

MTN 001 Study Specific Procedures Manual

Overview of Section Contents and Identification of Current Section Versions

Section Number	Section Title	Current Version Number	Current Version Date	Updates and Comments
1	Introduction	2.0	17 October 2008	<ul style="list-style-type: none"> • Update to contact information in Section 1.1 and include Figure 1-1 to outline MTN 001 Study Communication Contact Information
2	Protocol	2.0	17 October 2008	<ul style="list-style-type: none"> • Update to include Version 2.0 of the protocol, 03 September 2008
3	Documentation Requirements	2.1	5 November 2008	<ul style="list-style-type: none"> • Updated made to forms listed on Section Appendix 3-4, Section Appendix 3-5, and Section Appendix 3-6
4	Participant Accrual	2.3	10 August 2009	<ul style="list-style-type: none"> • Update to Section 4.1 to reflect change in accrual plan for study sites in Durban • Update Section 4.2.2 to clarify enrollment visit procedures must be conducted on the same day with the exception of obtaining informed consent • Update Section 4.2.6 to clarify the documentation of HIV testing • Updated Section 4.2.7.1 to clarify procedures for completing study prescription (s) at enrollment
5	Informed Consent	2.0	17 October 2008	<ul style="list-style-type: none"> • Update to Section 5.5 to include documentation procedures for the 21 week in –depth interview
6	Participant Follow-Up	2.2	10 August 2009	<ul style="list-style-type: none"> • Update Section 6.4 to clarify procedures for collecting rectal fluid samples • Update Section 6.6. to clarify procedures for completing prescriptions and/or Study Re-Supply during Follow-up • Updated Section 6.7 to clarify the documentation of HIV testing • Update to Section 6.12.6 to clarify the appropriate case report forms related to product hold/discontinuation to be completed at the study exit visit

Updated 11/23/2009

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7	Visit Checklists	2.2	18 September 2009	<ul style="list-style-type: none"> Updated to include procedures for collecting rectal fluid samples (applicable to the Bronx site only) and to clarify hematology testing procedures
8	Participant Retention	2.2	3 September 2009	<ul style="list-style-type: none"> Update to section 8.5 to add procedures for participants who discontinue participation in the study
9	Study Product Considerations For Non-Pharmacy Staff	2.1	18 May 2009	<ul style="list-style-type: none"> Update to Section 9.4 to remove reference to the MTN 001 Pharmacist Study Product Management Procedures manual
10	Clinical Considerations	2.4	24 August 2009	<ul style="list-style-type: none"> Update to Section 10.5.4 to clarify procedures for the documentation and reporting of expected non-menstrual bleeding associated with specimen collection
11	Adverse Event Reporting and Safety Monitoring	2.0	17 October 2008	<ul style="list-style-type: none"> Protocol version and date has been updated PSRT composition and contact information was updated on Section Appendix 11-3
12	Laboratory Considerations	2.4	23 November 2009	<ul style="list-style-type: none"> Update to Section 12.8 to clarify preparation and collection of rectal procedures for the Bronx site Update to Appendix 12-3 to clarify text for Algorithm for HIV testing at screening
13	Data Collection	2.0	5 November 2008	<ul style="list-style-type: none"> Updated to include updated SPA form, the Flow Cytometry form and the updated LDMS Specimen Tracking Sheets
14	Data Communiqués	2.0	17 October 2008	<ul style="list-style-type: none"> No changes
15	Study Reporting Plan	2.0	17 October 2008	<ul style="list-style-type: none"> MTN 001 SDMC Staff has been updated The CQC queries frequency in Table 15-1 was revised
16	Week 21 In-Depth Interviews	2.1	28 August 2009	<ul style="list-style-type: none"> Updated to reflect change in accrual plan for study sites in Durban

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Section 1. Introduction

This section specifies the sources of procedural information available to MTN 001 study staff, the responsibilities of MTN 001 Investigators of Record (IoRs), and the process by which each study site is approved to begin implementation of MTN 001. Also included is information on required submissions to Institutional Review Boards and/or Ethics Committees (IRBs/ECs).

1.1 Sources of Procedural Information

All study procedures must be conducted in accordance with the MTN 001 protocol (see Section 2). The purpose of this manual is to supplement the protocol, not to replace or substitute for it. In the event that this manual is inconsistent with the protocol, the specifications of the protocol take precedence. Please alert the MTN Coordinating and Operations Center (CORE) of any such inconsistencies.

Any study implementation questions that arise should be managed as follows (see also Figure 1-1):

- Questions related to interpretation and proper implementation of the MTN 001 protocol should be directed to the MTN CORE: Kailazarid Gomez and Sherri Johnson.
- Questions related to data collection and management should be directed to the MTN Statistical and Data Management Center (SDMC): Karen Patterson.
- Questions related to the collection, processing, testing, storage, and/or shipment of laboratory specimens should be directed to the MTN Network Laboratory (NL): Charlene Dezzutti and Edward Livant.
- Questions related to the investigational study products should be directed by the study site Pharmacist of Record to the DAIDS Protocol Pharmacist and the MTN CORE Pharmacist: Debra S. Mérés and Cindy Jacobson.
- Questions related to community involvement and/or the CWG should be directed to the Community Program Manager: Rhonda White
- When in doubt as to whether questions pertain to protocol interpretation, data collection, laboratory procedures, or product related, contact the MTN 001 Management Team: mtn001mgmt@mtnstopshiv.org.

Current contact details for the above-listed contact persons are found in Figure 1-1 as well as in the MTN Directory at: <http://mtnstopshiv.org/?q=search/user>

Figure 1-1: MTN-001 STUDY COMMUNICATION

Protocol Implementation and Procedural Related		
Kailazarid Gomez	919.544.7040 x11282	kgomez@fhi.org
Sherri Johnson	703-516-9779 x12127	sjohnson@fhi.org
Community Involvement Related		
Rhonda White	919.544.7040 x11515	rwhite@fhi.org
Data Management Related		
Karen Patterson	206-667-7052	karen@scharp.org
Laboratory Related		
Ted Livant	412.641.3772	livantew@upmc.edu
Product Related		
Debra Mérés,	301-451-2775	depayne@niaid.nih.gov
Cindy Jacobson	412.641.8913	cjacobson@mail.magee.edu
Clinical Management/PSRT Related		
Katherine Bunge	412.917.9936 (pager)	kbunge@mail.magee.edu
Nancy Connolly	206.523.1177	nancycsc@gmail.com
Ross Cranston	412.647.4007	cranstonr@dom.pitt.edu

1.2 Investigator Responsibilities

MTN 001 must be conducted in accordance with the United States (US) Code of Federal Regulations and the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (GCP). Copies of these regulations and guidelines are referenced in the MTN Manual of Operations (MOP) which is available at:

<http://www.mtnstopshiv.org/?q=node/398>

The Division of AIDS (DAIDS) Standard Operating Procedures (SOPs) for Essential Documents and Source Documentation are useful for interpreting and operationalizing the applicable regulations and guidelines in accordance with DAIDS expectations. Copies of these SOPs are provided in Section 16 of this manual.

At each site, MTN 001 also must be conducted in accordance with all site-specific regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular. Each site should file copies of all such regulations, policies, and guidelines in their MTN 001 essential document files (see also Section 3.1).

The IoR at each study site must sign both a protocol signature page and an FDA Form 1572 to formally indicate his/her agreement to conduct MTN 001 in accordance with the study protocol, applicable US regulations, and MTN policies. A copy of the protocol signature page can be found in the protocol in Section 2 of this manual. The obligations and responsibilities assumed by the IoR when signing the FDA Form 1572 are listed on the form itself, which can be found in Section 3.4.1 of the MTN MOP. IoRs may delegate their obligations and responsibilities for conducting MTN 001 to other study staff members, however delegation does not relieve the IoR of his/her ultimate responsibility for all study procedures performed and all study data collected. Delegation of IoR responsibilities must be formally documented throughout study implementation.

1.3 Study Activation Process

Prior to undertaking any study procedures, each study site must obtain approval to conduct MTN 001 from all responsible regulatory authorities and IRBs/ECs. Each site also must complete Protocol Registration procedures with the DAIDS Regulatory Compliance Center and Study Activation procedures with DAIDS and the MTN CORE, MTN SDMC, and MTN NL. Detailed information on the requirements of these pre-implementation procedures can be found in Section 10 of the MTN MOP. On a site-by-site basis, the MTN CORE will issue a Site-Specific Study Activation Notice when all study activation requirements have been met. At each site, no protocol-specified study procedures may be undertaken prior to issuance of the Site-Specific Study Activation Notice.

1.4 IRB/EC Submissions

Figures 1-2 and 1-3 list IRB/EC submission and approval requirements pertinent to MTN 001. Figure 1-2 lists requirements that must be met prior to study initiation. Figure 1-3 lists requirements that must be met during and following study implementation.

Each study site must submit all required documents to all responsible IRBs/ECs; however IRB/EC approval is not required for all documents. Documents requiring approval per US regulations and GCP guidelines are indicated in Figures 1-2 and 1-3. Additional approvals beyond those indicated in the figures may be required by individual IRBs/ECs; in such cases, all required documents must be submitted to and approved by the IRBs/ECs.

Study sites are encouraged to request an acknowledgement of receipt for all documents submitted to the IRBs/ECs, and to request that the IRBs/ECs note the effective and expiry dates of all approvals. Procedures for IRB/EC communication must be documented in site-specific SOPs. Documentation of all correspondence to and from all responsible IRBs/ECs (i.e., complete copies of all submissions, responses, and approvals) must be maintained in on-site essential document files.

**Figure 1-2
IRB/EC Submissions Required Prior to Initiation of MTN 001**

Document	Written Approval Required*
MTN 001 Protocol, Version 1.0 MTN 001 Protocol, Version 2.0 <i>Note: Some sites will be required to submit only Version 2.0 of the protocol.</i>	Yes
Informed consent forms: -Screening -Enrollment -Specimen Storage <i>Note: Informed consent forms may contain information on participant incentive amounts and schedules; however incentives may be approved through submission of separate materials.</i>	Yes
Investigator of Record current CV	No
Tenofovir Disoproxil Fumarate (TDF) Investigator's Brochure	No
Tenofovir 1% Vaginal Gel (Tenofovir Gel) Investigator's Brochure	No
Participant recruitment materials (prior to use)	Yes
Other written information for study participants (prior to use)	Yes
Other documentation required/requested by the IRB/EC	If required by IRB/EC

*Denotes approvals required by US regulations and GCP guidelines.

**Figure 1-3
IRB/EC Submissions Required During and Following Conduct of MTN 001**

Document	Written Approval Required*
Study status reports/updates (at least annually)	Yes
Protocol clarification memos (submission encouraged but not required by DAIDS)	No
Protocol amendments (including full amendments (to a new protocol version) and letters of amendment)	Yes
Amended informed consent forms (including forms that are amended due to protocol amendments as well as forms that are amended for site-specific reasons, e.g., to update participant incentive information or to update site contact information) <i>Note: Informed consent forms may contain information on participant incentive amounts and schedules; however incentives may be approved through submission of separate materials. If incentive information is not presented in the informed consent forms, the supplemental materials must be updated, submitted, and approved prior to modification of the incentive amounts or schedules.</i>	Yes
Tenofovir Disoproxil Fumarate (TDF) Investigator's Brochure updates	No
Tenofovir 1% Vaginal Gel (Tenofovir Gel) Investigator's Brochure updates	No
New information that may affect adversely the safety of study participants or the conduct of the study (e.g., IND Safety Reports) [§]	No
Reports of adverse events, serious adverse events, and/or events meeting criteria for expedited reporting to DAIDS (per IRB/EC requirements)	No
Protocol departures/deviations/violations (per IRB/EC requirements and/or as directed by DAIDS)	No
Investigator of Record current CV (if Investigator of Record changes during study)	No
Updated/additional participant recruitment materials (prior to use)	Yes
Updated/additional written information for study participants (prior to use)	Yes
Other documentation required/requested by the IRB/EC	If required by IRB/EC
Final study report/closure report	No

*Denotes approvals required by US regulations and GCP guidelines.

[§]Safety information will be distributed by the DAIDS RCC or the MTN CORE. All distributions will include instructions related to IRB/EC submission of the safety information.

Section 2. Protocol

This section contains a complete reference copy of the MTN 001 protocol. At the time of this printing, protocol Version 2.0, dated 3 September 2008, reflects current protocol specifications.

To ensure that this manual continues to reflect current protocol specifications in the future:

- Upon receipt of any protocol clarification memos, add a copy of the memo to this section.
- Upon receipt of any letters of amendment, add a copy of the letter of amendment to this section.
- Upon receipt of any full protocol amendments, replace the contents of this section with the amended protocol.

Further information on the content and required handling of protocol clarification memos, letters of amendment, and full amendments is available in Section 9.2 of the MTN Manual of Operations.

MTN-001

**Phase 2 Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations
of Tenofovir**

A Study of the Microbicide Trials Network

**Sponsored by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institutes of Health**

**Grant #:
5-U01-AI068633-03**

DAIDS Protocol #10617

**Co-Sponsored by:
CONRAD
Gilead Sciences, Inc.**

IND# 55,690

**Protocol Chair:
Craig W. Hendrix, MD**

Version 2.0

03 September 2008

MTN-001

Phase 2 Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir

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Phase 2 Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir

LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
ALT	alanine transaminase
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
BMD	bone mineral density
BV	bacterial vaginosis
CBC	complete blood count
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
C _{max}	maximum serum concentrations
C _{min}	minimum serum concentrations
CONRAD	Contraceptive Research and Development Organization
CRPMC	Clinical Research Products Management Center
CT	Chlamydia trachomatis
CTA	Clinical Trial Agreement
CVL	cervicovaginal lavage
CWG	community working group
DAIDS	Division of AIDS
DNA	deoxyribonucleic acid
EAE	expedited adverse event
EC	Ethics Committee
EC ₅₀	50% effective concentration
ELISA	Enzyme Linked Immunosorbent Assay
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practices
HBsAg	Hepatitis B surface antigen
HCG	human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus—Type 1
HPTN	HIV Prevention Trials Network
HSV	Herpes Simplex Virus
HSV-2	Herpes Simplex Virus—Type 2
IATA	International Air Transport Association
IND	investigational new drug
IoR	Investigator of Record
IRB	Institutional Review Board
IUD	intrauterine device
LDMS	Laboratory Data Management System
MSM	men who have sex with men
MTN	Microbicide Trials Network
NIAID	National Institute of Allergy and Infectious Disease

NIH	National Institutes of Health
PBMC	peripheral blood mononuclear cell(s)
PK	pharmacokinetic(s)
PMPA	9-[2-(Phosphonomethoxy)propyl]adenine
PoR	Pharmacist of Record
PPD	Pharmaceutical Product Development, Inc
ppts	participants
PrEP	pre-exposure prophylaxis
PSRT	Protocol Safety Review Team
RCC	Regulatory Compliance Center
RNA	ribonucleic acid
RT	reverse transcriptase
RTI	reproductive tract infection
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SD	standard deviation
SDA	Strand Displacement Assay
SDMC	Statistical Data Management Center
SMC	Study Monitoring Committee
SOP	standard operating procedure(s)
SSP	study specific procedure(s)
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate
ULN	upper limits of normal
US	United States
VOICE	Vaginal and Oral Interventions to Control the Epidemic

MTN-001

Phase 2 Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir

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MTN-001

**Phase 2 Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations
of Tenofovir**

INVESTIGATOR SIGNATURE FORM

**Version 2.0
03 September 2008**

A Study of the Microbicide Trials Network (MTN)

Sponsored by:

Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institutes of Health

Co-Sponsored by:

CONRAD
Gilead Sciences, Inc.

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for the study gel and/or tablets for the indication in which it was/they were studied. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the US Food and Drug Administration is notified. Publication of the results of this study will be governed by MTN policies. Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee, DAIDS, CONRAD, and Gilead Sciences, Inc. for review prior to submission.

I have read and understand the information in the Investigator's Brochure(s) and Package Insert(s), including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Name of Investigator of Record

Signature of Investigator of Record

Date

MTN-001

Phase 2 Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir

PROTOCOL SUMMARY

Short Title: Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir

Clinical Phase: 2

IND Sponsor: DAIDS (for both oral TDF 300 mg tablet and tenofovir 1% vaginal gel)

Protocol Chair: Craig W. Hendrix, MD

Sample Size: Approximately 144 evaluable participants (including 72 for intensive pharmacokinetic sub-study at domestic sites)

Study Population: Sexually active, HIV-uninfected women between the ages of 18 and 45 years

Participating Clinical Research Sites (CRS):

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- Botha's Hill CRS, Durban, KwaZulu-Natal, South Africa
- Makerere University - JHU Research Collaboration {MUJHU CARE LTD} CRS, Kampala, Uganda
- Alabama Microbicide CRS, Birmingham, USA
- Bronx-Lebanon Hospital Center CRS, Bronx, USA
- Case CRS, Cleveland, USA
- Pitt CRS, Pittsburgh, USA

Study Design: Phase 2, multi-site, randomized, six sequence, three period, open label crossover study

Study Duration: Approximately 21 weeks per participant, with projected six calendar months of accrual

Study Regimen:

Table 1: Study Regimen

	N	Period 1: 6 WEEKS	1 WK Wash-out	Period 2: 6 WEEKS	1 WK Wash-out	Period 3: 6 WEEKS	1 WK Wash-out
Sequence A	24	Oral		Vaginal		Oral + Vaginal	
Sequence B	24	Vaginal		Oral		Oral + Vaginal	
Sequence C	24	Oral + Vaginal		Oral		Vaginal	
Sequence D	24	Oral + Vaginal		Vaginal		Oral	
Sequence E	24	Oral		Oral + Vaginal		Vaginal	
Sequence F	24	Vaginal		Oral + Vaginal		Oral	

Primary Objectives:

- To compare adherence to and acceptability of three daily regimens of tenofovir (oral, vaginal, and dual use)
- To compare systemic and local pharmacokinetics (PK) among three regimens of tenofovir (oral, vaginal, and dual use) in a subset of participants

Primary Endpoints:

- **Adherence.** Participant self reported product use. For each woman, adherence to each regimen will be computed by dividing the number of daily doses she reports having taken (numerator) by the number of expected doses if she were fully adherent (denominator).
- **Acceptability.** The proportion of participants who indicate that they would be “unlikely” to use the study product in the future.
- **PK.** Area under the curve (AUC), maximum serum concentrations (C_{max}), and minimum serum concentrations (C_{min}) associated with oral, vaginal, and dual use regimens.

Secondary Objectives:

- To identify factors associated with product adherence, and whether these differ when women use one of three daily regimens of tenofovir (oral, vaginal, and dual use)
- To examine whether sexual activity or male condom use varies when women use one of three daily regimens of tenofovir (oral, vaginal, and dual use)
- To assess the timing of product use with sexual intercourse
- To determine the level of sharing of study products with non-participants (and to assess with whom products are shared)

- To characterize the differential safety profiles of three daily regimens of tenofovir (oral, vaginal, and dual use)

Secondary Endpoints

- Proportion of women who report taking at least 90% of expected daily doses, frequency of use during the follow-up interval using an ordinal measure (5 categories of use, never to always); number of days product missed or not used during the previous week
- Frequency (ordinal measures) of sexual activity and male condom use
- Time interval between product usage and sexual intercourse; sequence of product use and sexual intercourse
- Reported sharing of study product; quantity of shared study product
- Grade 3 or higher toxicity for systemic and local effects as defined by DAIDS Adverse Event (AE) Grading Table Version 1.0, December 2004, or Grade 3 or higher genital infection, pain or epithelial lesion as defined by the Female Genital Grading Table for Use in Microbicide Studies which cannot be directly attributed to another cause, and judged as definitely, probably, possibly, or probably not related to the study gel, applicator, or study tablet

Exploratory Objectives

- To build a PK model of intracellular-extracellular tenofovir levels in the systemic and female genital tract compartments
- To examine the impact of oral tenofovir and vaginal tenofovir gel on mucosal immunity in the female genital tract
- To assess correlation of PK and adherence measures

Exploratory Endpoints

- PK measures (blood, intracellular, and tissue values for C_{min} , C_{max} , and AUC)
- Intrinsic antimicrobial activity and mediators of mucosal immunity at Enrollment and at the end of each study period
- Adherence measures as outlined above for the primary and secondary objectives

1 KEY ROLES

1.1 Protocol Identification

Protocol Title: Phase 2 Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir

MTN Protocol Number: MTN-001

Date: 03 September 2008

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2 INTRODUCTION

2.1 Oral Pre-Exposure Prophylaxis and Microbicides in HIV/AIDS Prevention

More than twenty years after the first diagnosis of human immunodeficiency virus (HIV) was made, the epidemic continues to grow at an alarming rate. While recent developments in treatment have made dramatic improvements in life expectancy and quality of life for persons living with HIV and Acquired Immune Deficiency Syndrome (AIDS), these regimens are not cures, and remain inaccessible for much of the world. The XVI AIDS Conference highlighted these issues, as well as ongoing efforts to develop new strategies for the prevention of HIV transmission, particularly pre-exposure prophylaxis (PrEP) and microbicides.

Pre-exposure prophylaxis refers to the use of oral antiretroviral (ARV) medication to prevent HIV infection. Due to encouraging evidence from recent animal studies, scientific interest in PrEP continues, despite the closure of studies of PrEP using tenofovir in Cambodia and Cameroon due to local pressure. Pre-exposure prophylaxis has been controversial for several reasons. There is a concern about the cost of the regimen, especially in developing nations where cost-effective prevention strategies are needed most. More concerning, in particular for the HIV/AIDS activist community, is the perception that widespread use of PrEP could lead to problems with toxicity, ARV resistance, and behavioral disinhibition. The urgent need for new prevention strategies and the many unanswered questions surrounding PrEP call for further study on its potential as a safe, effective, and acceptable means of HIV prevention. The ideal PrEP drug would be safe, effective, have no or limited impact on HIV drug resistance, easy to use, and cost-effective. Such a product is yet to be identified.

Microbicides are being developed as substances intended to reduce or prevent transmission of HIV and/or other sexually transmitted infections (STIs) when applied topically to genital mucosal surfaces. A significant body of *in vitro*, animal, and preliminary clinical data suggests that tenofovir holds promise as a safe and effective vaginal microbicide. However, a potential weakness for single-compound ARV microbicides, such as tenofovir, is drug resistance. Exposure to HIV resistant to the ARV in a microbicide might result in protection levels that are less than those perceived by the user. It remains unclear whether drug resistance (and associated limitations in future treatment options) could occur with a microbicide containing a single ARV that is not significantly systemically absorbed. It has been posited that drug levels would likely be too low to select for drug resistant virus, but there are currently no data on this.

To address many of the unanswered questions, the MTN proposes to conduct a large scale safety and effectiveness study of both oral and vaginal tenofovir, MTN-003, the Vaginal and Oral Interventions to Control the Epidemic (VOICE) Study. Tenofovir will be studied because of its favorable toxicity and resistance profile, demonstrated efficacy against HIV-1 infection in some animal studies, and relatively rapid development path for use as a vaginal microbicide. The comparison of oral vs. vaginal tenofovir is being undertaken because each approach carries specific theoretical and operational advantages: while vaginal use may confer less systemic toxicity, oral use is less closely linked to sexual practices, and possibly could be administered by the woman without knowledge of her partner.

There are theoretical reasons to favor either approach for efficacy and/or selection of resistance, and only a head-to-head trial of these two approaches will begin to answer these questions. However, before a large efficacy trial comparing oral and vaginal preparations is undertaken, it is prudent to estimate the rates of adherence for both oral and vaginal regimens of tenofovir. While not strictly a feasibility study, MTN-001 will provide data on adherence to and PK of both oral and vaginal regimens of tenofovir that will inform the design of a large Phase 2B trial to compare the potential effectiveness of these two prevention strategies.

The behavioral factors associated with adherence to different prevention strategies are still being described. The full complement of HIV prevention strategies in the future arguably could include both orally and vaginally formulated agents. Different strategies will likely appeal to different risk populations, or even to the same woman at different times in her life. A woman's adherence to a particular prevention strategy would impact its effectiveness, as well as its effect on her health. Different levels of adherence to PrEP or ARV-based vaginal microbicide use could also have variable effects on the development of drug-resistant virus in a woman unknowingly infected with HIV. Thus, understanding how and why women are willing or able to commit to a particular formulation is vital to the development of safe and effective drug-based prevention strategies.

2.2 Tenofovir Disoproxil Fumarate (TDF)

2.2.1 Description

Tenofovir disoproxil fumarate is currently approved under the trade name Viread[®] for the treatment of HIV-1 infection in adults.¹ Tenofovir disoproxil fumarate is the oral pro-drug of tenofovir, an acyclic nucleotide analog (9-R-2-phosphonomethoxypropyl adenine, PMPA) with activity *in vitro* against retroviruses, including HIV-1 and HIV-2, as well as hepadnaviruses. Further information on TDF is available in the current version of the Viread[®] Package Insert.

2.2.2 Mechanism of Action

Once absorbed, TDF is rapidly converted by diester hydrolysis to tenofovir. Tenofovir is phosphorylated by cellular enzymes to tenofovir diphosphate, which is a competitive inhibitor of HIV-1 reverse transcriptase (RT) that terminates the growing deoxyribonucleic acid (DNA) chain.

2.2.3 Strength of Study Product

The strength of the TDF tablets will be the dose approved by the FDA for the indication of treatment of HIV-1 infection in adults (300 mg). For the treatment of HIV-1 infection, TDF is administered once daily as one 300 mg tablet and has excellent activity against wild type and many drug resistant viruses.

2.3 Tenofovir 1% Gel (Tenofovir Gel)

2.3.1 Description

Tenofovir gel contains 1 gm/100 mL of 9-[2-(Phosphonomethoxy)propyl]adenine (PMPA), an acyclic nucleotide analogue with activity against retroviruses, including HIV-1 and HIV-2, as well as hepadnaviruses.² Further information is available in the current version of the tenofovir gel investigator's brochure.

2.3.2 Mechanism of Action

Tenofovir is an acyclic nucleotide analogue of adenosine monophosphate. Tenofovir requires subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate (PMPApp). Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α , β , and mitochondrial DNA polymerase γ .

2.3.3 Strength of Study Product

The strength of tenofovir gel will be the dose (1%) previously tested in HPTN 050/IND 55,690, CONRAD A04-095/IND 73,382, CONRAD A04-099/IND 73,382, HPTN 059/IND 55,690, and MTN-002/IND 55,690. The application proposed in this study will deliver approximately 40 mg of tenofovir to the vaginal compartment.

2.4 *In Vitro* Studies

Anti-HIV-1 Activity

The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes.¹ The EC₅₀ (50% effective concentration) values for tenofovir were in the range of 0.04 µM to 8.5 µM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, zalcitabine, zidovudine), additive synergistic effects were observed. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G, and O (EC₅₀ values ranged from 0.5 µM to 2.2 µM) and strain specific activity against HIV-2 (EC₅₀ values ranged from 1.6 µM to 4.9 µM).

2.5 Animal Studies

2.5.1 Tenofovir and Tenofovir Disoproxil Fumarate

Toxicology

Tenofovir and TDF administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6 fold those observed in humans caused bone toxicity.¹ In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Four gravid rhesus monkeys were administered tenofovir subcutaneously once daily from 20 to 150 days of gestation (30 mg/kg; term: 165 ± 10 days).³ Fetuses were monitored sonographically, and maternal and fetal blood and urine samples were collected to assess hematologic parameters, clinical chemistry, insulin-like growth factor (IGF) levels, and bone biomarkers. Fetuses were delivered by hysterotomy near term for necropsy and evaluation of bone-related mechanical properties. Results of these studies showed 1) normal fetal development, although overall body weights and crown-rump lengths were less than those for age-matched controls ($p \leq .03$); 2) a significant reduction in circulating IGF-I ($p < .001$); 3) a small reduction in fetal bone porosity ($p \leq .03$); and 4) transient alterations in maternal body weights and bone-related biomarkers during treatment. Results of these studies suggest that chronic fetal exposure to subcutaneous tenofovir at the maternal dose of 30 mg/kg throughout gestation can alter select fetal parameters and transiently affect maternal bone biomarkers.

Evidence of renal toxicity was noted in 4 animal species.¹ Increases in serum creatinine, blood urea nitrogen, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Carcinogenesis and Mutagenesis

Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV infection.¹ At the high dose in female mice, liver adenomas were increased at exposures 16 times that observed in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose. Tenofovir disoproxil fumarate was mutagenic in the *in vitro* mouse lymphoma assay, but negative in an *in vitro* bacterial mutagenicity test (Ames test). In an *in vivo* mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice.

Reproductive Toxicity

There were no effects on fertility, mating performance or early embryonic development when TDF was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation.¹ There was, however, an alteration of the estrous cycle in female rats. Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

2.5.2 Tenofovir 1% Gel

Pharmacokinetics

Single-dose PK in female rabbits has been previously examined (0.5 mL, 1% weight/volume (w/v) tenofovir, 5 mg per animal, 50 μ Ci/kg).² Plasma concentrations of radioactivity were highest at the first sample time point (0.5 hr) and below the level of quantification at 24 hours. Pharmacokinetic parameters including the proportion of dose absorbed systemically could not be estimated, due to the very low plasma concentrations.

In a tissue distribution study using the same tenofovir vaginal gel formulation, dose and strength as the above study, eighteen female rabbits were administered an intravaginal dose using a gavage needle.² An additional eighteen rabbits received an intravaginal dose of 3% w/v tenofovir (15 mg per animal). Analysis of vaginal tissue sections found no clear relationship between tissue concentration and dose, with no consistent pattern of distribution. Very little radioactivity was recovered in non-vaginal tissues. Concentrations in blood (0.002 to 0.047 μ g-eq/g of tissue) exemplified the variability of distribution of the product.

The PK, excretion and tissue distribution of ¹⁴C-PMPA were evaluated in rats following intravaginal administration of an earlier formulation of tenofovir gel containing propylene glycol.⁴ Four female rats received a single intravaginal dose administered as an aqueous gel containing 20 mg tenofovir/g. Plasma concentrations of total radioactivity were highly variable; this was attributed to inconsistent retention of the formulation

within the vagina. The apparent C_{max} for tenofovir occurred at the earliest time point (15 minute), suggesting that absorption from the vagina was relatively rapid. Thereafter plasma concentrations declined with an approximate half-life of 1.6 hours. The bioavailability of intravaginal tenofovir was estimated by comparison of the observed $AUC_{(0-24)}$ with historical AUC data for an intravenous dose of 10 mg/kg tenofovir in rats (9.71 $\mu\text{g hr/mL}$). The observed systemic bioavailability of intravaginal tenofovir was 7.9%.

In the excretion and distribution study, two groups of four additional rats received a single intravaginal dose of ^{14}C -PMPA (approximately 10 mg/kg, 100 $\mu\text{Ci/kg}$) administered as an aqueous gel containing 20 mg tenofovir/g. This study found that much of the dose was lost from the vaginal orifice by leakage. Vaginal tissue contained 0.1% of the dose and less than 0.01% of the dose was recovered in the ovaries and uterus.

The PK of radiolabeled tenofovir was evaluated via plasma and vaginal biopsies collected from four rhesus monkeys following single-dose intravaginal administration of tenofovir 1% vaginal gel.² Radioactivity was detected starting at 15 minutes post application, with peak concentration of tenofovir in tissue at 8 hours and remaining high at 12 hours. No significant radioactivity was detected in whole blood or plasma.

The systemic and vaginal tissue bioavailability was assessed in female white New Zealand rabbits following single and multiple intravaginal doses (twice a day for 7 or 14 days) of 1mL of 1% tenofovir gel or a single intravenous (IV) solution of 10mg tenofovir.² Vaginal tissue was rinsed and samples collected at either 4 or 8 hours post-dose. System absorption following a single intravaginal dose was barely detectable, and only within the first 30 minutes. Multiple intravaginal administrations of tenofovir 1% gel and the single IV administration of 10mg tenofovir resulted in systemic levels of tenofovir (see Table 2).

Table 2: Tenofovir Bioassay Data

	Mean 1st Rinse Vaginal Surface (ng/mL)	Mean Vaginal Tissue Concentration (ng/gm)	C_{max} (ng/mL)	AUC (0-4 hr) (ng*hr/mL)
Single IV, 8 hr	362 (19-990)	950 (120-5,019)	10,221	4,013 (3,192-4,503)
Single vaginal, 8 hr	97 (7-415)	940 (10-7,277)	3	--
Single vaginal, 4 hr	1,441 (2-5,100)	2,817 (35-11,780)	5	--
Twice daily x 7d vaginal, 4 hr	1,086 (145-4,369)	3,146 (448-14,429)	239 (29-808)	342 (54-1,037)
Twice daily x 14d vaginal, 4 hr	3,361 (33-8,000)	11,409 (245-50,102)	71 (24-197)	94 (12-229)

Toxicology

The preclinical toxicity of tenofovir gel has been evaluated in 14-day rat and 10-day rabbit vaginal irritation and toxicity studies.^{5,6} Daily intravaginal administration of tenofovir gel produced no vaginal irritation in rats ($\leq 10\%$ tenofovir) and minimal to mild vaginal irritation in rabbits (3% or 10% tenofovir).

2.6 Clinical Studies

2.6.1 Tenofovir Disoproxil Fumarate 300 mg Tablet

Additional safety information from clinical studies on the TDF 300 mg tablet is available in the Viread[®] package insert.¹ Tenofovir disoproxil fumarate PK have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir PK are similar between these populations.

Pharmacokinetics

Tenofovir disoproxil fumarate is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from TDF in fasted patients is approximately 25%. Following oral administration of a single dose of TDF 300 mg to HIV-1 infected patients in the fasted state, C_{max} are achieved in 1.0 ± 0.4 hrs. Maximum serum concentration and AUC values are 296 ± 90 ng/mL and 2287 ± 685 ng-hr/mL, respectively. The PK of tenofovir are dose proportional over a TDF dose range of 75 to 600 mg and are not affected by repeated dosing. Tenofovir PK are similar in male and female patients.

Safety

Gilead Study 903, a randomized, double-blind trial conducted in the United States, Europe and South America, was designed to compare the efficacy and safety of a treatment regimen of TDF, lamivudine (3TC) and efavirenz to a regimen of stavudine (d4T), lamivudine and efavirenz in 600 antiretroviral-naïve HIV-1 infected patients. In Gilead Study 903 through 144 weeks of study treatment, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients receiving TDF + lamivudine + efavirenz ($-2.2\% \pm 3.9$) compared with patients receiving stavudine + lamivudine + efavirenz ($-1.0\% \pm 4.6$). Changes in BMD at the hip were similar between the two treatment groups ($-2.8\% \pm 3.5$ in the TDF group vs. $-2.4\% \pm 4.5$ in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of TDF-treated patients vs. 21% of the stavudine treated patients lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the TDF group and 6 patients in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) in the TDF group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1.25 Vitamin D levels

were also higher in the TDF group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of TDF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

Tenofovir is eliminated by renal elimination, including tubular secretion. Thus, dose-interval adjustments are necessary for TDF in patients with significant renal impairment. TDF-induced nephrotoxicity has been reported, especially in patients with other medical problems or pre-existing renal dysfunction.

The most common (occurring in 2% or more of recipients) treatment-emergent adverse events in the Gilead 903 study in HIV-infection treatment naive adults receiving TDF + lamivudine + efavirenz included whole body (headache, pain, fever, abdominal pain, back pain, asthenia), gastrointestinal (diarrhea, nausea, dyspepsia, vomiting), musculoskeletal (arthralgia, myalgia), nervous system (depression, insomnia, dizziness, anxiety), respiratory (pneumonia), and skin rash. The most frequent laboratory abnormalities were elevations in fasting cholesterol, creatine kinase, amylase, or aspartate aminotransferase (AST) or alanine transaminase (ALT), hematuria, and decreased absolute neutrophil count. The frequency of all these events and laboratory abnormalities was similar or lower in the TDF treated group compared to the stavudine treated group.

A Phase 1, 17-day, open label, two-way crossover, randomized PK study to evaluate the relative bioavailability and bioequivalence between a single dose of TDF oral powder and tablet formulation was conducted in healthy male and female participants.¹. The primary objective of this study was to determine the relative bioavailability between the investigational oral powder and the 300 mg tablet formulations of TDF. A total of 32 healthy adult participants (including non-pregnant, non-lactating females) were recruited at a single US site and received TDF in the study.

Preliminary results of this completed study indicate that TDF administered as the 300 mg tablet or oral powder formulation was well tolerated. No participant discontinued the study because of an adverse event. All treatment-emergent adverse events after administration of the oral powder and tablet were Grade 1 in severity. No serious adverse events or deaths occurred. Two participants discontinued the study by withdrawing consent. Treatment-emergent AEs were reported in 12 of 30 participants (40%, 18 events) after administration of the oral powder compared with 15 of 32 participants (47%, 29 events) after administration of the tablet. Headache, experienced by 4 participants (13%), was the most frequently reported treatment-emergent AE after the oral powder. The most frequently reported treatment-emergent AE after administration of the tablet were headache (6 participants, 19%) and dizziness (4 participants, 13%). Treatment-emergent AEs considered by the investigator to be related to study drug included flatulence (2 participants, 7 %), hot flush (1 participant, 3%) and increased ALT (1 participant, 2%); all related AEs were Grade I in severity and resolved without therapy. No AEs were considered related to study drug after administration of the tablet.

Peterson, et al. evaluated the safety of TDF 300 mg daily versus placebo for prevention of HIV-1 infection in women in a Phase 2 double-blind study conducted at 3 sites in West Africa.⁷ The study closed prematurely resulting in insufficient power to evaluate efficacy. In the primary safety analysis, with 428 person-years (p-y) of follow up, there was no significant difference in the rate of safety endpoints (defined as grade 2 or higher serum creatinine, grade 3 or 4 transaminase elevation, or grade 3 or 4 phosphate abnormality). Among the 368 participants on TDF, none had grade 3 or 4 transaminase elevation or grade 2 or higher creatinine. One TDF recipient had self-limited grade 3 phosphate.

Several other studies examining the safety and effectiveness of oral tenofovir as PrEP are underway or in later stages of planning. These include the following:

- The Bangkok Tenofovir Study (safety and efficacy of daily tenofovir to prevent parenteral HIV infection among injection drug users, CDC)
- Botswana TDF/FTC Oral HIV Prophylaxis Trial (Safety and Efficacy of Daily Oral Antiretroviral Use for the Prevention of HIV Infection in Heterosexually Active Young Adults in Botswana, CDC)
- Extended Safety Study of Tenofovir Disoproxil Fumarate (TDF) Among HIV-1 Negative Men (clinical and behavioral safety and tolerability of oral daily TDF use as pre-exposure prophylaxis (PrEP) to prevent HIV infection in uninfected men, CDC)
- Chemoprophylaxis for HIV Prevention in Men (IND# 71,859)
- FHI 2/Phase III daily Truvada or daily oral placebo for prevention of HIV-1 infection
- Parallel Comparison of Tenofovir and Emtricitabine/Tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples (IND #75,365)
- Safety and Effectiveness of Tenofovir Disoproxil Fumarate (TDF) in high-risk, West African women (FHI)

2.6.2 Tenofovir 1% Gel

Pharmacokinetics

A Phase 1 Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel, also known as HPTN 050, is a recently completed study of tenofovir vaginal gel with published data.⁸ Eighty-four (60 HIV negative and 24 HIV positive) women applied

either 0.3% or 1% tenofovir gel once or twice daily for 14 days. Systemic absorption was limited (maximum serum levels 3.1-25.8 ng/mL).

Safety

In HPTN 050, the tenofovir 1% gel formulation was well tolerated in both HIV negative and HIV positive women. Although 92% reported at least 1 AE, the majority (87%) were mild and limited to the genitourinary tract (77%). Product concentration, sexual activity and HIV status were not associated with a specific AE pattern. No clinically significant systemic toxicity was observed. Tenofovir gel showed no negative effect on vaginal microflora in this study. No new resistance mutations evolved in plasma or cervicovaginal lavage (CVL) after 14 days of tenofovir gel use but 3 women had plasma mutations associated with low level tenofovir resistance at day 0 and 14 (M41L, L210M, \pm T215I/Y). The AE and safety profile in HPTN 050 was reviewed by the FDA who subsequently permitted the initiation of the HPTN 059 extended safety protocol for vaginal tenofovir. Tenofovir gel was highly acceptable to both women and men in HPTN 050, with 94% of the women and 81% of the men indicating that they would definitely or probably use tenofovir gel in the future.

In a male tolerance study of tenofovir 1% gel (CONRAD A04-099) (IND #73,382), tenofovir gel was well tolerated in men following seven days of once daily exposure, for 6 to 10 hours, to the penis. There were few reported and observed genital findings after product use including mild pain (burning, irritation, discomfort) and pruritis². All observed findings were classified as mild, were small in size and required no treatment. All reported symptoms were mild, of short duration and resolved by the final visit. There were no noticeable differences between signs and symptoms of genital irritation observed in the circumcised compared to the uncircumcised group.^{2,9}

A Phase 2 study of tenofovir 1% gel (HPTN 059) has completed follow up. This study assessed safety and acceptability of, and adherence to a regimen of tenofovir gel for vaginal use in HIV-uninfected women versus a placebo gel. Exploratory objectives included measurement of vaginal flora characteristics, assessment of the effects of gel on genital cytokine and chemokine expression, and the evaluation of cytokine and chemokine expression to correlate expression with evidence of inflammation, epithelial disruption and genital symptoms. The study was a Phase 2 four arm, three site, randomized, controlled trial comparing gel used once daily and gel used prior to intercourse, to placebo gel, with 6 months gel exposure and follow-up. The study was conducted among 200 women in Pune, India; Birmingham, Alabama, USA; and New York, New York, USA. Participants were sexually active, HIV-uninfected women between ages 18 and 50, but not menopausal or post menopausal. Participants had six months of study gel exposure and six months of follow-up. They were randomized to either once daily or coitally dependent group, and received either tenofovir or placebo gel. Participants received single use unit dose tubes and single use applicators.

No statistically significant differences were seen between those receiving active and placebo gels in complete blood count, liver function tests, or renal function tests. Among those using a study gel daily, no participants had pelvic exam findings involving

generalized erythema or severe edema or deep epithelial disruption at any follow-up visit during the study. At the Week 24 Visit, no participants had exam findings suggestive of vaginitis, cervicitis, superficial disruption, disrupted blood vessels, or intermenstrual bleeding. Adherence to study gel was high, and was supported by PK data. 79% of women reporting gel use in past 12 hours had low but detectable plasma tenofovir supporting self-reported adherence data. Daily and coital use was highly acceptable to women. These data suggest a favorable safety and acceptability profile of tenofovir gel, and support routine monitoring for genital findings among women without genital symptoms at six month intervals.¹⁰

Several other tenofovir gel studies are ongoing or in development. These include:

- CONRAD A04-095: Single Dose and 14-Day Once or Twice-daily Pharmacokinetic Study of the Vaginal Microbicide Agent 1% Tenofovir Gel (IND #73,382)
- CAPRISA 004: Safety and Effectiveness Study of a Candidate Vaginal Microbicide for Prevention of HIV (proposed Phase 2B, two-arm, double-blinded, randomized, placebo controlled trial comparing 1% tenofovir gel with a placebo gel)
- MTN-002: Phase 1 Study of the Maternal Single-Dose Pharmacokinetics and Placental Transfer of Tenofovir 1% Vaginal Gel among Healthy Term Gravidas
- MTN-003: Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate (TDF) Tablet and TDF-Emtricitabine Tablet for the Prevention of HIV-1 Infection in Women
- MTN-006: Phase 1 Rectal PK Study of Tenofovir 1% Gel
- MTN-007: Phase 1 Rectal Safety of Tenofovir 1% Gel

2.7 Study Hypothesis and Rationale

2.7.1 Study Hypothesis

MTN-001 hypothesizes that:

- There will be no differences in rates of adherence among the three study regimens
- There will be no difference in rates of acceptability among the three study regimens
- Tissue levels of PMPA will be similar irrespective of the route of administration

- Oral TDF will be associated with higher concentrations of PMPA in the blood compared to topical administration of PMPA
- Neither tenofovir 1% gel nor oral TDF regimens will adversely impact the genital tract environment

2.7.2 Rationale

Adherence

The microbicide field will benefit from evaluating the behavioral factors associated with adherence to oral and vaginal formulations. The full complement of HIV prevention strategies in the future may include orally or vaginally formulated agents or combinations of both. Accordingly, efficacy trials should also include regimens of oral, vaginal, or both types of formulations. Different strategies will likely appeal to different risk populations, or even to the same woman at different times in her life. A woman's level of adherence to a particular prevention modality would impact its effectiveness, depending on her use pattern and the drug's half-life, as well as its effect (if any) on her health. It has also been posited that different levels of adherence to PrEP or ARV-based vaginal microbicide use could have variable effects on the development of drug-resistant virus in a woman unknowingly infected with HIV.

Understanding how product formulation affects adherence and acceptability as well as sexual risk taking (particularly condom use) is important to the design of the MTN-003 trial. Including adherence and acceptability assessments in MTN-001 permits the opportunity to pilot measures that would be used in MTN-003. Behavioral adherence data could complement interpretation of PK results.

Pharmacokinetics

No head to head comparison controlling for intra-individual variability has yet been performed to compare the relative efficiency of oral versus vaginal tenofovir dosing to achieve measurable and "adequate" (biologically active based on *in vitro* data) tenofovir levels in tissue. MTN-001 will evaluate intracellular tenofovir diphosphate concentrations (active moiety) in tissue and blood to inform PK models.

Based on data from HPTN 050, only one-third of the participants are expected to yield measurable levels in blood after vaginal dosing of tenofovir gel. An intensive PK sampling cohort is planned to provide frequent blood samples and carefully timed corresponding cervicovaginal lavage (CVL) and vaginal biopsy, one per woman, at pre-specified times after dosing to provide data for a sparse sampling analysis. For this reason and for reasons of technical capacity, all participants at the United States (US) sites will enter the Intensive PK substudy.

2.8 Justification of Dosing

Tenofovir 1% Vaginal Gel

Choice of the tenofovir 1% vaginal gel concentration for MTN-001 is based on both animal and clinical evidence suggesting an appropriate safety profile and potency. Animal and human studies have demonstrated minimal vaginal irritation at this concentration. A rabbit vaginal irritation test identified tenofovir 1% gel as being histopathologically identical to sham or control treatment, while on a qualitative basis 3% gel was more irritating to vaginal epithelia.² The tolerability of the 1% gel was confirmed in the HPTN 050 Phase 1 study, the Phase 1 dose ranging study of tenofovir gel (0.3% once daily, then 1.0% once daily, then 0.3% twice daily followed by 1% twice daily).^{2, Error! Bookmark not defined.} In this study, of the two doses and frequencies studied in the dose finding cohort, the 1% gel applied intravaginally twice daily for 14 days was well tolerated and was identified as the highest practical dose and frequency for further study in subsequent cohorts.

The second line of evidence is from vaginal transmission inhibition studies performed in non-human primates.² Six separate studies provided evidence for efficacy of the gel over a range of tenofovir concentrations of 1% to 10%. Although the total data are limited and a powered statistical determination as to the efficacy of tenofovir 1% gel versus 0.3% and 10% cannot be made, empirical examination of the efficacy data identifies tenofovir 1% gel as the lowest efficacious concentration tested when given within two hours of infection.

Finally, limited vaginal PK tenofovir data in primates demonstrate that tenofovir gel is broadly distributed in vaginal tissues following vaginal application and can penetrate to epithelial tissues.¹¹ The amount of tenofovir administered by intravaginal application of 4 grams of a 1% dose (40 mg) is highly active against HIV and results in a reduction of plasma HIV ribonucleic acid (RNA) of 1.5 log₁₀ copies / mL after daily administration for 21 days. Comparison of the predicted cervicovaginal concentrations of tenofovir gel delivered to those achieved systemically at the standard treatment dose of 300 mg TDF, and tenofovir's characteristic prolonged intracellular half-life (diphosphate form, nine to 50 hours depending upon cell type), suggest that an initial and potentially durational barrier to HIV transmission may be possible. In terms of weighing potential risks and benefits, the tenofovir 1% gel minimizes the potential risks of vaginal epithelial toxicity while providing the potential benefit of delivering sufficient tenofovir to achieve an initial and possibly durational barrier to infection.

Tenofovir Disoproxil Fumarate 300 mg Tablets

Choice of the 300 mg strength of the TDF tablet is based upon practical and scientific considerations. The TDF 300 mg tablet, or Viread[®], is the medication US FDA approved for the indication of treatment of HIV-1 infection. More than 12,000 people have been treated with TDF alone or in combination with other antiretroviral medications for periods of 28 days to 215 weeks in Phase 1–3 clinical trials and expanded access studies. A total of 1,544 patients have received TDF 300 mg once daily in Phase 1–3 clinical trials and over 11,000 people have received TDF in expanded access studies. A

significant body of safety data has been accumulated for daily use of the TDF 300 mg tablet. In addition, data on tenofovir PK and anti-viral activity in humans suggest a reasonable expectation of effectiveness as a prevention strategy.

3 OBJECTIVES

3.1 Primary Objectives

- To compare adherence to and acceptability of three daily regimens of tenofovir (oral, vaginal, and dual use)
- To compare systemic and local PK among three regimens of tenofovir (oral, vaginal, and dual use) in a subset of participants

3.2 Secondary Objectives

- To identify factors associated with product adherence, and whether these differ when women use one of three daily regimens of tenofovir (oral, vaginal, and dual use)
- To examine whether sexual activity or male condom use varies when women use one of three daily regimens of tenofovir (oral, vaginal, and dual use)
- To assess the timing of product use with sexual intercourse
- To determine the level of sharing of study products with non-participants (and to assess with whom products are shared)
- To characterize the differential safety profiles of three daily regimens of tenofovir (oral, vaginal, and dual use)

3.3 Exploratory Objectives

- To build a PK model of intracellular-extracellular tenofovir levels in the systemic and female genital tract compartments
- To examine the impact of oral and vaginal tenofovir gel on mucosal immunity in the female genital tract
- To assess correlation of PK and adherence measures

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-001 will be a Phase 2, multi-site, randomized, six sequence, three period open label crossover study of adherence to and PK of TDF 300 mg tablet and tenofovir 1% gel.

4.2 Summary of Major Endpoints

- Participant self-reported product use. For each woman, adherence to each regimen will be computed by dividing the number of daily doses she reports having taken (numerator) by the number of expected doses if she were fully adherent (denominator).
- The proportion of participants who indicate they would be "unlikely" to use the study product in the future.
- AUC, C_{max} , and C_{min} associated with oral, vaginal, and dual use regimens.

4.3 Description of Study Population

The study population will include approximately 144 evaluable generally healthy 18-45 year-old women who are HIV-uninfected, non-pregnant, sexually active and using adequate contraception, as described in Section 5.2. Among the total approximately 144 evaluable participants, the 72 participants enrolled at all US study sites will undergo more intensive specimen collection for PK analysis. These participants are hereafter referred to as "Intensive PK participants."

4.4 Time to Complete Enrollment

The approximate time to complete study enrollment is expected to be six months. The time of total study duration is expected to be a minimum of approximately one year, including the study follow-up period.

4.5 Study Groups

Six study sequences are planned. The 144 planned participants will be randomized equally across all 6 sequences in a 1:1:1:1:1:1 ratio. All study participants will be assigned to complete each study period (oral, gel, oral plus gel) once in an order that will be randomly assigned. Up to 204 women may be enrolled to reach the target of 144 evaluable women (i.e., women who have at least one follow-up visit with adherence data in each of the three periods of the study). The need to enroll replacement participants for enrollees will be dependent on whether the enrollee had at least one full period of the study with no follow-up adherence data. Details on procedures for

participant replacement are outlined in the MTN-001 Study Specific Procedures (SSP) Manual (www.mtnstopshiv.org).

4.6 Sequence and Duration of Trial Periods

The total duration of participation from the Enrollment Visit to the Termination Visit is 21 weeks, including three six-week study periods and three one-week washout periods. Visits may be completed within specified windows around target dates. Detailed information regarding visit windows will be thoroughly described in the MTN-001 SSP Manual.

4.7 Expected Duration of Participation

The expected duration of participation for individual enrolled participants is 21 weeks. No study data will be collected after the 21-Week Termination Visit unless the participant has an AE that has not resolved or stabilized, or is pregnant at the Termination Visit, or is a participant in the in-depth interview with applicable characteristics described in Section 7.6.

Participants who have AEs at the Termination Visit that have not resolved or stabilized will be followed beyond the Termination Visit until a clinically acceptable resolution of the AE(s) is confirmed and documented. Clinical acceptability of resolution will be determined by the site IoR in consultation with the Protocol Safety Review Team (PSRT). For participants who are pregnant at the Termination Visit, study site staff will make every effort to follow the participant until such time that her pregnancy outcome can be ascertained and documented.

4.8 Sites

Seven study sites are planned for this trial:

- Umkomaas CRS, Durban, KwaZulu-Natal, South Africa
- Botha's Hill CRS, Durban, KwaZulu-Natal, South Africa
- Makerere University - JHU Research Collaboration {MUJHU CARE LTD} CRS, Kampala, Uganda
- Alabama Microbicide CRS, Birmingham, USA
- Bronx-Lebanon Hospital Center, Bronx, USA
- Case CRS, Cleveland, USA
- Pitt CRS, Pittsburgh, USA

5 STUDY POPULATION

5.1 Selection of the Study Population

The inclusion and exclusion criteria outlined in Sections 5.2 and 5.3 will be utilized to ensure the appropriate selection of study participants for MTN-001.

5.1.1 Recruitment

Participants will be recruited from family planning and other health clinics, colleges, and other venues. Site IRB-approved media advertisements, telephone scripts, and fliers may be used.

5.1.2 Retention

Each site will establish participant retention procedures. Study site staff members at each site are responsible for developing and implementing site-specific standard operating procedures (SOPs) to target high rates of retention. Further information on retention of participants is provided in Section 10.6.

5.1.3 Enrollment Guidelines

Women with participation in any other investigational drug or device trial in the 30 days prior to enrollment will not be enrolled in this study. Study participants will be required to refrain from enrollment in other clinical trials involving investigational or prohibited drugs or investigational devices during their involvement in this study. Participants who report after enrollment their concurrent participation in such trials will be discussed by the PSRT and may be discontinued from use of study product(s). In this case they will be encouraged to remain in the study and will be followed with all safety evaluations deemed clinically appropriate by the Investigator and the NIH medical officer.

5.2 Inclusion Criteria

Women must meet all of the following criteria to be eligible for inclusion in the study:

- 1) Age 18-45 years (inclusive) at screening, verified per site SOP
- 2) Willing and able to provide written informed consent for screening and enrollment
- 3) Willing and able to provide adequate locator information, as defined in site standard operating procedures
- 4) HIV-uninfected based on testing performed by study staff during screening procedures (per applicable algorithm in Appendix II)

- 5) In general good health at screening and enrollment, as determined by the site IoR or designee
- 6) Per participant report at screening, usual menstrual cycle with at least 21 days between menses (does *not* apply to participants who report using a progestin-only method of contraception at screening, e.g., Depo-Provera)
- 7) Calculated creatinine clearance at least 70 mL/min by the Cockcroft-Gault formula where creatinine clearance (female) in mL/min = $(140 - \text{age in years}) \times (\text{weight in kg}) \times 0.85/72$ (serum creatinine in mg/dL)
- 8) Per participant report at screening, sexually active, defined as having had penile-vaginal intercourse at least four times in the four weeks prior to screening
- 9) Per participant report at screening and enrollment, intending to continue penile-vaginal intercourse at least once per week for the duration of study participation
- 10) Per participant report at enrollment, use of an effective method of contraception at enrollment, and intending to use same method for the duration of study participation and one month thereafter; effective methods include hormonal methods (except vaginal ring); intrauterine contraceptive device (IUCD) inserted at least 30 days prior to enrollment; and sterilization (of participant or her sexual partner or partners as applicable, self-report acceptable)
- 11) Normal Pap smear result at screening or adequately documented normal Pap smear result per SSP within the 12 calendar months prior to screening
- 12) At screening and enrollment, agrees not to participate in other research studies involving drugs, medical devices, or vaginal products for the duration of study participation

5.3 Exclusion Criteria

Women who meet any of the following criteria will be excluded from the study:

- 1) Participant reported history of:
 - a) Known adverse reaction to either of the study products (ever)
 - b) Known adverse reaction to latex (ever)
 - c) Any current male sex partner with known history of adverse reaction to latex (ever)
 - d) More than three partners in the month prior to screening

- e) Pathologic bone fracture not related to trauma
 - f) Last pregnancy outcome within 90 days or less prior to enrollment
 - g) Gynecologic or genital procedure (e.g., biopsy, tubal ligation, dilation and curettage) 90 days or less prior to enrollment
 - h) Participation in any other research study involving drugs, medical devices, or vaginal products 30 days or less prior to enrollment
 - i) Non-therapeutic injection drug use in the 12 months prior to Screening
 - j) As determined by the site investigator, any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease, including active tuberculosis, or any other medical condition that could make participation unsafe
- 2) Pregnant at screening or enrollment, or per participant report intending to become pregnant during the period of study participation
 - 3) Per participant report, breastfeeding at screening or enrollment
 - 4) At screening:
 - a) any liver function test result greater than 1.5 X the site laboratory ULN (upper limit of normal)
 - b) serum creatinine greater than the site laboratory ULN for women
 - c) hemoglobin less than 10.0 g/dl
 - d) platelet count less than 100,000/mm³
 - e) serum phosphate level below site laboratory LLN (lower limit of normal)
 - f) positive for hepatitis B surface antigen (HBsAg)
 - g) 2+ or greater dipstick urinalysis results for protein
 - 5) At screening or enrollment, unwilling to comply with study participation requirements, including attendance at all scheduled study visits
 - 6) At screening or enrollment,

- a) Has a clinically apparent pelvic exam finding (observed by study staff) involving Grade 2 or higher genital lesions, erythema, and/or edema (grading per the Female Genital Grading Table for Use in Microbicide Studies)
 - b) Has any other abnormal physical or pelvic exam finding that, in the opinion of the investigator or designee, would contraindicate study participation
- 7) At screening, is diagnosed with RTI requiring treatment per current WHO guidelines or UTI. Reproductive tract infections requiring treatment include symptomatic bacterial vaginosis (BV), symptomatic vaginal candidiasis, other vaginitis, trichomoniasis, chlamydia, gonorrhea, syphilis, active HSV lesions, chancroid, pelvic inflammatory disease, genital sores or ulcers, cervicitis, genital warts of the labia minora, vagina, or cervix, or any other symptomatic genital warts. Presence of genital warts exterior to labia minora requiring treatment is also exclusionary. Note that HSV-2 seropositive with no active lesions is allowed (since treatment is not required).

If diagnosed at screening: otherwise eligible participants with any of the above RTIs/conditions requiring treatment and/or UTI may be enrolled after completing treatment and all symptoms have resolved, as long as treatment is completed and all symptoms have resolved within 30 days of obtaining informed consent for screening.

- 8) Per participant report, use of the following at enrollment, and/or anticipated use during the period of study participation:
- a) use of a diaphragm, vaginal ring, and/or spermicide for contraception
 - b) acyclovir or valacyclovir
 - c) post-exposure prophylaxis for HIV exposure
 - d) TDF/emtricitabine
 - e) non-study vaginal products
- 9) At screening or enrollment, has any social or medical condition that, in the investigator's opinion, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

5.4 Selection of Participants for In-Depth Interviews

A subset of participants will be eligible for participation in an in-depth interview regarding their experiences using the study products. As outlined in Section 7.7, a random sample of women will be invited back for an in-depth interview before the study

activities are completed. Data on acceptability and factors affecting adherence will be collected during these in-depth interviews. As one of the purposes of collecting data during the in-depth interview is to facilitate the examination of variance in participant responses noted among different data collection modalities, responses during in-depth interviews need not be reconciled with data collected in other study measures.

6 STUDY PRODUCT

6.1 Regimen

Study participants will be randomized to one of the six study regimen sequences (see Table 2). Each study sequence will consist of three study periods and three wash out periods, for a total duration of 21 weeks. The study period duration is six weeks. A one week wash out period will immediately follow each six-week study period.

Study participants will receive the study products which are tenofovir 1% gel and tenofovir disoproxil fumarate 300 mg tablet. The daily regimen for each six week study period will consist of either single formulation of tenofovir 1% gel or tenofovir disoproxil fumarate 300 mg tablet. The dual formulation use will consist of tenofovir 1% gel and tenofovir disoproxil fumarate 300 mg tablet. All participants will be instructed to complete each study period, which will include the vaginal use of tenofovir 1% gel, the oral use of tenofovir disoproxil fumarate 300 mg tablet, and the dual use of both, in the order designated by their randomized sequence.

Table 3: Study Regimen

	N	Period 1: 6 WEEKS	1 WK Wash- out	Period 2: 6 WEEKS	1 WK Wash- out	Period 3: 6 WEEKS	1 WK Wash- out
Sequence A	24	Oral		Vaginal		Oral + Vaginal	
Sequence B	24	Vaginal		Oral		Oral + Vaginal	
Sequence C	24	Oral + Vaginal		Oral		Vaginal	
Sequence D	24	Oral + Vaginal		Vaginal		Oral	
Sequence E	24	Oral		Oral + Vaginal		Vaginal	
Sequence F	24	Vaginal		Oral + Vaginal		Oral	

6.2 Administration

Tenofovir 1% Gel (Single Formulation Period)

Study participants will be instructed to insert one dose (the entire contents of one applicator) of tenofovir 1% gel into the vagina once daily for the 6-week study period. Vaginal administration of study product should occur before bedtime, usually in the evening, or the longest period of rest.

If a participant misses a dose, she must insert vaginally the missed dose as soon as possible, unless the next dose is estimated to be due within 6 hours. If the next dose is

estimated to be due within 6 hours, the missed dose must be skipped. The next dose will be inserted vaginally as originally scheduled.

Tenofovir Disoproxil Fumarate 300 mg Oral Tablet (Single Formulation Period)

Study participants will be instructed to take one tenofovir disoproxil fumarate 300 mg tablet, by mouth, once daily for the 6-week study period. Tenofovir disoproxil fumarate 300 mg should be taken at bedtime, usually in the evening, or the longest period of rest, without regard to meals. If a participant misses a dose, she must take the missed dose, by mouth, as soon as possible, unless the next dose is estimated to be due within 6 hours. If the next dose is estimated to be due within 6 hours, the missed dose must be skipped. The next dose must be taken, by mouth, as originally scheduled.

Tenofovir 1% Gel and Tenofovir Disoproxil Fumarate 300 mg Oral Tablet Period (Dual Formulation Period)

Study participants will be instructed to insert one dose (the entire contents of one applicator) of tenofovir 1% gel into the vagina and take one tenofovir disoproxil fumarate 300 mg tablet by mouth once daily for the 6-week study period. Both vaginal and oral study products should be administered approximately at the same time, before bedtime, usually in the evening, or the longest period of rest.

If a participant misses a dose of tenofovir 1% gel, she must vaginally insert the missed tenofovir 1% gel as soon as possible unless the next dose is estimated to be due within 6 hours. If a participant misses a tenofovir disoproxil fumarate tablet dose, she must take the missed dose, by mouth, as soon as possible, unless the next dose is estimated to be due within 6 hours. If either dose is estimated to be due within 6 hours, the missed dose should be skipped. The next dose must be taken as originally scheduled.

6.3 Study Product Formulation

6.3.1 Tenofovir 1% Gel

Tenofovir 1% gel (weight/weight) is a gel formulation of tenofovir (PMPA, 9-[(R)-2-(phosphonomethoxy)propyl]adenine monohydrate), formulated in purified water with edetate disodium, citric acid, glycerin, methylparaben, propylparaben, hydroxyethylcellulose, and pH adjusted to 4-5. Tenofovir 1% gel is a transparent, viscous gel that will be filled into applicators to form pre-filled, single-use applicators. Each pre-filled applicator will contain a dose of approximately 4 grams (equal to 4 mL) of tenofovir 1% gel for delivery. Tenofovir 1% gel must be stored at controlled room temperature, 25°C (77°F), at all times. Excursions are permitted between 15°C and 30°C (59°F and 86°F).

6.3.2 Tenofovir Disoproxil Fumarate 300 mg Tablets

Tenofovir disoproxil fumarate (Viread[®], TDF) oral tablet, is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil. Tenofovir disoproxil fumarate tablets should be stored and dispensed in the original container. Each bottle should contain a silica gel desiccant to protect the product from humidity, and this should remain in the container. Tenofovir disoproxil fumarate should be stored at 25°C (77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F).

6.4 Study Product Supply and Accountability

6.4.1 Study Product Supply

Tenofovir 1% Gel

Tenofovir 1% gel will be supplied by CONRAD (Arlington, VA, USA). Under direction from CONRAD, DPT Laboratories, Ltd (San Antonio, TX, USA) which is a contract manufacturing facility, will manufacture the tenofovir 1% gel, and analyze/release tenofovir 1% gel under current good manufacturing practices (cGMP). DPT Laboratories Ltd will fill the applicators with tenofovir 1% gel to create pre-filled applicators and package each applicator and plunger in a wrapper. DPT Laboratories will over-wrap the pre-filled applicators and plungers. There will be 14 wrapped applicators and plungers packed in each carton. The cartons will be shipped under a temperature controlled carrier to the NIAID Clinical Research Products Management Center (CRPMC).

Tenofovir Disoproxil Fumarate 300 mg Tablets

Tenofovir disoproxil fumarate 300 mg tablets will be supplied by Gilead Sciences, Inc. (Foster City, CA, USA). Each bottle of tenofovir disoproxil fumarate will contain 30 tablets. The tablets will be shipped under a temperature controlled carrier to the CRPMC.

Tenofovir 1% Gel and Tenofovir Disoproxil Fumarate 300 mg Tablets

Study products supplied by CONRAD and Gilead Sciences, Inc. will be available through the CRPMC. The Pharmacist of Record can obtain the study products for this protocol by following the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section Study Product Control.

6.4.2 Dispensing

Study products are dispensed only to enrolled participants, upon receipt of a written prescription from an authorized prescriber. Depending on the study period in which the participant is currently enrolled, single formulation or dual formulation, she will receive either a bottle of 30 tenofovir disoproxil fumarate tablets, 28 pre-filled applicators, or 30

tenofovir disoproxil fumarate tablets and 28 pre-filled applicators (two cartons of 14 applicators), at each regularly scheduled study visit, except the End of Study Period Visits, and the Termination Visit. See Section 7 Study Procedures, for study visit schedule.

6.4.2.1 Pharmacokinetic Visit

As described in Section 7.8 Pharmacokinetic Procedures, all participants will have one timed PK measure at the end of each period of study product administration. These PK measures will occur at the end of the study period visit during their vaginal gel period, the oral period and during the combined oral and vaginal gel period. Participants will be instructed to take the tenofovir disoproxil fumarate tablet by mouth, insert the tenofovir 1% gel, or both, the evening before the end of the study period clinic visit as throughout the study period.

Participants will be instructed to return any unused study product to the clinic at the end of the study period visit. One of the doses the participant brings to this visit will be administered for the timed PK measures. This will be the final dose of study product for that study period. The dose for the timed PK measure will be administered in the clinic.

6.4.2.2 Male Condoms and Panty Liners

All participants will receive male condoms and be offered panty liners. The condoms and panty liners will be dispensed by the clinic staff, and made available in the clinic.

6.4.3 Accountability

Each site PoR is required to maintain complete records of all study products received from the CRPMC and subsequently dispensed. All unused study products must be returned to the CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are provided in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section Study Product Control.

6.4.4 Retrieval of Unused Study Products

Study participants will be instructed to return all unused study products to the site at each scheduled study visit. In the event that unused study products are not returned at the end of each study period visit, study staff members will make every effort to encourage participants to return study product as soon as possible. Participants who are permanently discontinued from study product use will be instructed to return all

unused study product to the site. The PoR will store returned unused study products in designated areas within the study pharmacy.

6.5 Participant Counseling

Adherence counseling will be provided to study participants upon enrollment into the study, and every visit thereafter to help ensure high rates of study product use. Condom counseling will be provided to all study participants. Counseling will be provided in accordance with standard study methods that will address such topics as participant-centered strategies to remember to use the study gel and/or tablet daily (depending on study period) and to ensure the availability of the study product both in the home and away from home. Counseling also will include reminders to contact study staff with questions about study product use and requests for additional supplies. For participants who have adherence problems, every effort will be made to identify adherence strategies to increase their rates of study product use throughout the course of the study. Participants will be counseled to avoid douching as this will alter exposure to study gel.

Participants also will be instructed to:

- Only use the study gel vaginally
- Not insert vaginal products other than study gel and tampons during menstruation
- Not use other participants' study products
- Not distribute their study products to other people

Participant behaviors regarding condom and study gel use data will be collected via standardized questions developed by the Protocol Team in conjunction with study site staff and community representatives, to maximize the accuracy of self-reported data.

6.6 Assessment of Participant Adherence

Assessment of participant adherence will be addressed using a quantitative instrument and in-depth qualitative interviews (conducted with a subset of study participants).

6.7 Concomitant Medications

With the exception of medications listed as prohibited, enrolled study participants may use concomitant medications during study participation. All concomitant medications reported throughout the course of the study will be recorded on case report forms designated for that purpose. Prescription medications, over-the-counter preparations, vitamins and nutritional supplements, recreational drugs, and herbal preparations will all be recorded on forms for concomitant medications.

6.7.1 Prohibited Medications and Procedures

Study participants should not use the following medications concurrent with use of study products: acyclovir, valacyclovir, and tenofovir disoproxil fumarate/emtricitabine. Should participants report use of any of these medications, they will be required to discontinue use of study products, but will continue to complete all scheduled study visits. Participants who report medication use for post-exposure prophylaxis for possible HIV exposure will be advised to discontinue use of study products and complete all scheduled study visits.

The following devices and preparations should not be used during study participation: diaphragm, vaginal ring, and/or spermicide and all non-study vaginal products other than tampons during menstruation. Participants who report current use of these preparations and devices will be counseled regarding the use of alternative methods and provided or referred to family planning services as needed for provision of alternative methods. Participants are not expected to require gynecologic surgical procedures during follow-up; however, should such a procedure be required, the site IoR or designee will consult the PSRT regarding ongoing product use by the participant

6.7.2 Recommended Medications and Procedures

Study sites will provide a single brand of latex male condoms and a single brand of panty liners to study participants for use during study participation. Instructions and counseling on use of these products will be provided as needed throughout study participation. Male condoms will not be impregnated or coated with spermicide. In the event that a participant needs additional male condoms or panty liners between visits, she may request these from clinic staff at any time.

7 STUDY PROCEDURES

An overview of the study visits and evaluations schedule is presented in Appendix I. Presented in this section is additional information on visit-specific study procedures. A detailed instruction guide will be provided in the MTN-001 SSP Manual.

In addition to any Interim Visits that may occur in accordance with guidance outlined in Section 7.5, the following visits should take place for study participants:

- Screening
- Enrollment (Period 1 Start)
- 3-Week Visit (Mid-Study-Period Visit)
- 6-Week Visit (Period 1 End)
- 7-Week Visit (Period 2 Start)

- 10-Week Visit (Mid-Study-Period Visit)
- 13-Week Visit (Period 2 End)
- 14-Week Visit (Period 3 Start)
- 17-Week Visit (Mid-Study-Period Visit)
- 20-Week Visit (Period 3 End)
- 21-Week Visit (Termination Visit)

Participants will be in an oral dosing period, vaginal dosing period, and dual dosing period, once each (with the order depending on randomization) during the three six-week study periods (Study Period 1, Study Period 2, and Study Period 3). The Enrollment Visit will be considered Day 0 and will occur no more than 30 days following provision of informed consent for screening. The 3-Week, 10-Week, and 17-Week Visit are at the approximate midpoints of Study Periods 1, 2, and 3. These three visits will all follow the format of the Mid-Study-Period Visit. Each of the three study periods is followed by a one-week washout period. These washout periods are between the 6- and 7-Week Visit, the 13- and 14-Week Visit, and the 20- and 21-Week Visit.

7.1 Screening Visit

After providing written informed consent, potential participants may be screened for eligibility over two or more visits if necessary, and eligibility must be confirmed at the enrollment visit. For participants who do not meet the eligibility criteria, screening will be discontinued when ineligibility is determined.

For participants who are found to be presumptively eligible based on the evaluations listed below at these visits, final eligibility will be confirmed at the Enrollment Visit, scheduled to take place within 30 days of the initial Screening Visit. Unless otherwise specified in the protocol or MTN-001 SSP Manual, laboratory testing for the purpose of determining eligibility will occur prior to (and does not include testing during) the Enrollment Visit.

Table 4: Screening Visit

Screening Visit (up to 30 days prior to Enrollment Visit)	
Component	Procedure/Analysis
Administrative	<ul style="list-style-type: none"> • Obtain written informed consent for screening • Assign Participant ID (PTID) • Collect demographic information • Collect locator information • Assess behavioral eligibility • Provide reimbursement for study visit • Schedule next visit
Clinical	<ul style="list-style-type: none"> • Collect medical/menstrual history • Collect concomitant medications • Perform physical exam (See Appendix III) • Perform pelvic exam (See Appendix III) • Provide counseling <ul style="list-style-type: none"> ○ Contraceptive ○ HIV pre- and post-test ○ HIV/STI risk reduction and male condom • *Treat for UTI/RTIs/STIs, treat or refer for other findings • Provide male condoms
Urine	<ul style="list-style-type: none"> • Collect urine sample <ul style="list-style-type: none"> ○ Qualitative hCG ○ Dipstick UA (*and culture if positive for leukocyte esterase or nitrates; may omit if culture not standard of care for UTI diagnosis) ○ SDA for chlamydia and gonorrhea
Blood	<ul style="list-style-type: none"> • Collect blood samples <ul style="list-style-type: none"> ○ Complete blood count ○ Liver function tests ○ Serum chemistries ○ Syphilis serology (confirmatory tests as needed) ○ HIV-1 test (confirmatory tests as needed) ○ HBsAg
Pelvic	<ul style="list-style-type: none"> • Collect pelvic samples <ul style="list-style-type: none"> ○ Vaginal pH ○ Vaginal fluid for wet mount (BV, Candida, Trichomonas) ○ *Herpes culture (at sites where standard of care for diagnosis) ○ **Pap smear

*If indicated (see also MTN-001 SSP Manual) **If no documented normal pap result within 12 months of screening is available.

7.2 Enrollment Visit

Table 5: Enrollment Visit

Enrollment Visit (Study Period 1 Start)	
Component	Procedure/Analysis
Administrative	<ul style="list-style-type: none"> • Obtain written informed consent for enrollment (incl. compr. checklist) • Review/update locator information • Confirm behavioral eligibility, required for eligibility assessment • Schedule next study visit • Provide reimbursement for visit • Follow procedures for randomization assignment
Clinical	<ul style="list-style-type: none"> • Update medical/menstrual history, required for eligibility assessment • Update concomitant medications, required for eligibility assessment • Document pre-existing conditions, required for eligibility assessment • Perform physical exam (See Appendix III), required for eligibility assessment • Perform pelvic exam (See Appendix III), required for eligibility assessment • *Treat for UTI/RTIs/STIs, treat or refer for other findings • Provide counseling <ul style="list-style-type: none"> ○ Contraceptive ○ *HIV pre- and post-test ○ HIV/STI risk reduction and male condom ○ Protocol adherence, product use/adherence • Provide male condoms and watch device, offer panty liners
Behavioral	<ul style="list-style-type: none"> • Administer baseline behavioral assessment
Urine	<ul style="list-style-type: none"> • Collect urine sample <ul style="list-style-type: none"> ○ Qualitative hCG, required for eligibility assessment ○ *SDA for chlamydia and gonorrhea ○ *Dipstick UA (*and culture if positive for leukocyte esterase or nitrates; may omit if culture not standard of care for UTI diagnosis)
Blood	<ul style="list-style-type: none"> • Collect blood specimens <ul style="list-style-type: none"> ○ Complete blood count (not for eligibility assessment) ○ Liver function tests (not for eligibility assessment) ○ Serum chemistries (not for eligibility assessment) ○ *Syphilis serology (confirmatory tests as needed) ○ *HIV-1 test (conf. tests as needed) (per standard in site SOP) ○ Plasma for storage
Pelvic Samples	<ul style="list-style-type: none"> • Collect vaginal pH • Collect vaginal fluid for wet mount (BV, Candida, Trichomonas) • Collect CVL for vaginal flora proteomics and markers of inflammation • *Collect herpes culture (at sites where standard of care for diagnosis)
Study Product Supply	<ul style="list-style-type: none"> • Appropriate number of doses of study product(s)

*If indicated (see also MTN-001 SSP Manual)

7.3 Follow-up Visits

Table 6: Mid-Study-Period Visit

Mid-Study-Period Visit (3-Week Visit, 10-Week Visit, and 17-Week Visit)	
Component	Procedure/Analysis
Administrative	<ul style="list-style-type: none"> • Review/update locator information • Schedule next study visit • Provide reimbursement for study visit
Clinical	<ul style="list-style-type: none"> • Collect interval medical/menstrual history • Review/update concomitant medications • Record/update adverse events • Perform physical exam (See Appendix III) • Perform pelvic exam (See Appendix III) • *Treat for UTI/RTIs/STIs, treat or refer for other findings • Reinforce counseling <ul style="list-style-type: none"> ○ Contraceptive ○ HIV/STI risk reduction and male condom ○ Protocol adherence, product use/adherence • Provide male condoms, offer panty liners • *Provide watch device
Behavioral	<ul style="list-style-type: none"> • Administer behavioral assessment
Urine	<ul style="list-style-type: none"> • Collect urine sample <ul style="list-style-type: none"> ○ Qualitative hCG ○ *Dipstick UA (*and culture if positive for leukocyte esterase or nitrates; may omit if culture not standard of care for UTI diagnosis) ○ *SDA for chlamydia and gonorrhea
Blood	<ul style="list-style-type: none"> • Collect blood <ul style="list-style-type: none"> ○ Liver function tests ○ Serum chemistries ○ Tenofovir ○ *Syphilis serology (confirmatory tests as needed) ○ *HBsAg
Pelvic Specimens	<ul style="list-style-type: none"> • *Collect vaginal pH • *Collect vaginal fluid for wet mount (BV, Candida, Trichomonas) • *Collect herpes culture (at sites where standard of care for diagnosis)
Study Product Supply	<ul style="list-style-type: none"> • Collect unused study product (gel and/or tablets) • Appropriate number of doses of study product(s)

*If indicated (see also MTN-001 SSP Manual)

Table 7: End of Study Period Visit

End of Study Period Visit (6-Week Visit, 13-Week Visit and 20-Week Visit)	
Component	Procedure/Analysis
Administrative	<ul style="list-style-type: none"> • Review/update locator information • Schedule next study visit • Provide reimbursement for study visit
Clinical	<ul style="list-style-type: none"> • Collect interval medical/menstrual history • Review/update concomitant medications • Record/update adverse events • Perform physical exam (See Appendix III) • Perform pelvic exam (See Appendix III) • *Treat for UTI/RTIs/STIs, treat or refer for other findings • Reinforce counseling <ul style="list-style-type: none"> ○ Contraceptive ○ HIV/STI risk reduction and male condom ○ Protocol adherence • Male condoms, panty liners
Behavioral	<ul style="list-style-type: none"> • Administer behavioral assessment
Urine	<ul style="list-style-type: none"> • Collect urine sample <ul style="list-style-type: none"> ○ Qualitative hCG ○ *SDA for chlamydia and gonorrhea ○ *Dipstick UA (*and culture if positive for leukocyte esterase or nitrates; may omit if culture not standard of care for UTI diagnosis)
Blood	<ul style="list-style-type: none"> • Insert lock for specimen collection (may be omitted for non-intensive PK) • Collect blood specimens (see also Section 7.8 for time points) <ul style="list-style-type: none"> ○ Pre-dose <ul style="list-style-type: none"> ▪ Liver function tests ▪ Serum chemistries ▪ Flow cytometry (at sites with capacity) ▪ Tenofovir ▪ Plasma for storage ▪ Peripheral blood mononuclear cells (PBMC) for intracellular tenofovir diphosphate (sites with capacity) ○ Post-dose <ul style="list-style-type: none"> ▪ Tenofovir ▪ PBMC for intracellular tenofovir diphosphate (sites with capacity) ○ *Syphilis serology (confirmatory tests as needed) ○ *HBsAg • *Remove lock after specimen collection completed (as indicated)

(CONTINUED)

**End of Study Period Visit
(6-Week Visit, 13-Week Visit and 20-Week Visit) (CONTINUED FROM PREVIOUS PAGE)**

Component	Procedure/Analysis
Pelvic Specimens	<ul style="list-style-type: none"> • Collect vaginal pH • Collect vaginal fluid for wet mount (BV, Candida, Trichomonas) • Collect CVL for vaginal flora proteomics, markers of inflammation, and tenofovir level (see also Section 7.8 for time points) • Intensive PK/Sub-study ONLY (see also Section 7.8 for time points) <ul style="list-style-type: none"> ○ Collect cervical cytology brush for tenofovir ○ Collect vaginal biopsies for tenofovir • *Collect herpes culture (at sites where standard of care for diagnosis)
Study Product Supply	<ul style="list-style-type: none"> • Collect unused study product (gel and/or tablets) • *Dispense observed dose(s) of study product(s) (if participant does not bring sufficient unused study product to visit for use as observed dose(s), study product(s) will be dispensed to participant during the study visit)

*If indicated (see also MTN-001 SSP Manual), **Intensive PK/Sub-study (US sites) participants only (see also Section 7.8)

Table 8: 7-Week and 14-Week Study Visit

7-Week and 14-Week Study Visits (Study Period 2 Start, Study Period 3 Start)	
Component	Procedure/Analysis
Administrative	<ul style="list-style-type: none"> • Review/update locator information • Schedule next study visit • Provide reimbursement for study visit
Clinical	<ul style="list-style-type: none"> • Collect interval medical/menstrual history • Review/update concomitant medications • Record/update adverse events • Perform physical exam (See Appendix III) • Perform pelvic exam (See Appendix III) • *Treat for UTI/RTI/STIs, treat or refer for other findings • Reinforce counseling <ul style="list-style-type: none"> ○ Contraceptive ○ HIV/STI risk reduction and male condom ○ Protocol adherence, product use/adherence • Provide male condoms, offer panty liners • Provide HIV pre- and post-test counseling
Urine	<ul style="list-style-type: none"> • Collect urine sample <ul style="list-style-type: none"> ○ Qualitative hCG ○ *Dipstick urinalysis (*and culture if positive for leukocyte esterase or nitrates; may omit if culture not standard of care for UTI diagnosis) ○ *SDA for chlamydia and gonorrhea
Blood	<ul style="list-style-type: none"> • Collect blood specimens <ul style="list-style-type: none"> ○ Complete blood count ○ Liver function tests ○ Serum chemistries ○ HIV-1 test (confirmatory tests as needed) ○ *Syphilis serology (confirmatory tests as needed) ○ *HBsAg
Pelvic	<ul style="list-style-type: none"> • *Collect vaginal pH • *Collect vaginal fluid swab for wet mount for BV, Candida, Trichomonas • *Collect herpes culture (at sites where standard of care for diagnosis)
Study Product Supply	<ul style="list-style-type: none"> • *Collect any unused study product (gel and/or tablets) • Dispense appropriate number of doses of study product(s)

*If indicated (see also MTN-001 SSP Manual)

Table 9: 21-Week Visit

21-Week Visit (Study Termination Visit)	
Component	Procedure/Analysis
Administrative	<ul style="list-style-type: none"> • Review/update locator information • *Schedule next study visit • Provide reimbursement for study visit
Clinical	<ul style="list-style-type: none"> • Collect interval medical/menstrual history • Review/update concomitant medications • Record/update adverse events • *Perform physical exam (See Appendix III) • *Perform pelvic exam (See Appendix III) • *Treat UTI/RTIs/STIs, treat or refer for other findings • Provide HIV pre- and post-test counseling • Reinforce counseling <ul style="list-style-type: none"> ○ Contraceptive ○ HIV/STI risk reduction and male condom • Provide male condoms
Behavioral	<ul style="list-style-type: none"> • Conduct in-depth interview (subset of participants, see Section 7.7)
Urine	<ul style="list-style-type: none"> • Collect urine sample <ul style="list-style-type: none"> ○ Qualitative HCG ○ *Dipstick urinalysis (*and culture if positive for leukocyte esterase or nitrates; may omit if culture not standard of care for UTI diagnosis) ○ *SDA for chlamydia and gonorrhea
Blood	<ul style="list-style-type: none"> • Collect blood specimens <ul style="list-style-type: none"> ○ Complete blood count ○ Liver function tests ○ Serum chemistries ○ HIV-1 test (confirmatory tests as needed) ○ Plasma for storage ○ *Syphilis serology (confirmatory tests as needed) ○ *HBsAg
Pelvic	<ul style="list-style-type: none"> • *Collect vaginal pH • *Collect vaginal fluid swab for wet mount for BV, Candida, Trichomonas • *Collect herpes culture (at sites where standard of care for diagnosis)
Study Product Supply	<ul style="list-style-type: none"> • *Collect any unused study product (gel and/or tablets)

*If indicated (see also MTN-001 SSP Manual)

7.4 Follow up Procedures for Participants who Discontinue Study Product

Participants who discontinue study product will be encouraged to remain in the study if they are willing, for safety evaluations according to the study follow up schedule with the exceptions described below.

7.4.1 Participants Who Seroconvert to HIV

Study staff will capture seroconversions on study CRFs. As discussed in Section 13.9.2, participants may be offered participation in the MTN Seroconverter Study (MTN-015). Protocol-specified procedures will continue except:

- HIV serology
- All PK assessments
- Provision of study gel
- Provision of study tablets
- Product use/adherence counseling
- Counseling for HIV/STI risk reduction. Counseling will be modified to address primary and secondary HIV/STI prevention for infected women.

7.4.2 Participants Who Become Pregnant

All protocol-specified study procedures will continue except:

- Provision of study gel
- Provision of study tablets
- Product use/adherence counseling
- All PK assessments

7.4.3 Participants Who Become Infected with Hepatitis B

All protocol-specified study procedures will continue except:

- Provision of study gel
- Provision of study tablets
- Product use/adherence counseling
- All PK assessments

7.4.4 Participants Who Voluntarily Discontinue Study Gel and/or Tablets

All protocol-specified study procedures will continue except:

- Provision of discontinued study product(s)
- Product use/adherence counseling (if both products are discontinued)
- All PK assessments applicable during the discontinuation period

7.4.5 Participants Who Are Discontinued from Study Gel and/or Tablet Use by the Site Investigator

All protocol-specified study procedures will continue except:

- Provision of discontinued study product(s)
- Product use/adherence counseling (if both products are discontinued)
- All PK assessments applicable during the discontinuation period

7.5 Interim Contacts and Visits

Interim contacts and visits (those between regularly scheduled follow up visits) may be performed at participant request or as deemed necessary by the investigator or designee at any time during the study. Participants will have a urine pregnancy test at each interim visit. All interim contacts and visits will be documented in participants' study records and on applicable case report forms.

Some Interim Visits may occur for administrative reasons. For example the participant may have questions for study staff or require additional study supplies. Other interim contacts and visits may occur in response to AEs experienced by study participants. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care.

Table 10: Interim Visits and Contacts

Interim Visits and Contacts	
Component	Procedure/Analysis
Administrative	<ul style="list-style-type: none"> • Review/update locator information • *Schedule next study visit
Clinical	<ul style="list-style-type: none"> • Collect interval medical/menstrual history • Review/update concomitant medications • Record/update adverse events • *Perform physical exam (See Appendix III) • *Perform pelvic exam (See Appendix III) • *Treat UTI/RTIs/STIs, treat or refer for other findings • *Reinforce counseling <ul style="list-style-type: none"> ○ Contraceptive ○ HIV risk reduction and male condom ○ Product use/adherence ○ Protocol adherence • *Provide HIV pre- and post-test counseling • *Provide male condoms, offer panty liners • *Provide watch device
Urine	<ul style="list-style-type: none"> • Collect urine sample <ul style="list-style-type: none"> ○ Qualitative hCG ○ *Dipstick urinalysis (*and culture if positive for leukocyte esterase or nitrates; may omit if culture not standard of care for UTI diagnosis) ○ *SDA for chlamydia and gonorrhea
Blood	<ul style="list-style-type: none"> • *Collect blood specimens <ul style="list-style-type: none"> ○ *Complete blood count ○ *Liver function tests ○ *Serum chemistries ○ *HIV-1 test (confirmatory testing as needed) ○ *Tenofovir ○ *Syphilis serology (confirmatory testing as needed) ○ *HBsAg
Pelvic	<ul style="list-style-type: none"> • *Collect vaginal pH • *Collect vaginal fluid swab for wet mount for BV, Candida, Trichomonas • *Collect herpes culture (at sites where standard of care for diagnosis)
Study Product Supply	<ul style="list-style-type: none"> • *Collect any unused study product (gel and/or tablets) • *Dispense doses of product(s)

*If indicated (see also MTN-001 SSP Manual)

7.6 Clinical Evaluations and Procedures

See Appendix III for an outline of physical exam and pelvic exam components.

7.7 Behavioral Measures

The primary behavioral study aims will be addressed using a quantitative instrument and in-depth qualitative interviews (conducted with a subset of study participants). Counts of unused study products, which will be returned to the clinics, also will be compared to reports of adherence.

1. The quantitative instrument will be structured around the following topics:
 - Sexual activity
 - Product adherence (frequency and duration of use)
 - Male condom use (frequency and in combination with study products)
 - Timing of sexual activity in relationship to product use
 - Intra-vaginal practices
 - Sharing of study products, including with whom products shared (also selling of products and product theft)
 - Experiences using study products, including obstacles to use, side effects and partner involvement

2. We will identify a random sample of eight participants from five sites (Umkomaas CRS, Botha's Hill CRS, Makerere University-JHU Research Collaboration CRS, Case CRS, and Pitt CRS) to complete an in-depth interview that addresses use of study drugs and male condoms during the trial. These interviews will be conducted by a trained study interviewer and will follow a structured questionnaire guide. They will be approximately 30 minutes in duration and will be conducted at the 21-Week study visit. Participants will be compensated for their completion of the in-depth interview. These interviews will be digitally recorded using a handheld digital voice recorder and this file will be transcribed and translated for analysis.

If, at a particular site, women with differential adherence between study products are not included in the random sample of in-depth interview participants, up to two additional participants from that site, who did report differential adherence between products, will be invited to complete an in-depth interview as well. Reported adherence levels will be monitored by site staff so that eligible women can be identified. These interviews will be conducted within one month of the 21-Week study visit.

The interviews will include the following topics:

- Challenges to use of study products
- Perceived benefits of use
- Preferences between oral and vaginal formulations

- Preferences between a single and dual use regimen
- Partner knowledge of study participation and reaction to product use
- Who knew that they had access to anti-retroviral drugs
- Whether they were ever asked to share (or sell) the product or if someone tried to take it away from them

7.8 Pharmacokinetic Procedures

7.8.1 Pharmacokinetic Procedures: All Participants

During all three study periods (single formulation and dual formulation), participants will provide specimens for PK measures. There are two types of visits that include PK measures: the Mid-Study-Period Visits and the End of Study Period Visits. As noted below and except where limited by site capacity, some PK procedures will be applicable for all participants.

Mid-Study-Period Visits

All participants will provide blood samples for tenofovir levels at Mid-Study-Period Visits (3-Week, 10-Week, and 17-Week). Every effort will be made to record the three doses of tenofovir taken prior to these visits with hour: minute accuracy. These visits do NOT include an observed dose of study product(s) in the study clinic.

End of Study Period Visits

Both US and non-US participants will have an observed dose of study product(s) at these visits.

All participants will provide a blood sample prior to their observed dose of study product(s) at the End of Study Period Visits (6-Week, 13-Week, and 20-Week). This blood sample will be used for:

- Blood tenofovir level
- *At sites with capacity*, cell lysate (intracellular tenofovir diphosphate)
- *At sites with capacity*, cell counts by flow cytometry. These cell counts serve as surrogate markers for cell activation and proliferation, respectively, and will be used as covariates during intracellular model building.

7.8.2 Pharmacokinetic Procedures: Non-Intensive PK Participants

At non-US sites, participants will take part at End of Study Period Visits (6-Week, 13-Week, and 20-Week) in the collection of samples for a Non-Intensive PK portion of the study.

Table 11: Non-Intensive PK Participants Only

	PRE-DOSE	POST-DOSE TIMING		
		1-3 HOURS	3-5 HOURS	5-7 HOURS
Blood: <ul style="list-style-type: none"> Flow cytometry (at sites with capacity) 	Study Regimen Sequences A, B, C, D, E, and F			
Blood: <ul style="list-style-type: none"> PBMC cell lysate (intracellular tenofovir diphosphate) (at sites with capacity) Tenofovir 	Study Regimen Sequences A, B, C, D, E, and F	Study Regimen Sequences E and F	Study Regimen Sequences A and B	Study Regimen Sequences C and D
CVL <ul style="list-style-type: none"> Tenofovir Proteomics and markers of inflammation 		Study Regimen Sequences E and F	Study Regimen Sequences A and B	Study Regimen Sequences C and D

For simplicity, Non-Intensive PK Participants will be assigned to a sampling window based on their sequence randomization assignment:

- 1-3 hours, Sequences E and F
- 3-5 hours, Sequences A and B
- 5-7 hours, Sequences C and D

Thus, it is expected that Non-Intensive PK Participants will have one sampling time pre-dose (blood), and only one sampling time post-dose (blood and CVL).

For individual participants, post-dose blood and CVL samples will occur within 15 – 30 minutes of each other (either sample may be taken first). The times of these samples must be recorded with hour: minute accuracy. The same sampling time point (within 15 minutes) in each study period should be used for all of a participant’s End of Study Period Visits.

The time of the observed dose(s) of study product(s) administered in clinic and the three prior doses taken must be recorded with hour: minute accuracy. Participants will

receive a small watch or similar timekeeping device to assist them in remembering or recording (on a study-provided form) the times of these doses. An additional device may be provided in the event of a lost or stolen device.

7.8.3 Pharmacokinetic Procedures: Intensive PK Participants (US Sites)

All US sites will participate in Intensive PK measures (n=72). These Intensive PK measures will occur at the End of Study Period Visits during all three study periods. Participants in the Intensive PK portion of the study will provide cervical cells (collected by cytology brush) and vaginal tissue (collected by biopsy at two locations in the vagina) which will be used for measurement of tenofovir levels.

The time of the dose administered in clinic and the three prior doses taken must be recorded with hour: minute accuracy. Participants will receive a small watch or similar timekeeping device to assist them in remembering or recording the times of these doses. Participants taking part in the Intensive PK measures will not follow procedures outlined in Table 10.

For the Intensive PK cohorts at US sites, the End of Study Period sample timing will require a second randomization which will be stratified within each of the two sites. All 72 participants will be randomized into groups (shown below as M, N, O, and P) to provide collection of pelvic exam specimens, either pre-dose, 2, 4, or 6 hours after dosing, providing up to 18 women per time point.

- All Intensive PK participants (ppts) will have blood collected within 15 – 30 minutes of the scheduled dose (pre-dose), and at 1, 2, 4, 6, and 8 hours following dosing. Blood from these specimens will be used for flow cytometry (at pre-dose only), tenofovir levels, and cell lysate (intracellular tenofovir disphosphate).
- Blood, cervical cells (cytology brush), CVL fluid, and vaginal biopsies will be collected according to the schedule outlined in the table below.
- At these three visits, participants will take their assigned dose of oral and/or vaginal tenofovir at the clinic and will undergo collection of their blood, cervical cells, CVL fluids, and vaginal biopsy within 15 – 30 minutes of the assigned sampling time, either pre-dose **or** 2, 4, or 6 hours post-dose.
- The specific post-dosing time point for each participant will be determined as part of the participant's random assignment.

Table 12: Intensive PK Participants Only (US site participants only)

SPECIMEN	PRE-DOSE	POST-DOSE TIMING				
		1 HOUR	2 HOURS	4 HOURS	6 HOURS	8 HOURS
Blood draw <ul style="list-style-type: none"> • PBMC cell lysate (intracellular tenofovir diphosphate) (at sites with capacity) • Tenofovir 	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)
Blood draw <ul style="list-style-type: none"> • Flow cytometry (at sites with capacity) 	Groups M, N, O, and P)					
Cervical cytology brush <ul style="list-style-type: none"> • Cell lysates (intracellular tenofovir diphosphate) • Tenofovir 	12 ppts (Group M)		12 ppts (Group N)	12 ppts (Group O)	12 ppts (Group P)	
CVL <ul style="list-style-type: none"> • Tenofovir • Proteomics and markers of inflammation 	Group M		Group N	Group O	Group P	
Vaginal biopsies <ul style="list-style-type: none"> • Cell lysates (intracellular tenofovir diphosphate) • Tenofovir 	Group M		Group N	Group O	Group P	

The blood sample should be taken within 15 – 30 minutes of the vaginal and cervical samples and times recorded for all samples (blood, CVL, cervical cytology brush, and vaginal biopsies). For an individual participant, the same time point (within 15 minutes) in each study period should be used for the oral, vaginal, and dual formulation periods.

Blood, cervical cytology brush, CVL and vaginal biopsy samples will be analyzed for tenofovir concentration. Cells will be extracted from tissue biopsy samples for determination of intracellular tenofovir diphosphate levels. Cell lysates will be analyzed for intracellular tenofovir diphosphate levels. Blood and intracellular samples will be analyzed for routine PK parameters - C_{max} , T_{max} , AUC, and C_{min} .

7.9 Laboratory Evaluations

7.9.1 Local Laboratory Testing

Blood

- Complete blood count
- Serum chemistries
 - Phosphate
 - Creatinine (creatinine clearance calculated for every creatinine result)
- Liver function tests
 - AST
 - ALT
- HIV serology (rapid test or enzyme-linked immunoassay, WB if indicated; see Appendix II)
- Syphilis serology (confirmatory testing as indicated)
- HBsAg
- Flow cytometry (at sites with capacity)
- PBMC cell lysate isolation (at sites with capacity)

Urine

- Qualitative hCG
- Urinalysis
- Urine culture (if clinically indicated, at sites where this is standard of care)
- SDA for chlamydia and gonorrhea (may ship to a regional Network Laboratory as needed)

Pelvic Specimens

- Pap smear
- Vaginal pH
- Vaginal swabs for wet preparation slide
- Herpes culture (at sites where standard of care for diagnosis, and where capacity exists)

7.9.2 Herold Laboratory Testing

Cervicovaginal Lavage Fluid

- Vaginal flora proteomics
- Markers of inflammation

7.9.3 Network Laboratory Testing

Blood

- HIV-1 confirmatory testing as needed (see Appendix II)
- Tenofovir level

- Cell lysate (intracellular tenofovir diphosphate)
- Plasma archive

Urine

- SDA for chlamydia and gonorrhea (for US sites not currently able to perform this test on site)

Cervicovaginal Lavage Fluid

- Tenofovir level

Cervical Cytology Brush

- Intracellular tenofovir level for Intensive PK participants

Vaginal Tissue Biopsy

- Intracellular tenofovir level for Intensive PK participants

At selected sites, 3 x 5 mm (approximate size) vaginal tissue biopsies will be obtained from a subset of participants for the purpose of measuring tenofovir level in tissue, pending the development of a validated assay.

7.10 Specimen Collection and Processing

Each study site will adhere to the standards of good clinical laboratory practice, the HPTN-MTN Network Laboratory Manual (www.mtnstopshiv.org), DAIDS Laboratory Requirements (<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Labs/>), MTN-001 SSP Manual (www.mtnstopshiv.org), and site standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, and storage at the site laboratories will be documented when applicable using the Laboratory Data Management System (LDMS). In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-draw specimens that are intended for use in the screening process.

7.11 Specimen Handling

Specimens will be handled in accordance with Requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials (<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Labs/>).

7.12 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the CDC and NIH. All biological specimens will be transported using packaging mandated by CFR 42 Part 72.

All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. This applies to both US and international sites. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

7.13 Final Contact

The 21-Week Visit for all participants will include laboratory testing. In addition, some participants will have an in-depth interview as described in Section 7.7. As results are not expected to be available on the same day for participants, a final contact (in person or by telephone (except for HIV test results)) may be required to provide the final study test results, post-test counseling, and treatment from these visits. In addition, for participants who become pregnant prior to the study end date, an additional contact may be required to ascertain the participant's pregnancy outcome. Study sites may complete the final contact visit(s) at the study site or at community based locations, depending on site capacities and site and participant preferences. All final contacts must be documented in participant study records.

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

The study site Investigators are responsible for continuous close safety monitoring of all study participants, and for alerting the Protocol Team if unexpected concerns arise. A sub-group of the Protocol Team, including the Protocol Chair, DAIDS Medical Officer, MTN CORE Protocol Safety Physicians, SDMC Clinical Affairs Research Nurse, and Protocol Statistician, will serve as the PSRT; the PSRT will be chaired by the MTN CORE Protocol Safety Physicians. Not all of these members are required for quorum, which will be outlined further in the MTN-001 SSP Manual. The MTN SDMC will prepare routine safety data reports for review by the PSRT, which will meet via conference call approximately once per month or as needed throughout the period of study implementation to review safety data, discuss product use management and address any potential safety concerns. The content, format and frequency of safety data reports will be agreed upon by the PSRT and the SDMC in advance of study implementation.

8.2 Clinical Data Safety Review

A multi-tiered safety review process will be followed for the duration of this study. The study site investigators are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the PSRT if unexpected concerns arise. Participant safety is also monitored at the Network level through a series of routine reviews conducted by the SDMC Clinical Affairs staff, the PSRT and study

sponsors. Additional reviews may be conducted at each of these levels as dictated by the occurrence of certain events.

MTN SDMC Clinical Affairs staff will review incoming safety data on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification. Adverse event reports submitted in an expedited manner to the DAIDS Safety Office will be forwarded to the DAIDS Medical Officer and SDMC Clinical Affairs staff for review.

The PSRT will meet regularly via conference call to review clinical data reports generated by the MTN SDMC. The content, format and frequency of the clinical data reports will be agreed upon by the PSRT and the SDMC in advance of study implementation. In addition to the routine safety data reviews, the PSRT will convene on an ad hoc basis to make decisions regarding the handling of any significant safety concerns. If necessary experts external to the MTN representing expertise in the fields of microbicides, biostatistics, HIV transmission and medical ethics may be invited to join the PSRT safety review. A recommendation to stop the trial may be made by the PSRT at this time or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed.

Recommendations regarding permanent discontinuation of one or both study products in the study as a whole may involve sponsor consultation with the US Food and Drug Administration (FDA).

In the unlikely event that the protocol team or PSRT has serious safety concerns that lead to a decision to permanently discontinue one or both study products for all participants and stop accrual into the study, the protocol team or PRST will request a review of the data by the Study Monitoring Committee (SMC) before recommending that the study be stopped. Members of the SMC will be independent investigators with no financial interest in the outcomes of this study. If at any time, a decision is made to discontinue one or more study products in all participants, DAIDS will notify the US FDA and the site investigators of record will notify the responsible IRBs/ECs expeditiously.

8.3 Adverse Events Definitions and Reporting Requirements

8.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical research participant enrolled in a clinical trial and which does not necessarily have a causal relationship with an investigational product or study participation. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product or study participation, whether or not considered related to the product or study participation. This definition will be applied beginning from the time of random assignment. The term “investigational product” for this study refers to the TDF 300 mg tablets, tenofovir gel, and study gel applicator.

Study participants will be instructed to contact the study site staff to report any AEs they may experience. In the case of a life-threatening event, they will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek medical care where the study clinician is based, and to request that the clinician be contacted upon their arrival. With appropriate permission of the participant, whenever possible records from all non-study medical providers related to AEs will be obtained and required data elements will be recorded on study case report forms. All participants reporting an AE (including pelvic exam abnormalities) will be followed clinically until the AE resolves (returns to baseline) or stabilizes.

The site IoR will determine AE resolution or stabilization in their best clinical judgment, but may seek PSRT consultation regarding follow up or additional evaluations of an AE. The PSRT will review the query and provide a consensus response regarding follow up and/or additional evaluation to the site IoR.

Study site staff will report on study case report forms all AEs reported by or observed in enrolled study participants from the time of enrollment (random assignment) until study termination, regardless of severity and presumed relationship to study product. The Female Genital Grading Table for Use in Microbicide Studies (included in Appendix IV) will be the primary tool for grading adverse events for this protocol, with the exception of asymptomatic bacterial vaginosis which will not be a reportable AE. Adverse events not included in that table will be graded by the DAIDS AE Grading Table Version 1.0, December 2004. In cases where an AE is covered in both tables, the Female Genital Grading Table for Use in Microbicide Studies will be the grading scale utilized.

Participants will be encouraged to report to the study clinician any problems experienced by their male partners that might be potentially related to study product. If any such problems are reported, study staff should evaluate and document the occurrence and the Investigator of Record (or designee) should inform the PSRT, so that this information can be considered during routine PSRT safety data reviews. Should any concerns arise with regard to partner safety the PSRT will advise all study sites on appropriate action.

8.3.2 Serious Adverse Event

Serious adverse events (SAEs) will be defined per CFR 312.32 guidelines, as AEs occurring at any dose that:

- Result in death
- Are life-threatening adverse events
- Require Inpatient hospitalization or prolongation of existing hospitalization

- Result in persistent or significant disability/incapacity, or
- Are congenital anomalies/birth defects.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or require medical or surgical intervention to prevent one of the outcomes listed above.

8.3.3 Adverse Event Relationship to Study Product

The relationship of all AEs to study product will be assessed per the Manual for Expedited Reporting of Adverse Events to DAIDS (dated 6 May 2004), the tenofovir gel investigator's brochure, the Viread® package insert, and clinical judgment. Per the Manual for Expedited Reporting of Adverse Events to DAIDS, the relationship categories that will be used for this study are:

- *Definitely related:* adverse event and administration of study agent are related in time, and a direct association can be demonstrated with the study agent.
- *Probably related:* adverse event and administration of study agent are reasonably related in time, and the adverse event is more likely explained by the study agent than by other causes.
- *Possibly related:* adverse event and administration of study agent are reasonably related in time, and the adverse event can be explained equally well by causes other than the study agent.
- *Probably not related:* a potential relationship between administration of study agent and adverse event could exist, but is unlikely, and the adverse event is most likely explained by causes other than the study agent.
- *Not related:* the adverse event is clearly explained by another cause unrelated to administration of the study agent. Reportable events must have documentation to support the determination of "not related".

8.4 Expedited Adverse Event Reporting Requirements

Expedited Adverse Event Reporting to DAIDS

The expedited adverse event (EAE) reporting requirements and definitions for this study and the methods for expedited reporting of adverse events (AEs) to the DAIDS Regulatory Compliance Center (RCC) Safety Office are defined in "The Manual for Expedited Reporting of Adverse Events to DAIDS" (DAIDS EAE Manual), **dated May 6, 2004**. The DAIDS EAE Manual is available on the RCC website: <http://rcc.tech-res-intl.com/>.

AEs reported on an expedited basis must be documented on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form) available on the RCC website: <http://rcc.tech-res-intl.com>.

DAIDS EAE forms should be submitted to DAIDS through the Regulatory Compliance Center (RCC) Safety Office (rccsafetyoffice@tech-res.com) or call 1-800-537-9979 or 301-897-1709 or fax 1-800-275-7619 or 301-897-1710.

EAE Reporting Requirements for this Study

EAE Reporting Level

This study uses the Standard Level of expedited AE reporting as defined in the DAIDS EAE Manual.

Study Agents for Expedited Reporting to DAIDS

The study agents that must be considered in determining relationships of AEs requiring expedited reporting to DAIDS are: TDF 300 mg tablet, tenofovir 1% gel, and study gel applicator.

Grading Severity of Events

The Female Genital Grading Table for Use in Microbicide Studies (included in Appendix IV) will be the primary tool for grading adverse events for this protocol, with the exception of asymptomatic bacterial vaginosis which will not be a reportable AE. Adverse events not included in that table will be graded by the DAIDS AE Grading Table Version 1.0, December 2004. In cases where an AE is covered in both tables, the Female Genital Grading Table for Use in Microbicide Studies will be the grading scale utilized.

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December, 2004, is available on the RCC website at <http://rcc.tech-res-intl.com/>.

EAE Reporting Periods

AEs must be reported on an expedited basis at the Standard Level during the Protocol-defined EAE Reporting Period, which is the entire study duration for an individual participant (from study enrollment until study termination).

For each study participant, expedited AE reporting will be undertaken throughout the scheduled duration of follow-up, i.e., from the time of random assignment through completion of the 21-Week Visit. After the 21-Week Visit, pregnancy outcomes that meet criteria for expedited AE reporting (e.g., fetal losses, congenital anomalies) occurring among participants known to be pregnant at Week 21 will be reported. In addition, should site staff become aware of any serious, unexpected, clinical suspected adverse drug reactions after Week 21, such events also will be reported as EAEs.

8.5 Local Regulatory Requirements

Site investigators will submit AE information in accordance with local regulatory agencies' or other local authorities' requirements. This reporting will include site IRB/EC-mandated reporting of AEs, SAEs, and other relevant safety information.

8.6 Social Harms Reporting

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities. Social harms that are judged by the Investigator of Record to be serious or unexpected will be reported to responsible site Institutional Review Boards/Ethics Committees (IRBs/ECs) at least annually, or according to their individual requirements. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. While maintaining participant confidentiality, study sites may engage their Community Advisory Boards in exploring the social context surrounding instances of social harm.

9 CLINICAL MANAGEMENT

Guidelines for clinical management and product hold/discontinuation are outlined in this section.

In general, the site investigator has the discretion to hold study product at any time if s/he feels that continued product use would be harmful to the participant, or interfere with treatment deemed clinically necessary according to the judgment of the investigator. Unless otherwise specified below, the investigator should immediately consult PSRT for further guidance in restarting study drug(s) or progressing to permanent discontinuation.

9.1 Grading System

The grading system is located in the Female Genital Grading Table for Use in Microbicide Studies, which can be found in Appendix IV, and in the Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004, which can be found on the Regulatory Compliance Center (RCC) Web site: <http://rcc.tech-res-intl.com/eae/html/>.

9.2 Dose Modification Instructions

No dose reductions are allowed.

9.3 Discontinuation of Study Product(s) in the Presence of Toxicity

Grade 1 or 2

In general, participants who develop a Grade 1 or 2 AE regardless of relatedness to study product that is not specifically addressed below may continue use of both study products per protocol.

Grade 3

Participants who develop a Grade 3 adverse event or toxicity that is not specifically addressed below and is judged to be possibly, probably, or definitely related to study product should have that study product held. In general, and unless otherwise decided in consultation with the PSRT, the investigator should re-evaluate the participant at least weekly up to 2 weeks. If documentation is not available within 2 weeks to show that the adverse event is \leq Grade 2, the current study product must be permanently discontinued.

If the same Grade 3 adverse event recurs after reintroduction of study product, the current study product must be permanently discontinued if the investigator considers the adverse event probably not, possibly, probably, or definitely related to study product. However if the investigator determines that the toxicity is definitely not related to study product, participants may continue the study product and the PSRT must be notified.

Grade 4

Participants who develop a Grade 4 adverse event or toxicity that is not specifically addressed below (regardless of relationship to study product(s)) should have the current study product(s) held. If the investigator determines that the toxicity is definitely not related to study product(s), PSRT may be consulted to consider restarting study product(s), but product(s) should be held until a recommendation from PSRT is obtained. The participant should be re-evaluated at least weekly up to 2 weeks. If documentation is not available within 2 weeks to show that the adverse event is \leq Grade 2, the study product(s) must be permanently discontinued. If the same Grade 4 adverse event recurs at either Grade 3 or 4 level after reintroduction of study product(s), study product(s) must be permanently discontinued.

9.4 General Criteria for Discontinuation of Study Product

Participants may voluntarily discontinue one or both study products for any reason at any time. Site IoRs will temporarily hold or permanently discontinue participants from one or both study products per protocol for any of the specific criteria below, which may be further clarified in the SSP Manual. Site IoRs also may temporarily hold or permanently discontinue participants from one or both study products for use of prohibited medication (per Section 6.7.1), for reasons not shown here or in the SSP Manual, e.g., to protect participant safety and/or if participants are unable or unwilling to comply with study product use procedures. In such cases, the Site IoRs would temporarily hold product use and provide a written query with a request for permanent

study product discontinuation to the PSRT for review. The PSRT will provide a written response to the site indicating whether the PSRT has recommended permanent discontinuation of study product(s). Such recommendations regarding permanent discontinuation of one or both study products in individual participants will be made by the PSRT based on careful review of all relevant data.

The criteria for permanent discontinuation of further study product use of one or both study products for an individual participant are:

- Study product-related toxicity requiring permanent discontinuation of study product(s) per Section 9 of this protocol
- Completion of regimen as defined in the protocol
- Request by participant to terminate study product(s)
- Clinical reasons determined by the physician
- HIV infection
- Hepatitis B infection
- Pregnancy or breastfeeding

If a participant is permanently discontinued from oral study product, and if the Tenofovir 1% Gel Period has not yet begun for this participant, the investigator in consultation with the PSRT may decide that she may participate per protocol in the Tenofovir 1% Gel Period as scheduled according to her sequence randomization. If a participant is permanently discontinued from gel study product, and if the TDF 300 mg Oral Tablet Period has not yet begun for this participant, the investigator in consultation with the PSRT may decide that she may participate per protocol in the TDF 300 mg Oral Tablet Period as scheduled according to her sequence randomization.

However, a participant who has been permanently discontinued from either type of study product will not take any study product during the Dual Formulation Period (if this study period has not yet begun for an individual participant), but will be followed according to regularly scheduled evaluations of safety, according to Section 7.4.5.

Participants may initiate study product use per protocol in a subsequent study period (if applicable), provided other product hold guidelines do not apply. Participants must meet applicable criteria for restarting a particular study product before initiating that study product's use in a subsequent study period.

9.5 Management of Specific Toxicities

Specific guidance related to product hold is also noted here as it pertains to the clinical management of toxicities.

9.5.1 Nausea and Vomiting

Participants with Grade 1 and/or 2 nausea or vomiting may be treated symptomatically with hydration, oral antiemetic therapies or antiemetic suppositories. Participants should be instructed to take oral study product with food.

ORAL STUDY PRODUCT

Participants with Grade ≥ 3 nausea and/or vomiting must hold the study product until the toxicity grade returns to Grade ≤ 2 and be treated symptomatically. Therapy should be resumed using the full doses of study product. If Grade ≥ 3 nausea and/or vomiting recurs upon the resumption of study product despite symptomatic treatment, study product must be permanently discontinued.

VAGINAL STUDY PRODUCT

Unless other product hold guidelines apply, vaginal study product may be continued at the discretion of the investigator.

9.5.2 Diarrhea

Participants with diarrhea of any toxicity grade may be treated symptomatically with permitted antimotility agents and rehydration at the discretion of the site investigator.

ORAL STUDY PRODUCT

Participants with new onset Grade ≥ 3 diarrhea that is unresponsive to antimotility agents and for which an alternative etiology (e.g., infectious diarrhea) is not established must hold the oral study product until the toxicity grade returns to Grade ≤ 2 or to baseline and be treated symptomatically. Oral study product administration should be resumed using the full dose of oral study product. If Grade ≥ 3 diarrhea recurs upon the resumption of oral study product despite symptomatic treatment, oral study product must be permanently discontinued.

VAGINAL STUDY PRODUCT

Unless other product hold guidelines apply, vaginal study product may be continued at the discretion of the investigator.

9.5.3 AST/ALT Elevations

Careful assessments should be done to rule out the use of alcohol, non-study medication-related drug toxicity, or viral hepatitis as the cause of elevation in AST or ALT of any grade.

ORAL STUDY PRODUCT

The participant must be carefully assessed for any symptoms or signs of hepatotoxicity, including fatigue, malaise, anorexia and nausea, jaundice, acholic stools, RUQ pain or hepatomegaly. If the AST/ALT elevation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent, should be undertaken.

If symptoms or signs of clinical hepatitis are present, study treatment must be discontinued (see below). Careful assessments should be undertaken for alcohol use, non-study medication-related drug toxicity, the lactic acidosis syndrome, and viral hepatitis as the cause of the transaminase elevation. If the AST/ALT elevation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent, should be undertaken.

Grade 1

For study participants with Grade 0 ALT and AST at study entry, an increase to Grade 1 ALT or AST even in an asymptomatic participant may be of concern.

ALT and AST must be repeated as soon as possible (at most within 1 week) of a new Grade 1 ALT or AST. Study treatment may be continued while repeating ALT and AST at the discretion of the investigator provided the participant is asymptomatic.

Participants with a confirmed Grade 1 ALT or AST who are asymptomatic may continue study medications with continued close observation.

Grade 2

Participants should have ALT/AST re-checked as soon as possible (at most within 1 week) and then be followed weekly until levels are Grade ≤ 1 . The frequency of follow up may be altered at the discretion of the site investigator following consultation with the PSRT. Study treatment may continue at the discretion of the investigator provided the participant is asymptomatic.

Grade 3

Study product should be held for any ALT or AST of Grade 3.

Participants should have ALT/AST re-checked as soon as possible (at most within 1 week). Participants should then be followed weekly until levels are Grade ≤ 1 , at which point study medication may be restarted with close follow-up and in consultation with

the PSRT. If lab documentation is not available that levels have returned to Grade ≤ 1 within three weeks, study product must be permanently discontinued.

For participants who have restarted study product, any level of Grade 3 or above should result in permanent discontinuation of study product.

Grade 4

Study product should be permanently discontinued. ALT/AST must be followed at least weekly until Grade ≤ 1 .

VAGINAL STUDY PRODUCT

Unless other product hold guidelines apply, vaginal study product may be continued at the discretion of the investigator.

9.5.4 Creatinine Clearance

If the creatinine clearance is $<50\text{mL}/\text{min}$, it should be confirmed within 1 week of the receipt of the results in consultation with the PSRT.

ORAL STUDY PRODUCT

If the creatinine clearance is confirmed to be $<50\text{mL}/\text{min}$, the oral study product must be permanently discontinued. If the participant fails to have the creatinine clearance confirmed in one week, all attempts should be made by the site to contact the participant to have the creatinine clearance confirmed within three working days. Participants who fail to have a confirmed test will permanently discontinue the oral study product.

VAGINAL STUDY PRODUCT

Unless other product hold guidelines apply, vaginal study product may be continued at the discretion of the investigator.

9.5.5 Hypophosphatemia

For Grades 1 and 2 hypophosphatemia, the phosphate should be repeated within 2 weeks of the receipt of the results. Supplemental phosphate should be given with phosphate-rich food or fluid with or without neutral phosphate solution. For Grades 3 and 4 hypophosphatemia, the phosphate should be repeated within 1 week of the receipt of the results. Supplemental phosphate should be given with phosphate-rich food or fluid with or without neutral phosphate solution, and other causes of low phosphate should be investigated. During the time that supplemental phosphate is provided to the participant and the time that testing is repeated, sites should follow product hold guidelines described in Section 9.3.

ORAL STUDY PRODUCT

If documentation is not available within 1 week to show response to supplementation (resolution to Grade \leq 2), the oral study product must be permanently discontinued.

VAGINAL STUDY PRODUCT

Unless other product hold guidelines apply, vaginal study product may be continued at the discretion of the investigator.

9.5.6 Genital Sexually Transmitted Infection/Reproductive Tract Infection

Management of sexually transmitted infections commonly referred to as STIs and other forms of vaginitis and cervicitis will be in accordance with current WHO guidelines, available at <http://www.who.int/en/>.

ORAL STUDY PRODUCT:

Oral study product need not be held in the event of genital STI/RTI requiring treatment, unless other product hold guidelines apply.

VAGINAL STUDY PRODUCT

For Grade 2 genital STI(s)/RTI(s) requiring treatment, vaginal study product may be held until treatment is completed and symptoms have resolved at the judgment of the investigator. Once treatment is complete and any symptoms have resolved, vaginal study product use can be resumed unless other product hold guidelines apply.

9.6 HIV and Hepatitis B

Participants who are identified as infected with HIV and/or hepatitis B will be managed or referred for management according to the local standard of care. For additional guidance regarding participants who are identified as infected with HIV, please see Section 13.9.2.

NOTE: Participants who are identified as infected with HIV and/or hepatitis B will discontinue permanently all study product(s).

9.7 Clinical Management of Pregnancy

All study participants are required to be using an effective method of contraception according to Section 5.2 at enrollment, and intending to use same method for the duration of study participation. Study staff will provide contraceptive counseling to enrolled participants as needed throughout the duration of study participation and will facilitate access to contraceptive services through direct service delivery and/or active referrals to local service providers. Study staff also will provide participants with male condoms and counseling on use of condoms ideally during every sex act during study participation.

Pregnancy testing will be performed at all study visits and participants will be encouraged to report all signs or symptoms of pregnancy to study staff. The site IoR or designee will counsel any participants who become pregnant regarding possible risks to the fetus according to site-specific SOPs. The IoR or designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care.

Participants who are pregnant at the termination visit will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). Pregnancy outcomes will be reported on relevant case report forms; outcomes meeting criteria for EAE reporting also will be reported on EAE forms.

NOTE: Participants who become pregnant during the course of the study will discontinue permanently all study product(s).

9.8 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. Site IoRs may, with the approval of the PSRT, withdraw participants before their scheduled termination visit to protect their safety, and/or if participants are unable or unwilling to comply with study procedures. Participants also may be withdrawn if the study sponsors, government or regulatory authorities (including the Office of Human Research Protections (OHRP)), or site IRBs/ECs terminate the study prior to its planned end date. Site investigators are required to consult the Protocol Chair and Protocol Biostatistician prior to the termination of any study participant. Study staff will record the reason(s) for all withdrawals in participants' study records. In the event that participants who voluntarily withdraw from the study wish to re-join the study during their planned 21-week follow-up period, they may resume study procedures and follow-up at the investigator's discretion.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and General Design

This is a three-period, three treatment, multi-site, open label, crossover study. All the enrolled women will use all three treatments (i.e. oral TDF, tenofovir 1% gel, and a period of using both products), each in a separate period. The sequence of the three treatments will be randomly assigned. The total length of follow-up is 21 weeks: three periods of 6 weeks on treatment, each followed by a one-week washout period.

Each one-week washout period will be used to collect adverse events that may have resulted from product use during the previous period.

10.2 Study Endpoints

10.2.1 Study Primary Endpoints

Consistent with the primary study objectives, the following primary endpoints will be assessed:

- **Adherence.** Participant self reported product use. For each woman, adherence to each regimen will be computed by dividing the number of daily doses she reports having taken (numerator) by the number of expected doses if she were fully adherent (denominator).
- **Acceptability.** The proportion of participants who indicate that they would be “unlikely” to use the study product in the future.
- **PK.** AUC, C_{max} , and C_{min} associated with oral, vaginal, and dual use regimens.

10.2.2 Study Secondary Endpoints

Consistent with the secondary study objectives, the following secondary endpoints will be assessed:

- Proportion of women who report taking at least 90% of expected daily doses, frequency of use during the follow-up interval using an ordinal measure (5 categories of use, never to always); number of days product missed or not used during the previous week
- Frequency (ordinal measures) of sexual activity and male condom use
- Time interval between product usage and sexual intercourse; sequence of product use and sexual intercourse
- Reported sharing of study product; quantity of shared study product
- Grade 3 or higher toxicity for systemic and local effects as defined by DAIDS AE Grading Table Version 1.0, December 2004, or Grade 3 or higher genital infection, pain or epithelial lesion as defined by the Female Genital Grading Table for Use in Microbicide Studies which cannot be directly attributed to another cause, and judged as definitely, probably, possibly, or probably not related to the study gel, applicator, or study tablet

10.3 Study Hypotheses

The study hypotheses for the primary objective are:

- There will be no differences in rates of adherence among the three study regimens
- There will be no difference in rates of acceptability among the three study regimens
- Tissue levels of PMPA will be similar irrespective of the route of administration
- Oral TDF will be associated with higher concentrations of PMPA in the blood compared to topical PMPA
- Neither tenofovir 1% gel nor oral TDF regimens will adversely impact the genital tract environment

10.4 Sample Size

Sample size/power formulas for a parallel design with two arms (i.e. two different groups of women) can be used to compute sample size/power. Then, this sample size resulting from the assumption of independent groups can be adjusted to reflect that there will be intra-woman correlation in the crossover design. The sample size adjustment can be obtained by this formula:

$$N' = N (1 - \rho)/2$$

where N' is the sample size for a crossover study, N is the total number of women required in a parallel design with two arms ($N/2$ in each arm) and ρ is the correlation between responses within a single woman during different periods (intra-woman correlation).

For the adherence endpoint, we use preliminary data from HPTN 059 to estimate the standard deviation (SD) of daily gel use and make the assumption that the standard deviations of adherence to daily oral use and of adherence to dual use are similar to that for daily gel use. From the first 4 weeks and the first 8 weeks of daily gel use observed in HPTN 059, we have observed a SD of 11% and 16%, respectively (note that we do not have data in HPTN 059 for the first 6 weeks). Therefore, we use a conservative estimate for the SD for the first 6 weeks of 20%.

To our knowledge, there are no data available for estimating ρ . However, it is highly likely that this correlation will be positive and large. The following table gives the power to detect various differences in adherence with a sample size of 144 evaluable women:

Table 13: Minimum Detectable Difference in Adherence

	Rho			
	0.0	0.3	0.5	0.7
Minimum Detectable Absolute Difference in Adherence Between Any Two Regimens				
2.5%	18%	24%	32%	49%
5.0%	56%	72%	85%	97%
7.5%	89%	97%	99%	>99%

If there is no intra-woman correlation for adherence, the study will have $\geq 89\%$ power to detect absolute differences between the different study drug regimens of at least 7.5% with a two-sided alpha of 5%. Assuming a moderately high intra-woman correlation of 0.5 for adherence, the study will have $\geq 85\%$ power to detect an absolute difference of at least 5.0% with a two-sided alpha of 5%.

For the acceptability endpoint, based on previous studies we expect to observe acceptability $> 95\%$, which equates to $\leq 5\%$ of women reporting they would be “unlikely” to use the study product in the future. Power is computed by using formulas appropriate for the McNemar test (formula 3.1 in Ezzet and Whitehead).¹² For the computations, we assume that the pooled acceptability for two regimens is 90% giving a probability of 18% that a woman has two different outcomes in two different periods (i.e. finds one product acceptable and the other not acceptable). Under this assumption, and assuming a 2-sided test with $\alpha=0.05$, with 144 evaluable women we have 80% power to detect a log-odds ratio between acceptability rates in two groups of 1.10. If acceptability in one group is 95%, this corresponds to being able to detect a 13% difference (i.e., 5% versus 18% being “unlikely” to use study product in the future) in acceptability between different study product regimens. If acceptability in one group is 98%, this corresponds to being able to detect a 5% difference (i.e. 2% versus 7% being “unlikely” to use study product in the future) in acceptability between different study product regimens. Although the primary analysis for this endpoint will not rely on the McNemar test (see details in Section 10.7.2), the above computations provide a good approximation given that the range of individual acceptabilities observed in previous studies is rather homogenous. This leads to a small degree of heterogeneity; therefore negligible sample size adjustment is needed for the use of random effects model.

Finally, for the secondary endpoint assessing condom use rates during the different drug regimens, we use preliminary data from HPTN 035 to estimate the SD of percent condom use and make the assumption that the SDs of condom use for daily oral use and dual use are similar to that for daily gel use. From the first 2028 participants enrolled in HPTN 035 we have observed a condom use rate of 72% with a SD of 34% and we use this estimate of the SD for the power calculations.

Again, to our knowledge, there are no data available for estimating rho. However, it is highly likely that this correlation will be positive and large. The following table gives the

power to detect various differences in condom use rates with a sample size of 144 evaluable women:

Table 14: Minimum Detectable Difference in Condom Use

	Rho			
	0.0	0.3	0.5	0.7
Minimum Detectable Absolute Difference in Condom Use Between Any Two Regimens				
2.5%	9%	11%	14%	21%
5.0%	24%	32%	42%	62%
7.5%	46%	61%	75%	93%
10%	70%	85%	94%	>99%

If there is no intra-woman correlation for condom use, the study will have low power to detect absolute differences in condom use rates of <10% between the different study drug regimens. Assuming a moderately high intra-woman correlation of 0.5 for condom use, the study will have $\geq 75\%$ power to detect an absolute difference of at least 7.5% with a two-sided alpha of 5%.

Methods for sample size estimates for the sparse sampling population PK analysis are not available. However, experience indicates that 144 participants, especially when each contributes a pair of specimens the same dosing interval, should provide robust PK parameter estimates.

The more intensive PK sampling to be done at the domestic sites will involve 72 women. Based on data from Gilead in the package insert¹, the coefficient of variation for C_{max} , AUC, and total clearance (Cl/F) are 30%, 30%, and 11%, respectively. With 72 participants, assuming no intra-individual correlation, we have 90% power to detect a 0.38 SD unit difference between any two regimens being compared. This represents a 14% difference in C_{max} and AUC and a 5% difference in total clearance (Cl/F). If one assumes some correlation within a participant between periods – a very reasonable assumption – these estimates would be even lower. However, because we are using fewer sample points than used in the Gilead tenofovir studies in which the parameter estimates and SDs were determined, we expect that this may increase the variability of the estimates, so we will make no adjustments for intra-participant correlations.

In HPTN 050, blood levels after vaginal tenofovir were too low to allow variance estimates needed for sample size calculations since only one-third of the women had detectable levels of tenofovir in their blood following any given dose. Comparisons of oral and dual formulation arms will rely on imputations of values that are below the assay limits of quantitation which will have the effect of actually reducing the variance of the data which may falsely increase the apparent power of the study design.

10.5 Randomization Procedures

Randomization to product sequence will be stratified by site. Within each site, participants will be randomly assigned to one of six study sequences outlined in Table 15: Study Regimen below. In an unblinded trial, special care needs to be taken to assure that the study staff cannot control or guess assignment. The MTN Statistical and Data Management Center will coordinate the randomization procedures, which will be specified in the SSP Manual.

Table 15: Study Regimen

	N	Period 1: 6 WEEKS	1 WK Wash -out	Period 2: 6 WEEKS	1 WK Wash- out	Period 3: 6 WEEKS	1 WK Wash- out
Sequence A	24	Oral		Vaginal		Oral + Vaginal	
Sequence B	24	Vaginal		Oral		Oral + Vaginal	
Sequence C	24	Oral + Vaginal		Oral		Vaginal	
Sequence D	24	Oral + Vaginal		Vaginal		Oral	
Sequence E	24	Oral		Oral + Vaginal		Vaginal	
Sequence F	24	Vaginal		Oral + Vaginal		Oral	

Assignment to end of study period non-intensive PK sample timing will correspond to product sequence randomization for simplicity. For the intensive PK cohorts at domestic sites, the end of study period sample timing will require a second randomization which will be stratified within each of the two sites.

10.6 Participant Accrual, Follow-up, Retention, and Replacement

The accrual period will be 6 months. Up to 204 women may be enrolled to reach the target of 144 evaluable women, where evaluable women are women who have at least one follow-up visit with adherence data in each of the 3 periods of the study. Five of the 7 participating sites will recruit and enroll 24 evaluable participants each, and 2 of the participating sites will enroll 12 evaluable participants each for a total of 144 evaluable participants. The need to enroll replacement participants for enrollees will be dependent on whether the enrollee had at least one full period of the study with no follow-up adherence data. Details on procedures for participant replacement are outlined in the SSP Manual.

Each participant will be followed for 21 consecutive weeks (three periods of 7 weeks). In a crossover study, it is important to have completeness of the data such that the target retention should be set at 100%. Therefore, once a participant has enrolled in the study, the study site will make every reasonable effort to retain her for the entire study period so that she is evaluable. A maximum of 5% loss-to-follow-up of enrolled participants is targeted.

10.7 Data Monitoring and Analysis

10.7.1 Study Monitoring Committee (SMC)

No Data and Safety Monitoring Board oversight is planned for this study. The MTN SMC will conduct interim reviews of study progress, including rates of participant accrual, retention, completion of primary and main secondary endpoint assessments, and study or lab issues. These reviews will take place approximately every 4-6 months, or as needed. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

10.7.2 Primary Analysis

All analyses will be based on data from the 144 evaluable women (women with at least one follow-up visit in each period of the study) after assessing differences in baseline values between the evaluable women and those women lost to follow-up. These differences will be described and used to interpret the generalizability of the results. For the adherence endpoint, the primary analysis will evaluate the difference in product adherence using statistical methods for paired data controlling for period and sequence effects. Prior to this analysis, the presence of any carryover effects will be evaluated using a more liberal alpha level of 10%. Although carryover effects are not expected, if evidence of them is found, we will resort to analyzing only the data from the first period as a simple three arm parallel design using statistical methods for independent data. This will greatly reduce the power of testing. If adherence distributions do not allow the use of parametric tests, rank tests as those described in Koch and Strokes will be used instead.¹³

For the binary acceptability endpoint, similar measures to assess for carryover effects will be used and then for the main outcome, controlling for period and sequence effects, a generalization of McCullagh's proportional odds model for repeated measures will be performed by adding a random effect on the logit scale as proposed by Ezzet and Whitehead.¹⁴ Again, if carryover effects are present, the analysis will only use data from the first period.

Blood and intracellular samples will be analyzed for routine PK parameters - C_{max} , T_{max} , AUC, C_{min} - and described using descriptive statistics. Cervical and vaginal samples will be analyzed using sparse sampling population PK methods to provide PK parameter estimates. Measures of drug exposure (AUC, C_{max}) will be compared between oral and vaginal and dual use concentration differences controlling for sequence and period effects. Post-biopsy blood samples will be evaluated for deviation from expected values. Model building will be attempted to relate blood and intracellular model drug levels if sufficient samples have detectable drug levels.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study case report forms will be developed by the SDMC. Quality control reports and queries routinely will be generated and distributed by the SDMC to the study sites for verification and resolution.

11.2 Source Documents and Access to Source Data/Documents

Source documents and access to source data/documents will be maintained in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. The investigator will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with US regulations, the investigator will retain all study records on site for at least two years after study closure. Study records will not be destroyed prior to receiving approval for record destruction from DAIDS. Applicable records include source documents, site registration documents and reports, correspondence, informed consent forms, and notations of all contacts with the participant.

11.3 Quality Control and Quality Assurance

Quality control and quality assurance procedures for MTN-001 will be performed in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites.

11.4 Study Coordination

DAIDS holds the IND applications for this study. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed by DAIDS, CONRAD, and Gilead Sciences, Inc. Study site staff will be provided with the DAIDS SOPs for Source Documentation and Essential Documents, the Manual for Expedited Reporting of Adverse Events to DAIDS, and the DAIDS AE Grading Table. Training and written instructions outlining management and reporting, study gel dispensing, product accountability, and other study operations will be provided by FHI, SCHARP, and the MTN NL.

12 CLINICAL SITE MONITORING

Study monitoring will be carried out by PPD (Wilmington, NC). On-site study monitoring will be performed in accordance with Requirements for On-Site Monitoring of DAIDS Funded and/or Sponsored Clinical Trials. Site monitoring visits will be conducted to assess compliance with Health and Human Services (HHS) Regulations 45 Code of

Federal Regulations (CFR) Part 46 and 21 CFR Parts 50, 56, and 312. Study monitors will visit the site to:

- Verify compliance with human subjects and other research regulations and guidelines, including confidentiality procedures, informed consent process, and regulatory documentation
- Assess adherence to the study protocol, SSP Manual, and local counseling practices
- Confirm the quality and accuracy of information collected at the study site and entered into the study database, including the validation of data reported on case report and DataFax forms
- Assess the resolution of any past or ongoing issues identified at previous monitoring visits

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the MTN CORE, MTN NL, FHI, SCHARP, NIAID, local regulatory authorities, and US regulatory authorities. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

The investigators will make efforts to minimize risks to human participants. Volunteers and study staff members will take part in a thorough informed consent process. Before beginning the study, the investigators will have obtained IRB/EC approval and the protocol will have been submitted to the FDA. The investigators will permit audits by the NIH, CONRAD, Gilead Sciences, Inc., the FDA, or any of their appointed agents.

13.1 Institutional Review Boards

Each participating institution is responsible for assuring that this protocol and the associated informed consent documents and study-related documents are reviewed by an EC or IRB prior to implementation of the protocol. Any amendments to the protocol, informed consents, or other study-related documents must be approved by the IRB/EC and DAIDS prior to implementation.

13.2 Protocol Registration

Each study site will complete protocol registration with the DAIDS RCC Protocol Registration Office. Protocol registration material can be sent electronically to

epr@tech-res.com. For questions regarding protocol registration, please call (301) 897-1707. For additional information, refer to the protocol registration documents located at <http://rcc.tech-res.com/forms.htm>.

Protocol registration must occur as a condition for site-specific study activation; no participants may be screened or enrolled in this study prior to obtaining protocol registration approval and completing all other study activation requirements. MTN CORE (FHI) staff will notify each study site when all activation requirements have been met by issuing a site-specific study activation notice. Study implementation may not be initiated until the activation notice is issued.

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and DAIDS Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB/EC(s) and the RCC prior to implementing the amendment.

13.3 Risk Benefit Statement

13.3.1 Risks

Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection. Pelvic examination may cause mild discomfort and/or vaginal bleeding or spotting. Disclosure of STI status may cause sadness or depression in volunteers. Participation in clinical research includes the risks of loss of confidentiality and discomfort with personal nature of questions.

For sub-study participants, vaginal biopsy carries the risk of discomfort or pain during the procedure and for a few hours afterwards. Participants may have mild vaginal spotting (bleeding) for one or two days, and will be instructed to avoid sexual intercourse until bleeding stops. Some temporary discomfort with sexual intercourse may occur if the biopsy areas are still healing. There is a small risk of infection and heavier bleeding. Participants will be instructed to contact the clinic if symptoms are bothersome, if heavy bleeding is noted (soaking through a pad or tampon in an hour or less) or if the participant develops any abnormal odor or discharge from the vagina.

The most common side effects associated with oral TDF in patients with HIV infection are nausea, headache, diarrhea, vomiting, asthenia, flatulence, abdominal distension/pain and anorexia. Less common side effects of TDF include kidney toxicities and low blood phosphate. Other side effects reported in the post-marketing period include weakness, pancreatitis, low blood phosphate, dizziness, shortness of breath, and rash. In animal studies, tenofovir has been associated with decreased bone mineral density. These effects have not been seen in those taking tenofovir tablets for up to one year.

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and

"cushingoid appearance" have been observed in persons receiving antiretroviral drugs. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established. These effects are not expected in this study involving a brief exposure to antiretroviral drug.

Administration of tenofovir gel intravaginally at 0.3% and 1% concentrations in the HPTN 050 Phase1 study resulted in minimal local irritation and little or no systemic adverse effects were identified.⁸ Although 92% of participants reported at least 1 AE, 87% of those reported AEs were mild, and 70% of the AEs were limited to the genitourinary tract. Four severe AEs were reported, with only one, lower abdominal pain, thought to be product-related. The risks associated with tenofovir gel are believed to be less than those identified for systemic use. In the HPTN 050 Phase1 study of tenofovir gel, serum PK analysis in a subset of participants demonstrated that there is no clinically significant systemic toxicity. Fourteen of 25 women with PK results had low, but detectable, serum tenofovir levels.

Given that Phase 1 data demonstrates measurable plasma concentrations of tenofovir in some participants, participants with hepatitis B infection might be at risk for development of tenofovir resistant hepatitis B. However, participants with known hepatitis B infection will not be eligible for enrollment. It is not known what effect tenofovir gel could have on the HIV virus or HIV disease progression in HIV infected participants or their partners. There is a theoretical risk that tenofovir absorbed systemically from tenofovir gel could result in mutations of the HIV virus in participants who become infected with HIV during the study, or their partner, if the partner is infected with HIV. Limited resistance data from HPTN 050 show no new resistance mutations in plasma or CVL specimens after 14 days of tenofovir gel use. No participant had high level tenofovir mutations (e.g. K65R). Some of the possible side effects of the study gel are dryness, itching, burning, or pain in the genital area.

13.3.2 Benefits

Participation in this study likely will have no direct benefit to volunteers other than access to screening for RTIs/STIs and appropriate referral if RTIs/STIs are diagnosed. Some volunteers may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities in serology, blood count, liver or kidney function tests. Pap smear may offer the opportunity for early detection of a cervical and/or vaginal abnormality with expedient referral if an abnormality is detected. Lastly, the participant may appreciate the opportunity to contribute to the body of knowledge in the field of microbicide research.

13.4 Informed Consent Process

Written informed consent will be obtained from all potential study participants prior to the initiation of any study-related procedures. In obtaining and documenting informed consent, the investigators and their designees will comply with applicable local and

country-specific regulatory requirements and will adhere to Good Clinical Practices (GCP) and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. A comprehension checklist will be used to assess participants' comprehension of the enrollment informed consent document. Participants are provided with copies of the informed consent forms if they are willing to receive them. Each study site is responsible for developing study informed consent forms for local use, based on the templates in Appendices VI, VII, and VIII that describe the purpose of screening and of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The study site also is responsible for translating the template forms into local languages, and verifying the accuracy of the translation by performing an independent back-translation.

Prior to the beginning of the trial, site investigators will have IRB/EC written approval of the protocol, informed consent forms, and any other study-related information to be provided to participants.

The informed consent process will give individuals all of the relevant information they need to decide whether to participate, or to continue participation, in this study. Potential research participants will be permitted to ask questions and to exchange information freely with the study investigators. Listed study investigators or their designees will obtain informed consent from potential study participants. The investigators will keep research participants fully informed of any new information that could affect their willingness to continue study participation.

Community input has been sought for the development of the sample informed consent forms. The informed consent process covers all elements of informed consent required by research regulations. In addition, the process specifically addresses the following topics of import to this study:

- The importance of adherence to the study visit and procedures schedule.
- The potential risks of study participation (and what do if such risks are experienced).
- The potential social harms associated with study participation (and what do if such harms are experienced).
- The real yet limited benefits of study participation.
- The distinction between research and clinical care.
- The right to withdraw from the study at any time.

13.5 Participant Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Each study site will establish a standard operating procedure for confidentiality protection that reflects the local study implementation plan (e.g., whether community-based visits will be

conducted) and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them. In addition to local considerations, the protections described below will be implemented at all sites.

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. Data collection, process, and administrative forms, laboratory specimens, and other reports will be identified by a coded number only to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access. Participants' study information will not be released without their written permission, except as necessary for monitoring (see Section 12).

The MTN has obtained a Certificate of Confidentiality from the US Department of Health and Human Services that will be applicable for this study. This Certificate protects study staff from being compelled to disclose study-related information by any US Federal, State or local civil, criminal, administrative, legislative or other proceedings. It thus serves to protect the identity and privacy of study participants. Since the Certificate cannot be enforced outside of the US, it will apply only to US site staff and participants.

13.6 Special Populations

This section outlines considerations made for the inclusion or exclusion of special populations in this study.

13.6.1 Pregnant Women

Participants who test positive for pregnancy at screening or enrollment visits will not be eligible to participate in this study. A urine pregnancy test will be performed on all women at all clinic visits, and participants who test positive will be taken off product. During the informed consent process, women will be informed that oral tenofovir disoproxil fumarate and tenofovir gel are not methods of contraception and that the effects of oral tenofovir disoproxil fumarate and tenofovir gel on a developing human fetus are unknown.

Oral TDF is classified by the FDA as a Pregnancy Category B drug. Animal studies have failed to demonstrate a risk to the fetus, but there are no adequate and well-controlled studies in pregnant women that have been completed to date.

All potential participants will be required by the Eligibility Criteria for Screening and Enrollment to be currently using a reliable method of contraception, such as hormonal contraception (except vaginal ring), intrauterine device, or sterilization. Women who become pregnant during the study period following randomization and exposure to

study product will discontinue product use and the PK assessments but will not be excluded from analysis.

13.6.2 Children

The NIH has mandated that children be included in research trials when appropriate. This study meets “Justifications for Exclusion” criteria for younger children as set forth by the NIH. Specifically, “insufficient data are available in adults to judge potential risk in children” and “children should not be the initial group to be involved in research studies.” Oral TDF is not currently approved for children under 18 years old. This study does not plan to enroll children under 18 years old.

13.7 Incentives

Pending IRB/EC approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits, child care, and time away from work.

13.8 Communicable Disease Reporting

Study staff will comply with all applicable local requirements to report communicable diseases including HIV identified among study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.

13.9 Access to HIV-related Care

13.9.1 HIV Counseling and Testing

HIV pretest and post-test counseling will be provided to all potential study participants who consent to undergo HIV screening to determine their eligibility for this study. Participants must receive their HIV test results to take part in this study. Participants who have positive or indeterminate results will have standard post-test counseling as well as limited follow-up confirmatory testing provided by the study. Referral for additional counseling related to testing or diagnosis will occur if needed or requested by the participant.

13.9.2 Care for Participants Identified as HIV-Infected

Study staff will provide participants with their HIV test results in the context of post-test counseling. According to site SOPs, study staff will refer participants found to be HIV-infected to available sources of medical and psychological care, social support, and local research studies for HIV-infected women. At applicable sites, participants may be offered participation in MTN-015, the MTN Seroconverter Study.

13.10 Study Discontinuation

This study may be discontinued at any time by NIAID, the MTN, CONRAD, Gilead Sciences, Inc., the US FDA, the OHRP, other government or regulatory authorities, or site IRBs/ECs.

14 PUBLICATION POLICY

DAIDS and MTN policies and a Clinical Trial Agreement (CTA) between CONRAD, Gilead Sciences, Inc. and NIAID will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted by the Investigator to the MTN Manuscript Review Committee, DAIDS, CONRAD, and Gilead Sciences, Inc., for review prior to submission.

15 APPENDICES

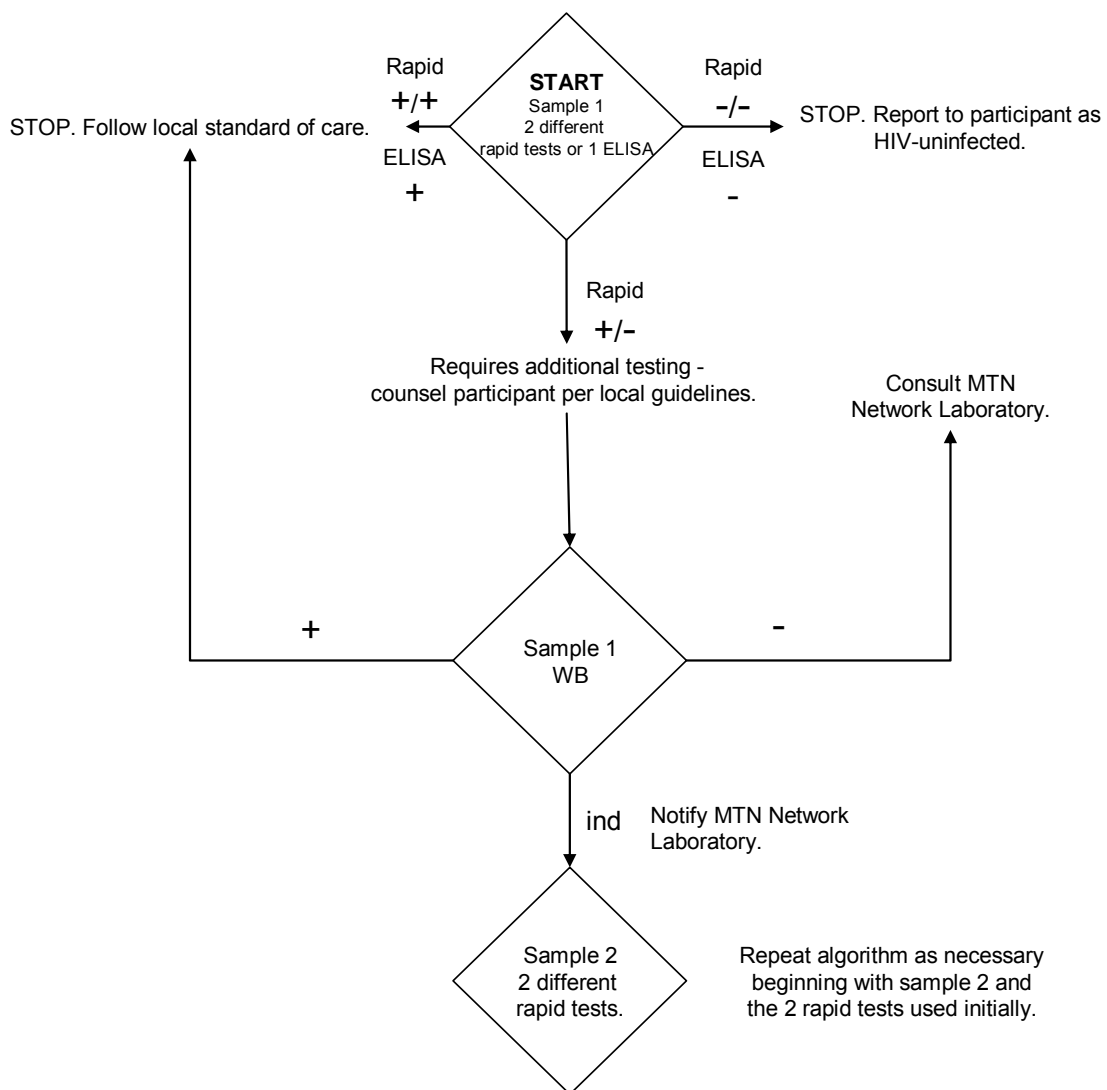
APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

	SCR	PERIOD 1		PERIOD 2			PERIOD 3					
	SCR	ENR	3W	6W	7W	10W	13W	14W	17W	20W	21W	INT.
Informed Consent	X	X										
PTID	X											
Demographics	X											
Locator Information	X	X	X	X	X	X	X	X	X	X	X	X
Behavioral Eligibility	X	X										
Reimbursement	X	X	X	X	X	X	X	X	X	X	X	
Randomization		X										
Schedule Next Visit	X	X	X	X	X	X	X	X	X	X	*	*
Med./Menstrual History	X	X	X	X	X	X	X	X	X	X	X	X
Con. Meds.	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X
Pre-existing Conditions		X										
Physical Exam	X	X	X	X	X	X	X	X	X	X	*	*
Pelvic Exam	X	X	X	X	X	X	X	X	X	X	*	*
Contraceptive Coun.	X	X	X	X	X	X	X	X	X	X	X	*
Pre-/Post-Test Coun.	X	*			X			X			X	*
Protocol Adherence Coun.		X	X	X	X	X	X	X	X	X		*
HIV/STI Risk Red. Coun.	X	X	X	X	X	X	X	X	X	X	X	*
Product Use/Adherence		X	X		X	X		X	X			*
Male Condom Coun.	X	X	X	X	X	X	X	X	X	X	X	*
Treat and/or Refer	*	*	*	*	*	*	*	*	*	*	*	*
Behav. Assessment		X	X	X		X	X		X	X		
In-Depth Interview (subset)											X	
Qualitative Urine hCG	X	X	X	X	X	X	X	X	X	X	X	X
Dipstick Urinalysis	X	*	*	*	*	*	*	*	*	*	*	*
Urine Culture	*	*	*	*	*	*	*	*	*	*	*	*
Urine SDA for CT/GC	X	*	*	*	*	*	*	*	*	*	*	*
CBC	X	X			X			X			X	*
Liver Function	X	X	X	X	X	X	X	X	X	X	X	*
Serum Chemistries	X	X	X	X	X	X	X	X	X	X	X	*
Syphilis Serology	X	*	*	*	*	*	*	*	*	*	*	*
Confirmation Syphilis	*	*	*	*	*	*	*	*	*	*	*	*
HIV-1 Test	X	*			X			X			X	*
Confirmation HIV-1	*	*			*			*			*	*
HBsAg	X		*	*	*	*	*	*	*	*	*	*
Plasma for Storage		X		X			X			X	X	
Tenofovir			X	X		X	X		X	X		*
Insert Lock/Remove Lock				*			*			*		
Flow Cytometry				++			++			++		
Intracel.Ten./Ten. Diphos.				++			++			++		
Vaginal pH	X	X	*	X	*	*	X	*	*	X	*	*
Wet Mount	X	X	*	X	*	*	X	*	*	X	*	*
Herpes Culture	*	*	*	*	*	*	*	*	*	*	*	*
Pap Smear (if >12 months)	*											
CVL		X		X			X			X		
Provide Male Condoms	X	X	X	X	X	X	X	X	X	X	X	*
Offer Panty Liners		X	X	X	X	X	X	X	X	X		*
Supply Study Products		X	X	X	X	X		X	X			*
PK Dose Dispensing				X			X			X		
Collect Unused Prod.			X	X	*	X	X	*	X	X	*	*
Watch Device		X	*			*			*			*
Cytology Brush/Biopsies				●			●			●		

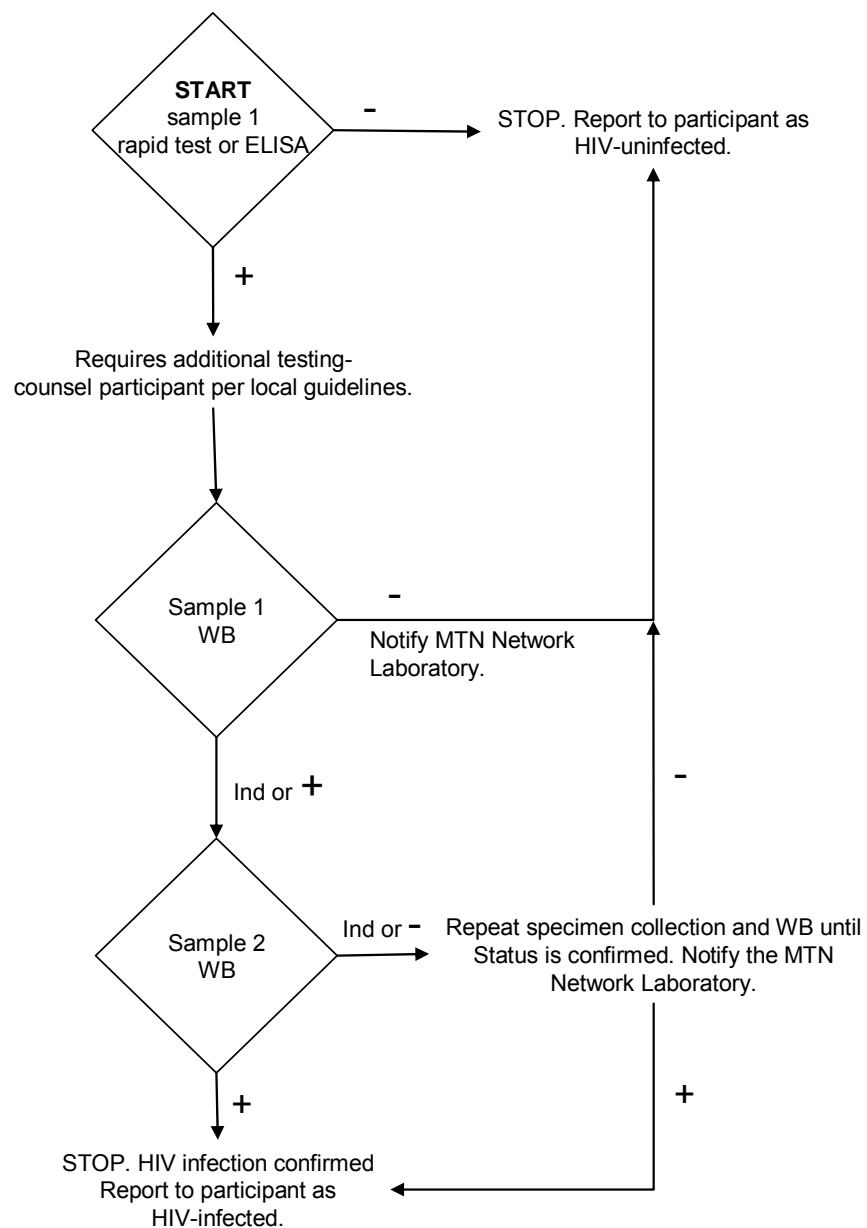
X Protocol specified proc., *If indicated, ● Intensive PK participants only, ++ At sites with capacity, 7.8 for time points

APPENDIX II: HIV ANTIBODY TESTING ALGORITHMS

Algorithm for HIV antibody testing – Screening (and Enrollment if applicable)



Algorithm for HIV antibody testing during follow-up



APPENDIX III: COMPONENTS OF EXAMINATIONS

Physical Exam

- Height (may be omitted after the Enrollment Visit)
- Weight (must be repeated with each Physical Exam)
- Vital signs
 - Temperature
 - Pulse
 - Blood pressure
- General appearance
- Abdomen
- Other components as indicated by participant symptoms

Pelvic Exam

- Vulva
- Perianal area
- Speculum exam
 - Vagina (including vaginal discharge)
 - Cervix (including cervical discharge)
- Bimanual exam, if clinically indicated
 - Cervix
 - Uterus
 - Adnexae

APPENDIX IV: TOXICITY TABLES

The Female Genital Grading Table for Use in Microbicide Studies will be the primary tool for grading adverse events for this protocol, with the exception of asymptomatic bacterial vaginosis which will not be a reportable AE. Adverse events not included in that table will be graded by the DAIDS AE Grading Table Version 1.0, December 2004. In cases where an AE is covered in both tables, the Female Genital Grading Table for Use in Microbicide Studies will be the grading scale utilized.

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December, 2004, is available on the RCC website at <http://rcc.tech-res-intl.com/>.

Female Genital Grading Table for Use in Microbicide Studies

INDIVIDUAL SIGNS/SYMPTOMS					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
GENERAL					
Odor	No complaint	Mild-moderate unpleasant odor	Severe unpleasant odor	NA	NA
PAIN AND TENDERNESS (Specify Area: Vulvar/Perineum, Vagina, Cervix (including cervical motion tenderness), Uterus, Adnexae, Pelvic/Lower Abdominal, or Ovulatory)					
*Note – if both pain and tenderness are present, only report the one with the most severe grade					
Pain* ¹	None	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities or the need for non-narcotic medication	Pain causing inability to perform usual social & functional activities or the need for narcotic medication	Disabling pain causing inability to perform basic self-care functions OR hospitalization (other than emergency room visit) indicated
Tenderness* ¹	None	Mild tenderness	Moderate tenderness	Severe tenderness	NA
Dyspareunia (pain with sexual activity)	None	Pain causing no or minimal interference with sexual function	Pain causing greater than minimal interference with sexual function	NA	NA
Dysmenorrhea/cramping with menses	None	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities or the need for non-narcotic medication	Pain causing inability to perform usual social or functional activities or the need for narcotic medication	NA

¹ If pain or tenderness is included in the grading of another category (e.g., PID), it should not be graded again in the pain or tenderness category.

Female Genital Grading Table for Use in Microbicide Studies

INDIVIDUAL SIGNS/SYMPTOMS					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
GENITOURINARY SIGNS/SYMPTOMS – VULVA					
Vulvar/vaginal itching	None	Itching causing no, mild, or moderate interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities; may require intervention such as antihistamine or bathing to provide relief	NA	NA
Vulvar edema	None	Mild, non-pitting edema	Moderate, 1-2+ pitting edema	3+ pitting edema, severe enough to require urinary drainage, or weeping edema ± skin breakdown	NA
Vulvar erythema	None	Erythema covering < 50% of vulvar surface	Erythema covering ≥ 50% of vulvar surface	NA	NA
Vulvar lesions (findings seen only by colposcopy should not be included here)	Normal variants including skin tags, moles, scars, etc.	Blisters, ulcerations, or pustules - no treatment indicated	Blisters, ulcerations or pustules, with treatment indicated	Severe epithelial disruption with hospitalization indicated	NA
Vulvar rash	None	Rash covering < 50% of vulvar surface	Rash covering ≥ 50% of vulvar surface	Severe epithelial disruption with hospitalization indicated	NA
Bartholin's or Skene's gland	No findings	Cyst with no inflammation	Cyst or abscess with outpatient intervention indicated	Cyst or abscess with hospitalization indicated	Necrotizing fasciitis from Bartholin's abscess
GENITOURINARY SIGNS/SYMPTOMS – VAGINA					
** Note – if vaginal discharge is present both by history and on examination, only report the one with the most severe grade					
Vaginal edema	None	Mild-moderate engorgement	Loss of rugae and friability	NA	NA

Female Genital Grading Table for Use in Microbicide Studies

INDIVIDUAL SIGNS/SYMPTOMS					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Vaginal erythema	None	Erythema covering < 50% of vaginal surface	Erythema covering ≥ 50% of vaginal surface	NA	NA
Vaginal dryness	No complaint	Dryness causing no or minimal interference with usual sexual, social, & functional activities	Dryness causing greater than minimal interference with usual sexual, social, & functional activities	NA	NA
Vaginal discharge by participant report **	Participant's usual amount of discharge, regardless of color or quantity	Mild-moderate increase in amount above participant baseline - no sanitary protection required	Profuse increase in discharge requiring pad use or other hygienic intervention	NA	NA
Vaginal discharge as observed by clinician ** (red or brown discharge should be reported under bleeding, not discharge)	Slight amount of discharge, any color	Mild-moderate increase in amount	Significant increase in amount with pooling in vagina on examination	NA	NA
Vaginal abrasions or lacerations (including probable applicator injuries)	None	Superficial disruptions and disruptions extending through the mucosa with minimal impact on life	Large disruptions extending through the mucosa or large superficial disruptions, hospitalization not indicated	Large disruptions extending through the mucosa or large superficial disruptions, hospitalization indicated	Lacerations extending into the peritoneal cavity, bladder, or rectum
Vaginal lesions (findings seen only by colposcopy should not be included here)	Normal variants including skin tags, moles, scars, etc.	Blisters, ulcerations, or pustules, no treatment indicated	Blisters, ulcerations, or pustules with treatment indicated	Severe epithelial disruption requiring hospitalization	NA
Vaginal and Cervical masses (polyps, myomas, or possible malignancy)	None or normal variants such as Nabothian cyst or Gartner duct cyst	Polyp or myoma or undiagnosed mass without symptoms	Polyp, myoma, or undiagnosed mass causing mild symptoms, e.g., bleeding/pain not requiring more than mild analgesia	Polyp, myoma, or undiagnosed mass causing severe symptoms, e.g., bleeding/pain affecting bladder and bowel function	Visible cervical cancer

Female Genital Grading Table for Use in Microbicide Studies

INDIVIDUAL SIGNS/SYMPTOMS					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
GENITOURINARY SIGNS/SYMPTOMS – CERVIX					
Cervical edema and friability	None	Edema without friability	Friable cervix	NA	NA
Cervical erythema	None	Erythema covering < 50% of cervix	Erythema covering ≥ 50% of cervix	NA	NA
Cervical discharge	White or clear discharge	Small amount of purulent discharge at os	Purulent discharge extending onto cervix or vagina	NA	NA
Visible cervical lesions (findings seen only by colposcopy should not be included here)	Normal variants including skin tags, moles, scars, etc.	Blisters, ulcerations, or pustules, no treatment indicated	Blisters, ulcerations, or pustules with treatment indicated	NA	NA
GENITOURINARY SIGNS/SYMPTOMS – UTERUS					
Uterine masses/enlargement based on bimanual examination	Normal to 8 week size, no palpable myomas	Enlarged uterus and mild symptoms, e.g., bleeding/pain requiring mild analgesics	Enlarged uterus/myoma with moderate pain or symptoms, e.g., bleeding	Mass causing severe bleeding/pain or with impact on bowel/bladder function	Uterine mass that requires transfusion or surgery
Polyp, submucosal fibroid, or thickened endometrium detected by transvaginal ultrasound (new or increasing in size from prior exam)	None or unchanged/reduced in size from prior exam	New myomas < 6 cm diameter (single or multiple) or diameter increased < 6 cm since prior exam	New myomas ≥ 6 cm diameter (single or multiple) or diameter increased ≥ 6 cm since prior exam	Hospitalization and/or surgery indicated	NA
GENITOURINARY SIGNS/SYMPTOMS – ADNEXA					
Not pregnancy- or infection-related adnexal masses based on bimanual exam (use if no ultrasound done; if ultrasound done, use ultrasound categories below)	None, ≤ 4 cm, normal size ovary	> 4 cm with minimal or no symptoms	> 4 cm with severe symptoms, e.g., pain, but hospitalization not indicated (see footnote #1)	> 4 cm with severe symptoms, e.g., pain and hospitalization indicated (see footnote #1)	NA

Female Genital Grading Table for Use in Microbicide Studies

INDIVIDUAL SIGNS/SYMPTOMS					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Hydrosalpinx based on ultrasound	None	Asymptomatic, suspected hydrosalpinx	Hydrosalpinx with pain, but without evidence of infection or ectopic pregnancy	Signs/symptoms of infection with hospitalization and/or surgery indicated	NA
Adnexal mass based on ultrasound	None	Simple cyst, asymptomatic	Simple cyst, symptomatic	Mass suspicious for malignancy	Malignant mass
GENITOURINARY SIGNS/SYMPTOMS – ABDOMEN					
Abdominal mass not palpable on pelvic exam of unknown diagnosis	None or known (pre-existing) mass unchanged in size	New mass or increased size of known mass requiring mild analgesia with minimal impact	New mass or increased size of known mass with moderate symptoms	Mass causing severe bleeding/pain with impact on bladder/bowel function or with hospitalization indicated	Malignancy
GENITOURINARY SIGNS/SYMPTOMS – URINARY TRACT					
Urinary frequency	None	Up to 2 times participant's normal frequency	> 2 times participant's normal frequency	NA	NA
Dysuria	None	Superficial only	Deep ± superficial	Inability to void due to pain	NA
Hematuria	None	Microscopic, no intervention indicated (beyond evaluation for infection)	Gross blood in urine or medical intervention/evaluation indicated (beyond evaluation for infection)	Persistent bleeding with transfusion, hospitalization or intervention indicated to obtain hemostasis (endoscopy, interventional radiology, or operative)	Profuse hemorrhage with shock or orthostatic dizziness

Female Genital Grading Table for Use in Microbicide Studies

COMPOSITE SIGNS/SYMPTOMS (Use instead of individual categories if 2 or more signs/symptoms are present)					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD (Use if all signs/ symptoms would individually be Grade 0 or 1)	GRADE 2 MODERATE (Use if one or more signs/symptoms would individually be Grade 2 and all others Grade 0 or 1)	GRADE 3 SEVERE (Use if one or more signs/symptoms would individually be Grade 3)	GRADE 4 POTENTIALLY LIFE- THREATENING
NO ORGANISM IDENTIFIED BUT INADEQUATE TESTING PERFORMED					
Vulvovaginitis (combinations of pain, itching, erythema, edema, rash, tenderness, or discharge)	None	Mild signs/ symptoms	Moderate signs/ symptoms	Severe signs/ symptoms	NA
Cervicitis (combinations of dyspareunia, erythema, edema, tenderness, and discharge)	None	Mild signs/ symptoms	Moderate signs/ symptoms	Severe signs/ symptoms	NA
PID (if Gonorrhea or Chlamydia identified use that category)	None	NA	Cervicitis with mild uterine tenderness, ± mild cervical motion tenderness, no signs of peritoneal irritation	More diffuse tenderness, any signs of peritoneal irritation, or indications for hospitalization	Tubo-ovarian abscess or surgery required for resolution
NO ORGANISM IDENTIFIED AFTER APPROPRIATE TESTING PERFORMED					
Vulvovaginitis (combinations of pain, itching, erythema, edema, rash, tenderness, or discharge)	None	Mild signs/ symptoms	Moderate signs/ symptoms	Severe signs/ symptoms	NA
Cervicitis (combinations of dyspareunia, erythema, edema, tenderness, and discharge)	None	Mild signs/ symptoms	Moderate signs/ symptoms	Severe signs/ symptoms	NA
PID (if Gonorrhea or Chlamydia identified use that category)	None	NA	Cervicitis with mild uterine tenderness, ± mild cervical motion tenderness, no signs of peritoneal irritation	More diffuse tenderness, any signs of peritoneal irritation, or indications for hospitalization	Tubo-ovarian abscess or surgery required for resolution

Female Genital Grading Table for Use in Microbicide Studies

INFECTIONS AND DYSPLASIA					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
GENITOURINARY INFECTIONS					
Genital herpes	No lesions	Characteristic ulcerative or vesicular lesions confirmed by culture, PCR, Tzanck prep or other diagnostic test of lesion or previous type-specific serology, covering < 25% of vulva, vagina, or cervix	Same criteria as mild but covering 25-50% of vulvar, vaginal, or cervical surface	Same criteria as mild but covering > 50% of vulvar, vaginal, or cervical surface	Symptoms of significant systemic involvement, e.g., encephalitis, hepatitis
Candida	Absence of symptoms regardless of candida test results	Positive culture, wet mount, or other laboratory test for yeast, with mild symptoms	Positive culture, wet mount, or other laboratory test for yeast, with moderate to severe symptoms	NA	NA
Trichomonas	Negative	NA	Positive wet mount, culture, PCR or other licensed test, excluding pap smear, showing T. vaginalis, regardless of symptoms	NA	NA
Bacterial Vaginosis (BV)	Negative	Asymptomatic BV diagnosed by Amsel criteria, wet mount, Gram stain, or licensed diagnostic test	Symptomatic confirmed by wet mount, Gram stain, or any licensed diagnostic test	NA	NA

Female Genital Grading Table for Use in Microbicide Studies

INFECTIONS AND DYSPLASIA					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Chlamydia	Negative	NA	Positive culture or other diagnostic test for Chlamydia, asymptomatic or with mild uterine or cervical motion tenderness (no signs of peritoneal irritation)	Positive test for Chlamydia with abdominal or uterine or adnexal tenderness on examination, with or without adnexal mass, diffuse tenderness, any signs of peritoneal irritation, or indications for hospitalization	Tubo-ovarian abscess or surgery required for resolution
Gonorrhea	Negative	NA	Positive culture or other diagnostic test for Gonorrhea, asymptomatic or with mild uterine or cervical motion tenderness (no signs of peritoneal irritation)	Positive test for Gonorrhea with abdominal or uterine or adnexal tenderness on examination, with or without adnexal mass, diffuse tenderness, any signs of peritoneal irritation, or indications for hospitalization	Tubo-ovarian abscess or surgery required for resolution or disseminated gonococcal infection
Urinary tract infection (by urinalysis and urine culture)	Negative	5-10 WBC/hpf on urinalysis with a negative culture per protocol definition (with or without symptoms)	> 10 WBC/hpf on urinalysis OR a positive culture per protocol definition (with or without symptoms)	Pyelonephritis	Sepsis (septicemia) due to urinary tract infection

Female Genital Grading Table for Use in Microbicide Studies

INFECTIONS AND DYSPLASIA					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Syphilis	Negative treponemal or non-treponemal test or both positive with known treatment and stable titers (< 4 fold increase)	NA	Syphilis diagnosed by a positive treponemal test along with a positive non-treponemal test and no previous treatment or a four-fold rise in titer on the non-treponemal test after previous treatment regardless of symptoms or non-oral lesions positive by darkfield exam for treponemes	Criteria for Grade 2 Syphilis in the presence of neurologic symptoms or a positive CSF VDRL or FTA-ABS	NA
GENITAL DYSPLASIA					
Condyloma (specify site: cervical, vaginal, vulvar, perianal)	None	Condylomata causing no or mild interference with daily function	Condylomata causing moderate interference with daily function	Condylomata causing severe interference with daily function, secondary infection, or hospitalization indicated	NA
Intraepithelial Neoplasia by biopsy (VIN, CIN, VAIN)	None	Intraepithelial Neoplasia 1 (IN1)	Intraepithelial Neoplasia 2 (IN2)	Carcinoma in situ (CIS)	Invasive carcinoma
Pap (use this category <u>only</u> if treatment performed without diagnostic testing, otherwise use biopsy category above)	nI PAP	ASCUS or LSIL	HSIL	Carcinoma in situ or Carcinoma	NA

Female Genital Grading Table for Use in Microbicide Studies

UTERINE BLEEDING AND PREGNANCY COMPLICATIONS					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
ABNORMAL UTERINE BLEEDING UNRELATED TO PREGNANCY					
Menorrhagia ² (prolonged and/or heavy menstrual bleeding)	Participant report of normal bleeding relative to her baseline	Increase from usual with no or minimal interference with usual social & functional activities (including sexual functioning)	Increase from usual with moderate interference with usual social & functional activities (including sexual)	Incapacitating or severe interference with usual social & functional activities (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock
Metrorrhagia ² (intermenstrual or frequent bleeding)	None or any expected nonmenstrual bleeding	Increase from usual with no or minimal interference with usual social & functional activities (including sexual functioning)	Increase from usual with moderate interference with usual social & functional activities (including sexual)	Incapacitating or severe interference with usual social & functional activities (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock
Unexplained infrequent bleeding (excludes expected absence of menses due to hormonal contraception or pregnancy/postpartum)	Participant report of normal or expected bleeding frequency	No menses for 1-3 months (missed menses)	No menses for > 3 months (oligomenorrhea/ amenorrhea)	NA	NA
Postcoital bleeding	None	Occasional (< 25% of coital acts) OR Increase from usual with no or minimal interference with usual social functioning (including sexual functioning)	Frequent (25-75% of coital acts) OR Increase from usual with moderate interference with usual social functioning (including sexual)	Consistent (> 75% of coital acts) OR Incapacitating or severe interference with usual social functioning (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock

² If both Menorrhagia and Metrorrhagia are present, a single adverse event should be reported as "Menometrorrhagia" and graded per the Menorrhagia grading scale.

Female Genital Grading Table for Use in Microbicide Studies

UTERINE BLEEDING AND PREGNANCY COMPLICATIONS					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
COMPLICATIONS OF PREGNANCY					
First trimester bleeding	None	Spotting or bleeding less than menses with continuation of pregnancy	Bleeding like menses or heavier with continuation of pregnancy	Spontaneous abortion, or profuse bleeding with dizziness or orthostatic hypotension, transfusion indicated	Spontaneous abortion with profuse bleeding and/or shock
Postabortal endometritis/salpingitis	None	Low grade fever and uterine tenderness, resolved with oral antibiotics	Moderate symptoms, requiring \leq 3 days of parenteral antibiotics	Severe symptoms requiring > 3 days of IV antibiotics or development of tubo-ovarian abscess	Ruptured TOA or diffuse peritonitis or severe uterine infection for which operative intervention indicated
Postpartum hemorrhage	EBL < 500 cc for vaginal delivery or < 1000 cc after CS or reported as normal	EBL 500-1000 for vaginal delivery or 1000-1500 for CS or reported as slightly increased	EBL > 1000 for vaginal delivery or > 1500 for CS, with or without mild dizziness, no transfusion required	Hemorrhage at a level for which transfusion of 1-2 units of packed cells, but no other blood products indicated	Hemorrhage with shock or coagulopathy, for which transfusion of > 2 units of packed cells or any amount of other blood components is indicated
Postpartum endometritis	None	Low grade fever and uterine tenderness, resolved with oral antibiotics	Moderate symptoms, treated by \leq 3 days of parenteral antibiotics	Severe symptoms treated with > 3 days of IV antibiotics or addition of heparin	Severe infection or infection for which operative intervention is indicated
Chorioamnionitis	None	Fever (38°C – 38.4°C or 100.4°F – 100.9°F) with two or more: FHR > 160 BPM, maternal HR > 120, uterine tenderness between contractions or purulent AF or preterm labor	Same as Grade 1 plus fever 38.5°C – 40°C or 101°F – 104°F	Criteria for Grade 2 plus fetal distress or fever > 40°C or 104°F	Criteria for Grade 3 plus either fetal demise or maternal symptoms of shock

Female Genital Grading Table for Use in Microbicide Studies

UTERINE BLEEDING AND PREGNANCY COMPLICATIONS					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Episiotomy infection	None	Mild erythema, edema, and tenderness of wound	Fever > 38°C or 100.4°F with erythema, edema, and tenderness of wound	Fever with wound dehiscence or debridement required	Fever with signs of wound infection and shock or necrotizing fasciitis
Second/third trimester bleeding	None	Bleeding less than menses	Bleeding like menses or greater, but not requiring intervention	Bleeding requiring delivery or other intervention, e.g., transfusion	Bleeding with fetal demise or coagulopathy
Preterm rupture of membranes	None	NA	Preterm rupture with hospitalization but not resulting in delivery at less than 37 weeks' gestation	Delivery at 33-36 weeks' gestation or 1501-2500 grams birth weight	Delivery < 33 weeks' gestation or ≤ 1500 grams birth weight
Preterm contractions	None	Preterm contractions which resolve without medical intervention	Preterm contractions with cervical change which result in medical intervention but not resulting in preterm delivery	Delivery at 33-36 weeks' gestation or 1501-2500 grams birth weight	Delivery < 33 weeks' gestation or ≤ 1500 grams birth weight
Poor fetal growth	At or above 10th percentile	Fetal growth < 10th percentile but ≥ 3rd percentile for gestational age by ultrasound or newborn exam	NA	Fetal growth < 3rd percentile for gestational age by ultrasound or newborn exam	NA

APPENDIX V: MANUAL FOR EXPEDITED REPORTING OF ADVERSE EVENTS TO DAIDS

The Manual for Expedited Reporting of Adverse Events to DAIDS, Final 1.0, 6 May 2004 is available at: <http://rcc.tech-res.com/eae.htm>

APPENDIX VI: SAMPLE INFORMED CONSENT FORM (SCREENING)

Phase 2 Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir

Version 2.0
03 September 2008

PRINCIPAL INVESTIGATOR: [insert]
PHONE: [insert]
Short Title for the Study: Adherence and Pharmacokinetics Study of Oral and Vaginal Tenofovir

INTRODUCTION

You are being asked to take part in these screening exams and tests because you are a woman between the ages of 18 and 45 years, and you may be able to join the research study named above. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. The screening exams and tests include interview questions, urine and blood tests, a physical exam, and an examination of your vagina.

This is a screening consent form. It gives you information about the screening exams and tests. The study staff will explain the exams and tests to you and what is expected of you. You are free to ask questions about the screening exams and tests at any time. If you agree to have the screening exams and tests, you will be asked to sign or make your mark on this consent form in front of a witness. You will be given a copy of this form to keep.

Please note that your participation in this research is entirely voluntary. You may decide to withdraw from the study at any time without losing the benefits of your standard medical care.

WHY ARE THE SCREENING EXAMS AND TESTS BEING DONE?

These exams and tests are being done to see if you can be in this study. The exams and tests will check to see if you are eligible for the study.

WHAT IS THE PURPOSE OF THE STUDY?

This study is being done to understand women's experiences in taking a product called tenofovir several different ways; by experiences we mean safety and how women feel about taking the product. Women in this research study will take tenofovir tablets by mouth once a day for six weeks, tenofovir gel by vagina once a day for six weeks, and both products (oral plus gel) once a day for six weeks. The study will also do different tests on blood and genital specimens to see how much tenofovir goes to those areas of

the body. For example, we will measure how much tenofovir passes from the gel and goes into the blood. We are studying the “pharmacokinetics” of tenofovir; pharmacokinetics is what the body does to a drug, such as where the drug passes and in what amounts.

WHAT DO I HAVE TO DO IF I TAKE PART IN THE SCREENING EXAMS AND TESTS?

The Screening Visit will take about two hours. You will be asked to do these things if you decide you want to be in the study:

- Sign or make your mark on this form after you have read it or had it explained to you and had the chance to ask questions about the study
- Answer questions about yourself, such as where you live, your education, your behavior, including your sexual behavior, your medical history, menstrual period history, and any medicines that you may take and how we can contact you
- Have a physical exam and pelvic exam
- Hear about
 - different ways to avoid getting pregnant
 - how to avoid infections passed during sex
 - the meaning of your test results, including your HIV test results
 - how to use male condoms
- Get treatment for any infections passed during sex or urinary tract infection that you may have, or find out from the study staff where you can get care or treatment
- Provide a urine sample to get tested for pregnancy, urinary tract infection, and chlamydia and gonorrhea
- Provide a blood sample (about 11mL) [SITES TO INSERT LOCAL EQUIVALENT] to check these things:
 - The health of your blood, liver, and kidneys
 - HIV test, Hepatitis B test, and a syphilis test
- Provide a few drops of vaginal fluid to get tests for bacterial vaginosis, vaginal yeast infection, and Trichomonas
- [AT APPLICABLE SITES] Have a genital swab for herpes if you have signs of herpes
- Provide some cells from your cervix for a Pap smear if you do not have results with you today of a Pap smear that was done in the past 12 months (a Pap smear is a test for cervical cancer). If your Pap result is not normal, you might not be able to be in the study; the study staff can discuss this with you.
- Receive male condoms from the study staff
- It will take about [INSERT LENGTH OF TIME] to get the results of your screening tests. We will give you the results of these tests when they are available.

WHY WOULD THE DOCTOR STOP THE SCREENING PROCEDURES EARLY?

The study doctor may need to stop the screening exams and tests early without your permission if:

- The study is cancelled by the US Food and Drug Administration (FDA), US National Institutes of Health (NIH), the MTN, the drug company supporting this study, the Ethics Committees, the US Office for Human Research Protections, the local government or regulatory agency, or the Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research participants).
- Your exams, tests and answers to the questions show you cannot join the study.
- The study staff feels that having the screening exams and tests would be harmful to you.
- You do not want to find out your HIV test result.
- You are not able to come to the visits or complete the screening exams and tests.
- Other reasons that may prevent you from completing the study.

WHAT ARE THE RISKS OF THE SCREENING VISIT TESTS?

Risk of Blood Draws:

- You may feel discomfort or pain when your blood is drawn.
- You may feel dizzy, faint or lightheaded.
- You may have a bruise, swelling, or infection where the needle goes into your arm.

Risk of Genital Exams:

- You may feel discomfort or pressure during the exam of your genital area and inside your vagina.
- You may have mild vaginal bleeding (spotting). The mild bleeding will stop shortly after the exam.

Other Possible Risks:

- You may become embarrassed, worried, or nervous when discussing personal questions about your sexual behavior, ways to protect against HIV and other infections passed during sex, and your test results.
- You may become worried or nervous while waiting for your test results.
- If you have HIV or other infections, knowing this could make you worried or nervous. A trained counselor will help you deal with any feelings or questions you have.

We will make every effort to protect your privacy while you are having the screening exams and tests. Your visits here will take place in private. However, it is possible that others may learn that you are taking part in the study here. Because of this, they may treat you unfairly. For example, you could have problems getting or keeping a job, or being accepted by your family or community.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

You may get no direct benefit from the screening exams and tests. However, you may benefit from the following:

- Physical exam and a pelvic exam

- Tests for sexually transmitted infections, other vaginal infections, and HIV (which may detect infections that have no symptoms). If you have any of these infections, you will be referred for treatment if needed. You can bring your male partner(s) here so that we can also provide them with referral for diagnosis and treatment for potential STIs.
- Tests to check your general health and the health of your liver, kidneys, and blood. This study cannot provide you with medical care, but study staff will refer you to other available sources of care.
- A Pap test if you have not had one in the past 12 months. If your Pap test result is not normal, you will be referred for treatment at the [INSERT NAME OF PROVIDER/CENTER].
- Safer sex counseling and free male condoms
- If your tests show that you are infected with HIV, you will be referred for medical care, counseling, and other services available to you. Medical care for HIV infection will not be part of this study. You will need to get medical care for your HIV infection from your own health care provider or we will provide you with a referral to a center where you can receive care. We will help you to access the right treatment for HIV infection if you need it.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

You do not have to participate in this study, if you choose not to do so. [SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE: There may be other studies going on here or in the community for which you may be eligible. If you wish, we will inform you about other studies that are being conducted locally. There also may be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.] Please talk to your doctor about these and other choices that may be available to you.

WHAT ABOUT CONFIDENTIALITY?

This study is being conducted according to ethical guidelines and efforts will be made to keep your personal information private. Your physical and vaginal exams will be done in private. We cannot guarantee absolute confidentiality. In some situations, including emergencies, legal and professional rules may force us to share confidential information about you. If this study is published, your name will not be used and you will not be personally identified. You are encouraged but not required to tell sexual partners about your being in this study.

Your records may be reviewed by:

- The US Food and Drug Administration (FDA)
- US National Institutes of Health (NIH)
- US Office for Human Research Protections (OHRP)
- Local regulatory authorities
- [INSERT NAME OF SITE] IRB
- Study staff
- Study monitors
- Ethics committees

- The companies that make the gel and the tablets

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE:]

[LOCAL/STATE/NATIONAL] regulations require study staff to report the names of people who test positive for HIV and other infections passed during sex to the [LOCAL HEALTH AUTHORITY]. Outreach workers from the [HEALTH AUTHORITY] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [HEALTH AUTHORITY].

[For US sites only:] In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been requested from the US Federal Government for this study. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. Even with the Certificate of Confidentiality, however, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

WHAT ARE THE COSTS TO ME?

There is no cost to you for the screening exams and tests.

WILL I RECEIVE ANY PAYMENT?

You will be paid for your time and effort for each screening visit. You will receive [INSERT SITE - SPECIFIC AMOUNT OF MONEY] for each visit. You will also be paid for other costs to you for coming to the screening visits [SUCH AS CHILD CARE, TRAVEL, AND LOSS OF WORK TIME – SITES TO COMPLETE]. There may be one or more screening visits.

WHAT HAPPENS IF I AM INJURED (EXPERIENCE HARM)?

If you are injured as a result of being in this study, the [INSTITUTION] will give you immediate treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. The US National Institutes of Health (NIH) does not have a program to provide money or other forms of compensation for your injuries. Signing this consent form does not change your legal rights.

[SITES TO SPECIFY INSTITUTIONAL POLICY]

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in the screening exams and tests is completely voluntary. You may choose not to have the screening exams and tests any time. You will be treated the same no matter what you decide. If you choose to not have the screening exams and tests, you will not lose the benefit of services to which you would normally have at this clinic.

We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE PROBLEMS OR QUESTIONS?

For questions about the screening exams and tests or if you have a research-related injury, you should contact:

- [SITE INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

For questions about your rights as a research participant, contact:

- [SITE INSERT NAME OR TITLE OF PERSON ON THE INSTITUTIONAL REVIEW BOARD (IRB) OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

SIGNATURE

[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB]

If you have read the informed consent (or had it read and explained to you), and all your questions have been answered and you agree to take part in this study, please sign your name or make your mark below.

Participant's Name (print)

Participant's Signature or Mark and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness's Signature and Date

APPENDIX VII: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT)

Phase 2 Open Label Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir

Version 2.0
03 September 2008

PRINCIPAL INVESTIGATOR: [insert]
PHONE: [insert]
Short Title for the Study: Adherence and Pharmacokinetics Study of Oral and Vaginal Tenofovir

INTRODUCTION

You are being asked to take part in this research study because you are a woman between the ages of 18 and 45 years and have passed the screening for this study. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. Before you decide if you want to join this study, we want you to know about the study.

This is an enrollment consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign or make your mark on this consent form in front of a witness. You will be given a copy of this form to keep. Please note that your participation in this research is entirely voluntary. You may decide to withdraw from the study at any time without losing the benefits of your standard medical care.

WHY IS THIS STUDY BEING DONE?

This study is being done to understand women's experiences in taking a product called tenofovir several different ways; by experiences we mean safety and how women feel about taking the product. Women in this research study will take tenofovir tablets by mouth once a day for six weeks, tenofovir gel by vagina once a day for six weeks, and both products (oral plus gel) once a day for six weeks. The study will also do different tests on blood and genital specimens to see what level of tenofovir goes to those areas of the body. For example, we will measure how much tenofovir passes from the gel and goes into the blood. We are studying the "pharmacokinetics" of tenofovir; pharmacokinetics is what the body does to a drug, such as where the drug passes and in what amounts.

The strength of the tenofovir **tablets** is the dose approved by the Food and Drug Administration (FDA) for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infection in adults. The strength of the tenofovir **gel** has been previously tested and is currently being evaluated in other studies, but is not approved by the FDA for the

treatment or prevention of HIV. HIV is the virus that causes AIDS. This study is not testing to see if tenofovir prevents HIV infection.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

There are three different Study Periods in this study: the Gel Period, the Tablet Period, and the Gel Plus Tablet period. These study visits are part of this study: Enrollment, 3 Week, 6-Week, 7-Week, 10-Week, 13-Week, 14-Week, 17-Week, 20-Week, and 21-Week.

Enrollment Visit:

This visit will take about two hours. At this visit, we will ask you to:

- Sign or make your mark on this consent form after you have had the chance to have all of your questions answered, and if you agree to be in the study
- Answer questions, including questions about your sexual behavior and medical and menstrual history (some of these questions will be asked to make sure that you can be in the study)
- Let us know if there are any changes in how we may contact you
- Tell us about any changes in your medical and menstrual history
- Tell us about any medicines that you are taking now
- Have a brief physical exam
- Have a pelvic exam
- Get treatment for any infections passed during sex or urinary tract infection that you may have, or find out from the study staff where you can get care or treatment
- Hear about:
 - ways to avoid pregnancy
 - how to use male condoms
 - how to avoid infections that may be passed during sex, including HIV
 - the study and how to use the study products the right way
 - what your HIV test results mean (if you have an HIV test today)
- Have your urine tested for pregnancy (your urine may also be tested for urinary tract and/or chlamydia and gonorrhea infection if you are having symptoms)
- Provide blood (14mL) [SITES TO INSERT LOCAL EQUIVALENT] for:
 - tests to check the health of your blood, liver, and kidneys
 - an HIV test (if this is the policy of the study clinic, or the study doctor feels that it is important for your health)
 - a syphilis test (if you have signs of syphilis at this visit)
 - storage at the clinic (this blood may be sent to a laboratory in the US and used for tests on how the body responds to infection)
- Provide a few drops of vaginal discharge (collected by swabs) for testing for infections (only if you are having symptoms of an infection)
- Provide some vaginal and cervical fluid by cervicovaginal lavage (CVL); for CVL, a clinician rinses your vagina and cervix with about 2 teaspoons [SITES TO INSERT LOCAL EQUIVALENT] of sterile fluid and collects that fluid into a tube for testing. A laboratory in the United States will test the fluid to look for

protective proteins and cytokines. Cytokines are very small parts of the fluid that sometimes can be seen when there is inflammation. The protective proteins may help to protect women from infections. These tests do not say if a person has a certain disease or infection. In the future, these tests may help scientists learn more about the safety of different vaginal products. Because doctors do not yet understand enough about what these test results might mean, the results will only be seen by the researchers.

- [AT APPLICABLE SITES] Have a genital swab for herpes if you have signs of herpes
- Receive male condoms from the study staff
- Receive panty liners from the study staff if you use panty liners; a panty liner is a soft absorbent kind of paper that you can place in your panties to catch vaginal discharge or bleeding
- Receive study product(s)
- Receive a small watch and diary card to help you remember or write down what time it is when you take certain dose(s) of study product(s) (we will ask you to tell us the dates and times of your certain doses of study product(s) before coming to your Mid-Study-Period and End of Study Period Visits)

For your study product, you will receive ONE of these ways to take tenofovir today:

1. 28 doses of tenofovir 1% gel already in applicators (an applicator holds the gel and is made to be put in the vagina to insert the gel)

OR

2. 30 tenofovir 300 mg tablets in a bottle

OR

3. 28 doses of tenofovir 1% gel **PLUS** 30 tenofovir 300 mg tablets in a bottle (this means using the gel **AND** taking a tablet every day at about the same time)

By random chance (like flipping a coin [SITES TO INSERT LOCAL EQUIVALENT]) you will be put in a group that takes the study products in a certain order. There are six different groups. For example, one group will use gel first for six weeks, then take tablets for six weeks, and then take both gel and tablets for six weeks. The other groups will have the Gel Period, Tablet Period, and Gel Plus Tablet Period in a different order. All groups will have a week with no study gel or tablets between the study periods, and one week with no study gel or tablets at the end of the study. The study staff will tell you more about how to take care of your gel and tablets and how to use them.

You cannot pick which group you are in (what order you get the study products). The study staff cannot change your group or order of study products. You will only get some of your doses today because you will get more study products at other study visits. There are several times in this study where you will give blood or genital fluid to check for the level of tenofovir. You will not receive the results of these tests because there is not a way to use these results for your medical care.

Mid-Study-Period Visits (3–Week, 10-Week, and 17-Week):

These visits will take about an hour each. At these visits, we will ask you to:

- Tell us if your address has changed, or if there is a new way to reach you
- Tell us about anything new in your medical history, menstrual periods, medicines that you are taking
- Tell us if you are having any health problems or other problems having to do with being in the study
- Have a physical exam
- Have a pelvic exam
- Get treatment or find out where to get treatment for problems (including some infections passed during sex) that the study staff might find
- Hear about:
 - ways to avoid getting pregnant
 - how to use male condoms
- Answer questions about how often you took your study products
- Answer questions about your behavior, including sexual behavior
- Have your urine tested for pregnancy (and infection if you have signs or symptoms)
- Have your blood (6mL) [SITES TO INSERT LOCAL EQUIVALENT] tested for
 - the health of your liver and kidneys
 - tenofovir
 - syphilis (if you have signs of syphilis at this visit)
- Give a few drops of vaginal fluid to be tested for vaginal infections (only if you are having symptoms of vaginal infections, like vaginal itching, for example)
- [AT APPLICABLE SITES] Have a genital swab for herpes if you have signs of herpes
- Receive male condoms
- Receive panty liners, if you wish
- Bring back any study product that you did not use
- Receive more doses of study product

7-Week and 14-Week Visits

These visits will take about an hour and a half each. At these visits, you will have most of the same procedures as the Mid-Study-Period Visits. We will also ask you to:

- Have a test to check the health of your blood (7mL) [SITES TO INSERT LOCAL EQUIVALENT]
- Have an HIV test and hear about what the results mean
- Hear about the study product(s) you will be starting, and how to use them
- Get a new supply of study products

[ONLY **NON-US SITES** TO USE THE FOLLOWING TEXT ON END OF STUDY PERIOD VISITS FOR NON-INTENSIVE PK]

End of Study Period Visits for Non-Intensive PK (6-Week 13-Week, and 20-Week):

These visits will take up to nine hours. These visits take longer because we will check your blood twice over a period of 8 hours. These visits will not be scheduled during your menstrual period.

At these visits, you will have many of the same procedures as the Mid-Study-Period Visits. We will also ask you to:

- Take one dose of study gel one tablet, or both in the clinic on the day of your visit, depending on what group you are in
- Give blood (54mL) [SITES TO INSERT LOCAL EQUIVALENT]) for:
 - the level of tenofovir before you take your dose
 - the level of tenofovir one time after your dose of study product(s) in the clinic, either between 1-3 hours, 3-5 hours, or 5-7 hours after your dose, depending on which group you are in. Your group will be decided by a process using random chance (like flipping a coin [SITES TO INSERT LOCAL EQUIVALENT]). You will be able to find out today how long you will have to stay at the clinic for these visits.
 - [AT SITES WITH CAPACITY] flow cytometry -- this test counts certain kinds of cells in your blood and helps us understand why some people's blood takes up more tenofovir than others.
 - tests to check the health of your liver and kidneys
 - storage at the clinic (this blood may be sent to a laboratory in the US and used for tests on how the body responds to infection)
 - [AT SITES WITH CAPACITY] a test to check how much tenofovir gets into different parts of your blood and tissue
- [SITES TO INSERT IF APPLICABLE] Before you give blood for these tests, the study staff may put a special kind of device under your skin in your arm vein called a lock that will let them take your blood without putting a needle into your skin every time. This lock would be removed today after we are done taking the blood samples.
- Provide some vaginal and cervical fluid by CVL. A laboratory in the United States will test the fluid to look for protective proteins and cytokines. We will also check the amount of tenofovir in the fluid.
- It will take about [INSERT TIME] to get the results of your tests. We will give you your results when they are ready. You will not receive the results of some tests (tenofovir levels, flow cytometry), because there is no way to use the results for your medical care. Because doctors do not yet understand enough about what these test results might mean, the results will only be seen by the researchers.

[US SITES ONLY TO INSERT THE FOLLOWING TEXT ON END OF STUDY PERIOD VISITS FOR INTENSIVE PK]

End of Study Period Visits for Intensive PK (6-Week, 13-Week, and 20-Week)

This visit will take up to nine hours. This visit takes longer because we will check your blood six times over a period of 8 hours. These visits will not be scheduled during your menstrual period.

At this visit you will have many of the same procedures as the Mid-Study-Period Visits. We will also ask you to:

- *Tell us when you took your last two doses of study product before coming to the clinic*
- *Take one dose of study gel one tablet, or both in the clinic on the day of your visit, depending on what group you are in*
- *Give blood (134 mL) [SITES TO INSERT LOCAL EQUIVALENT] for these tests:*
 - *flow cytometry--this test counts certain kinds of cells in your blood and helps us understand why some people's blood takes up more tenofovir than others.*
 - *the level of tenofovir before you take a dose of your study product in the clinic*
 - *the level of tenofovir at 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours after your dose of study product(s)*
- *Before you give blood for these tests, the study staff may put a special kind of device under your skin in your arm vein called a lock that will let them take your blood without putting a needle into your skin every time. This lock would be removed today after we are done taking the blood samples.*
- *Give cells from your cervix to check the level of tenofovir there. The cells will be taken with a cytology brush, which is a small brush that is the same kind used to get cells for a Pap smear. (Although the cells will be collected the same way cells are collected for a Pap smear, they will be used for a different kind of test [tenofovir level] so you will not get the results for a Pap smear [a test for cervical cancer] from this test).*
- *Give tissue from two places in your vagina (each about 3 by 5 mm around, or as big as a grain of rice) to check for the level of tenofovir there. We will collect the tissue by taking a biopsy (a biopsy is a sample of tissue) with a special medical tool that is made for this purpose.*
- *Provide some vaginal and cervical fluid by cervicovaginal lavage (CVL); a laboratory in the United States will test the fluid to look for protective proteins and cytokines. We will also check the amount of tenofovir in the fluid*
- *The cervical cells, CVL, and vaginal biopsy samples will be taken one time at each intensive PK visit either before your dose of study product, or at 2, 4, or 6 hours after you receive your study product, depending on random chance (like flipping a coin [SITES TO INSERT LOCAL EQUIVALENT]).*
- *It will take about [INSERT TIME] to get the results of your tests. We will give you your results when they are ready. You will not receive the results of some tests*

(tenofovir levels, flow cytometry), because there is no way to use the results for your medical care. Because doctors do not yet understand enough about what these test results might mean, the results will only be seen by the researchers.

Twenty-One-Week Visit

This visit will take about one and a half hours. At the 21-Week Visit, you will have most of the same procedures as the Mid-Study-Period Visits. You will also:

- Have an HIV test and hear about the meaning of the results.
- Give blood for a test to check the health of your blood. (7mL) [SITES TO INSERT LOCAL EQUIVALENT]

The study site staff will give you your test results as soon as they are available. We will ask you to come back to the clinic or, with your permission; we may visit you at your home or a place in your community.

In-Depth Interview

This interview will take about 30 minutes (in addition to the one and a half hours for the other parts of the 21-Week Visit). About eight to ten participants at each study site will be asked to answer extra questions at the 21-Week Visit about what they thought about the study products. The group of possible participants will be chosen by random chance, like flipping a coin [SITES TO INSERT LOCAL EQUIVALENT]. Being in this part of the study (like being in other parts of the study) is voluntary. The interviewers will ask questions about any problems you may have had using the study products, whether you liked using the products or not, any reaction your partner(s) may have had to the product(s), and whether anyone ever wanted you to share or sell them your study products. Since your response to these questions is so important, we will be recording the interview using a handheld digital voice recorder so we can make sure that all the information you provide is captured. Every effort will be made to ensure that all information provided during the interview remains confidential.

AFTER YOU FINISH USING THE GEL AND TABLETS:

During this study you may have a chance to take part in additional studies. If you choose not to take part in any of our additional studies, your participation in this study remains the same. If you have any problems or concerns regarding your health after using the study gel and tablets, let the study staff members know. You can contact the study site staff at any time after you have finished using the study gel and tablets. The study site staff will want to let the study sponsor (the company or organization who provides the study products) know about any serious problems you tell them about.

ANY TIME DURING THE STUDY:

If either you or the study staff members think you may have become pregnant, you will give urine for a pregnancy test. Also, if you are having health problems that may be caused by STIs, you will:

- Have an exam of your genital area and inside your vagina.

- Give blood or urine to test for STIs.
- Get referral for treatment for STIs if you need it.

You are asked to tell the study staff about any medical problems you have. You can contact the study staff between regular visits to report these problems. The study staff will examine you as necessary. They will refer you for medical care that you may need.

When possible, please tell the study site before starting any new medications, supplements, or herbal/traditional remedies.

If the staff members find that study gel and/or study tablets are causing you problems, they may ask you to stop using the study gel and/or study tablets, either for a short time or permanently. The study staff will ask you to stop using the study gel and/or tablets if you become pregnant or if you become infected with HIV or Hepatitis B. Even if you stop using the study gel and/or tablets, you will be asked to stay in the study and have your follow up visits. You will also have some or all of the originally planned exams and tests that the study staff would like you to have to check on your health.

If you have an STI that your partner also may have, you can bring him here for counseling and referral for testing and treatment. You can have extra counseling and testing for HIV at any time during the study. If you wish, your partner can have counseling with you. If you become infected with HIV, you can stay in the study but you cannot keep using the study gel or tablets and you should return any used and unused applicators or tablets to the study clinic. The study staff will give you counseling and refer you to available sources of medical care and other services you may need.

At each study visit, the study staff will update information on where you live and how to keep in contact with you. They will use this information to remind you of scheduled visits. If you miss a visit, the study staff will try to contact you by [SITE-SPECIFIC METHODS]. If you give your permission, they also may visit your home to find you. They will try to reach you through the contact people that you list. If they talk to these people, they will not tell them why they are trying to reach you.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE:]

[LOCAL/STATE/NATIONAL] regulations require study staff to report the names of people who test positive for HIV and other infections passed during sex to the [LOCAL HEALTH AUTHORITY]. Outreach workers from the [HEALTH AUTHORITY] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [HEALTH AUTHORITY].

HOW MANY WOMEN WILL TAKE PART IN THIS STUDY?

Approximately 144 women will take part in this study: about 24 each from 5 of the sites (Botha's Hill, Durban, South Africa, Umkomaas, Durban, South Africa, Cleveland, USA, Kampala, Uganda, and Pittsburgh, USA), and 12 each from Birmingham, USA and

Bronx, USA. At US sites (Birmingham, Bronx, Cleveland and Pittsburgh), 72 women will participate in the Intensive PK sampling.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study about 21 weeks. The total time you will be in the study, including the time to complete the screening exams and tests and the main study is about 23 weeks.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- The study is cancelled by the US Food and Drug Administration (FDA), US National Institutes of Health (NIH), a drug company supporting this study, the Ethics Committee, the US Office for Human Research Protections (OHRP), the MTN, the local government or regulatory agency, or the Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research participants).
- The Study Monitoring Committee (SMC) recommends that the study be stopped early (A SMC reviews the progress of the study and the kinds of effects that people report while they are participating in the study).
- You are not able to keep appointments.
- Other reasons that may prevent you from completing the study successfully.

The study doctor will ask you to stop using the study gel or tablets but continue to come in for your follow up visits and procedures if:

- You are pregnant.
- You are breastfeeding.
- You become infected with HIV.
- The study doctor decides that using the study gel or tablets would be harmful to you or your partner.
- You require a treatment that you may not take while using the study gel or tablets.
- You have a bad reaction to the study gel or tablets.

If the study doctor asks you to stop using the study gel or tablets, you will still be advised to come in for all of the scheduled follow-up visits that are described above, including things like the physical exam, vital signs, pelvic exam, blood tests, and questionnaires. You will stop using the study gel or tablets until the study doctor decides it is safe for you to start using the study gel or tablets again, if possible.

WHAT ARE THE RISKS OF THIS STUDY?

Risks of Blood Draws:

You may feel discomfort or pain when your blood is drawn and/or where a lock device for blood draws is inserted. You may feel dizzy, faint or lightheaded. You may have a bruise, swelling, or infection where the needle goes into your arm.

Risks of Genital Exams:

You may feel discomfort or pressure during the exam of your genital area and inside your vagina. You may have mild vaginal spotting (bleeding). The mild bleeding will stop shortly after the exam.

Risks of Cervicovaginal Lavage:

You may feel discomfort or pressure in your vagina and/or pelvis during the CVL.

[US SITES TO ADD THE FOLLOWING LANGUAGE RELATED TO VAGINAL BIOPSIES].**Risks of Vaginal Biopsies:**

You may feel slight to moderate pain at the time of the biopsy (like being pinched) which usually resolves quickly but could last for a few hours. You may have spotting (small amounts of vaginal bleeding) for one or two days. You should not have vaginal intercourse until you stop bleeding. You may have a little discomfort (soreness) if you have vaginal intercourse during the time that the biopsy areas are still healing. There is a small risk of the biopsy area becoming infected or having bleeding that is heavier than spotting. Exposure to an STI during vaginal intercourse before complete healing of biopsies might increase your risk of getting an STI. If you have bleeding heavier than your usual menstrual period, a foul odor or a heavier vaginal discharge (more than usual), you should contact the study clinic right away.

Other Possible Risks:

You may become embarrassed, worried, or nervous when discussing sexual behaviors and HIV. You may become worried or nervous while waiting for your STI and HIV test results. If you have HIV, knowing your HIV status could make you worried or nervous. You will talk with a trained staff member who will help you deal with any feelings or questions you have.

Risks of the Study Gel:

It is very important to use the study gel as instructed by staff. The study gel used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these products. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning additional study product side effects please ask the study staff.

Some of the effects of the tenofovir gel are still unknown. Some possible effects are dryness, itching, burning, or pain in the genital area. You may also have discharge if the study gel comes out of the vagina. In about half of the women tested before, there was a small amount of irritation in the genital area.

It is possible that tenofovir gel could be absorbed from the vagina into the blood. Based on an earlier study of tenofovir gel, a small amount of tenofovir gel from the vagina was absorbed into the blood in about half of the women tested (about 1% of the amount that

is absorbed when the oral pill is taken). If the tenofovir in the study gel is absorbed into the blood, it is not known whether this will cause any bad effects. If bad effects did occur, they might be like the ones listed below for the tenofovir tablet.

If you are HIV positive you should not receive the study gel. This is because it is not known what effect tenofovir gel could have on the HIV virus. There is a small possibility that tenofovir could change the virus. If the virus changes, normal treatment for HIV may not work on the virus.

If you have a positive test for hepatitis B you should not receive the study gel. It is not known what effect tenofovir gel could have on the hepatitis B virus. There may be a risk that tenofovir will change the hepatitis B virus. If the virus changes normal treatment for hepatitis B may not work on the virus. It is not known what effect tenofovir gel could have on the disease condition in people with hepatitis B virus.

Your male sexual partners will be protected from potential risks associated with exposure to tenofovir gel through:

- Consistent use of approved male condoms during penile-vaginal sex
- Avoidance of oral-vaginal sex

Risks of the Study Tablet (Tenofovir or TDF 300 mg Tablet)

General Disclaimer

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning additional study drug side effects please ask the medical staff at your site.

Use of Combination Antiretroviral Drugs

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs and arms
- Breast enlargement

Tenofovir itself is not a combination antiretroviral drug, but is one of the drugs that is used in some combination antiretroviral drugs.

Nucleotide Analogue

Lactic acidosis (elevated lactic acid levels in the blood) and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may result in liver failure, other complications or death have been reported with the use of antiretroviral nucleoside analogues alone or in combination. The liver complications and death have been seen

more often in women on these drug regimens. Some nonspecific symptoms that might indicate lactic acidosis include: unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, cramps, muscle pain, weakness, dizziness and shortness of breath.

Tenofovir Disoproxil Fumarate (Tenofovir DF, TDF, Viread®)

Gilead Sciences, Inc.

The following side effects have been associated with the use of tenofovir:

- Upset stomach, vomiting, gas, loose or watery stools
- Dizziness
- Abdominal pain
- Lack of energy
- Kidney damage or failure
- Inflammation or swelling and possible damage to the pancreas
- Shortness of breath
- Rash
- Low phosphate, a chemical in the blood
- Increase of liver functions tests in children
- Allergic reaction, which may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath or a general feeling of illness
- Changes in bone growth and strength were seen in study animals given tenofovir. Bone thinning has been seen in adults and children taking tenofovir.

NOTE: If you are infected with both Hepatitis B and HIV, you should be aware that your liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen if tenofovir is stopped. People with hepatitis B infection are not permitted to join this study. If you think you might have been exposed to hepatitis B infection, please tell the study site.

There is a risk that taking tenofovir tablets could change the type of HIV virus in you or your sexual partner's body, if either of you have an HIV infection. This kind of change can make an HIV infection more difficult to treat with HIV medicines. People with HIV infection are not permitted to join this study. If you think you might have been exposed to HIV infection, please tell the study site. If you have questions about side effects, ask a member of the study staff. You should report any new or continuing symptoms to the study staff right away.

Possible Risks to Your Privacy

We will make every effort to protect your privacy while you are in this study. However, it is possible that you could have problems if people learn that you are in this study. They might think that you are infected with HIV or at risk of HIV because of sexual behavior or illegal drug use. Because of this, others may treat you unfairly. For example, you could have problems getting or keeping a job. You also could have problems being accepted by your family or community. There also is a risk to your privacy if someone else taking part in this study knows you.

Are There Risks Related To Pregnancy?

Taking tenofovir gel and tenofovir tablets are not ways to prevent pregnancy. The study gel should not be used during pregnancy. You must agree to try to not become pregnant during the study. It is not known if the study gel used in this study harms unborn babies. You and your partner must be willing to use an effective method of birth control such as birth control pills or another hormonal based method (except for vaginal rings), an intrauterine device or IUD, already be sterilized, or have sex with a partner who is sterilized. You should discuss this with the study staff. Some of these services may be available at your study site.

The study staff will provide male condoms to you free of charge. You must have a pregnancy test before you enter this study. The test must show that you are not pregnant.

Oral tenofovir disoproxil fumarate is classified by the FDA as a pregnancy category B drug. This means that animal studies have not shown a risk to the fetus (unborn baby), but there are no adequate and well-controlled studies in pregnant women that have been completed to date.

NOTE: Because there is only a small amount of information on tenofovir in pregnant women, tenofovir should be used during pregnancy only if clearly needed.

Again, you must agree to try to not become pregnant in this study, and you should tell the study staff if you think you might be pregnant.

What If I Have A Positive Pregnancy Test During The Study?

If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices. If you have a positive pregnancy test while using the study gel or tablets, we will ask you to stop using the study gel or tablets and return all used and unused applicators and tablets, but will ask you to continue to be in the study and to come in for your follow up visits. There are no anticipated additional risks to you if you choose to continue to take part in this study.

If you are pregnant and choose to continue the pregnancy, this study will not provide care related to your pregnancy, the delivery of your baby, or the care of the baby. Your baby may have been exposed to tenofovir if you received tenofovir gel and/or tablets, and we do not know if this will affect unborn babies. The study staff will contact you to ask you a few questions about the outcome of your pregnancy. You must arrange for your care and your baby's care outside of this study. This study cannot provide care related to termination of pregnancy, though study staff can provide you with information regarding your access to termination of pregnancy as part of counseling you about your pregnancy test results.

Breastfeeding

It is unknown if there are any effects of tenofovir on breast milk. It is not known if tenofovir tablets or gel will pass through breast milk and cause harm to your infant. You

must agree to not breastfeed during this study. Women who are currently breastfeeding may not enroll in this study.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

No one knows if the study gel or tablets will prevent HIV infection. Information learned from this study may help in the development of ways to prevent the spread of HIV in the future. You will receive pelvic exams and counseling and testing for HIV and STIs. You will also have tests to check the overall health of your liver, kidneys, and blood cells. This study cannot provide you with medical care, but study staff will refer you to other available sources of care. If your Pap test result shows anything that is not normal, you will be referred for advice and/or treatment.

You will get counseling and testing for HIV. You will get free male condoms. If you are infected with HIV, you will be referred for medical care, counseling, and other services available to you. Medical care for HIV infection will not be part of this study. You will need to get medical care for your HIV infection from your own health care provider or we will provide you with referral to a center that can provide you with appropriate care. We will help you to access the right treatment for HIV infection if you need it. You will get counseling and testing for STIs. If you have an STI diagnosed, you will get medicine to treat it, if needed. You can bring your partner here for counseling and referral for testing and treatment for STIs if this is needed.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

You do not have to participate in this study, if you choose not to. [SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE: There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about. There also may be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.] Please talk to your health provider about these and other choices that may be available to you.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. In some situations, including emergencies, legal and professional rules may force us to share confidential information about you. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:

- The US Food and Drug Administration (FDA)
- US National Institutes of Health (NIH)
- US Office for Human Research Protections (OHRP)
- Local regulatory authorities
- [INSERT NAME OF SITE] IRB
- Study staff
- Study monitors
- Ethics committees

- The companies that make the gel and the tablets

[For US sites only:] In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been requested from the US Federal Government for this study. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. Even with the Certificate of Confidentiality, however, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

You are encouraged but not required to tell sexual partners about your being in this study.

WHAT ARE THE COSTS TO ME?

There is no cost to you for study related visits, study products, physical examinations, laboratory tests or other procedures.

WILL I RECEIVE ANY PAYMENT?

You will receive payment for your time and effort in this study. You will receive [INSERT SITE-SPECIFIC AMOUNT OF MONEY] per visit. You will also receive payment for activities affected by your participation in this study [SUCH AS CHILD CARE, TRAVEL, LOSS OF WORK TIME – SITES TO COMPLETE].

WHAT HAPPENS IF I AM INJURED (EXPERIENCE HARM)?

If you are injured as a result of being in this study, the [INSTITUTION] will give you immediate treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. The US National Institutes of Health (NIH) does not have a program to provide money or other forms of compensation for your injuries. Signing this consent form does not change your legal rights.

[SITES TO SPECIFY INSTITUTIONAL POLICY]

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. You will be treated the same no matter what you decide. If you choose not to participate or to leave the study, you will not lose the benefit of services to which you would otherwise be entitled at this clinic. We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff members know.

WHAT DO I DO IF I HAVE PROBLEMS OR QUESTIONS?

For questions about this study or a research-related injury, contact:

- [SITE INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]

- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

For questions about your rights as a research participant, contact:

- [SITE INSERT NAME OR TITLE OF PERSON ON THE INSTITUTIONAL REVIEW BOARD (IRB) OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

SIGNATURE

[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB]

If you have read the informed consent (or had it read and explained to you), and all your questions have been answered and you agree to take part in this study, please sign your name or make your mark below.

Please mark one of the following boxes if you are chosen to participate in the in-depth interview:

- I agree to participate in the in-depth interview

- I do not agree to participate in the in-depth interview but would still like to participate in this study

Participant's Name (print)

Participant's Signature or Mark and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness's Signature and Date

APPENDIX VIII: SAMPLE INFORMED CONSENT (STORAGE AND FUTURE TESTING OF SPECIMENS)

Phase 2 Open Label Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir

**Version 2.0
03 September 2008**

PRINCIPAL INVESTIGATOR: [insert]
PHONE: [insert]
Short Title for the Study: Adherence and Pharmacokinetics Study of Oral and Vaginal Tenofovir

INTRODUCTION

You have decided to take part in a Division of AIDS research study. While you are in this research study there may be some samples of tissue, blood and/or fluid from your cervix and vagina taken from you that might be useful for future research. You are being asked to agree to the storage of these samples. This consent form gives you information about the collection, storage and use of your samples. The study staff will talk with you about this information. Please ask any questions, if you have some. If you agree to the storage of your samples, you will be asked to sign or make your mark on this consent form. You will be given a copy of this form copy to keep.

HOW WILL YOU GET THE SAMPLES FROM ME?

The research doctors want to save any extra tissue, blood and cervical and vaginal fluid leftover from your tests during the study. This leftover blood and cervical and vaginal fluid will be kept and used for future research.

HOW WILL YOU USE MY SAMPLES?

Your samples will be used to look for ways that your body responds to infection (such as cells, proteins, and other chemicals in your body). Tests may also include checking your genes (material passed from parent to child that determines the make-up of the body and mind), since they might affect how your body responds to disease. Your genes might make you more or less likely to get an infection, affect your responses to infection, or make your responses to treatment stronger or weaker. No other kinds of genetic test will be done on your stored samples without first explaining the test to you and getting your permission. The researchers do not plan to contact you or your regular doctor with any results from tests done on your stored samples. This is because research tests are often done with experimental procedures, so the results from one research study are generally not useful for your medical care. If a rare situation came up where the researchers decided that a test result would provide important information for your health, the researchers would tell your study doctor and your study doctor would try to contact you. If you wish to be contacted with this type of test result, you must give the study doctor or nurse any change to your address and/or phone number. If you want

your regular doctor to be told about this type of test result, you must provide the study doctor or nurse with your regular doctor's name, address and phone number. Your samples will not be sold or used directly to produce products that can be sold for profit.

Research studies using your samples will be reviewed by the National Institutes of Health and a special committee at the researcher's institution (an Institutional Review Board) whose purpose is to protect you as a research participant.

HOW LONG WILL YOU KEEP MY SAMPLES?

There is no time limit on how long your samples will be stored.

HOW WILL MY SAMPLES BE STORED?

Your samples will be stored at special facilities at your study site and/or in the United States that are designed to store samples securely. The storage facilities are made so that only approved researchers will have access to the samples. An Institutional Review Board will oversee the storage facilities to protect you and other research volunteers from harm.

DOES STORAGE OF MY SAMPLES BENEFIT ME?

There are no direct benefits to you.

WHAT ARE THE RISKS?

There are few risks related to storing your samples. When tests are done on the stored samples there is a small but possible risk to your privacy. It is possible that if others found out information about you from tests (such as information about your genes) it could cause you problems with your family (having a family member learn about a disease that may be passed on in families or learning who is the biological parent of a child) or problems getting a job or insurance.

WHAT ABOUT CONFIDENTIALITY?

To keep your information private, your samples will be labeled with a code that can only be traced back to your research clinic. Your personal information (name, address, phone number) will be protected by the research clinic. When researchers are given your stored samples to study they will not be given your personal information. The results of future tests will not be included in your health records.

[For US sites only:] We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have applied for a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with the research, such as the court system, about your participation. Also, any publication of the research will not use your name or identify you personally.

People who may review your records include: [INSERT NAME OF SITE] IRB, National Institutes of Health (NIH), US Office for Human Research Protections, US Food and Drug Administration, study staff, study monitors, and their designees. Having a

Certificate of Confidentiality does not prevent you from giving information about yourself and your participation in the study. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

WHAT ARE MY RIGHTS?

Allowing your samples to be stored is completely voluntary. You may decide not to have any samples stored other than what is needed to complete this study and still be in this research study or any future study. If you decide now that your samples can be stored for future research, you may change your mind at any time. You must contact your study doctor or nurse and let them know that you do not want your samples used for future research. Your samples will then not be used and will be destroyed.

WHAT DO I DO IF I HAVE QUESTIONS?

For questions about the storage of your samples, contact (*insert the name of the investigator*) at (*insert telephone number*).

For questions about your rights related to the storage of your samples for research, contact (*insert the name or title of person on the Institutional Review Board*) at (*insert telephone number*).

SIGNATURE PAGE

[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB]

If you have read the informed consent (or had it read and explained to you), and all your questions have been answered and you agree to this specimen storage and future testing, please sign your name or make your mark below.

Participant's Name (print)

Participant's Signature or Mark and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness's Signature and Date

REFERENCES

- 1 Gilead Sciences. Viread (tenofovir disoproxil fumarate) tablets. Package Insert, May 2008.
- 2 CONRAD. Investigator's Brochure: Tenofovir Gel (GS-1278). Third Edition, 11 January 2008.
- 3 Tarantal AF, Castillo A, Ekert JE et al. Fetal and maternal outcome after administration of tenofovir to gravid rhesus monkeys (*Macaca mulatta*). *JAIDS* 2002; 29: 207-220.
- 4 Lund B, Weber S. Pharmacokinetics and distribution of intravaginal [¹⁴C] PMPA (GS-1278) following single dose administration to rats. Gilead Sciences Report No. 96-DDM-1278-004. October 1, 1996.
- 5 Creek MR. Pharmacokinetics and tissue distribution study of PMPA (GS-1278) following intravaginal administration in female New Zealand White Rabbits. SRI Report No. B010-97. November 6, 1997.
- 6 Fairchild D. 14-day vaginal tissue irritation and toxicity study of PMPA in rats. Report No. M016-97. June 30, 1997.
- 7 Peterson L, Taylor D, Roddy R, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2 double-blind randomized placebo-controlled trial. *PLoS Clin Trials* 2(5): e27.doi:10.1371/journal.pctr.0020027
- 8 Mayer K, Maslankowski L, Gai F, et al. Safety and tolerability of tenofovir vaginal gel in abstinent and sexually active HIV-infected and uninfected women. *AIDS* 2006;20:543-551.
- 9 CONRAD Protocol #A04-099 (Study Report), Male Tolerance Study, July 19, 2007.
- 10 Hillier SL. Safety and acceptability of daily and coitally dependent use of 1% tenofovir over six months of use. In: *Microbicides 2008*; New Delhi.
- 11 NIAID Study 97-101. Pharmacokinetic Study in Three Monkeys.
- 12 Ezzet F, Whitehead J. A Random Effects Model for Binary Data from Crossover Clinical Trials. *Applied Statistics* 1992;41(1):117-126.

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- ¹³ Koch GG, Stokes ME. Chi-Square Tests: Numerical Examples. In Kotz S and Johnson N, eds. Encyclopedia of Statistical Sciences, Volume 1. New York, NY:John Wiley & Sons, 1982:457-472.
- ¹⁴ McCullagh P. Regression models for ordinal data. Journal of the Royal Statistical Society, Series B, 1980;42:109-142.

Section 3. Documentation Requirements

Study staff are responsible for proper collection, management, storage, quality control, and quality assurance of all study-related documentation. This section contains information on the Essential Documents that each study site must maintain throughout the study. It also contains information related to establishing adequate and accurate participant research records — commonly referred to as participant “case history records” — for MTN 001.

3.1 Essential Documents

The Division of AIDS (DAIDS) Standard Operating Procedure (SOP) for Essential Documents specifies the essential documents that study sites must maintain for DAIDS-sponsored studies, including MTN 001. The DAIDS SOP for Essential Documents can be found at: <http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Regulatory.htm>. When required documents are modified or updated, the original and all modified or updated versions must be maintained. Although all required documentation must be available for inspection at any time, all documents need not be stored together in one location.

Section Appendix 3-1 presents a suggested essential documents filing structure for MTN 001. Study sites are not required to adopt the suggested structure, but are encouraged to consider it when developing their filing approach for MTN 001. Study sites also are encouraged to establish an SOP to document their filing approach. Further clarifications of the suggested filing structure are as follows:

- Essential documents may be stored in files and/or in binders. The files/binders listed in Section Appendix 3-1 may be further subdivided, consolidated, and/or re-organized if desired.
- It is recommended that a contents sheet be maintained and inserted as the first page(s) of each file/binder. Within each file/binder, it is recommended that documents be filed in ascending date order (most recent documents in front).
- To ensure study integrity, certain documents related to the investigational study products will be stored in site pharmacies. A listing of essential documents to be maintained in the pharmacies is provided in Section 3.3, rather than Section Appendix 3-1.
- To facilitate routine inspection by study monitors, certain laboratory-related essential documents should be stored in the main study essential documents files/binders (see items 26-28 in Section Appendix 3-1). Other lab-related essential documents (e.g., lab SOPs) may be filed in site laboratories.
- The suggested filing structure assumes that MTN 001 participant case history records will be stored separately from the other essential documents listed in Section Appendix 3-1. Section 3.2 below provides information on the required contents of these records. The suggested filing structure also assumes that the MTN 001 Screening and Enrollment Log, Participant Name-ID Number Link Log, and Randomization Envelope Tracking Record (which are described in Section 4 of this manual) will be stored in the study clinic or data management area, and not necessarily with the other essential documents listed in Section Appendix 3-1.

3.2 Participant Case History Documentation

Study sites must maintain adequate and accurate participant case history records containing all information pertinent to MTN 001 for each study participant. Per Section 13.5 of the MTN 001 Protocol, all study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to authorized study staff. Data collection, process, and administrative forms, laboratory specimens, and other reports will be identified by a coded number only to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access. Participants' study information will not be released without their written permission, except as necessary for monitoring (see Section 12 of the MTN 001 Protocol).

3.2.1 Case History Contents

Participant case histories should contain all of the following elements:

- Basic participant identifiers.
- Documentation that the participant provided written informed consent to screen for and participate in the study prior to the conduct of any screening or study procedures, respectively.
- Documentation that the participant met the study's selection (eligibility) criteria.
- A record of the participant's random assignment.
- A record of the participant's exposure to the investigational study products.
- A record of all contacts, and attempted contacts, with the participant.
- A record of all procedures performed by study staff during the study.
- Study-related information on the participant's condition before, during, and after the study, including:
 - Data obtained directly from the participant (e.g., interview responses and other self-reported information)
 - Data obtained by study staff (e.g., exam and lab findings)
 - Data obtained from non-study sources (e.g., non-study medical records)

In addition to the above, DAIDS requires that all protocol deviations be documented in participant records, along with reasons for the departures and/or attempts to prevent or correct the departures, if applicable. The MTN Protocol Deviation Report Form is posted on the MTN Web site. Site staff are encouraged to submit a draft form for review and comment by the CORE (FHI) Clinical Research Manager prior to broader distribution of the form, to help ensure that the form is complete and accurate prior to distribution. Once the form is finalized, it will be distributed to the Protocol Chair, CORE Clinical Research Manager, SDMC Project Manager, NL representative, and DAIDS Medical Officer.

3.2.2 Concept of Source Data and Source Documentation

The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (ICH-E6) defines the terms source data and source documentation as follows:

Source data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source documents: Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the trial).

Source documents are commonly referred to as the documents —paper-based or electronic— upon which source data are first recorded. All study sites must adhere to the standards of source documentation specified in the DAIDS SOP for Source Documentation, which can be found at <http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/ClinicalSite.htm>. The DAIDS SOP specifies both requirements and recommendations. Study sites must comply with all requirements and are encouraged, but not required, to comply with all recommendations.

MTN 001, it is expected that participant case history records will consist of the following source documents:

- Narrative chart notes
- Randomization envelopes, Randomization form, and prescriptions documenting participants' random assignments
- Investigational product dispensing and chain of custody records
- Visit checklists and/or other site-specific flowsheets
- Local laboratory testing logs and result reports
- DataFax and Non-DataFax forms provided by the MTN Statistical and Data Management Center (SDMC)
- Other source documents (e.g., site-specific worksheets, non-study medical records)

As a condition for study activation, each study site must establish an SOP for source documentation that specifies the use of the above-listed documents as source documents. Although it is the responsibility of each site to determine the most appropriate source document for each required case history element, Section Appendix 3-2 provides a guide that sites may follow for this study. Supplemental information on the use of chart notes, visit checklists, and forms provided by the MTN SDMC is provided below. Detailed information on proper completion, maintenance, and storage of participant randomization and product dispensing documentation is provided in Sections 4, 6, and 9 of this manual. Detailed information on proper completion of DataFax and Non-DataFax forms provided by the MTN SDMC is provided in Section 13 of this manual.

Chart Notes: Study staff must document every contact with a study participant in a signed and dated chart note specifying the date, type, purpose, and location of the contact, and the general status of the participant. The time at which a contact takes place, or at which particular procedures take place, also should be specified when necessary to document adherence to protocol requirements. Chart notes also must be used to document the following:

- The screening and enrollment informed consent processes (see also Section 5)
- Procedures performed that are not recorded on other source documents
- Pertinent data about the participant that are not recorded on other source documents
- Protocol departures that are not otherwise captured on other source documents

Study sites are strongly encouraged to adopt a common format — such as the Subjective-Objective-Assessment-Plan (SOAP) format — for all chart notes, to help ensure adequacy and consistency of note content and maximize adherence to GCP standards. Further information on the SOAP note format and several sample notes in SOAP format are provided in Section Appendix 3-3.

Visit Checklists: The checklists in Section 7 of this manual represent convenient tools to fulfill the requirement of documenting all study procedures performed with each study participant. Note, however, that checklists alone may not be sufficient for documenting all procedures. For example, chart notes may be required to document procedures performed at unscheduled study visits, and/or to explain why procedures in addition to those listed on a checklist may have been performed or why procedures listed on a checklist were not performed. Chart notes also may be required to document the content of counseling sessions and/or other in-depth discussions with participants (e.g., related to adherence to protocol requirements).

DataFax and Non-DataFax Forms Provided by the MTN SDMC: The case report forms for this study are designed for use with the DataFax data management system described in Section 13 of this manual. The SDMC will provide these forms to each site. The SDMC also will provide several study-specific non-DataFax forms to each site. See Section Appendix 3-4 for a listing of all DataFax and non-DataFax forms to be provided for this study.

The SDMC will provide all forms in pre-assembled packets for each protocol-specified study visit; i.e., Screening, Enrollment (Period 1 Start), 3-Week Visit (Mid-Study-Period 1 Visit), 6-Week Visit (Period 1 End), 7-Week Visit (Period 2 Start), 10-Week Visit (Mid-Study-Period 2 Visit), 13-Week Visit (Period 2 End), 14-Week Visit (Period 3 Start), 17-Week Visit (Mid-Study-Period 3 Visit), 20-Week Visit (Period 3 End), 21-Week Visit (Termination

Visit). A packet of other “as needed” forms also will be provided. The packets will be produced at a US-based printing company, and will be shipped from the printing company to each study site. For non-US sites, forms will be printed on A4 paper and four-hole punched. For the US sites, forms will be printed on letter size paper and three-hole punched. For all sites, forms that are administered directly to participants will be available in local languages relevant to the site.

As shown in Section Appendices 3-5 and 3-6, many of the DataFax and non-DataFax forms provided by the SDMC have been designed to serve as source documents. Each study site must document the forms that routinely will be used as source documents in its SOP for source documentation, and must follow the specifications of this SOP consistently for all study participants. In the event that study staff are not able to record data directly forms designated as source documents, the following procedures should be undertaken:

- Record the data onto an alternative source document
- Enter the alternative source document into the participant’s study chart
- Transcribe the data from the alternative source document onto the appropriate form
- Enter a chart note stating the relevant study visit date and the reason why an alternative source document was used

3.2.3 Document Organization

Study staff must make every effort to store all study records securely and confidentially. Case history records must be stored in the same manner for all participants, in areas with access limited to authorized study staff only. Study staff are responsible for purchasing file folders, binders, storage cabinets, and any other equipment or supplies needed to properly store all records.

Study-related documentation collected during the screening process should be stored in file folders or thin notebooks for each potential participant. All screening documentation — for potential participants who eventually enroll in the study as well as for those who do not enroll — must be maintained and available for monitoring throughout the study. This documentation also must be available for reference should participants present to the site for re-screening. For participants who enroll in the study, screening documentation should be transferred into large ring binders that will serve as participants’ study notebooks for the duration of their participation in the study.

All documents contained in participant case history records must bear a participant identifier, which generally will consist of either the participant identification number (PTID) or the participant name. Any documents transferred or transmitted to a non-study site location — including DataFax forms and Expedited Adverse Event Forms — must be identified by PTID only.

Regardless of whether the identifier on a particular document consists of the participant name or PTID, the original identifier may not be obliterated or altered in any way, even if another identifier is added. When necessary to maintain confidentiality, identifiers may be obliterated on copies of original source documents. For example, if medical records obtained from a non-study health care provider bear the participant's name, the original documents bearing the name must be stored unaltered with other study documents bearing the name. However, a copy of the original documents could be made, the PTID could be entered onto the copies, and then the participant name could be obliterated from the copies. Copies handled in this way could then be stored in participants' study notebooks and/or transferred or transmitted to non-study site locations.

All on-site databases must be secured with password-protected access systems. Any lists, logbooks, appointment books, or other documents that link PTIDs to other participant identifiers should be stored securely in a location separate from records identified by either participant name or PTID. When in use, these documents should not be left unattended or otherwise accessible to study participants, other study clinic patients, or any other unauthorized persons.

As a condition for study activation, each study site must establish an SOP for data management. This SOP minimally should contain the following elements:

- Procedures for assigning PTIDs, linking PTIDs to participant names, and storing the name-PTID link log
- Procedures for establishing participant files/charts/notebooks
- During-visit participant chart and case report form review procedures
- Post-visit participant chart and case report form review procedures and timeframes
- Data transmission procedures, including timeframes, case report form storage locations before and after faxing, and mechanisms for identifying when forms have been transmitted
- Procedures for resolving data quality control notes from the SDMC
- Procedures for handling and filing field workers' logs, worksheets, etc.
- Storage locations for blank case report forms
- Storage locations for documents identified by participant names or other personal identifiers
- Storage locations for documents identified by PTID
- Procedures for back up of electronic study data (if applicable)
- Confidentiality protections
- Other ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements (if not specified elsewhere)
- QC/QA procedures related to the above (if not specified elsewhere)

3.3 Study Product Accountability, Chain of Custody, and Dispensing Documentation

The following essential documents should be maintained in study site pharmacies:

- Current MTN 001 protocol
- Current Investigator's Brochures for Tenofovir Disoproxil Fumarate (TDF) and Tenofovir 1% Vaginal Gel (Tenofovir Gel) (if brochures on file in the clinic essential document files are not easily accessible to pharmacy staff)
- Current MTN 001 FDA Form 1572
- Current list of authorized prescribers and staff authorized to sign MTN 001 Study Product Request Slips (names and signatures)
- Pharmacy Establishment Plan
- MTN 001 pharmacy and product-related SOPs
- MTN 001 PTID list (provided by the MTN SDMC)
- MTN 001 product import documentation (if applicable)
- MTN 001 product shipping and receipt documentation
- MTN 001 product storage temperature logs
- MTN 001 investigational agent accountability records
- MTN 001 participant-specific records (including prescriptions, study product hold/resume/pK supply/re-supply slips, dispensing records, and DataFax forms as applicable)
- MTN 001 monitoring visit reports
- MTN 001 communications with site clinic staff
- MTN 001 communications with the DAIDS Pharmaceutical Affairs Branch (PAB), the NIAID Clinical Research Product Management Center, and MTN Research Pharmacist
- MTN 001 communications with the MTN Coordinating and Operations Center (CORE)
- MTN 001 communications with the MTN SDMC
- Other MTN 001 communications
- Other locally-required administrative, operational, and/or regulatory documentation

Pharmacy staff will document the receipt, dispensing, and final disposition of the investigational products used in the study, i.e., TDF and Tenofovir 1% Gel. Separate accountability records must be maintained for each product, per instructions provided in the MTN 001 Pharmacist Study Product Management Procedures Manual available from the DAIDS PAB.

Pharmacy staff also will maintain in the study pharmacies randomization materials for all enrolled study participants and product dispensing records for all participants, per instructions in the MTN 001 Pharmacist Study Product Management Procedures Manual. Study clinic staff will contribute to the documentation of product dispensation and chain of custody as described in Sections 4, 6, and 9 of this manual.

The specifications related to document security and participant confidentiality described in Section 3.2 also apply to records maintained in the study pharmacies. All records must be stored securely in the pharmacies with access limited to authorized study pharmacy staff only.

To preserve study integrity, neither study clinic staff nor study participants will be provided access to product-related documentation maintained in the study pharmacies. Pharmacy staff may provide copies of some participant-specific documentation maintained in the study pharmacies (e.g., chart notes) to clinic staff for purposes of communication and operational coordination. However, decisions to provide such documentation to clinic staff will be made by pharmacy staff only, and under no circumstances will documentation released from the pharmacy include participants' product dispensing records or other information related to participants' random assignments (see also Section 9.1 of this manual).

3.4 Record Retention Requirements

All study records must be maintained for at least two years after the investigation is discontinued and the US Food and Drug Administration (FDA) is notified. Study product records must be stored in the study pharmacies, with access limited to authorized study pharmacy staff only. DAIDS will provide further instructions for long-term storage of study records after the study is completed.

Section Appendix 3-1
Suggested Filing Structure for MTN 001 Essential Documents

<p>File/Binder #1: MTN 001 Protocol and Current Informed Consent Forms</p> <ol style="list-style-type: none"> 1. MTN 001 Protocol (including copy of signed and dated protocol signature page): Version 1.0 and any subsequent protocol Clarification Memos, Letters of Amendment, and Amendments issued after Version 1.0 2. Currently-approved MTN 001 informed consent forms
<p>File/Binder #2: Regulatory Authority Documentation (if applicable)</p> <ol style="list-style-type: none"> 3. Regulatory Authority Correspondence/Authorization/Approval/Notification of Protocol (if applicable; if more than one regulatory authority has oversight responsibility for research performed at the study site, include subsections for each authority)
<p>File/Binder #3A: IRB/EC Documentation for [IRB/EC A]</p> <ol style="list-style-type: none"> 4. FWA documentation for IRB/EC A 5. Roster of IRB/EC A (if available) 6. Relevant IRB/EC A Submission Requirements/Guidelines/SOPs 7. IRB Correspondence for IRB/EC A: File complete copies of all correspondence to and from the IRB/EC; include all enclosures/attachments for all submissions, even if copies of the enclosures/attachments are filed elsewhere; include all approval documentation.
<p>File/Binder #3B: IRB/EC Documentation for [IRB/EC B]</p> <ol style="list-style-type: none"> 8. FWA documentation for IRB/EC B 9. Roster of IRB/EC B (if available) 10. Relevant IRB/EC B Submission Requirements/Guidelines/SOPs 11. IRB Correspondence for IRB/EC B: File complete copies of all correspondence to and from the IRB/EC; include all enclosures/attachments for all submissions, even if copies of the enclosures/attachments are filed elsewhere; include all approval documentation.
<p>File/Binder #4: Product Safety Information</p> <ol style="list-style-type: none"> 12. Investigator's Brochure for TDF: current version and any subsequent updates 13. Investigator's Brochure for Tenofovir 1% Gel: current version and any subsequent updates 14. Product Safety Information/Reports/Memos <p>Notes:</p> <ul style="list-style-type: none"> • It is assumed that expedited adverse event reports will be stored in participant study notebooks. • It is assumed that documentation of IRB/EC submission of above-listed documents (if applicable) will be maintained in the relevant IRB/EC Files/Binders (i.e., File/Binder #3A and #3B).
<p>File/Binder #5: MTN 001 Study-Specific Procedures (SSP) Manual</p> <ol style="list-style-type: none"> 15. Final version 2.0 (when available) and any subsequent updates <p>Notes:</p> <ul style="list-style-type: none"> • For this reference copy of the SSP Manual, do not discard out-dated pages or sections when updates are issued; retain all versions of all pages as a complete historical record. • The SSP Manual contains reference versions of all study case report forms, therefore additional (blank) copies of the case report forms need not be stored elsewhere in the essential document files.
<p>File/Binder #6: MTN 001 Study-Specific Standard Operating Procedures</p> <ol style="list-style-type: none"> 16. Final approved version of each SOP, and any subsequent updates to each

Section Appendix 3-1
Suggested Filing Structure for MTN 001 Essential Documents

File/Binder #7: MTN 001 Staffing Documentation

17. FDA Form 1572 (copy of original and dated form submitted to the RCC for Protocol Registration, and any subsequent updates)
18. MTN 001 Investigator of Record CV (copy of CV submitted to the RCC for Protocol Registration; ensure that the CV is current prior to initiating MTN 001; it is recommended that CVs be signed and dated to document at least annual updating)
19. Financial Disclosure Forms (original signed and dated forms, and any subsequent updates)
20. Study Staff Roster (original submitted to MTN CORE for study activation, and any subsequent updates)
21. Study Staff Identification and Signature Sheet (if not combined with staff roster; original and any subsequent updates)
22. Study Staff Delegation of Duties (if not combined with staff roster; original and all updates)
23. CVs for Study Staff other than the IoR (ensure that all CVs are current prior to initiating MTN 001; it is recommended that CVs be signed and dated to document at least annual updating)
24. Study Staff Job Descriptions
25. Documentation of Study Staff Training

File/Binder #8: Local Laboratory Documentation

26. Local Laboratory Certification(s), Accreditation(s) and/or Validation(s): file documentation current at time of study activation and all subsequent updates
27. Local Laboratory Normal Ranges: file documentation of relevant normal ranges for all protocol-specified tests current at time of study activation and all subsequent updates
28. Laboratory Manager CV (or cross-reference to CV contained in File/Binder #7)

Note:

- It is recommended that a cross-reference be included in this file/binder specifying the storage location(s) of other lab-related essential documents filed in the local lab(s).

File/Binder #9: Monitoring Visit Documentation

29. Monitoring Visit Log
30. Initiation and Monitoring Visit Reports and Documentation of Response to Visit Findings

File/Binder #10: Documentation of Other MTN Site Visits

31. (Non-Monitoring) Site Visit Log
32. MTN CORE Site Visit Reports and Documentation of Response to Visit Findings
33. MTN SDMC Site Visit Reports and Documentation of Response to Visit Findings
34. MTN Network Lab Site Visit Reports and Documentation of Response to Visit Findings
35. Other Site Visit Reports and Documentation of Response to Visit Findings

File/Binder #11: Study-Related Sponsor Communications

36. Study-Related Communications to and from DAIDS
37. Communications to and from DAIDS RCC (includes copies of all submissions to the DAIDS Protocol Registration Office, which will be prepared by the sites with copies provided to the MTN CORE, as well as the current monthly DAIDS IB/PI listing and year-end and current monthly DAIDS Comprehensive Safety Distribution Report)

Notes:

- Communications related to individual MTN 001 study participants will be filed in individual participant study records.
- Product-related communications with DAIDS PAB (and its contractors) will be stored in the study pharmacy.

Section Appendix 3-1
Suggested Filing Structure for MTN 001 Essential Documents

<p>File/Binder #12: Other Study-Related Communications</p> <p>38. Study-Related Communications to and from MTN CORE 39. Study-Related Communications to and from MTN SDMC 40. Study-Related Communications to and from MTN Network Lab 41. Other Study-Related Communications</p> <p>Notes:</p> <ul style="list-style-type: none"> • Communications related to individual MTN 001 study participants will be filed in individual participant study records. • Product-related communications with DAIDS PAB and MTN Research Pharmacist (and its contractors) will be stored in the study pharmacy.
<p>File/Binder #13: Study Site Staff Meeting Documentation</p> <p>42. MTN 001 Staff Meeting Agendas, Participant Lists/Sign-In Sheets, and Summaries</p> <p>Note:</p> <ul style="list-style-type: none"> • Meeting documentation should be filed beginning from the date of the MTN 001 Operational Walkthrough
<p>File/Binder #14: Conference Call Documentation</p> <p>43. MTN 001 Protocol Team and Protocol Co-Chairs Conference Call Summaries 44. MTN 001 Study Coordinators Group Conference Call Summaries 45. MTN 001 Community Educators Group Conference Call Summaries 46. Summaries of Other MTN 001 Conference Calls</p> <p>Note:</p> <ul style="list-style-type: none"> • Conference call summaries will be filed beginning from the date of the MTN 001 Protocol Development Call
<p>File/Binder #15: DAIDS and Other Reference Documentation</p> <p>47. DAIDS SOP for Source Documentation (Version 2.0 and any subsequent updates) 48. DAIDS SOP for Essential Documents (Version 2.0 and any subsequent updates) 49. DAIDS Protocol Registration Policy and Procedures Manual (August 2004 and any subsequent updates) 50. Manual for Expedited Reporting of Adverse Events to DAIDS 51. US Regulations Applicable to Conduct of MTN 001 (45 CFR 46; 21 CFR 50, 54, 56, and 312) 52. Any other relevant manuals or reference documents</p>
<p>File/Binder #16: Site-Specific Study Activation Documentation</p> <p>54. Site-Specific Study Activation Documents</p>

Section Appendix 3-2
Guide to Required Case History Elements and Source Documents for MTN 001

Required Case History Element	Source Documents*
Basic participant identifiers.	Locator form; Demographics forms.
Documentation that the participant provided written informed consent to screen for and participate in the study.	Signed and dated informed consent forms; signed and dated chart notes stating that informed consent was obtained prior to initiating study procedures.
Documentation that the participant met the study selection (eligibility) criteria.	Signed and dated informed consent forms; Demographics form, locator form; Screening Consent form; Screening Eligibility form (non-DataFax); Clinical Eligibility form (non-DataFax); Enrollment Eligibility form (non-DataFax); Baseline Genital Symptoms; Safety Laboratory Results form; Screening and Enrollment STI Laboratory Results form; HIV Test Results form; Baseline Medical History form (non-DataFax), Concomitant Medications Log form, Physical Exam form (non-DataFax), Pre-existing Conditions form; Screening and Enrollment Pelvic Exam form; Pelvic Laboratory Results; Pelvic Exam Diagrams (non-DataFax); local lab logs and result reports [§] ; signed and dated chart notes.
A record of the participant's random assignment.	MTN 001 Randomization Envelope Tracking Record; MTN 001 Randomization Envelope; MTN 001 Randomization Document (or MTN 001 Replacement Randomization Document, if a replacement participant).
A record of the participant's exposure to the investigational study products.	MTN 001 Prescription,, MTN 001 Study Product Hold/Resume/pK supply/Re-supply Slip, MTN 001 participant pharmacy dispensing records; dispensed product chain of custody logs, visit checklists.
A record of all contacts, and all attempted contacts, with the participant.	Signed and dated chart notes, and/or other worksheets or site-specific documents if designated in site SOPs.
A record of all procedures performed by study staff.	Completed visit checklists; signed and dated chart notes detailing (i) procedures performed in addition to those contained on the checklist and/or (ii) the reason why procedures contained on the checklist were not performed.
Information on the participant's condition before, during, and after the study.	All documents listed above; Screening Summary (non-DataFax); Enrollment form; Enrollment Behavior Assessment form, Follow-up Visit form; Study Product Adherence and Behavior Assessment; Acceptability Assessment form; Final Acceptability Assessment form; Product Sharing Assessment form; Follow-up Medical History Log (non-DataFax); Follow-up Genital Symptoms; Genital Bleeding Assessment form (non-DataFax); Follow-up Pelvic Exam form (non-DataFax); Pelvic Laboratory Results form; STI Laboratory Results form; Adverse Experience Log; Family Planning Methods form; Pharmacokinetics-Intensive form; Pharmacokinetics-Non-Intensive form; Product Hold/Discontinuation form; Pregnancy Report and History form; Pregnancy Outcome form; Interim Visit form; Missed Visit form; Participant Transfer form; Participant Receipt form; Termination form; End of Study Inventory form; Flow Cytometry form; local lab logs and result reports from the local lab [§] ; results of information pertinent to the study obtained from non-study sources; signed and dated chart notes.

*Other site-specific source documents also may be used.

[§]A clinician must review all local laboratory reports and document this review by signing and dating all reports.

Section Appendix 3-3 Guidelines and Examples on the SOAP Format for Chart Notes

Guidelines

The SOAP Format: The benefits of the SOAP format are that it can be tailored to any type of study or study visit and that, if done properly, will satisfy both the medical record needs for the continuing care of the client and the source documentation requirements for the study. Below is a broad definition of the components of the SOAP format and then three examples of how it might be used in specific scenarios.

• **S (SUBJECTIVE):** The subjective component is the client’s report of how he or she has been doing since the last visit, and this includes the current visit. Subjective comments made by client may range from no complaints (“I feel great”) to specific current complaints (“I’ve had a headache for 3 days”) to complaints that took place in the interim but have resolved (“3 weeks ago I had diarrhea for a couple of days”). For an infant’s record, the subjective component would include the mother’s (or caretaker’s) observations. Again, these may range from no complaints (“The baby is happy and healthy”) to a specific current complaint (“the baby’s been fussy lately”) to a complaint that has resolved (“the baby had a nappy rash, but it’s all better now”). The client should be asked directed questions about any complaints – current or reportedly resolved -- and ask appropriate follow-up questions and document all responses.

Reports of compliance with specific treatment regimens – whether study-related or not – should also be included here: “How much of your study medication did you take since your last visit? Did you miss any doses? Why?” or “At the last visit, you were given antibiotics for pneumonia. Do you have any pills left?”

• **O (OBJECTIVE):** The objective component is straightforward and includes vital signs (temperature, blood pressure, pulse, respiration), documentation of the physical examination that was done, and results of laboratory or other studies that may be done during the course of this visit. For a client with no complaints, the physical exam may be limited to meet study specific needs. For a client with a complaint, an appropriate focused physical exam should be completed in addition to or instead of the study-specific exam.

• **A (ASSESSMENT):** For this component, the clinician pulls together the subjective information gathered during the interview with the client and the objective findings of the physical exam (and, possibly, laboratory or other study results) and consolidates them into a short assessment: “This is a 26-year old woman here for a routine MTN 001 study visit; there are no clinical problems today” or “This is a 22-year old pregnant woman, here for a non-study visit due to chief complaint of increased nausea for 1 week and vomiting for 2 days”

• **P (PLAN):** The plan should include anything that will be done as a consequence of the assessment and could include:

- The collection of study-specific labs or special studies
- The collection of labs or special studies to address an acute complaint
- Intention to admit to the hospital
- Study-specific medications dispensed (name of drug, amount dispensed and dosing instructions)
- Non-study medications prescribed or dispensed for a specific acute or chronic complaint (name of drug, amount dispensed and dosing instructions)
- Follow-up instructions to the client (for example: “return to the clinic if this problem does not resolve”)
- Date of next appointment

Section Appendix 3-3
Sample Chart Notes for MTN 001 in Subjective-Objective-Assessment-Plan (SOAP) Format

Sample Chart Note for Screening:

13 OCT 2008: Participant presented for MTN 001 screening. Obtained written informed consent for screening before initiating any procedures. Procedures were completed per protocol, visit checklist and SOPs.

S: Participant reported no current health problems.

O: Pregnancy test negative, participant behaviorally eligible per the Screening Eligibility form, tested HIV negative.

A: Participant is eligible for the study thus far.

P: Enrollment scheduled for 27 October 2008.

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Sample Chart Note for Screening:

13 OCT 2008: Participant presented for MTN 001 screening. Obtained written informed consent for screening before initiating any procedures. Procedures were completed per protocol, SOPs and visit checklist, with the additions listed here.

S: Participant complained of current genital itching and yellowish discharge, no other current health problems.

O: Participant behaviorally eligible per the Screening Eligibility form, tested negative for pregnancy and HIV.

A: Other than genital symptoms, participant appears eligible for the study thus far. Syndromic treatment provided [insert details here]; participant must be symptom free at next visit in order to enroll in study.

P: Enrollment scheduled for 28 OCT 2008, participant counseled to contact site if symptoms do not resolve in 5-7 days.

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Sample Chart Note for Enrollment:

27 OCT 2008: Participant presented for MTN 001 enrollment visit. Procedures completed per protocol, SOPs and visit checklist. Enrollment was discontinued at this visit due to ineligibility.

S: Participant reported no current health problems.

O: Screening GC and CT lab tests were negative, but today's pregnancy test was positive. Enrollment discontinued upon finding this result.

A: Participant is pregnant — not eligible for study.

P: Participant informed that she is pregnant and referred to [clinic name] for antenatal care.

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Sample Chart Note for Mid-Study Follow-up Visit:

4 NOV 2008: Participant presented for MTN 001 Week 10 visit. Procedures completed per protocol, visit checklist and SOPs.

S: No issues/problems reported since last visit.

O: Pregnancy test negative.

A: No issues of concern.

P: Week 13 visit scheduled for 25 NOV 2008.

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Sample Chart Note for Week-20 Follow-up Visit:

13 JAN 2009: Participant presented for MTN 001 Week 20 visit. Procedures completed per protocol, visit checklist and SOPs.

S: No issues/problems reported since last visit.

O: Participant tested negative for pregnancy and for HIV. Pelvic exam and wet mount normal (see test results and exam findings on DataFax forms).

A: No issues of concern.

P: Termination visit scheduled for 20 JAN 2009.

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Section Appendix 3-4
MTN 001 DataFax and Non-DataFax Forms

DataFax Forms	Non-DataFax Forms
Screening Consent	Clinical Eligibility (non-DataFax)
Demographics	Screening Summary (non-DataFax)
Screening and Enrollment Pelvic Exam	Enrollment Eligibility (non-DataFax)
Pelvic Laboratory Results	Genital Bleeding Assessment (non-DataFax)
Safety Laboratory Results	Follow-up Medical History Log (non-DataFax)
Screening and Enrollment STI Laboratory Results	Physical Exam (non-DataFax)
Concomitant Medications	Pelvic Exam Diagrams (non-DataFax)
Baseline Genital Symptoms	Screening Eligibility (non-DataFax)
Follow-up Genital Symptoms	Baseline Medical and Menstrual History (non-DataFax)
Pharmacokinetics-Intensive	
Pharmacokinetics-Non-intensive	
Product Sharing Assessment	
Flow Cytometry	
STI Laboratory Results	
Acceptability Assessment	
Family Planning Methods	
Enrollment Behavior Assessment	
Pre-Existing Conditions	
Enrollment	
Final Acceptability Assessment	
HIV Test Results	
Product Hold/Discontinuation	
Pregnancy Report and History	
Pregnancy Outcome	
Adverse Experience Log	
Follow-up Visit	
Study Product Adherence and Behavior Assessment	
Interim Visit	
Missed Visit	
Participant Transfer	
Participant Receipt	
Follow-up Pelvic Exam	
Termination	
End of Study Inventory	

Section Appendix 3-5
Use of MTN 001 DataFax Forms as Source Documents
(Forms listed in alphabetical order)

Form Name	Is form source?	Comments
Acceptability Assessment	Mixed	MTN 001 Randomization Document (or MTN 001 Replacement Randomization Document, if a replacement participant) is source for item 1. Form is source for the rest of the items on the form, as participant responses are recorded directly onto the form.
Adverse Experience Log	Yes	Form and/or participant chart notes may be source for all items.
Baseline Genital Symptoms	Yes	Form is interviewer-administered; participant responses are recorded directly onto this form.
Concomitant Medications	[Yes]	[It is expected that sites will record concomitant medication information directly and initially on to this form. If, instead, other documents such as the participant chart notes routinely will serve as the source documents for this information, then this form is not considered a source document and the actual source document should be specified here.]
Demographics	Yes	Form is interviewer-administered; participant responses are recorded directly onto the form.
End of Study Inventory	No	All items are based on source data recorded on other forms.
Enrollment	No	The Enrollment Informed Consent form is source for item 1. The Specimen Storage Informed Consent form is source for items 2 and 2a. The MTN 001 Randomization Envelope Tracking Record is source for items 3-5. The MTN 001 Randomization Document (or MTN 001 Replacement Randomization Document, if a replacement participant) is source for items 6-8. The SCHARP-provided list of participants requiring replacement should serve as source for item 9. The participant pharmacy dispensing record is source for items 10-12. The non-DataFax Physical Exam form is source for item 13.
Enrollment Behavior Assessment	Yes	Form is interviewer-administered; participant responses are recorded directly onto this form.
Family Planning Methods	No	The non-DataFax Baseline Medical and Menstrual History form will serve as the source document at the Screening and Enrollment Visits. The participant chart notes will serve as the source document at follow-up visits.
Final Acceptability Assessment	Mixed	The MTN001 Randomization Document (or MTN 001 Replacement Randomization Document, if a replacement participant) is source for item 1. Form is source for the rest of the items on the form, as participant responses are recorded directly onto the form.
Flow Cytometry	[No or Yes (site to choose one)]	[Form is not source if all items are based on data recorded on a local laboratory report or assay result data output. Form is source if results are read and recorded directly onto the form].

Form Name	Is form source?	Comments
Follow-up Genital Symptoms	Yes	Form is interviewer-administered; participant responses are recorded directly onto this form.
Follow-up Pelvic Exam	[Yes]	[It is expected that this form routinely will serve as a source document, with supplemental information recorded on the Pelvic Diagrams, and in the participant chart notes if needed. If, instead, other documents such as participant chart notes routinely will serve as the source documents for pelvic exam information, this should be specified here.]
Follow-up Visit	[Mixed]	[Form may serve as source for item 1 if result is not documented on a local laboratory report or clinic log, but is recorded directly onto the form. Form may also serve as source for item 1a. Participant chart notes and/or AE Log forms are source for items 2-2a. Form or pharmacy record may serve as source for items 3-4. Participant pharmacy dispensing record is source for items 5-6.]
HIV Test Results	[Mixed]	Local laboratory report (and network laboratory report, if needed) is source for items 1-4. [Form may serve as source for item 5.]
Interim Visit	Mixed	Participant chart notes and/or form may serve as source for items 1-1f, 2a, and 3. Form may serve as source for item 2 if result is not documented on a local laboratory report or clinic log, but is recorded directly onto the form. Form or pharmacy record may serve as source for items 4-5. Participant pharmacy dispensing record is source for items 6-7.
Missed Visit	[Yes]	[Form and/or participant chart notes may be source to document that the visit was missed and the reason why the visit was missed.]
Participant Receipt	No	Participant Transfer form may be source for items 1-2. Informed Consent forms are source for items 3-4a.
Participant Transfer	Yes	Form may be source for all items.
Pelvic Laboratory Results	[Mixed]	[For items 1a-1f, the form may serve as source in cases where results are not documented on a local lab report, but are recorded directly onto the form. Otherwise, the local laboratory report may serve as source. Local laboratory report is source for items 2 and 3.]
Pharmacokinetics-Intensive	Mixed	The non-DataFax Physical Exam form is source for item 1. Form may be source for items 2-14.
Pharmacokinetics- Non-Intensive	Mixed	The non-DataFax Physical Exam form is source for item 1. Form may be source for items 2-10.
Pre-Existing Conditions	No	All items are based on source data recorded on the non-DataFax Baseline Medical and Menstrual History form, non-DataFax Physical Exam form, Screening and Enrollment Pelvic Exam forms, Baseline Genital Symptoms form, non-DataFax Pelvic Exam Diagrams, and participant chart notes.
Pregnancy Outcome	Yes	Form may be source for all items if medical records are not available and the data recorded on the form are based on participant self-report.
Pregnancy Report and History	Mixed	Form may be source for item 2. All other items are based on source data recorded on the non-DataFax Baseline Medical and Menstrual History form and non-DataFax Follow-up Medical History Log.

Form Name	Is form source?	Comments
Product Hold/Discontinuation	Mixed	Form may be source for all items EXCEPT item 3. Participant chart notes, the Pregnancy Report and History form, the STI Laboratory Results form, the HIV Test Results form, and/or AE Log form may serve as source for item 3.
Product Sharing Assessment	Yes	Form is interviewer-administered; participant responses are recorded directly onto the form.
Safety Laboratory Results	[Mixed]	[Form may serve as source for items 1a-1c in cases where results are not documented on a local lab report or log, but are recorded directly on the form. Otherwise, the local laboratory report or log may serve as source. Local laboratory report is source for items 1d-3d. Form may serve as source for item 4.]
Screening and Enrollment Pelvic Exam	[Yes]	[It is expected that this form routinely will serve as a source document, with supplemental information recorded on the Pelvic Diagrams, and in the participant chart notes if needed. If, instead, other documents such as participant chart notes routinely will serve as the source documents for pelvic exam information, this should be specified here.]
Screening and Enrollment STI Laboratory Results	No	Local laboratory report (and network laboratory report, if needed) will serve as source.
Screening Consent	[Mixed]	Form [may be] source for item 1. Items 2 and 2a are based on source data recorded in the participant chart notes and on the screening informed consent form.
STI Laboratory Results	No	Local laboratory report (and network laboratory report, if needed) is source for items 1-3c.
Study Product Adherence and Behavior Assessment	Mixed	The MTN001 Randomization Document (or MTN 001 Replacement Randomization Document, if a replacement participant) is source for item 1. Documentation from the participant or the form (if participant does not provide documentation) is source for items 2-3c. Form is source for remaining form items, as participant responses are recorded directly onto the form.
Termination	No	All items are based on source data recorded on other documents.

Section Appendix 3-6
Use of MTN 001 Non-DataFax Forms as Source Documents
(Forms listed in alphabetical order)

Form Name	Is form source?	Comments
Baseline Medical and Menstrual History	Yes	Form is source for all items. Data recorded on this form is based on participant self-report, and may also be supplemented with data recorded on other source documents (e.g., non-study medical records).
Clinical Eligibility	No	All items are based on data recorded on other documents as source.
Enrollment Eligibility	Mixed	Enrollment informed consent form is source for item 1. Form is source for items 2-15; items are interviewer-administered. [Form may be source for item 16 if result is not documented on a local laboratory report or clinic log, but is recorded directly onto the form. Form or participant chart notes may be source for item 17.]
Follow-up Medical History Log	Yes	Form may be source for all items.
Genital Bleeding Assessment	Mixed	[Form or participant chart notes may be source for items 1-11g and 13a-14a.] The Concomitant Medications Log may be source for items 12-13. The AE Log form is source for item 14b.
Pelvic Exam Diagrams	Yes	Form may be source for all items.
Physical Exam	Yes	Form may be source for all items.
Screening Eligibility	Mixed	Screening informed consent form is source for item 1. The local participant locator form is source for item 2. The Screening and Enrollment Log is source for item 3. Form may serve as source for item 4 if documentation of a normal Pap result (in the 12 calendar months prior to screening) is NOT available. Form is source for items 5-25; these items are interviewer-administered. [Form may be source for item 26 if result is not documented on a local laboratory report or clinic log, but is recorded directly onto the form. Form or participant chart notes may be source for item 27.]
Screening Summary	No	All items are based on data recorded on other documents as source.

Section 4. Participant Accrual

This section provides information on requirements and procedures for recruiting, screening, and randomizing/enrolling participants in MTN 001.

4.1 Study Accrual Plan and Site-Specific Accrual Targets

The MTN 001 study will be conducted among approximately 144 evaluable women — 72 from the US and 72 from the non-US sites. For this protocol, evaluable women are defined as women who have at least one follow-up visit with adherence data in each of the three study periods. Up to 204 women may be enrolled in order to reach the total study accrual target of 144 evaluable women. It is expected that accrual for this study will require approximately six months. For each site, accrual will begin after all applicable approvals are obtained and a site-specific study activation notice is issued by the MTN Coordinating and Operations Center (CORE). (See Protocol Section 10.6 for additional detail on Participant Accrual)

Table 4-1 presents monthly accrual targets for each site. Each site is allowed to accrue beyond the specified targets shown in Table 4-1, as long as accrual does not surpass the total site target. A site's total accrual target may change in the event that enrollment slots need to be transferred from one site to another, as authorized by the SDMC.

**Table 4-1
MTN 001 Accrual Plan – Participants Enrolled Per Month**

Accrual Months	Non-US Sites			US Sites				All Sites
	Umkomaas	Botha's Hill	Kampala	Alabama	Bronx-Lebanon	Cleveland	Pittsburgh	
1	5	5	2	2	2	2	2	20
2	6	5	3	2	2	3	3	24
3	7	2	4	2	2	4	4	25
4	7	0	5	2	2	5	5	26
5	6	0	5	2	2	5	5	25
6	5	0	5	2	2	5	5	24
TOTAL	36	12	24	12	12	24	24	144

Once accrual is initiated at each site, study staff will report the number of participants screened for and enrolled in the study to the MTN CORE (FHI) on a weekly basis throughout the accrual period. Based on this information, the MTN CORE will distribute a weekly consolidated cross-site accrual report to the Protocol Team. In addition, the SDMC will provide the Protocol Team with online access to a report, updated nightly, that shows the number of participants enrolled based on data received and entered into the study database.

Throughout the accrual period, and additionally as accrual comes to an end at each site, care must be taken to manage the recruitment, screening, and enrollment process in order not to exceed site-specific accrual targets. This is important in the last 4-8 weeks of accrual at each site; during this time enrollment must be monitored closely, and potential participants must be informed that although they may screen for the study, they may not be enrolled if the target sample size is reached before they are able to complete the screening and enrollment process. This may be difficult to explain to potential participants, especially those who are very interested in taking part in the study. Therefore all sites are advised to work with their community advisory board/group members to develop strategies to address this issue several weeks to months before the end of accrual at the site.

Site staff are responsible for establishing a standard operating procedure (SOP) for participant accrual and for updating the SOP and recruitment efforts undertaken if needed to meet site-specific accrual goals. The accrual SOP minimally should contain the following elements:

- Site-specific accrual goals
- Methods for tracking actual accrual versus accrual goals
- Recruitment methods and venues
- Methods for identifying the recruitment source of participant who present to the site for screening
- Methods for timely evaluation of the utility of recruitment methods and venues
- Pre-screening procedures (if any)
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements (if not specified elsewhere)
- QC/QA procedures related to the above (if not specified elsewhere)

4.2 Screening and Enrollment

The study screening and enrollment procedures are described in detail in Sections 7.1 and 7.2 of the MTN 001 Protocol and visit checklists contained in Section 7 of this manual. Informed consent procedures are described in Section 5 and instructions for performing clinical and laboratory screening procedures are included in Sections 10 and 12, respectively. Key screening and enrollment topics are described in Sections 4.2.1-4.2.7 below. Several possible screening and enrollment scenarios are presented for illustrative purposes in Section Appendix 4-1.

4.2.1 Definition of Screening

- The term “screening” refers to all procedures undertaken to determine whether a potential participant is eligible to take part in MTN 001. The study eligibility criteria are listed in protocol Sections 5.2 and 5.3. The screening and enrollment procedures are described in protocol Sections 7.1 and 7.2 and Figure 4-2 provides further information on the timing of assessment for each eligibility criterion.

It is the responsibility of the site Investigator of Record and other designated staff to ensure that only participants who meet the study eligibility criteria are enrolled in the study. Each study site must establish an SOP that describes how study staff will fulfill this responsibility. This SOP minimally should contain the following elements:

- Eligibility determination procedures, including:
 - During-visit eligibility assessment procedures
 - Post-visit eligibility assessment and confirmation procedures
 - Final confirmation and sign-off procedures prior to enrollment
 - Documentation
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements (if not specified elsewhere)
- QC/QA procedures related to the above (if not specified elsewhere)

Should site staff identify that an ineligible participant has inadvertently been enrolled in the study, the Investigator of Record or designee should contact the MTN 001 Protocol Safety Review Team (PSRT) for guidance on subsequent action to be taken. PSRT contact details are provided in Section 11 of this manual. Site staff must also complete a protocol deviation form in accordance with the guidelines in Section 15 of the MTN Manual of Operations, <http://www.mtnstopshiv.org/node/187>.

**Figure 4-2
Timing of Eligibility Assessments for MTN 001**

	Assessed At Screening Visit	Assessed At Enrollment Visit
Inclusion and Exclusion Criteria		
Between the ages of 18 and 45, inclusive, at the time of screening as verified by site SOP.	X	
Be willing and able to provide written informed consent	X	X
Be in general good health	X	X
Willing and able to provide adequate locator information	X	X
Be HIV uninfected	X	X*
Have a normal Pap Test, or be able to document a normal Pap Test (in the 12 calendar months prior to screening)	X	
Predictable menstrual cycle, w ≥ 21 days between menses (does not apply to pts using hormonal contraception; "between menses" defined as onset to onset of menses)	X	
Be sexually active, defined as having had penile-vaginal intercourse at a minimum average of at least four times in the four weeks prior to screening	X	
More than three partners in the previous month prior to screening	X	
Per participant report at screening and enrollment, intending to continue penile-vaginal intercourse at least once per week for duration of study participation	X	X
Be willing to use an effective method of contraception during the study, defined as either a hormonal based method (except vaginal rings); an IUCD (inserted at least 30 days prior to enrollment); female sterilization, or sexual activity with a documented vasectomized partner. <i>Note: Self-report is acceptable documentation for vasectomized partners.</i>	X	X
Calculated creatinine clearance at least 70 mL/min by the Cockcroft-Gault formula where creatinine clearance (female) in mL/min = $(140 - \text{age in years}) \times (\text{weight in kg}) \times 0.85/72 \times (\text{serum creatinine in mg/dL})$	X	
Agrees to not participate in other investigational drug or device research studies for the duration of study participation	X	X
Be willing to undergo all study related assessments (clinical and laboratory), including speculum examination, urine testing and blood draws, and, adhere to follow up schedule as required by the protocol	X	X
Willing to use study products as required	X	
Urine negative for pregnancy at screening and enrollment	X	X
Has not participated in any other device or drug study in the 30 days prior to enrollment	X	X
No history of adverse reaction to latex or any other component of study products	X	
No reported history of male sex partner having an allergic reaction to latex	X	
Not using at enrollment, or intention to use diaphragm, vaginal ring, and/or spermicide for contraception during study participation	X	X
Not using at enrollment, or intention to use acyclovir, valacyclovir, post-exposure prophylaxis for HIV exposure, TDF/emtricitabine, non-study vaginal products	X	X
Not pregnant or breastfeeding at screening or enrollment, has had any form of pregnancy within 90 days of enrollment or intends to become pregnant during the study	X	X

No uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infection disease	X	X
No pathologic bone fracture (not related to trauma)	X	
No gynecologic or genital procedure in 90 days prior to enrollment (e.g., biopsy, tubal ligation, dilation and curettage, etc.)	X	X
No clinically apparent pelvic exam finding involving Grade 2 or higher genital sores, erythema, and/or edema	X	X
No abnormal finding on physical or pelvic examination which precludes participation in the trial	X	X
Any liver function test result not greater than 1.5 X the site laboratory ULN (upper limit of normal)	X	
Serum creatinine not greater than the site laboratory ULN for women.	X	
Hemoglobin not less than 10.0 g/dl	X	
Platelet count not less than 100,000/mm ³	X	
Serum phosphorus level not below site laboratory LLN (lower limit of normal)	X	
Negative for Hepatitis B surface antigen (HBsAg)	X	
No 2+ or greater dipstick urinalysis results for protein	X	
No UTI or RTI at screening or enrollment requiring treatment (See protocol Section 5.3 for details)	X	X
No injection of non-therapeutic drugs in the 12 calendar months prior to screening	X	X

* If applicable, per site SOP

4.2.2 Definition of Enrollment

Participants will be considered enrolled in MTN 001 when they have been assigned an MTN 001 Randomization Envelope. Further information on methods and materials for random assignment is provided in Section 4.2.7.

Note: All Enrollment Visit procedures must be conducted on the same day with the exception of obtaining the enrollment informed consent, which may be obtained at a prior date. If the enrollment informed consent is obtained on a prior date, sites need to pay close attention to the screening to enrollment window and ensure the enrollment process takes place within 30 days of participant signing the informed consent.

4.2.3 Screening and Enrollment Timeframe

All protocol-specified screening and enrollment procedures must take place within a 30-day period. The Enrollment Visit must take place within 30-days from the initial screening visit. This 30-day period begins on the day following the day the potential participant provides written informed consent for screening. For example:

- A potential participant who signs or marks her screening informed consent form on 1 October could be enrolled on any day up to and including 31 October.

OCTOBER 2008						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1 Screening Consent	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31 Last Day To Enroll	

To help ensure that the 30-day screening period is not exceeded, study staff are strongly encouraged to highlight the allowable screening period on their screening and enrollment visit checklists (as shown in Section 7 of this manual).

If all screening and enrollment procedures are not completed within 30 days of obtaining informed consent for screening, the participant must repeat the entire screening process, including the screening informed consent process; however, the PTID will remind the same (see Section 4.2.5). The term “screening attempt” is used to describe each time a participant screens for the study.

To avoid a heavy caseload of follow-up visits on the last day of each month, study sites are advised to limit the scheduling of potential enrollment visits on the last day of months with 31 days.

4.2.4 Screening and Enrollment Logs

The DAIDS SOP for Essential Documents requires study sites to document screening and enrollment activity on screening and enrollment logs. Screening and enrollment logs may be maintained separately or combined into one log. Figure 4-3 presents a sample screening and enrollment log suitable for use in MTN 001. Study sites are encouraged to reference the item numbers on the Screening Summary non-DataFax form (see Section 13) when recording the reason for screening failure/discontinuation on the screening and enrollment logs.

Figure 4-3
Sample Screening and Enrollment Log for MTN 001

Sample MTN 001 Screening and Enrollment Log						
Site Name, Clinic Name, and Location:						
	Participant ID	Date Screened/ Consent Signed*	Eligible?	Enrollment/ Randomization Date	If not enrolled, specify reason (include all applicable codes).	Staff Initials
1			Y N			
2			Y N			
3			Y N			
4			Y N			
5			Y N			
6			Y N			
7			Y N			
8			Y N			
9			Y N			
10			Y N			
11			Y N			
12			Y N			

* Note: Women should not be considered screened unless they have completed the screening informed consent process.

4.2.5 Assignment of Participant ID Numbers

The MTN SDMC will provide each study site with a listing of Participant ID (PTID) numbers for use in MTN 001. As shown in Figure 4-4, the listing will be formatted such that it may be used as the log linking PTIDs and participant names at each site.

Further information regarding the structure of PTIDs for MTN 001 can be found in Section 13 of this manual. PTIDs will be assigned to all potential participants who provide informed consent for screening, regardless of whether they enroll in the study. Only one PTID will be assigned to each potential participant, regardless of the number of screening attempts she undergoes. Site staff are responsible for establishing SOPs and staff responsibilities for proper storage, handling, and maintenance of the PTID list such that participant confidentiality maintained, individual PTIDs are assigned to only one participant, and individual participants are assigned only one PTID.

Figure 4-4
Sample Site-Specific PTID List for MTN 001

	Participant ID	Participant Name	Date	Staff Initials
1	XXX-00001-7			
2	XXX-00002-7			
3	XXX-00003-7			
4	XXX-00004-7			
5	XXX-00005-7			
6	XXX-00006-7			
7	XXX-00007-7			
8	XXX-00008-7			
9	XXX-00009-7			
10	XXX-00010-7			

4.2.6 Screening HIV Testing

Instructions for performing HIV tests during screening are provided in Section 12. US sites must perform testing in laboratories certified by the Clinical Laboratory Improvement Amendment (CLIA) for HIV testing. At all sites, all tests must be documented on local laboratory log sheets or other laboratory source documents, such documents must capture the start and end/read times of each test. Also for all HIV testing done in non-CLIA certified labs or clinics, a second independent clinic or laboratory staff member trained in proper HIV testing and result recording procedures must review, verify, and sign-off on test results within the timeframe of the tests and prior to disclosure of results to participants. In addition to initialing or signing the testing logs to document review and verification of the results, the second staff member must also record the time at which the results were reviewed and verified.

4.2.7 Random Assignment

Overview

At all study sites, participants will be randomly assigned to one of six study sequences (see Figure 4.5 below). In addition to randomization to product sequence, participants will be randomized for End of Study Period PK testing procedures. Participants at the African sites will undergo non-intensive PK procedures and participants at the US sites will undergo intensive specimen collection for PK analysis, also known as Intensive PK. The Non-Intensive PK participants will be assigned to a sampling window based on their sequence randomization assignment, while Intensive PK cohorts will require a second randomization which will be stratified within each of the four US sites.

Figure 4-5 presents the expected distribution of participants across sequence groups.

Figure 4-5

	N	Period 1: 6 WEEKS	1 WK Wash -out	Period 2: 6 WEEKS	1 WK Wash- out	Period 3: 6 WEEKS	1 WK Wash- out
Sequence A	24	Oral		Vaginal		Oral + Vaginal	
Sequence B	24	Vaginal		Oral		Oral + Vaginal	
Sequence C	24	Oral + Vaginal		Oral		Vaginal	
Sequence D	24	Oral + Vaginal		Vaginal		Oral	
Sequence E	24	Oral		Oral + Vaginal		Vaginal	
Sequence F	24	Vaginal		Oral + Vaginal		Oral	

Overview of MTN 001 Randomization Plan

The SDMC will generate and maintain the study randomization scheme and associated materials, which consist of the following:

- MTN 001 Randomization Envelopes (Figures 4-6a, 4-6b, and 4-6c)
- MTN 001 Randomization Envelope Tracking Records (Figure 4-7)
- MTN 001 Randomization Documents (Figures 4-8a and 4-8b)
- MTN 001 Replacement Randomization Documents (Figures 4-9a and 4-9b)

MTN 001 Randomization Envelopes (see Figure 4-6a and 4-6b) will be shipped from the SDMC to each study clinic. They will be stored in the clinic and assigned in sequential order to participants who have been confirmed as eligible and willing to take part in the study. Envelopes must be assigned in sequential order, and only one envelope may be assigned to each participant. Once an envelope is assigned to a participant, it may not be re-assigned to any other participant. All envelopes are sealed with blue security tape that, when opened, reveals the word “OPENED” in the residue of the tape (see Figure 4-6c).

Figure 4-6a
Sample MTN 001 Randomization Envelope — Full View

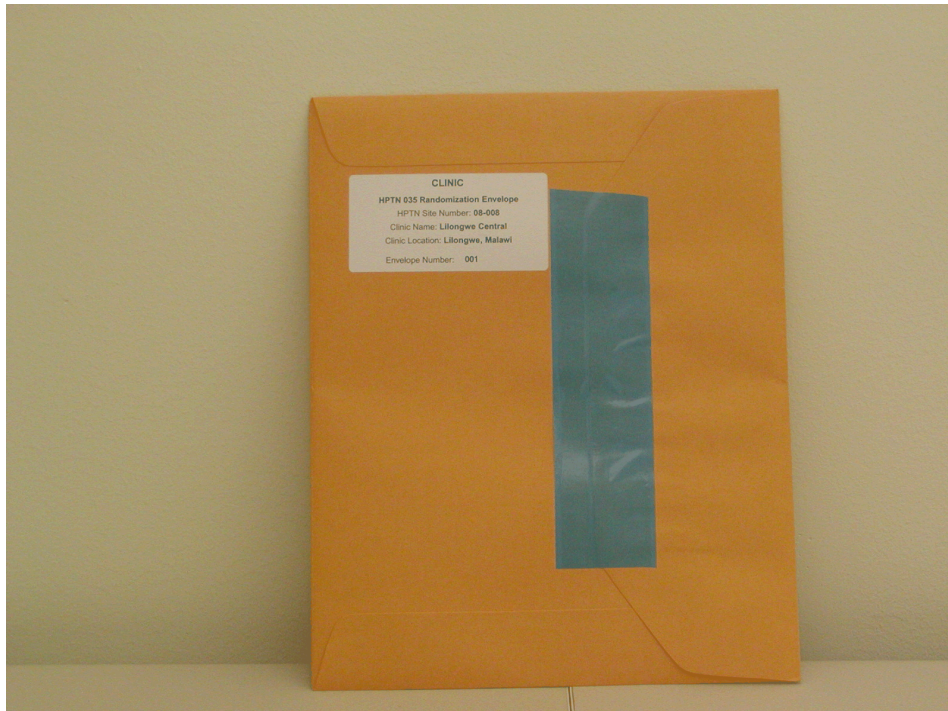


Figure 4-6b
Sample MTN 001 Randomization Envelope — Close-Up View of Label

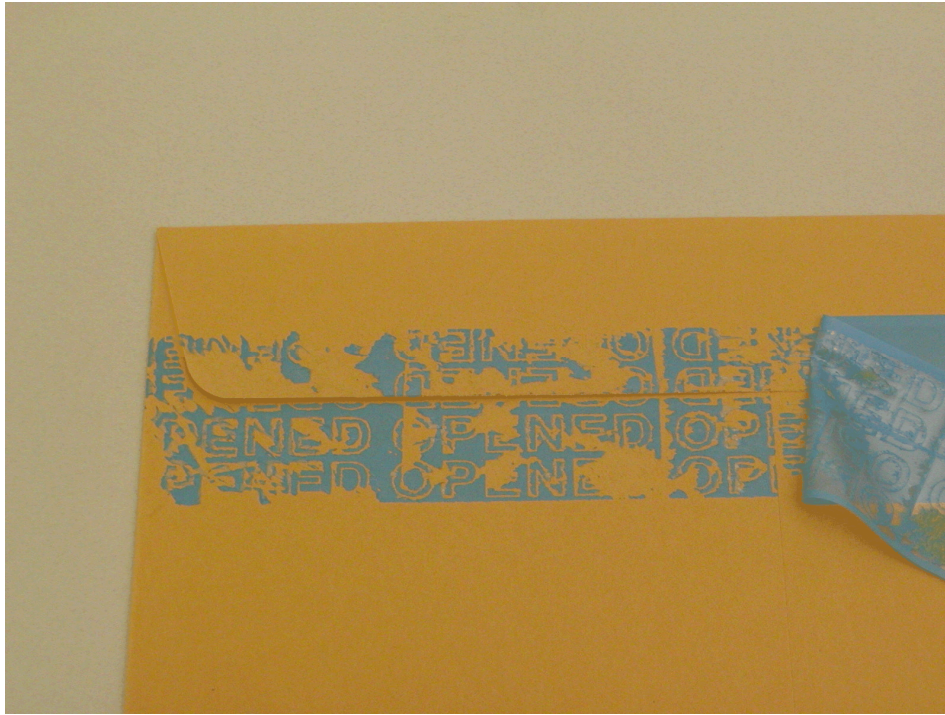
MTN 001 Randomization Envelope

Site Name: **Umkomaas**

Site Location: **Durban, South Africa**

Envelope Number: **501**

Figure 4-6c
Sample Opened MTN 001 Randomization Envelope



Envelope assignment to eligible participants will be documented in the MTN 001 Randomization Envelope Tracking Record (see Figure 4-7) that will accompany the initial envelope shipment to each site. The act of assigning a Randomization Envelope to a participant is considered the effective act of randomization and enrollment in the study. Once a Randomization Envelope is assigned, the participant is considered enrolled in the study.

The MTN 001 Randomization Envelopes will contain a two-part no carbon required (NCR) Randomization Document pre-printed with the site name, site location, Randomization Envelope number, study regimen sequence, indication as to whether the participant will complete the in-depth interview at Week 21 (See Protocol Section 7.7), and PK procedure randomization assignment (see Figure 4.8). After recording the PTID and other details on the randomization form, clinic staff will separate the two parts of the form and deliver the white original form to the pharmacy. The pharmacy will use this form to verify against the prescription to ensure the correct product is being dispensed during the correct time period. The envelope and the yellow copy of the prescription will be retained in the participant's study notebook.

Figure 4-8b
Sample MTN 001 Randomization Document – US Sites

MTN 001 RANDOMIZATION - US

Instructions: All entries must be made in dark ink. Press firmly when completing this form. Corrections may be made by drawing a single line through incorrect entries, recording correct information, and initialing and dating the correction.

Site Name:		Case					
Site Location:		Cleveland, USA			Randomization Envelope #:	999	
Study Regimen Sequence:	Z	Study Period 1:	Oral	Study Period 2:	Oral+Vaginal	Study Period 3:	Vaginal
Intensive PK sampling time point for collection of genital samples:					2 hours		
Is participant selected to complete in-depth interview at Week 21?					No		

Participant ID: - -

Did the participant provide written informed consent for enrollment into MTN 001?..... ^{yes} ^{no} Clinic Staff Initials: _____

Clinic Staff Instruction: Complete all items in this box. After initialing and dating, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Clinic Staff Initials: _____ Date envelope opened: - -
dd MMM yy

Pharmacy

4.2.7.1 Prescription Overview

The MTN 001 Study Prescription is a two-part no carbon required (NCR) document that is available from the DAIDS Clinical Research Product Management Center (CRPMC). The MTN 001 Study Prescriptions should be ordered simultaneously with the study product prior to study initiation.

An authorized prescriber will complete a prescription based on the participant randomization information on the participant's MTN 001 Randomization Document or MTN 001 Replacement Randomization Document, if a replacement participant. If the participant is in the dual use period, the authorized prescriber will need to complete one prescription for oral tenofovir and one prescription for vaginal tenofovir gel. When completing the prescription(s), site clinic staff should record the site name, site number, and site location at the top of the prescription. The site name and site location must be identical to the site name and site location preprinted on the MTN 001 Randomization Document for the given participant. After recording the PTID and other details on the prescription, site clinic staff will separate the two parts of the form and deliver the white original form to the pharmacy. The white original form must be delivered to the pharmacy prior to study product dispensation. The envelope yellow copy of the prescription will be retained in the participant's study notebook.

Participant-Specific Procedures

For each participant, random assignment will take place after the participant has been confirmed as eligible and willing to take part in the study, as documented by her signing or marking an informed consent form for enrollment. Random assignment also will take place after the participant has completed the Enrollment Behavior Assessment and has provided blood for plasma archive. The in-clinic and in-pharmacy randomization procedures are listed below.

In Clinic:

- C1. FOR NON-REPLACEMENT PARTICIPANTS: Obtain the next sequential MTN 001 Randomization Envelope and inspect it to verify that the correct envelope has been obtained and there is no evidence that the envelope has previously been opened or otherwise tampered with. Assign the envelope to the participant and document assignment on the MTN 001 Randomization Envelope Tracking Record by recording the PTID, date assigned, time assigned, and authorized clinic staff initials in the row corresponding to the assigned envelope number.

FOR REPLACEMENT PARTICIPANTS: Obtain the MTN 001 Randomization Document of the next sequential participant who is to be replaced per the list provided by the SDMC. Verify that the PTID on the randomization document is identical to the PTID on the list.

- C2. FOR NON-REPLACEMENT PARTICIPANTS: Open the assigned MTN 001 Randomization Envelope; alternatively, allow the participant to open it herself. Remove the MTN 001 Randomization Document inside the envelope and verify that the envelope number printed on the randomization document corresponds to the envelope number printed on the randomization envelope label. If the envelope does not contain a randomization document, or if any information pre-printed on the randomization document appears to be incorrect, contact the SDMC Project Manager and Study Coordinator or designee. Do not proceed with randomization of this or any other participant until instructed to do so by the SDMC.

FOR REPLACEMENT PARTICIPANTS: Obtain a blank MTN 001 Replacement Randomization Document for the replacement participant. Transcribe the randomization information from the MTN 001 Randomization Document of the participant being replaced onto the MTN 001 Replacement Randomization Document of the replacement participant.

C3. Complete the randomization document as follows:

In the middle section of the randomization document, record the PTID and mark whether the participant provided informed consent to take part in the study. The person who marks the informed consent check box is responsible for confirming the presence of a properly signed/signed and dated informed consent form for enrollment prior to recording his/her initials beside these boxes.

The bottom section of the randomization document may be completed by any clinic staff member authorized in the site's delegation of duties to perform randomization procedures. For non-replacement participants, if this section is completed by a staff member other than the person who opened the Randomization Envelope, he/she must have access to other source documentation of the date upon which the Randomization Envelope was opened.

C5. Complete the prescription as follows:

Prescriptions must be completed by a study staff member designated in the site's delegation of duties as an authorized prescriber of study product. This person also must be listed as an investigator (either the Investigator of Record or Sub-Investigator) on the current FDA Form 1572.

All sites must complete an MTN-001 study prescription(s) at the start of each 6-week study period (the Enrollment, Week 7, and Week 14 Visits).

Each site has the discretion to determine if study prescriptions will be used to dispense additional study product at the mid-study period visits (the Week 3, Week 10, and Week 17 Visits), in which case completion of the MTN-001 Study Product Hold/Resume/pK Supply/Resupply Slip only will be required or if dispensation of new study product at the mid-study period visits requires completion of a new MTN-001 prescription(s).

For sites choosing to use the **MTN-001 Study Product Hold/Resume/pK Supply/Resupply Slip** to order new study product at the mid-study period visits, site clinic staff must follow the instructions outlined below:

At the start of each 6-week study period (the Enrollment, Week 7, and Week 14 Visits):

1. Complete the MTN-001 prescription(s) by recording the site name, site number, and site location on the top section of the prescription. The site name recorded on the prescription must be identical to the site name printed on the site's randomization envelope labels; unless an alternative site name or abbreviation is designated in the site SOP for product dispensation.
2. Record the Participant ID (PTID) assigned to the participant in the boxes provided.
3. Mark the box for current study period based on participant's randomization sequence: study period number (1, 2, or 3).
4. Complete the prescription by providing an authorized prescribers' printed name, signature and date in the provided area

*For the 'Refill/Repeat' item, record the number "1" to appears on the prescription as "Refill/Repeat 1" to indicate that the pharmacist may dispense study product [2 cartons of study gel (vaginal prescription) and/or one bottle of 30 study tablets (oral prescription)] at two intervals. The first interval will be the start of the study period and the second interval will be the mid study period visit.

***Note:** This number should never be greater than 1. The "Refill/Repeat" should never be left blank.

For sites choosing to complete new **MTN-001 Prescription(s)** to order new study product at the mid-study period visits, site clinic staff must follow the instructions outlined below:

At the start of each 6-week study period (the Enrollment, Week 7, and Week 14 Visits):

1. Complete the MTN-001 prescription(s) by recording the site name, site number, and site location on the top section of the prescription. The site name recorded on the prescription must be identical to the site name printed on the site's randomization envelope labels; unless an alternative site name or abbreviation is designated in the site SOP for product dispensation.
2. Record the Participant ID (PTID) assigned to the participant in the boxes provided.
3. Mark the box for current study period based on participant's randomization sequence: study period number (1, 2, or 3).
4. Complete the prescription by providing an authorized prescribers' printed name, signature and date in the provided area

*For the 'Refill/Repeat' item, record the number "0" to appears on the prescription as "Refill/Repeat 0" to indicate that the pharmacist may dispense study product [2 cartons of study gel (vaginal prescription) and/or one bottle of 30 study tablets (oral prescription)] for that designated study period. Any further dispensations study gel cartons or bottles of study tablets will require site clinic staff to complete new prescription(s).

***Note:** The "Refill/Repeat " should never be left blank.

- C6. Double-check the accuracy of all entries on both the randomization document and the prescription. Separate the two parts of the completed randomization document and completed prescription, and retain the yellow copies in the participant study notebook. Also retain the Randomization Envelope in the participant study notebook. Randomization Envelopes may be hole-punched after they have been opened and their contents have been removed.
- C7. Inform the participant of her sequence assignment and provide appropriate information, instructions, and counseling applicable to her assignment. Refer to study-specific informed consent support materials and the Frequently Asked Product Use Questions in Section Appendix 9-1 for reference as needed.
- C8. Deliver the white original randomization document and prescription to the study pharmacy, as follows:

OPTION A: Give the original randomization document and prescription to the participant to deliver to the pharmacy.

OPTION B: Deliver the original randomization document and prescription to the pharmacy.

OPTION C: Fax a copy of the original randomization document and prescription to the pharmacy for filling purposes only; deliver the original randomization document and prescription to the pharmacy by the time of product pick-up.

Note: In the event that pharmacy staff identifies possible errors on the original randomization document or prescription, they will return the original documents to clinic staff for clarification or correction. If corrections are required, corrections must be made on both the white original document and the yellow copy. A signed and dated note explaining the corrections also should be recorded on both copies of the corrected document. Identical corrections and notes should be recorded on both copies, on the same date, by the same person. Corrections should only be made by study staff authorized to complete original prescriptions.

In Pharmacy:

- P1. Receive the randomization document and prescription and:

Verify entries on both the randomization document and prescription and ensure the correct product is being dispensed during the correct time period. Document participant randomization sequence in the pharmacy dispensing records.

Verify the prescription has been completed correctly. If there are any errors on the prescription, the pharmacy should communicate with the clinic staff immediately to address the issue.

Proceed with dispensing study product and documenting dispensation per the MTN 001 *Pharmacist Guidelines* and *Instructions for DAIDS Clinical Trials Networks*.

File the prescription, randomization document, and Participant-Specific Pharmacy Dispensing Record, in participant-specific pharmacy files.

Figure 4-10a
Sample MTN 001 Prescription — Oral Tablets

**MTN 001
ORAL TDF 300 MG TABLETS
PRESCRIPTION**

Instructions: All entries must be made in blue or black ink. Press firmly when completing this form. Corrections may be made by drawing a line through incorrect entries, recording correct information, and initialing and dating the correction.

Site Name:		Site Number:	
Site Location:			

Participant ID:

Study Period: (check one) Sequence: ____

- Study Period 1
- Study Period 2
- Study Period 3

Tenofovir Disoproxil Fumarate 300 mg tablets

30

Directions: 1 tablet by mouth once each day before the longest period of rest (usually at night).

Refill/Repeat ____

Note to Pharmacist: May dispense 1 additional Tenofovir Disoproxil Fumarate 300 mg tablet if needed on day of pK visit without a new prescription.

Authorized Prescriber Name or ID (please print): _____

Authorized Prescriber Signature: _____

Date:
dd MMM yy

Clinic Staff Instruction: Deliver top copy to pharmacy. File bottom copy in participant study notebook.

Figure 4-10b
Sample MTN 001 Prescription — Vaginal Gel

**MTN 001
VAGINAL TENOFOVIR 1% GEL
PRESCRIPTION**

Instructions: All entries must be made in blue or black ink. Press firmly when completing this form. Corrections may be made by drawing a line through incorrect entries, recording correct information, and initialing and dating the correction.

Site Name:		Site Number:	
Site Location:			

Participant ID:

Study Period: (*check one*) Sequence: _____

- Study Period 1
- Study Period 2
- Study Period 3

Tenofovir 1% Gel (14 pre-filled applicators per carton)
2 cartons

Directions: Insert entire contents of one applicator vaginally once each day before the longest period of rest (usually at night).

Refill/Repeat _____

Note to Pharmacist: May dispense 1 additional applicator containing tenofovir 1% gel if needed on day of pK visit without a new prescription.

Authorized Prescriber Name or ID (*please print*): _____

Authorized Prescriber Signature: _____

Date:
dd MMM yy

Clinic Staff Instruction: Deliver top copy to pharmacy. File bottom copy in participant study notebook.

4.2.7.2 Replacing Participants

The purpose of replacing participants is to allow for a secondary analysis of adherence among a subgroup of participants who have adherence data in each of the three study periods. Only participants who were dispensed study product *and* returned to report on product use at least once in *each* of the three study periods are considered “evaluable” and will be included in this secondary analysis. Sites may enroll a combined total of up to 204 women in the study in order to achieve a study total of 144 evaluable women with adherence data in each of the three study periods. Participants who were not dispensed any study product and/or did not report on study product use for at least one full study period, regardless of the reason (i.e., safety, loss to follow-up), will need to be replaced. These participants should NOT be terminated from the study. Rather, site clinic staff should make every effort to retain these participants through the 21-Week Visit for purposes of continuing to monitor participant safety.

At designated time points throughout the study, the SDMC will provide each site with a site-specific list of all participants requiring replacement. The site will use the list to enroll one replacement participant for each participant on the list. Site clinic staff will *not* assign randomization envelopes to replacement participants. Rather, site clinic staff will complete an MTN 001 Replacement Randomization Document (Figures 4-9a and 4-9b) for each replacement participant by transcribing the randomization information from the MTN 001 Randomization Document of the participant being replaced onto the MTN 001 Replacement Randomization Document. For replacement participants, the act of completing the MTN 001 Replacement Randomization Document is the effective act of randomization and enrollment in the study. Once an MTN 001 Replacement Randomization Document is completed, the replacement participant is considered enrolled in the study.

In the event that a replacement participant lacks adherence data in each of the three study periods, the replacement participant will need to be replaced. Site clinic staff will transcribe the randomization information from the MTN 001 Replacement Randomization Document of the original replacement participant being replaced onto a blank MTN 001 Replacement Randomization Document of the new replacement participant.

Figure 4-9a
Sample MTN 001 Replacement Randomization Document – African Sites

MTN 001 REPLACEMENT RANDOMIZATION - AFRICA

Instructions: All entries must be made in dark ink. Press firmly when completing this form. Corrections may be made by drawing a single line through incorrect entries, recording correct information, and initialing and dating the correction.

Site Name:	Empilisweni
Site Location:	Cape Town, South Africa

To complete the table below, obtain the "MTN 001 Randomization" form assigned the participant being replaced. Complete the information below based on the randomization information contained on that form.

Participant ID of participant being replaced:			Randomization Envelope #:		
Study Regimen Sequence:	Study Period 1:	Study Period 2:	Study Period 3:		
Non-intensive PK post-dose sampling window for blood and CVL:					
Is participant selected to complete in-depth interview at Week 21?					

Participant ID: -

Did the participant provide written informed consent for enrollment into MTN 001? yes no

Clinic Staff Initials: _____

Clinic Staff Instruction: Complete all items in this box. After initialing and dating, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Clinic Staff Initials: _____

Date: -

dd MMM yy

Pharmacy

Figure 4-9b
Sample MTN 001 Replacement Randomization Document – US Sites

MTN 001 REPLACEMENT RANDOMIZATION - US

Instructions: All entries must be made in dark ink. Press firmly when completing this form. Corrections may be made by drawing a single line through incorrect entries, recording correct information, and initialing and dating the correction.

Site Name:	Case
Site Location:	Cleveland, USA

To complete the table below, obtain the "MTN 001 Randomization" form assigned the participant being replaced. Complete the information below based on the randomization information contained on that form.

Participant ID of participant being replaced:		Randomization Envelope #:	
Study Regimen Sequence:	Study Period 1:	Study Period 2:	Study Period 3:
Intensive PK sampling time point for collection of genital samples:			
Is participant selected to complete in-depth interview at Week 21?			

Participant ID: -

Did the participant provide written informed consent for enrollment into MTN 001?..... ^{yes} ^{no} Clinic Staff Initials: _____

Clinic Staff Instruction: Complete all items in this box. After initialing and dating, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Clinic Staff Initials: _____ Date: - -
dd MMM yy

Pharmacy

Section Appendix 4-1
Screening and Enrollment Scenarios for MTN 001

4.1	<p>Suppose Miss X begins the study screening process (i.e., signs or marks the screening informed consent) on October 1, and that based on the protocol-specified screening visit procedures she appears to be eligible for the study. When Miss X's screening lab results are received, however, she is found to have chlamydia. What do you do?</p> <ul style="list-style-type: none"> • When Miss X returns for the Enrollment visit (say on October 15), provide results and chlamydia treatment and continue the enrollment process. Ideally single-dose treatment will be provided, so that if Miss X is otherwise eligible for the study and free of STI/RTI symptoms, she may be enrolled at this visit. • If single dose treatment is not provided, schedule Miss X to return to the study site to complete the enrollment process immediately after treatment has been completed (assuming she remains free of STI/RTI symptoms at that time). <p>Why? Potential participants diagnosed with an STI or RTI during the screening process must complete treatment and be free of STI/RTI symptoms in order to be eligible for the study.</p>
4.2	<p>Continuing from Scenario 4.1, suppose Miss X is given a seven-day course of treatment on October 15 and returns to the study site on October 22. What should you do?</p> <ul style="list-style-type: none"> • On October 22 confirm that Miss X completed the seven-day course of treatment. If Miss X reports having completed treatment, proceed with the enrollment process. If Miss X reports not having completed treatment, provide education and counseling to encourage completion of treatment and provide additional medication if needed. Schedule Miss X to return to the study site to complete the enrollment process immediately after treatment has been completed (assuming she remains free of STI/RTI symptoms at that time). <p>Why? Potential participants diagnosed with an STI during the screening process must complete STI treatment and be free of STI/RTI symptoms in order to be eligible for the study.</p>
4.3	<p>Continuing from Scenario 4.2, suppose Miss X is given a seven-day course of treatment on October 22 but does not return to the study site until November 10. What do you do?</p> <ul style="list-style-type: none"> • Begin the entire screening process again from the beginning (including the screening informed consent process, but not including assignment of a new PTID). <p>Why? All screening and enrollment procedures must be completed within 30 days. If more than 30 days elapse from the day when the participant signed or marked the screening informed consent form, all screening procedures including the screening informed consent process must be repeated.</p>
4.4	<p>Suppose Miss X reports at her screening visit that she gave birth 1 month prior to the visit, but she is not breastfeeding and appears to otherwise be eligible and interested in taking part in the study. What should you do?</p> <ul style="list-style-type: none"> • Discontinue the current screening attempt and if she is not breastfeeding, schedule Miss X to return at least 90 days after giving birth to re-start the screening process. <p>Why? Potential participants are ineligible for enrollment in the study if fewer than 90 days have elapsed since their last pregnancy outcome. That is, enrollment must take place on or after the 90th day after the pregnancy outcome date. For Miss X, only one month has elapsed since her last pregnancy outcome. Since all screening and enrollment procedures must be completed within 30 days, Miss X should be scheduled to return 2 months later to re-start the screening process. At that time she will be required to sign another informed consent form for screening. Confirm Miss X is not breastfeeding before re-starting the screening process.</p>

Section Appendix 4-1
Screening and Enrollment Scenarios for MTN 001

4.5	<p>Suppose Miss X reports at her screening visit that she had a miscarriage 70 days prior to the visit, but appears to otherwise be eligible and interested in taking part in the study. What should you do?</p> <ul style="list-style-type: none"> Continue the screening process. Schedule Miss X’s Enrollment visit (when enrollment may take place) to occur at least 20 (but not more than 29) days later. <p>Why? Potential participants are ineligible for the study if fewer than 90 days have elapsed since their last pregnancy outcome. That is, enrollment must take place on or after the 90th day after the pregnancy outcome date. Seventy days have elapsed since Miss X’s last pregnancy outcome. Therefore she cannot be enrolled for another twenty days.</p>
4.6	<p>Suppose Miss X begins the study screening process on October 1, and she appears to be eligible. At her Enrollment visit, which takes place on October 15, Miss X does not report any STI/RTI symptoms, and otherwise appears to be eligible for the study, but she is diagnosed with bacterial vaginosis (BV) based on Amsel’s criteria. What do you do?</p> <ul style="list-style-type: none"> Enroll Miss X in the study on October 15. <p>Why? Asymptomatic BV does not require treatment per WHO guidelines. Miss X is free of STI/RTI symptoms and therefore is eligible for the study on May 15 despite having been diagnosed with BV that day.</p>
4.7	<p>Suppose in Scenario 4.6 that, rather than being asymptomatic, Miss X reports abnormal vaginal discharge and is diagnosed with BV based on Amsel’s criteria at her Enrollment visit. What do you do?</p> <ul style="list-style-type: none"> Provide treatment for BV (ideally single-dose). Schedule Miss X to return to the study site to complete the enrollment process as soon as possible after treatment is expected to be completed and symptoms are expected to have resolved (say on October 24). Assuming treatment was completed and all STI/RTI symptoms have resolved at that time, and the 30-day screening window has not elapsed, continue the enrollment process. Note: Assuming all STI/RTI symptoms have resolved when Miss X returns on October 24, a repeat screening pelvic exam is not required prior to enrollment on October 24, since she had no exclusionary pelvic exam findings on October 15 and “no test of cure” is required for treatment of BV. <p>Why? Symptomatic BV requires treatment per WHO guidelines and all STI/RTI symptoms must be resolved prior to enrollment in the study.</p>
4.8	<p>Suppose Miss X begins the study screening process on October 1, and she appears to be eligible. At the Enrollment visit, which takes place on October 8, Miss X does not report any STI/RTI symptoms, and otherwise appears to be eligible for the study, but yeast is identified on her wet mount. What do you do?</p> <ul style="list-style-type: none"> Enroll Miss X in the study on October 8. <p>Why? The MTN 001 protocol specifies that symptomatic candidiasis requires treatment; however treatment is not required in the absence of symptoms. Miss X is free of STI/RTI symptoms and therefore is eligible for the study on October 8 despite the finding of yeast that day.</p>

Section Appendix 4-1
Screening and Enrollment Scenarios for MTN 001

4.9	<p>Suppose Miss X begins the study screening process on October 1, and that she appears to be eligible after Screening Part 1. At the enrollment visit, which takes place on October 8, a grade 2 finding involving epithelial disruption is observed on pelvic exam, but no other STI/RTI signs or symptoms are present. What do you do?</p> <ul style="list-style-type: none"> • Schedule Miss X to return to the study site for a repeat screening pelvic examination as soon as possible after the observed finding is expected to be resolved. Assuming the finding is resolved at that time, and the 30-day screening window has not elapsed, continue the screening and enrollment process. (Note: If syphilis is suspected, also collect blood and perform syphilis serology.) <p>Why? A grade 2 pelvic exam finding is exclusionary for this study.</p>
4.10	<p>Suppose in Scenario 4.9 that the observed grade 2 finding involving epithelial disruption is consistent with a genital herpes (HSV-2) outbreak. What do you do?</p> <ul style="list-style-type: none"> • Provide Miss X with treatment and schedule her to return to the study site for a repeat pelvic examination as soon as possible after treatment is expected to be completed and the finding involving epithelial disruption is expected to be resolved. Assuming the finding is resolved at that time, no STI/RTI symptoms are present, and the 30-day screening window has not elapsed, continue the screening and enrollment process. <p>Why? A grade 2 pelvic exam finding is exclusionary for this study, and genital herpes outbreaks should be treated per WHO guidelines.</p>
4.11	<p>Suppose Miss X begins the study screening process on October 8, and she reports back pain and painful and frequent urination. What do you do?</p> <ul style="list-style-type: none"> • Perform dipstick urinalysis. If results indicate urinary tract infection (UTI), provide treatment per site SOP. • Schedule Miss X to return to the study site after treatment is complete and symptoms have resolved. If the treatment is complete and all symptoms have resolved within the 30-day screening window, continue with the enrollment process. <p>Why? Grade 2+ dipstick urinalysis results are exclusionary for this study. Following treatment and resolution of symptoms, and assuming Miss X is otherwise eligible, she may return to the study clinic within 30 days and continue with her enrollment visit.</p>
4.12	<p>Suppose Miss X begins the screening process on October 20 and appears to be eligible. Between her Screening and Enrollment visits her lab test results are received and a Grade 3 liver function test result is reported. At the Enrollment visit, which takes place on October 27, Miss X reports that she rarely drinks alcohol, but two days before the Screening visit she attended her sister's wedding and had several glasses of wine. What do you do?</p> <ul style="list-style-type: none"> • If Miss X appears otherwise eligible for the study, additionally draw blood to repeat her liver function tests. • Schedule another visit to take place when the liver function test results are expected to be available (but no later than November 19). • Defer the study informed consent process and all enrollment procedures until the next visit. <p>Why? A liver function test result greater than 1.5X the ULN is exclusionary for this study. However, tests may be repeated during the screening process and enrollment may proceed if a non-exclusionary result is documented within 30 days of providing informed consent for screening.</p>

Section Appendix 4-2
Randomization and First Product Dispensation Scenarios for MTN 001

4.13 On the day of enrollment/randomization, pharmacy staff identify an inconsistency between the participant's MTN 001 Randomization Document and her prescription (e.g., the "date randomization envelope opened" on the randomization document is different than the date on the prescription). What do you do?

Pharmacy Staff: Return the original randomization document and prescription to clinic staff and inform them of the error that must be corrected in order for product to be dispensed.

Clinic Staff: Review the dates on the MTN 001 Randomization Document and prescription, and determine which document needs correction. If the randomization document requires correction, both the white original and the yellow copy must be corrected by clinic staff authorized to complete original randomization documents. If the prescription requires correction, both the white original and the yellow copy must be corrected by clinic staff authorized to complete original prescriptions. Refer to the participant's study chart as needed to determine the correct entries to be added to the randomization document or prescription. Retrieve the yellow copy of the document requiring correction from the participant's study notebook and record identical corrections on both the white original and the yellow copy. Write identical signed and dated notes explaining the corrections on both the original and the copy. Identical corrections and notes should be recorded on both copies, on the same date, by the same person. Deliver the corrected white original randomization document and prescription to pharmacy staff. Retain the yellow copies in the participant's study notebook.

Pharmacy Staff: Receive the corrected prescription and/or randomization document, verify that all entries are now correct, and dispense product per standard procedures. File the original white copies of the randomization document and prescription in participant-specific pharmacy files.

4.14 On the day of enrollment/randomization, pharmacy staff notice that the participant's prescription does not match the study product she is randomized to use in her first study period, per the randomization document (e.g., the prescription is for vaginal tenofovir, but the randomization document indicates that the participant's first study period is oral). What do you do?

Pharmacy Staff: Return the original randomization document and prescription to clinic staff and inform them of the error that must be corrected in order for product to be dispensed.

Clinic Staff: Verify that the incorrect prescription has been completed for the given study period per the randomization document. If the prescription is incorrect, place the white original copy of the prescription on top of the yellow copy, then draw a diagonal line across the original copy so that the correction shows on the yellow copy. Write a note at the top of the incorrect prescription that states, "Incorrect prescription completed in error." Initial and date the note. Identical corrections and notes should be recorded on both copies, on the same date, by the same person. Only site clinic staff authorized to complete original prescriptions should make these corrections on both the white original and yellow copy of the incorrect prescription. File the incorrect prescription in the participant's study notebook. Site clinic staff authorized to complete original prescriptions should complete a new, correct prescription per the participant's randomization document. Deliver the white original of the correct prescription, along with the white original of the randomization document, to pharmacy staff. Retain the yellow copies in the participant's study notebook.

Pharmacy Staff: Receive the new prescription and the randomization document, verify that both are now correct, and dispense product per standard procedures. File the original white copies of the randomization document and prescription in participant-specific pharmacy files.

Section Appendix 4-2
Randomization and First Product Dispensation Scenarios for MTN 001

4.15	<p>On the day of enrollment/randomization, a participant is given her prescription to bring to the study pharmacy. On the way to the pharmacy she loses the prescription. She re-traces her steps back to the clinic but still cannot find the prescription. What do you do?</p> <p><u>Clinic Staff:</u> Make a photocopy of the yellow clinic copy of the prescription and obtain another original authorized prescriber signature and signature date on the photocopy. Document the occurrence and action taken in a signed and dated chart note. Deliver the signed photocopy of the prescription and a photocopy of the chart note to the pharmacy. The documents may be delivered to pharmacy staff by the participant or by study staff. In this case, because the prescription is a signed photocopy, it is advisable for clinic staff to escort the participant back to the pharmacy and explain the situation to pharmacy staff.</p> <p><u>Pharmacy Staff:</u> Dispense product per the signed photocopy of the prescription. File the signed photocopy of the prescription and the photocopy of the clinic staff note in participant-specific pharmacy files.</p> <p>Note: These same steps would be taken if a prescription were to be lost by a clinic staff member or product runner.</p>
4.16	<p>Continuing from Scenario 4.14, suppose another woman finds the lost prescription and brings it to the pharmacy to request product for herself. What do you do?</p> <p><u>Pharmacy Staff:</u> Product will be dispensed only if prescriptions are delivered along with the randomization document. The randomization document is used to verify the prescription, to ensure the correct product is being dispensed during the correct time period and in this case, to the correct person. Pharmacy staff will contact the clinic staff to discuss the situation.</p> <p><u>Pharmacy and/or Clinic Staff:</u> In a manner deemed most appropriate by supervisory clinic staff (e.g., Clinic Coordinator, Study Coordinator, or Investigator of Record), address the situation with the woman who presented the prescription. Document the occurrence and action taken in a memo to file.</p>
4.17	<p>On the day of enrollment/randomization, a participant is given her randomization document to bring to the study pharmacy. On the way to the pharmacy she loses the randomization document. She re-traces her steps back to the clinic but still cannot find the randomization document. What do you do?</p> <p><u>Clinic Staff:</u> Make a photocopy of the yellow clinic copy of the randomization document and obtain another original authorized prescriber signature and signature date on the photocopy. Document the occurrence and action taken in a signed and dated chart note. Deliver the signed photocopy of the randomization document and a photocopy of the chart note to the pharmacy. The documents may be delivered to pharmacy staff by the participant or by study staff. In this case, because the randomization document is a signed photocopy, it is advisable for clinic staff to escort the participant back to the pharmacy and explain the situation to pharmacy staff.</p> <p><u>Pharmacy Staff:</u> Dispense product per the signed photocopy of the randomization document and the participant's prescription. File the original prescription, signed photocopy of the randomization document, and the photocopy of the clinic staff note in participant-specific pharmacy files.</p> <p>Note: These same steps would be taken if a randomization document were to be lost by a clinic staff member or product runner.</p>

Section Appendix 4-2
Randomization and First Product Dispensation Scenarios for MTN 001

4.18 On the day of enrollment/randomization for a replacement participant, pharmacy staff identify an inconsistency between the replacement participant's MTN 001 Replacement Randomization Document and the MTN 001 Randomization Document of the participant being replaced (e.g., the "study regimen sequence" on the replacement randomization document is different than on the randomization document of the participant being replacement). What do you do?

Pharmacy Staff: Return the original replacement randomization document and prescription to clinic staff and inform them of the error that must be corrected in order for product to be dispensed.

Clinic Staff: Retrieve the yellow copy of the MTN 001 Randomization Document of the participant being replaced. Compare the randomization information on the randomization document of the participant being replaced with the randomization information on the replacement randomization document of the replacement participant. Determine what transcription errors need to be corrected on the replacement randomization document so that it matches exactly the randomization information on the randomization document of the participant being replaced. Both the white original and the yellow copy of the replacement randomization document must be corrected by clinic staff authorized to complete original randomization documents. Retrieve the yellow copy of the replacement randomization document from the replacement participant's study notebook and record identical corrections on both the white original and the yellow copy. Write identical signed and dated notes explaining the corrections on both the original and the copy. Identical corrections and notes should be recorded on both copies, on the same date, by the same person. Deliver the corrected white original replacement randomization document and prescription to pharmacy staff. Retain the yellow copies in the participant's study notebook.

Pharmacy Staff: Receive the corrected replacement randomization document and prescription, verify that all entries are now correct, and dispense product per standard procedures. File the original white copies of the replacement randomization document and prescription in the replacement participant's participant-specific pharmacy files.

Section Appendix 4-2
Randomization and First Product Dispensation Scenarios for MTN 001

4.19 Two days after receiving her first carton of study gel, a participant returns to the clinic and reports that she has tried to use the applicators (which she has brought with her) but they seem empty. What do you do?

Based on information provided by the participant, determine whether (a) the participant may need refresher instructions on how to use the applicators or (b) the participant may have received defective gel supplies.

Clinic Staff: Discuss the participant's current understanding of how to use the applicators and provide refresher instructions as needed. Then ask the participant to try to apply the gel again in a private on-site location (using one of the applicators she brought back with her; give her a suitable container in which to place the applicator and wrapper before and after use).

- If the participant is able to apply the gel, no further follow-up action is required. Assist the participant in disposing of the used applicator and wrapper in accordance with applicable biowaste requirements. Instruct the participant to return at any time with questions about how to use the applicators. Document the occurrence and action taken in a signed and dated chart note.
- If the participant still is unable to apply the gel, contact pharmacy staff for further consultation. Collect the unused applicators that the participant has with her for return to the pharmacy. Complete a Vaginal Tenofovir Gel Prescription to order replacement gel supplies for the participant. Document the occurrence and action taken in a signed and dated chart note. Attach a photocopy of the note to the new prescription and deliver the note, the prescription, and the applicators to the pharmacy. Pharmacy staff then will proceed with storing the applicators and contacting the DAIDS Protocol Pharmacist as described below.

Pharmacy Staff: If the participant may have received defective gel supplies, collect the supplies she has with her and dispense replacement supplies. Document dispensation per standard procedures. Store the applicators collected from the participant in a designated 'quarantine' area for returned applicators. Inform the DAIDS Protocol Pharmacist immediately; the Protocol Pharmacist will inform CONRAD, MTN CORE Clinical Research Managers, and MTN SDMC Project Managers. Follow any further instructions provided by the DAIDS Protocol Pharmacist and document all further action taken.

Inform clinic staff of the outcome/resolution of the participant's report and provide written documentation for inclusion in the participant's study chart (e.g., a photocopy of signed and dated pharmacy staff notes or a separate signed and dated note or memo to file). Be sure the documentation provided does not contain coded information related to the participant's random assignment.

Section 5. Informed Consent

This section provides information on informed consent procedures for MTN 001. MTN 001 involves three types of informed consent:

- Informed consent for screening
- Informed consent for enrollment
- Informed consent for long term specimen storage and possible future research testing

Potential study participants must provide written informed consent for screening in order to undergo protocol-specified procedures for determining eligibility for study participation. Potential participants who are found to be eligible for the study must then provide written informed consent to enroll in the study and undergo protocol-specified “on study” procedures, including random assignment, use of study products and completion of follow-up visits and procedures. For enrolled participants, informed consent for long term specimen storage and possible future research is optional. Participants may choose not to consent to long term specimen storage and possible future research testing and still be enrolled in the study. The participant can consent later in the study to long term storage and possible future research testing (does not have to consent at enrollment), as long as she gives her consent before the samples are stored.

This section contains general information and instructions applicable to all three types of informed consent required for MTN 001. In addition, detailed guidance is provided for the standardized approach to the enrollment informed consent process that must be followed at all sites.

5.1 Overview of Informed Consent Requirements and Procedures

Informed consent is a process by which an individual voluntarily expresses her willingness to participate in research, after having been informed of all aspects of the research that are relevant to her decision. Informed consent is rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process, involving information exchange, comprehension, voluntariness, and documentation. Each of these aspects of the process are described in greater detail below. Please also refer to Section 4.8 of the ICH GCP guideline and the informed consent section of the DAIDS SOP for Source Documentation for further guidance on the informed consent process and documentation requirements.

As noted above, for MTN 001, informed consent is first obtained for screening procedures only. Then, for participants found to be eligible, informed consent is obtained for enrollment. For both screening and enrollment, informed consent must be obtained prior to undertaking screening and enrollment procedures, respectively. For enrolled participants, informed consent also must be construed as an ongoing process that continues throughout the study follow-up period.

Enrolled study participants are asked to provide informed consent for long term storage of blood specimens for possible future research testing. Participants may choose to not have their specimens stored for possible future research testing and still enroll/remain in the study.

US regulations (45 CFR 46) specify the elements of informed consent that must be conveyed to research participants through the informed consent process. It is the responsibility of the Investigator of Record (IoR), and by delegation all study staff involved in the informed consent process, to deliver all required information to potential study participants.

Based on the technical and regulatory reviews that are completed as part of the MTN protocol development and study activation processes, there is adequate assurance that once a site has been “activated” for study implementation, the site-specific informed consent form specifies all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate informed consent form. It also is the responsibility of the IoR and designated study staff to:

- Deliver all required information in a manner that is understandable to potential study participants
- Assure that informed consent is obtained in a setting free of coercion and undue influence
- Confirm that the participant comprehends the information
- Document the process

If the participant is not literate, an impartial literate witness must be present during the entire informed consent process/discussion with the participant. As part of the documentation steps detailed below, the witness will be asked to sign and date the informed consent form to attest that the information in the consent form was accurately explained to, and apparently understood by, the participant, and that informed consent was freely given by the participant. The ICH GCP guideline identifies an “impartial” witness as a person who is independent of the study, who cannot be unfairly influenced by people involved with the study. The MTN CORE received guidance from the US Food and Drug Administration’s GCP office stating that the witness need not be “totally unaffiliated with the study. It may be possible, for example, to designate a "subject advocate" who would be available at each site ...” Please refer to Section Appendix 5-1 of this manual for a summary of considerations for obtaining informed consent from illiterate participants.

When a witness is present during the informed consent process, care should be taken to minimize the perception of coercion due to the presence of the witness. For example, the purpose of having the witness present should be clearly explained to the participant, with emphasis on the fact that the witness is there as a protection for the participant, not as an agent of the study per se.

As a condition for study activation, each study site must establish an SOP for obtaining informed consent from potential study participants that ensures that all of the above-listed requirements are met. The SOP must be consistent with the DAIDS SOP for Source Documentation. It is recommended that the SOP contain the elements listed below and that each site seek IRB/EC review and approval of the SOP.

- The minimum legal age to provide independent informed consent for research at the study site
- Procedures for ascertaining participant identity and age
- Procedures for ascertaining participant literacy
- Procedures for providing all information required for informed consent to the participant
- Procedures for ascertaining participant comprehension of the required information

- Procedures to ensure that informed consent is obtained in a setting free of coercion and undue influence
- Procedures for documenting the informed consent process
- Considerations and requirements for illiterate participants, including specification of who may serve as a witness to the informed consent process
- Storage locations for blank informed consent forms
- Storage locations for completed informed consent forms
- Procedures (e.g., color-coding) to ensure that the many different study informed consent forms are easily distinguished and used appropriately
- Procedures for implementing a change in the version of the informed consent form used
- Procedures to document and identify participants that have consented to participate in the 21-Week In-depth interview (for applicable sites)
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements (if not specified elsewhere)
- QC/QA procedures related to the above (if not specified elsewhere)

5.2 Informed Consent for Screening

At each study site, the informed consent process for screening will be conducted according to site SOPs. Informed consent for screening must be obtained prior to performing any study screening procedures. For participants who do not consent to screening, no screening procedures should be performed and no data that can be linked to the participant's name or other personal identifier(s) should be recorded.

5.3 Informed Consent for Enrollment

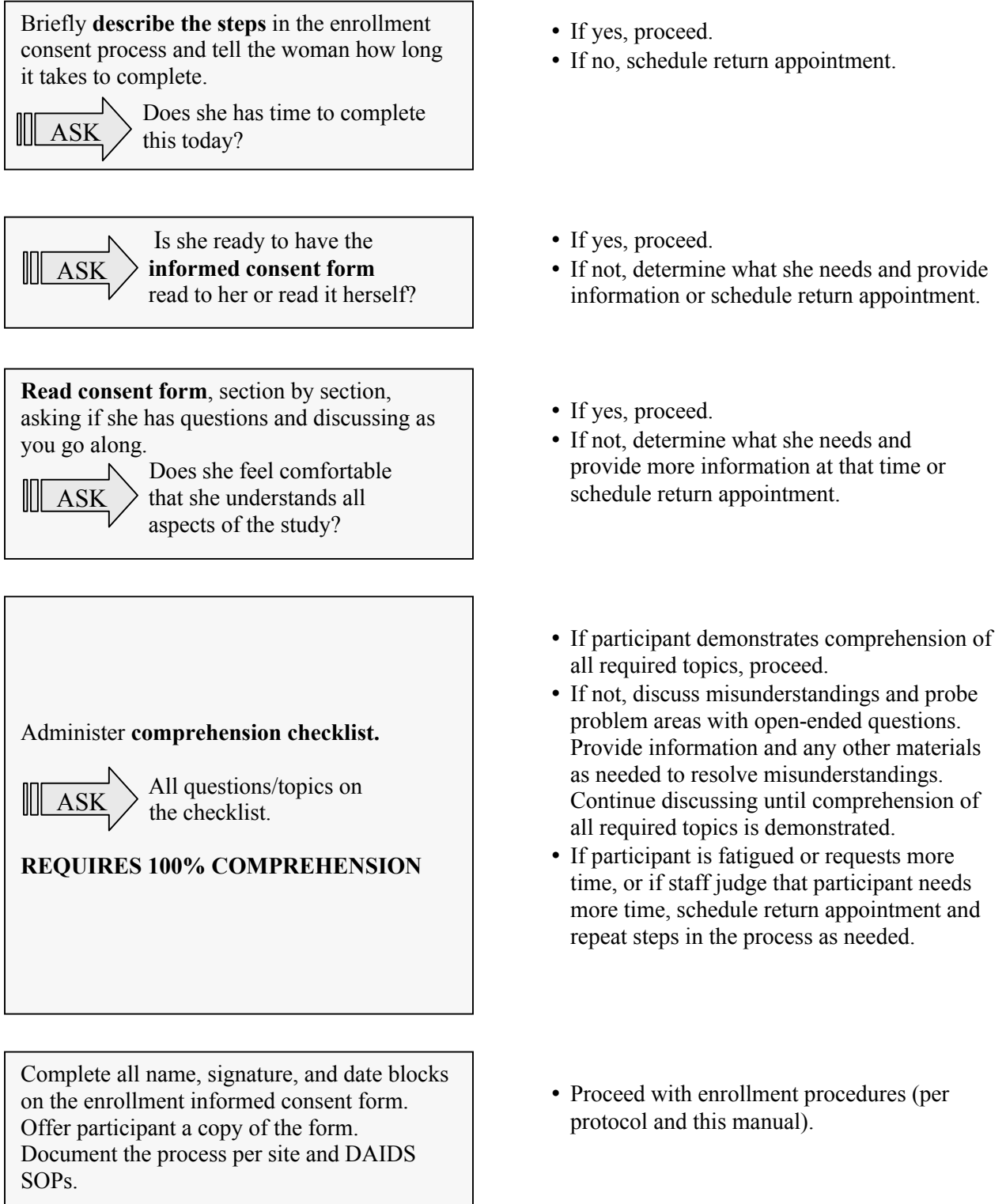
At each study site, the informed consent process for enrollment will be conducted according to site SOPs. However, site SOPs must reflect the standardized approach to the enrollment informed consent process that is described in this section. Informed consent for enrollment must be obtained prior to performing any study enrollment or "on-study" procedures. An overview of the standardized approach to the enrollment informed consent process is provided in Figure 5-1. Additional details related to key steps in the process are provided in the remainder of this section.

5.3.1 Informed Consent Support Materials

- **Site-specific informed consent forms:** The informed consent forms used at all sites must be reviewed and approved by study site IRBs/EC and DAIDS prior to their use. After the forms are approved, each site is responsible for preparing bulk supplies of their approved forms and for only using the currently approved versions of the forms at all times during the study.

It is recommended that all sites consider the use of color-coding or other techniques to ensure that the various study informed consent forms are easily distinguished and used appropriately (such as a yellow cover sheet for screening, blue for enrollment, etc.). At the beginning of the study, bulk supplies of the screening and enrollment informed consent forms should be prepared. Care must be taken to use the correct forms for long term specimen storage and possible future research testing.

**Figure 5-1
Overview of MTN 001 Enrollment Informed Consent Process**



- **Visual Aids:** Use of visual aids is encouraged throughout the informed consent process to facilitate participant comprehension. Each site should determine the most appropriate visual aids for its study population and ensure that a “kit” containing each of these aids is available in each room where informed consent discussions take place. In addition to the visual aids decided upon at each site, it may be helpful to point out such things as a locked file cabinet, a referral clinic across the way, or a calendar on the wall. It is not necessary to use each visual aid with each participant. Study staff should use their best judgment of each participant’s information needs and how best to address those needs.

Suggested visual aids for each site to consider using are as follows:

- Calendar
- Sample gel applicator
- Sample pill container
- Sample product carton
- Urine specimen cup
- Watch (for recording time of study product dosage for PK measures)
- Blood collection tubes
- Vaginal and/or pelvic model
- Speculum
- Sample randomization envelopes
- Other randomization explanation visual aids (e.g., sack or box containing six items of different colors)

When using vaginal and pelvic models, remember that participants may not be familiar with such models. Introduce the models in a sensitive manner and use information, rapport, and humor to help make the participant feel comfortable with the models.

When using a vaginal model to demonstrate gel use, be sure to lubricate the sample applicator before insertion. If this is done while the participant is present, point out that women normally have some lubrication, and you are just adding some to the model to make it more realistic. Always hold the applicator in the middle of the barrel and insert it so that half is inserted inside and half is visible on the outside of the vagina. After inserting the applicator, point out that there is plenty of room for the applicator inside.

When using a pelvic model to demonstrate gel use, it may be necessary to first orient the participant to the model and the anatomical parts shown. Be sure that all staff who may use the model are able to explain what each part is. Point out that the vaginal opening starts at the outside edge of the plastic model. Hold the applicator in the middle of the barrel and also hold your fingers against the outside edge of the model, so that the applicator is only inserted half-way. Otherwise, it could appear to the participant that the applicator is jabbing against the cervix.

Regardless of use of the vaginal and pelvic models, study staff who take part in informed consent discussions should be prepared to “imitate” the application of gel with two hands between their legs.

5.3.2 Comprehension Assessment

The staff person conducting the enrollment informed consent process with a potential participant is responsible for determining whether the participant comprehends the information provided to her. The sample MTN 001 Enrollment Informed Consent Comprehension Checklist (see Section Appendix 5-3) will assist staff in assessing participant comprehension and targeting follow-up educational efforts to ensure that participants understand all information required to make an informed decision about whether to enroll in the study. Sites may choose to adapt the checklist, however all checklists require approval from the MTN CORE (FHI) prior to use.

The comprehension checklist will be administered to each potential participant after she has completed the informed consent discussions described above and before she is asked to sign or mark on the enrollment informed consent form. The checklist should not be presented to participants as a “test,” but rather as a way of double-checking that study staff have fulfilled their responsibility to provide all information needed for the participant to make an informed decision about enrolling in the study.

It is expected that the checklist will be administered by the same staff member who conducted the enrollment informed consent discussion with the participant, however this is not a requirement per se. If more than one staff member spent time with the potential participant during the informed consent process, the checklist should be administered by the person who most recently spoke with her or who spent the most time with the participant.

The checklist is structured around open-ended questions that correspond with the required elements of informed consent for research. Each question should be read to the potential participant, giving her time to respond to each one.

Each question should be satisfactorily answered by the participant before moving to the next question. For each question, the checklist specifies particular points that must eventually be included in the participant’s response. When the potential participant mentions one of the required points, study staff should check off that point. If the participant does not mention one or more of the required points, study staff should follow-up with another open-ended question to elicit a response about that point. For example, one of the required points in the sample checklist, Question 1 is “study is testing one gel and one oral pill.” If the potential participant does not mention this in her initial response to Question 1, the study staff member may then ask “Can you tell me how many products are being tested in this study?” If the participant responds correctly, the point may then be checked off. All required points must be satisfactorily addressed by the participant, and checked off, before proceeding to the final informed consent decision and signing or marking of the enrollment informed consent form.

When responding to the various questions, potential participants may report back more information than is included on the checklist. This is acceptable, as long as the required information is reported back. If the additional information reported by the participant applies to another question on the checklist, study staff may go ahead and check off that point. If any misinformation is reported back, study staff may explain the correct information before proceeding to another question, or defer explanation of the correct information until after the entire checklist has been administered.

Once administration of the comprehension checklist discussion begins, it is possible that the participant may spontaneously mention many of the required points, without each separate question being asked. In these cases, study staff should check off the relevant points on the checklist and then ask the remaining questions, or probe about the remaining points. It doesn't hurt to ask a question that a participant may have already answered in her response to a previous question. However, if staff is confident that a previous response was adequate, the specific question and/or point do not need to be repeated.

It is expected that study staff administering the informed consent process and checklist will be sufficiently knowledgeable about MTN 001 to make good judgments about potential participants' grasp of the required information. It is possible that a participant might repeat the correct information, yet the staff member may not be convinced that she really understands it. In these cases the staff should decide if further explanation or discussion is needed before proceeding to the final informed consent discussion and signing or marking of the informed consent form. The further explanation or discussion could take place at the same visit or another visit might be suggested/scheduled.

Whenever additional information or explanation is needed, all the informed consent support materials may be used. Study staff should decide which materials may be most helpful to each participant. Some potential participants may be more comfortable interacting with the same study staff person throughout the informed consent process. However, another staff member may be consulted, if necessary or desired, to help explain problematic concepts and/or respond to participant questions or concerns.

The comprehension checklist is considered a study source document that should be completed, handled, and retained in the participant's study chart like any other source document. After administering the checklist, study staff should carefully review the checklist to verify that all required points have been satisfactorily addressed by the participant and that this is adequately documented on the checklist (i.e., with a check mark beside each point). Failure to document participant comprehension of all required points on the checklist will be considered an informed consent and enrollment violation. Comments may be recorded in the designated column on the checklist (and on the back of the checklist if additional space is needed), however this is not required. Lastly, after the enrollment consent process is completed, the final outcome of the process should be recorded in the bottom left corner of the checklist and the staff member who completed the checklist should ensure his/her signature in the space provided.

5.4 Informed Consent for Specimen Storage and Possible Future Research Testing

At each study site, the informed consent process for specimen storage and possible future research testing will be conducted according to site SOPs among enrolled study participants. For participants who do not consent to specimen storage and possible future research testing, specimens collected and stored on-site per protocol will be retained until the study is completed and all protocol-specified testing has been completed. Thereafter, any remaining specimens collected from these participants will be destroyed.

5.5 Documenting the Informed Consent Process

US regulations require that informed consent be documented by "the use of a written informed consent form approved by the IRB/EC and signed and dated by the subject or the subject's legally authorized representative at the time of consent."

To fulfill this requirement, complete all signature and date blocks on the informed consent form in ink. Legal names should be used. Fabricated/falsified names should not be used. Initials may not be used in place of a participant's full surname, and it is strongly recommended that initials not be used in place of a participant's full first name. However, if a participant commonly signs her name using an initial for her first name, the initial may be used, provided this practice is acceptable per the policies of the study site institution(s).

If the participant is not literate, the witness who was present during the informed consent discussion must sign and date the informed consent form to attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant, and that informed consent was freely given by the participant. The participant printed name, signature, and signature date blocks on the informed consent form should be completed as follows:

- The study staff member who completes the informed consent process/discussion with the participant should enter the participant's name below the "participant's printed name" block, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry.
- The participant should make her mark in the "participant's signature" block.
- The study staff member who completes the informed consent process/discussion with the participant should enter the date upon which the participant made her mark on the informed consent form below the "participant signature date" block, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry.

The DAIDS SOP for Source Documentation lists detailed requirements and suggestions for documenting the informed consent process. All requirements listed in the DAIDS SOP must be met. In order to also meet some of the suggestions listed in the DAIDS SOP, site staff may use an informed consent "coversheet" similar to the example included in Section Appendix 5-2. Sites choosing to use a coversheet should list the coversheet as a source document in their SOPs for Source Documentation for MTN 001 and should use the coversheet consistently to document all informed consent processes with all participants.

In addition to completing the documentation requirements on the informed consent form itself, each informed consent process must be documented in a signed and dated chart note. It is essential that the note (as well as the dates on the informed consent form itself) document that informed consent was obtained prior to the initiation of any study procedures. The note should also document adherence to the requirements of the informed consent section of the DAIDS SOP for Source Documentation. However, if an informed consent coversheet is used, it is not necessary to transcribe information recorded on the coversheet into the chart note.

Additionally, at site conducting the 21-Week In-depth Interview behavioral assessment, it is important the site develop a method to document and identify which participants have consented to participate in this interview.

Finally, regulations require that participants be given a signed copy of the informed consent forms. If a participant opts not to receive a copy, document this in a chart note and offer the participant an alternate form of study contact information (e.g., a contact card or appointment card) in lieu of the full informed consent form.

Section Appendix 5-1
Summary of Considerations for Obtaining Informed Consent from Illiterate Persons

- Each site must specify procedures for obtaining and documenting informed consent from illiterate persons in its SOP for obtaining informed consent. These procedures must be consistent with the DAIDS SOP for Source Documentation and must be followed each time informed consent is obtained. It is recommended that each site seek IRB/EC review and approval of these procedures.
- An impartial witness must be present during the entire informed consent discussion with an illiterate participant. The witness must sign and date the informed consent form to attest that the information in the consent form was accurately explained to, and apparently understood by, the participant, and that informed consent was freely given by the participant.
- The site SOP for obtaining informed consent should define who may serve as the witness to the informed consent process.
- Take care to minimize the perception of coercion due to the presence of the witness.
- The study staff member who completes the informed consent process/discussion with the participant should enter the participant's name below the "participant's printed name" block, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry.
- The participant should make her mark in the "participant's signature" block.
- The study staff member who completes the informed consent process/discussion with the participant should enter the date upon which the participant made her mark on the informed consent form below the "participant signature date" block, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry.
- Refer to Section 4.8 of the ICH GCP guideline and the informed consent section of the DAIDS SOP for Source Documentation for additional information.

Section Appendix 5-2
Sample Informed Consent Coversheet for MTN 001

Participant Name (or PTID):	
Name of study staff person completing informed consent process/discussion (and this coversheet):	
Is the participant of legal age to provide independent informed consent for research?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ STOP. Participant is not eligible for MTN 001.
Date of informed consent process/discussion:	
Start time of informed consent process/discussion:	
Language of informed consent process/discussion:	
Was the informed consent process/discussion conducted according to site SOPs for MTN 001?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Record and explain departures from site SOPs below.
Can the participant read?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ A literate impartial witness should be present during the entire informed consent process/discussion. Refer to site and DAIDS SOPs for specific instructions. Record name of witness here: <p style="text-align: center;">Record relationship of witness to participant here:</p>
Version number/date of informed consent form used during informed consent process/discussion:	
Was all information required for the participant to make an informed decision provided in a language that was understandable to the participant?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Explain below.
Were all participant questions answered?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Explain below.
Did the participant comprehend all information required to make an informed decision?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Explain below.
Was the participant given adequate time/opportunity to consider all options before making her informed decision?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Explain below.
Did the participant accept a copy of the informed consent form?	<input type="checkbox"/> NA (participant chose not to provide informed consent) <input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Offer alternative form of study contact information to participant.
End time of informed consent process/discussion:	
Notes/Comments (continue on back if needed):	
Signature of study staff person completing informed consent process/discussion (and this coversheet):	

Section Appendix 5-3
MTN 001 Enrollment Informed Consent Comprehension Checklist

PTID:

Date:

Open-Ended Question/Statement		Required Points of Comprehension	✓	Comments
1	Please describe your understanding of the purpose of the study.	Study is testing an experimental gel and oral pill		
		Testing to learn if women like using the gel and/or pill		
		Testing to learn if the products are safe		
2	What do you understand that you are being asked to do in this study?	Use condoms and study product daily		
		Have pelvic exams and HIV tests		
		Not get pregnant in the next 21 weeks		
		Come for follow-up visits for 21 weeks		
3	What do you understand are possible risks to being in this study?	Possibility of social harms		
		Gel or pill may have other side effects		
		Gel may irritate skin inside or outside vagina		
4	What will happen if you do not join the study?	No effect on access to care		
		Free to make her own decision about joining		
5	Please tell me about the different groups in the study.	There will be 6 different sequences of 3 different study periods		
		All women will take both of the study products but at different times		
6	How will the information about you be protected?	Participant information kept under lock and key		
		Only people working on study have access		
7	What are the benefits to participating in the study?	Counseling, tests, clinical care, benefit to science or community		
8	What should you do if you have any questions about the study?	Must articulate how to contact staff		
Outcome: <input type="checkbox"/> Demonstrated comprehension of all required points, decided to enroll in study. <input type="checkbox"/> Demonstrated comprehension of all required points, decided not to enroll in study. <input type="checkbox"/> Demonstrated comprehension of all required points, deferred enrollment decision <input type="checkbox"/> Did not demonstrate comprehension of all required points (yet), needs more time/discussion. <input type="checkbox"/> Unable to demonstrate comprehension of all required points, consent process discontinued. <input type="checkbox"/> Other (specify): _____			Optional Comment Categories: a. Answered correctly on first try b. Could not answer at first, but answered correctly after probing c. Answered incorrectly at first, but answered correctly after discussion d. Not able to answer correctly at this time e. Other (describe)	
Staff Signature:				

Section 6. Participant Follow-up

This section provides information on requirements and procedures for participant follow-up.

6.1 Study Follow-up Plan and Participant Retention Targets

Each enrolled participant will be followed through twenty-one weeks post her enrollment date. The target accrual is expected to be completed within six months of study activation at each site. The protocol team will actively monitor and manage the study accrual process to ensure that the enrollment occurs within the specified timeframe.

To minimize bias and ensure accuracy of study results, each study site will target a minimum retention rate of at least 95% for all enrolled study participants. Further information on MTN 001 retention definitions and procedures is provided in Section 8.

6.2 Types of Follow-up Visits

Throughout the study follow-up period, two types of follow-up visits may be conducted:

- **Scheduled visits** are those visits required per protocol. The protocol specifies that follow-up visits occur at: enrollment, 3-week, 6-week, 7-week, 10-week, 13-week, 14-week, 17-week, 20-week, and 21-week. All scheduled follow-up visits are pre-assigned a visit code for purposes of data management as described in Section 13.
- **Interim visits** are those visits that take place between scheduled visits. There are a number of reasons why interim visits may take place (see protocol Section 7.5). Site staff may be required to assign visit codes to interim visits for purposes of data management as described in Section 13.

Additional information related to the scheduling and conduct of scheduled and interim visits is provided in the remainder of this section.

6.3 Follow-up Visit Scheduling

6.3.1 Target Visit Dates

Enrolled participants will be scheduled to complete follow-up visits throughout their participation in the study. For each participant, all follow-up visits are targeted to take place based on the participant's enrollment date. Each participant's enrollment date is defined as the date upon which she is assigned an MTN 001 Randomization Envelope or an MTN 001 Replacement Randomization Document (for replacement participants). For example, for a participant assigned a Randomization Envelope on 1 December, follow-up visits will be targeted to take place on 22 December, 12 January, 19 January, 9 February, 2 March, 9 March, 30 March, 20 April, and 27 April.

6.3.2 Allowable Visit Windows

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, the MTN 001 protocol allows for visits to be completed within a visit window. For each required study visit, there is an allowable visit window specifying on which study days (post-enrollment) the visit is "allowed" to be completed. The allowable visit windows are contiguous from visit to visit, and do not overlap. For example, a visit conducted on study day 38 is within the 6-Week visit allowable window (see figure 6-1).

Within each allowable visit window, there is a target visit window. The target visit window is the same for each visit, equal to +/- 3 days around the target visit date. For example, the target visit window for the 3-Week visit (target day 21) is day 18 to 24. Sites are encouraged to complete required study visits within the target window if at all possible. If it is not possible to complete the required visit within the target window, the visit may be completed within the allowable visit window. Visits completed outside of the target window but within the allowable visit window will be considered completed ("retained") visits, but they will be designated as being completed "early" or "late". For example, a 3-Week visit completed on day 25 will be listed as being completed "late" since it was completed outside of the target window. However, the participant is considered retained for the 3-Week visit since it was completed within the allowable window.

If the visit is not completed within the allowable visit window, the visit is considered "missed" and is documented using a Missed Visit case report form.

Note: During the "wash-out" periods (between the 6-Week and 7-week; 13-Week and 14-Week; and 20-Week and 21-Week visits), the allowable and target window dates are the same. For example, the 6-Week target and allowable windows both close on day 45. This is due to the short interval between these particular visits.

Although the visit windows allow for some flexibility, the intent of the protocol-specified visit schedule is to conduct follow-up visits at specific intervals, and every effort should be made to do so. The MTN SDMC will provide the Protocol Team with routine visit adherence reports for purposes of monitoring adherence to the weekly visit schedule (see Section 16).

Figure 6-1
MTN 001 Visit Windows

Visit	Visit Code	Window* Opens		Target Day	Window* Closes	
		Allowable	Target		Target	Allowable
Week 3	3.0	1	18	21	24	31
Week 6	4.0	32	39	42	45	45
Week 7	5.0	46	46	49	52	59
Week 10	6.0	60	67	70	73	80
Week 13	7.0	81	88	91	94	94
Week 14	8.0	95	95	98	101	108
Week 17	9.0	109	116	119	122	129
Week 20	10.0	130	137	140	143	143
Week 21	11.0	144	144	147	150	150

* All windows are listed in days

Figure 6-2
Example of Allowable Visit Windows for MTN 001

December-2008						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1 Enrollment Day	2 3W Allowable Window Opens	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19 3W Target Window Opens	20
21	22 3W Target Day	23	24	25 3W Target Window Closes	26	27
28	29	30	31			
January-2009						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
				1 3W Allowable Window Closes	2 6W Allowable Window Opens	3
4	5	6	7	8	9 6W Target Window Opens	10
11	12 6W Target Day	13	14	15 6W Target and Allowable Window Closes	16 7W Allowable and Target Window Opens	17
18	19 7W Target Day	20	21	22 7W Target Window Closes	23	24
25	26	27	28	29 7W Allowable Window Closes	30 10W Allowable Window Opens	31
February-2009						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
1	2	3	4	5	6 10W Target Window Opens	7
8	9 10W Target Day	10	11	12 10W Target Window Closes	13	14
15	16	17	18	19 10W Allowable Window Closes	20 13W Allowable Window Opens	21
22	23	24	25	26	27 13W Target Window Opens	28
March 2009						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
1	2 13W Target Day	3	4	5 13W Target and Allowable Window Closes	6 14W Allowable and Target Window Opens	7
8	9 14W Target Day	10	11	12 14W Target Window Closes	13	14
15	16	17	18	19 14W Allowable Window Closes	20	21
22	23	24	25	26	27	28
29	30	31				

3W = 3-Week Visit, 6W = 6-Week Visit, 7W = 7-Week Visit, 10W = 10-Week Visit, 13W = 13-Week Visit

6.3.3 Visits Conducted Over Multiple Days: “Split Visits”

All procedures specified by the protocol to be performed at a particular follow-up visit ideally will be completed at a single visit on a single day. In the event that all required procedures cannot be completed on a single day, (for example because the participant must leave the study site before all required procedures are performed), the remaining procedures may be completed on subsequent day(s) within the allowable visit window.

In the case of “end of study period” visits (6-Week, 13-Week, and 20-Week) when Pharmacokinetic (PK) procedures are conducted, every effort should be made to complete all PK procedures during this visit. These PK procedures may not be split over multiple days, meaning that all PK procedures must be completed on the same day. If a participant informs the staff that she will not be able to complete all required procedures during that visit and no PK procedures have been done, the participant can be rescheduled within the study window to complete the PK procedures. Since participants may not inform staff in a timely manner that they will not be able to complete procedures, they should be counseled about the importance of completing these procedures as scheduled. In addition, every effort should be made to schedule “end of study period” visits when the participant is not experiencing her menses. However, if the participant is on her menses, all PK procedures will be conducted, including collection of the Cervical Vaginal Lavage (CVL). There is not a need to reschedule a visit for PK procedures, including specimen collection, if a participant is on menses. As described in Section 13, all case report forms completed for a split visit are assigned the same visit code.

6.3.4 Missed Visits

For participants who do not complete any part of a scheduled visit within the allowable window, the visit will be considered “missed” and a Missed Visit case report form will be completed to document the missed visit (see Section 13). However, if a participant misses a “Study-Period Start” visit (7-Week and 14-Week), only the HIV counseling and testing procedures, and complete blood count testing, required at this missed visits must be conducted at the participants’ next visit. If the participant misses an “End of Study Period” visit (6-Week, 13-Week and 20-Week), only assessment of vaginal pH, and collection of vaginal fluid for wet mount required at the missed visit must be conducted at the participants’ next visit. For example, if a participant misses her 7-Week study visit and comes to the clinic when the window for the 10-Week visit has opened, you will conduct all the 10-Week required procedures, plus HIV counseling and testing, and complete blood count testing.

6.3.5 Follow-up Visit Scheduling Scenarios

Presented in Section Appendix 6-1 are several follow-up visit scenarios that may occur during MTN 001. These scenarios illustrate that the allowable visit windows impact whether a completed visit will be considered a scheduled visit or an interim visit. The examples also illustrate the complexities that may be encountered when scheduling and completing study follow-up visits in a “real world” setting. Given these complexities, SCHARP will provide each site a Microsoft Excel spreadsheet that will have the visit windows already programmed. When a participant is enrolled, the site will insert the Enrollment Date, and the spreadsheet will generate a participant visit calendar that will include the target dates and visit windows. It is strongly recommended that sites print this calendar and place it in the participant’s binder/file.

6.4 Follow-up Visit Procedures

Required follow-up visit procedures are listed in protocol Sections 7.1, 7.2 and 7.3. Highlighted for reference below are the primary procedural requirements:

- Perform physical exam at all scheduled visits, except 21-week when the exam is performed if indicated
- Perform pelvic exam at all scheduled visits, except 21-week when the exam is performed if indicated
- Urine pregnancy testing is conducted at every visit
- HIV test is conducted at screening, 7-week, 14-week, 21-week and if indicated at other visits
- Collect urine for Dipstick Urinalysis and SDA for Chlamydia and Gonorrhea at Screening Visit and as indicated at all other visits
- Blood draws are conducted at every visit
- Baseline behavioral questionnaire conducted at Enrollment and additional behavioral questionnaires conducted at the 3-week, 6-week, 10-week, 13-week, 17 week and 20-week visits
- Counseling for contraception, male condom, and HIV/STI risk reduction, conducted at all visits
- Protocol Adherence counseling conducted at all visits except 21-week; Product Use Adherence counseling conducted at Enrollment, 3-week, 7-week, 10-week, 14-week, and 17-week visits.
- In-depth qualitative interviews will be conducted with only a subset of study participants at 21-week visit
- The two types of visits that will include PK measures are the Mid-Study-Period and the End-of-Study-Period visits.
 - Mid-Study-Period: All participants will be asked to record the three doses of tenofovir taken prior to these visits with hour: minute accuracy. Participants will provide blood samples for tenofovir level.
 - End-of-Study-Period: All participants will be asked to record the three doses of tenofovir taken prior to these visits with hour: minute accuracy. Once at the site for their study visit, they will provide blood samples and then have an observed dose of study product(s). Post-dose blood and required vaginal samples will occur within 15 – 30 minutes of each other (either sample may be taken first). Participants at the Bronx-Lebanon Hospital Center CRS who opt to have rectal fluid samples taken, will have these samples taken after (within 15 minutes) the vaginal specimens are taken. The times of these samples must be recorded with hour: minute accuracy. The same sampling time point (within 15 minutes) in each study period should be used for all of a participant's End of Study Period Visits.
 - At the Non-US sites (non-intensive PK), participants will be assigned to a sampling window based on their sequence randomization assignment (See Section 7.8.2 of the protocol). At the US sites (intensive PK), participant randomization for PK procedures will be stratified within each of the sites, providing up to 18 women per time point (See Section 7.8.3 of the protocol). Figures 6-3 and 6-4 provides additional information on non-intensive and intensive PK procedures, respectively.

- Since PK procedures may not be split over multiple days, it is vital that participants are counseled of the importance of completing these visits on the scheduled date. Clinic staff should make all efforts to schedule these visits on a date that is the most convenient for the participant.
- To prevent dilution of the study product in the PK genital specimens and to minimize the impact on the levels of study product in the cervicovaginal tissue, participants will be asked to abstain from sexual activities, if possible, at least 24 hours prior to the End-of-Study-Period visit.

**Figure 6-3
Non-Intensive PK Sites**

	PRE-DOSE	POST-DOSE TIMING		
		1-3 HOURS	3-5 HOURS	5-7 HOURS
Blood: <ul style="list-style-type: none"> • Flow cytometry (at sites with capacity) 	Study Regimen Sequences A, B, C, D, E, and F			
Blood: <ul style="list-style-type: none"> • PBMC cell lysate (intracellular tenofovir diphosphate) (at sites with capacity) • Tenofovir 	Study Regimen Sequences A, B, C, D, E, and F	Study Regimen Sequences E and F	Study Regimen Sequences A and B	Study Regimen Sequences C and D
CVL <ul style="list-style-type: none"> • Tenofovir • Proteomics and markers of inflammation 		Study Regimen Sequences E and F	Study Regimen Sequences A and B	Study Regimen Sequences C and D

**Figure 6-4
Intensive PK Sites**

SPECIMEN	PRE-DOSE	POST-DOSE TIMING				
		1 HOUR	2 HOURS	4 HOURS	6 HOURS	8 HOURS
Blood draw <ul style="list-style-type: none"> • PBMC cell lysate (intracellular tenofovir diphosphate) (at sites with capacity) • Tenofovir 	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)
Blood draw <ul style="list-style-type: none"> • Flow cytometry 	Groups M, N, O, and P)					
Cervical cytology brush <ul style="list-style-type: none"> • Cell lysates (intracellular tenofovir diphosphate) • Tenofovir 	18 ppts (Group M)		18 ppts (Group N)	18 ppts (Group O)	18 ppts (Group P)	
CVL <ul style="list-style-type: none"> • Tenofovir • Proteomics and markers of inflammation 	Group M		Group N	Group O	Group P	
Vaginal biopsies <ul style="list-style-type: none"> • Cell lysates (intracellular tenofovir diphosphate) • Tenofovir 	Group M		Group N	Group O	Group P	
Rectal Fluid (Bronx-Lebanon Hospital Center CRS only)	Group M		Group N	Group O	Group P	

6.5 Follow-up Visit Locations

All visits must take place on-site.

6.6 Product Re-Supply During Follow-up

Study product(s) will be re-supplied only to enrolled participants, upon receipt of a written prescription from an authorized prescriber. Depending on the study period in which the participant is currently enrolled, she will receive either a bottle of 30 tenofovir tablets, or 28 pre-filled vaginal gel applicators (two cartons of 14 applicators), or 30 tenofovir tables and 28 pre-filled applicators at each regularly scheduled study visit, except the End of Study Period visits and the Termination visit.

At each follow-up visit, study staff will collect all unused study products to determine whether a participant remains eligible for continued study product use per protocol specifications. Protocol Section 9.4 lists conditions under which participants should be discontinued from study product use, either temporarily or permanently. The site Investigator of Record (IoR) is responsible for ensuring that these protocol specifications are followed for all participants.

At the start of each study period, an authorized prescriber will complete a prescription based on the participant randomization assignment. If the participant is in the dual period, the authorized prescriber will need to complete a prescription for both study products (vaginal gel and tablets).

Each site has the discretion to determine if study prescriptions will be used to dispense additional study product at the mid-study period visits (the Week 3, Week 10, and Week 17 Visits), in which case completion of the MTN-001 Study Product Hold/Resume/pK Supply/Resupply Slip only will be required or if dispensation of new study product at the mid-study period visits requires completion of a new MTN-001 prescription(s).

At the Mid-Study Period, the site will provide the Pharmacist with a new Prescription or a Study Product “Re-Supply” Slip, to have new study product supplies dispensed, according to site policies.

During follow-up visits, when a new prescription will be used at the mid study period visit, an authorized prescriber will complete a prescription in the same manner they are completed during enrollment.

- Record the Participant ID (PTID) assigned to the participant in the boxes provided.
- Mark the box for current study period based on participant’s randomization sequence: study period number (1, 2, or 3).
- Complete the prescription by providing an authorized prescribers’ printed name, signature and date in the provided area.
- Double-check the accuracy of all entries and then separate the two parts of the completed prescription. Retain the yellow copy in the participant study notebook. Deliver the white original to the study pharmacy in the same manner that enrollment prescriptions are delivered to the pharmacy. Both the original and clinic copy of the prescription may be hole-punched.

Section 9 of this Study-Specific Procedures Manual contains detailed information on site clinic staff procedures for the dispensation of study product, as well as the return of used and unused study products.

6.6.1 MTN 001 Study Product Hold/Resume/pK Supply Slip

The MTN 001 Study Product Hold/Resume/pK Supply Slip (Study Product Slip, See Appendix 6-4) is a two-part no carbon required (NCR) document that is available in from the DAIDS Clinical Research Product Management Center (CRPMC). The PoR will order bulk supplies of the pads for use by clinic staff throughout the course of the study. The Study Product Slip will be used to inform the pharmacy if product needs to be held (permanently or temporarily), resumed, or in the case that a participant does not bring product to the clinic for PK procedures, this form will be used to order a single dose of product (one applicator, one tablet, or one applicator and one tablet).

At the Mid-Study Period, when a Study Product “Re-Supply” Slip will be used at the mid study period visit, an authorized clinic staff will complete a Study Product “Re-Supply” Slip based on the participant randomization assignment.

Complete the Study Product Request Slip as follows:

- Record the PTID and the number of the Randomization Envelope assigned to the participant (as recorded on her Randomization Document) in the boxes provided.
- Mark the box for HOLD, RESUME, or pK SUPPLY to indicate the action to be taken by the study pharmacy.
 - When designating HOLD, mark the box for either permanent or temporary hold and then choose which product will be held. A participant may be temporarily or permanently discontinued from one study product and be eligible to use the other product; however, if a participant is discontinued from either study product, she cannot use any product during the dual period.
 - When designating RESUME, mark which product will be dispensed. If the participant is in the dual period, mark both products. When resuming product, a new prescription for the appropriate study product (tablets, vaginal gel, or tablets and vaginal gel) will need to be completed and sent to the pharmacy along with the Study Product Slip. Study product will not be dispensed from the pharmacy unless/until another slip marked RESUME is subsequently completed and received in the pharmacy, along with the new prescription.
 - When designating pK SUPPLY, indicate which product will be dispensed. It is not necessary to complete a new prescription.
- The clinic staff name, signature, and signature date must be completed by a clinic staff member authorized to order product supplies for participants during follow-up. DAIDS does not require that an authorized prescriber sign and date the Study Product Slips; however site-specific pharmacy regulations may be more stringent than DAIDS requirements. All sites must comply with local requirements.

- Double-check the accuracy of all entries and then separate the two parts of the completed Study Product Slip. Retain the yellow copy in the participant study notebook. Deliver the white original to the study pharmacy in the same manner that original prescriptions are delivered to the pharmacy. Both the original and clinic copy of the slip may be hole-punched.

6.7 HIV Testing During Follow-Up

At all sites, follow-up HIV testing will be performed according to the algorithm in protocol Appendix II, which is re-printed in Figure 6-5. Section Appendix 6-6 presents several HIV testing scenarios that illustrate the testing procedures required by the algorithm. Further information on the procedural and documentation requirements of the algorithm is provided in the remainder of this section.

In Step One, an FDA-approved rapid HIV test (i.e., either the OraSure OraQuick test or the Uni-Gold Recombigen test) or an ELISA test, that has been validated at the study site is performed. If the rapid test or ELISA in Step One is negative, testing will stop after Step One. If the rapid test or ELISA is positive, testing will proceed to Step Two, in which the same sample that tested positive in Step One will be tested with the FDA-approved Genetic Systems Western blot (WB).

At some sites, a second rapid test may be performed in Step One. For example, HIV counseling and testing guidelines at some sites require that two rapid tests be performed whenever rapid testing is utilized. Sites required or otherwise wishing to perform a second test in Step One must specify their site-specific testing procedures in their local laboratory SOPs for MTN 001, and must obtain MTN Network Laboratory (NL) approval of these SOPs prior to study activation. Once approved, these SOPs must be followed consistently for all study participants. For sites that perform two tests in Step One, testing will proceed to Step Two if either of the two tests is positive/reactive.

If the WB in Step Two is negative, testing will stop after Step Two. If the WB is positive or indeterminate, a second FDA-approved Genetic Systems WB must be performed on a second sample collected from the participant. This sample is referred to as “sample 2” in the algorithm and will be used for plasma archive if HIV infection is confirmed. For participants with confirmed HIV infection, plasma archived at enrollment will be tested at the NL for evidence of HIV infection, as described in Section 12.

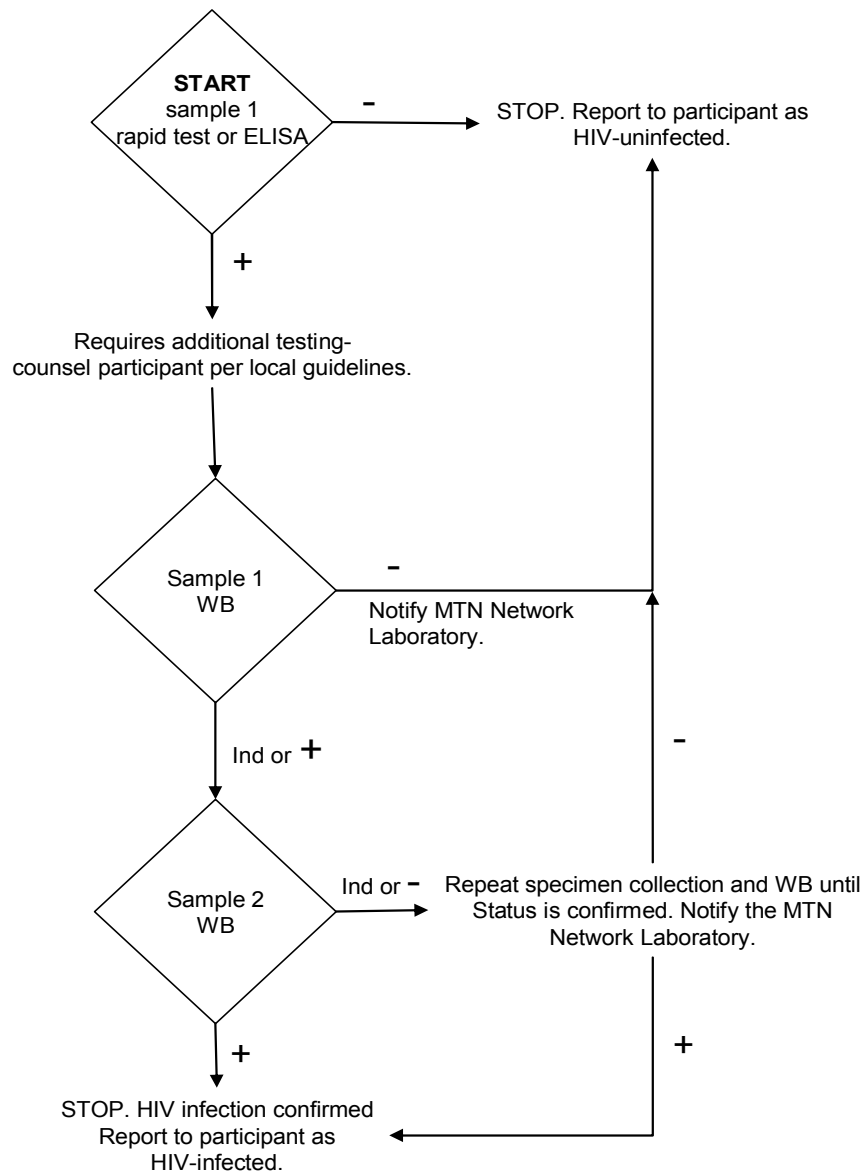
If the sample 2 WB is negative or indeterminate, additional WB testing must be performed on additional samples. In this case, inform the MTN NL via email of the sample 1 and sample 2 test results (copied to the MTN CORE and SDMC) and request NL input on next steps and timeframes for additional specimen collection and testing.

Further instructions for performing HIV tests during follow-up are provided in Section 12. All tests must be documented on local laboratory log sheets or other laboratory source documents, such documents must capture the start and end/read times of each test. A second independent clinic or laboratory staff member trained in proper HIV testing and result recording procedures must review, verify, and sign-off on test results within the timeframe of the tests and prior to disclosure of results to participants. For positive/reactive results, review, verification, and sign-off must be performed by a nurse, clinician, or physician. In addition to initialing or signing the testing logs to document review and verification of the results, the second staff member must also record the time at which the results were reviewed and verified.

Figure 6-5

Algorithm for HIV Antibody Testing During Follow-up in MTN 001

Algorithm for HIV antibody testing during follow-up



6.8 Modified Follow-up Procedures for Participants Who Become Pregnant

Participants who become pregnant after enrollment/randomization will be maintained in follow-up according to their original study follow-up schedule. Participants who are pregnant at the termination visit will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained).

While in scheduled follow-up, all protocol-specified study procedures, including routine pregnancy testing, will continue to be conducted for pregnant participants, with the following exceptions:

- Administration of study products (site staff will make every effort to recover any unused study product within 5 days once the site becomes aware of the pregnancy)
- Product use and adherence counseling will be discontinued.
- All pharmacokinetic measures
- For all participants who become pregnant, regardless of study treatment group, a Pregnancy Report and History form must be completed to report the pregnancy. A Pregnancy Outcome form also must be completed to document the outcome of the pregnancy. Certain pregnancy outcomes also must be reported on Adverse Experience Log case report forms (see Section 13.6) and/or DAIDS Expedited Adverse Event Forms, as described in Section 11 of this manual. Whenever possible, pregnancy outcomes should be ascertained based on medical records or other written documentation from a licensed health care practitioner. When medical records cannot be obtained, however, outcomes may be ascertained based on participant report.

Several illustrative pregnancy management scenarios are provided in Section Appendix 6-7. All study sites are strongly encouraged to use a pregnancy management worksheet similar to the sample in Section Appendix 6-8 to ensure proper documentation of the pregnancy and timely discontinuation and resumption (if applicable) of product use. Site pharmacy staff must be informed of the product hold/discontinuation in writing, product supplies previously dispensed to pregnant participants must be retrieved as soon as possible and within 5 days after the pregnancy is identified, and a Product Hold/Discontinuation case report form (see Section 13) must be completed and transmitted to the SDMC.

6.9 Modified Follow-up Procedures for Participants Who Become Infected with HIV

Participants who become infected with HIV after enrollment/randomization will be maintained in follow-up according to their original study follow-up schedule. All participants who become infected with HIV will be counseled and referred to available sources of medical and psychosocial care and support, as well as to any available research studies for HIV-infected persons. For any participants who become HIV-infected and also become pregnant during follow-up, every effort will be made to facilitate access to interventions such as single-dose nevirapine to reduce the probability of HIV transmission to the participant's infant.

While in scheduled follow-up, all protocol-specified study procedures will continue to be conducted for participants who become infected with HIV, with the following exceptions:

- After HIV infection is confirmed per the algorithm in Figure 6-3, and the participant's enrollment plasma specimen has been tested for evidence of HIV infection, if applicable, HIV testing will be discontinued.
- Product use will be permanently discontinued (site staff will make every effort to recover any unused study product immediately after the site becomes aware of the participant's HIV status)
- Counseling will be tailored to primary and secondary HIV/STI prevention for infected women.
- Product use and adherence counseling will be discontinued.
- All pharmacokinetic measures

Participants, who become infected with HIV, may be offered participation in the MTN Seroconverter Study (MTN-015).

6.10 Participant Transfers

During the course of the study, participants may leave the area in which they enrolled in the study and re-locate to another area where the study is taking place. To maximize participant retention, participants who re-locate from one study location to another should be encouraged to continue their study participation at their new location. To accomplish this, study staff at both the original site (called the "transferring" site) and the new site (called the "receiving" site) will complete the process of a participant transfer.

Upon identifying the need for a participant transfer to another site, the transferring site will notify the receiving site as well as the MTN CORE, MTN SDMC, MTN NL, and DAIDS Pharmaceutical Affairs Branch (PAB). After the logistical details of the transfer have been discussed and agreed upon by the two sites, the following steps will be completed:

- The SDMC will notify the transferring site of all outstanding data QC notes for the transferring participant; the transferring site will resolve these QCs.
- The transferring site will explain the transfer arrangements to the participant and obtain her written permission to provide copies of her study records to the receiving site.
- The transferring site will deliver copies of all of the participant's study records to the receiving site via courier or overnight mail service. Copies of participant-specific records maintained in the transferring site pharmacy must be delivered directly to the receiving site pharmacy, separate from the participant's clinic records. Pharmacy records may not be delivered in the same shipping envelope or carton as the clinic records. The transferring site (clinic and pharmacy) will document all materials sent to the receiving site and inform the receiving site of the shipment date and expected arrival date. The receiving site (clinic and pharmacy) will confirm receipt of the shipment.
- The transferring site will complete and transmit a Participant Transfer case report form to the MTN SDMC (see Section 13). The SDMC will forward a copy of this form to the MTN CORE, MTN NL, and DAIDS PAB for informational purposes.
- The receiving site will establish contact with the participant, obtain her written informed consent to continue in the study at the receiving site, and complete and transmit the Participant Receipt case report form to the SDMC (see Section 13).
- Upon receipt of the Participant Transfer and Participant Receipt forms, the SDMC will re-map the participant's study ID number (PTID) to reflect the change in site follow-up responsibility. The participant's original PTID and follow-up visit schedule will remain unchanged. Her random assignment also will remain unchanged. An authorized prescriber at the receiving site will be required to prepare an original signed and dated note to pharmacy staff stating that the participant has provided written informed consent to take part in the study at the receiving site and that the prescriber authorizes the participant to continue product use per the MTN 001 protocol at the receiving site. Clinic staff will deliver the original signed and dated note to pharmacy staff and retain a photocopy of the note in the participant's study chart. Upon receipt of the original signed and dated note, and a completed MTN 001 Study Product Prescription, pharmacy staff at the receiving site will dispense the product to the participant according to the random assignment documentation received from the transferring site pharmacy.
- If applicable, the transferring site will retain responsibility for storage and shipment of all specimens collected from the participant to the MTN NL, prior to her transfer, unless otherwise instructed by the MTN NL.

6.11 Resumption of Study Participation After Voluntary Withdrawal

As stated in protocol Section 9.8, regardless of the participant retention methods undertaken at each study site, participants may voluntarily withdraw from the study for any reason at any time. The protocol also allows, however, for participants who voluntarily withdraw from the study to reverse their decision and re-join the study during their planned 21-week follow-up period, resume study procedures and follow-up at the investigator's decision. If such cases arise, study staff are advised to contact the MTN CORE and SDMC for additional guidance on how to manage various aspects of protocol implementation and data collection as the participant resumes participation in the study. In general, however, the following instructions and requirements should be adhered to:

- The participant's original PTID and follow-up visit schedule will remain unchanged. Her random assignment also will remain unchanged and she will continue product use per her random assignment.
- An interval (since the last visit) medical/menstrual history should be taken and a pregnancy test should be performed as soon as the participant resumes study participation. Product use will be resumed only among participants who are not currently pregnant or within 90 days of last pregnancy outcome.
- A pelvic exam should be performed as soon as possible, and prior to re-instating gel use. A pelvic exam and other clinically-indicated evaluations also should be performed if the participant reports current genital symptoms. Gel use will be reinstated (if applicable) only after any genital symptoms have resolved, any STIs/RTIs requiring treatment per World Health Organization guidelines have been treated, and any pelvic exam findings involving deep epithelial disruption have resolved.
- If the participant missed her last scheduled HIV counseling and testing, it should be performed as soon as possible. Product use will only be re-instated for participants who are confirmed as HIV-uninfected per the algorithm in Figure 6-3.
- Clinic staff will communicate any re-instatement of product use to the study pharmacy in writing, using the MTN 001 Study Product Prescription.

6.12 Study Exit Considerations

Procedural requirements for conducting study exit visits are specified in protocol Sections 7, Table 8 and 7.13; further procedural guidance is incorporated in the Study Termination Visit checklist in Section 7 of this manual. Provided in the remainder of this section is additional information related to key aspects of study exit visits.

6.12.1 Certificate of Completion

All study sites are strongly encouraged to provide each participant who completes a scheduled study exit visit with a certificate of study completion. Sample certificates which may be tailored for use at each site are available on the MTN 001 web page:

<http://www.mtnstopshiv.org/node/71>.

As “written information to be provided to subjects,” certificates should be approved by site IRBs/ECs prior to use.

6.12.2 Participant Locator Information

As described in greater detail in Section 6.12.9, accurate participant locator information will be needed for post-study contact with study participants. As such, locator information should be actively reviewed and updated at all study exit visits and all participants should be counseled to contact the study site should their locator information change after study exit.

6.12.3 Final Study Contacts

Although the study exit visit is the last scheduled study visit, a final contact is required after the exit visit to provide the participant with her final study test results, post-test counseling, and treatment, if needed. Additional contacts also are required for:

- Participants who are pregnant at study exit (see Section 6.8 above)
- Participants with positive or indeterminate HIV Western blot (WB) test results (see Section 6.12.4 below)
- Participants with certain types of AEs that are ongoing at study exit (see Section 6.12.7 below)

For each participant, a final contact should be scheduled based on the participant’s overall clinical picture at study exit, as well as the time required to obtain all final study test results. Study staff may complete final contacts at the study site, by telephone, or at community-based locations, depending on site capacities and site and participant preferences. It is recommended that final contact plans be documented on a study exit worksheet similar to the sample provided in Section Appendix 6-9.

All final contacts must be documented in participant study records, but no case report forms are completed for these contacts.

6.12.4 HIV Counseling and Testing

HIV testing is performed at the study exit visit per the algorithm in Figure 6-3. For participants with one or more positive rapid test results, WB testing will be performed on the blood sample collected at the exit visit. If the WB is positive or indeterminate, additional specimen collection and testing will be required to clarify or confirm the participant’s HIV status; therefore, additional visits will be required after the study exit visit. HIV pre- and post-test counseling provided at the study exit visit should emphasize that additional counseling and testing will be provided to the participant after her study exit visit if needed to clarify or confirm her HIV status.

6.12.5 Plasma Archive

All anticoagulated blood remaining in the lavender top (EDTA) tube after HIV testing is performed at the study exit visit should be processed within 24 hours of collection into at least four 0.5 mL aliquots of plasma (see Section 12 of this manual for more information).

6.12.6 Product Hold/Discontinuation

All participants are discontinued from product use at their study exit visits. Therefore, for all participants at the study exit visit, the End of Study Inventory (ESI) CRF and Termination (TM) CRF should be completed and all unused product supplies should be collected from the participant and returned to the study pharmacy on the day of collection. In addition, clinic staff should add the participant's PTID to a cumulative listing of participants who have exited the study which should then be provided to pharmacy staff on a weekly basis.

Participants should be reminded to bring all unused product supplies to their exit visits. For participants who do not bring all unused supplies to their exit visits, arrangements must be made to collect the remaining supplies as soon as possible. It is recommended that plans to collect remaining product supplies be documented on a study exit worksheet similar to the sample provided in Section Appendix 6-9. If the study product is not collected within five working days after the study exit visit, the MTN 001 Protocol Safety Review Team (PSRT) must be informed, using the PSRT Query Form. When informing the PSRT, please describe the reason for the product hold (i.e., study exit), actions taken to try to collect the unused product, and plans and timelines for further action to collect the product.

6.12.7 AE Management and Documentation

All AE Log forms completed for each participant should be reviewed at the study exit visit and updated as needed. For AEs that are ongoing at the exit visit, the status/outcome of the AE should be updated to "continuing at end of study participation" and the AE Log form should be re-faxed to SCHARP DataFax.

For any serious or expedited AEs (SAEs/EAEs) that are continuing at a participant's study exit visit, the IoR/designee must establish a clinically appropriate follow up plan for the AE (see Section 11.1 of this manual for more information on SAEs and EAEs). At a minimum, the AE must be re-assessed by study staff 30 days after the participant's study exit visit; additional evaluations also may take place at the discretion of the IoR/designee. The same approach must be taken for any AEs that are found to have increased in severity at the study exit visit. It is recommended that AE follow-up plans be documented on a study exit worksheet similar to the sample provided in Section Appendix 6-9.

For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment will be re-assessed at least once within the 30-60 days after the study end date. The MTN 001 PSRT may advise study staff as to whether any additional follow-up may be indicated on a case by case basis.

For AEs that are re-assessed after study exit, information on the status of the AE at the time of re-assessment will be recorded in source documents only — no updates should be made to AE Log case report forms based on the re-assessments. All information related to the re-assessment of AEs should be documented in the participant's chart notes, including all efforts to contact the participant.

6.12.8 Referral to Non-Study Service Providers

After completing their study exit visits and final study contacts, participants will no longer have routine access to services provided through the study, such as reproductive health care and HIV counseling and testing. Participants should be counseled about this — ideally before and during their study exit visits — and provided information on where they can access such services after study exit. It is strongly recommended that all study sites develop a sample script which can be used when discussing this issue with exiting participants, as well as written referral sheets that can be given to participants at their study exit visits (after obtaining IRB/EC approval of the written information). A sample script which may be tailored for use at each site is provided in Section Appendix 6-10.

6.12.9 Post-Study Contacts

It is expected that all participants will be re-contacted by study staff approximately three to nine months after study completion, when it is expected that study results will be available for dissemination to all participants.

To facilitate post-study contact with participants, locator information should be updated at the study exit visit, and participants should be counseled to contact the study site should their locator information change after study exit. In addition, participant preferences for methods to be used for contacting them when study results are available should be documented in participant study records. It is recommended that participant preferences be recorded on a study exit worksheet similar to the sample provided in Section Appendix 6-9.

Lastly, for participants whom study staff may wish to contact regarding participation in future studies, permission for such contact should be sought from the participant and documented. It is recommended that participant permission (or lack thereof) for future studies be documented on a study exit worksheet similar to the sample provided in Section Appendix 6-9. In addition, for ease of retrieving information on participant permissions, it is recommended that study staff maintain future study contact permission logs similar to the examples provided in Section Appendix 6-11.

Section Appendix 6-1
Follow-up Visit Scheduling Scenarios for MTN 001

6.1	Suppose Miss X enrolls in the study on 3 April. What are the target dates for her visits in study weeks 3, 6, 7, and 10?		
		<u>Target</u>	
	3-Week	24 April	
	6-Week	15 May	
	7-Week	22 May	
	10-Week	12 June	
	Why? Target dates are set based on the participant's study enrollment date (day 0) and occur at 3, 6, 7, 10, 13, 14, 17, 20, and 21 weeks after enrollment.		
6.2	Continuing from scenario 6.1, what are the allowable and target windows for this participant?		
		<u>Target Window</u>	<u>Allowable Window</u>
	3-Week	21-27 April	4 April – 4 May
	6-Week	12-18 May	5 May – 18 May
	7-Week	19-25 May	19 May – 1 June
	10-Week	9-15 June	2-22 June
	Why? The allowable visit windows are contiguous from visit to visit starting with the day after enrollment (day 1), and do not overlap. Within each allowable visit window, there is a target visit window. The target visit window is the same for each visit, equal to +/- 3 days around the target visit date.		
6.3	Suppose Miss X completes her 3-Week visit on 21 April. What are the target and allowable dates for her visits in study weeks 6, 7, and 10?		
		<u>Target</u>	<u>Allowable</u>
	6-Week	15 May	5 May – 18 May
	7-Week	22 May	19 May – 1 June
	10-Week	12 June	2-22 June
	Why? Target dates always remain linked to the enrollment date. Target dates do not shift when a previous visit does not take place on the target date.		
6.4	Suppose Miss X does not complete her 6-Week visit on the target date of 15 May, but presents to the study site on 17 May. What do you do?		
	<ul style="list-style-type: none"> • Complete a 6-Week visit per protocol on 17 May. 		
	Why? 17 May is within the allowable 6-Week visit window.		
6.5	Suppose Miss X does not complete her 6-Week visit between 5 May and 18 May, but presents to the study site on 19 May. What do you do?		
	<ul style="list-style-type: none"> • On 18 May, consider the 6-Week visit missed. • On 19 May, complete a 7-Week visit per protocol. 		
	Why? The 6-Week visit window closed on 18 May, but the 7-Week visit window opened on 19 May.		

Section Appendix 6-1
Follow-up Visit Scheduling Scenarios for MTN 001

6.6	<p>Suppose Miss X completes all her 7-Week visit procedures on 24 May, but presents to the study site on 26 May to report genital bleeding. What do you do?</p> <ul style="list-style-type: none"> • On 26 May, complete interim visit required procedures, including a pregnancy test. • Perform pelvic exam to assess Miss X symptoms and manage accordantly. • Complete necessary documentation such as chart notes and AE log form. • Confirm and reinforce the scheduling of Miss X's 10-Week visit. <p>Why? The 7-Week visit procedures were completed, and the window for the 10-Week visit does not open until 2 June. Appendix I of the protocol lists the procedures that are required at each interim visit.</p>
6.7	<p>Continuing from scenario 6.6, suppose Miss X comes to the study site for follow-up on the genital bleeding on 3 June. What do you do?</p> <ul style="list-style-type: none"> • On 3 June, complete a 10-Week visit per protocol. <p>Why? The 10-Week visit opened on 2 June. A pelvic is a required procedure at the 10-Week study visit. Clinician should assess whether or not the genital bleeding has resolved and update documentation as appropriate.</p>
6.8	<p>Suppose Miss X does not complete her 6-Week visit between 5 May and 18 May, but presents to the study site on 19 May. What do you do?</p> <ul style="list-style-type: none"> • On 18 May, consider the 6-Week visit missed. • On 19 May, complete a 7-Week visit per protocol. • Additionally during the pelvic exam, collect swab for wet mount and assess vaginal pH specified for the missed 6-Week visit. <p>Why? The 6-Week visit window closed on 18 May and the 7-Week visit window opened on 19 May. When End-of-Study-Period visits are missed, during the pelvic exam at the next visit, you need to assess vaginal pH and collect vaginal fluid for wet mount.</p>
6.9	<p>Suppose Miss X presents to the study site for her 7-Week visit on 20 May, and completes some but not all of the protocol-specified procedures for 7-Week visits. What do you do?</p> <ul style="list-style-type: none"> • Document all procedures performed on 20 May as usual. Explain in chart notes why all protocol-specified procedures were not completed. • Schedule Miss X to return to the study site as soon as possible to complete the remaining 7-Week procedures. • When Miss X returns to the study site, provided the 7-Week visit window has not elapsed, perform an interval medical/menstrual history and pregnancy test, and all remaining 7-Week visit procedures. • Take care to document the actual date of all procedures performed in visit chart notes, on visit checklists, and all other documents and forms. • Confirm and reinforce the scheduling of Miss X's 10-Week visit. <p>Why? Since Miss X could not complete all protocol-specified procedures in a single visit, her 7-Week visit is considered a split visit. Split visits may be conducted over two or more days, provided the allowable visit window does not elapse. DataFax forms completed for all parts of a split visit are assigned the same scheduled visit code.</p>

Section Appendix 6-1
Follow-up Visit Scheduling Scenarios for MTN 001

<p>6.10 Suppose Miss X presents to the study site for her 13-Week visit on 28 June, and has to leave the site before completing some but not all of the protocol-specified PK procedures for 13-Week visits. What do you do?</p> <ul style="list-style-type: none">• Document all procedures performed on 28 June as usual. Explain in chart notes why all protocol-specified procedures were not completed, and all efforts to complete these procedures during this visit, including participant counseling.• Schedule Miss X to return to the study site as soon as possible (taking into consideration the visit window) to complete the remaining 13-Week procedures.• When Miss X returns to the study site, provided the 13-Week visit window has not elapsed, perform an interval medical/menstrual history and pregnancy test, and all remaining 13-Week visit procedures, <u>except</u> PK procedures.• Take care to document the actual date of all procedures performed in visit chart notes, on visit checklists, and all other documents and forms.• Confirm and reinforce the scheduling of Miss X's 14-Week visit. <p>Why? Since Miss X could not complete all protocol-specified procedures in a single visit, her 13-Week visit is considered a split visit. PK procedures cannot be completed at a later visit because some of the procedures had already started and PK procedures cannot be split.</p>	
<p>6.11 Re-considering scenario 6.10, suppose Miss X presents to the study site for her 13-Week visit on 28 June, and during registration informs the staff that she can only stay for a few hours and cannot complete all the procedures for 13-Week visit. What do you do?</p> <ul style="list-style-type: none">• Document all procedures performed on 28 June as usual. Explain in chart notes why all protocol-specified procedures were not completed.• If PK procedures cannot be completed all in one visit, do not start any PK procedures and complete these at the next visit.<ul style="list-style-type: none">○ For Non-US sites, if the participant is assigned to the 1-3 hours post-dose timing, it may be possible that there will be sufficient time to complete these procedures. Before any PK procedures are initiated, please ensure that it can be completed within this visit.• Schedule Miss X to return to the study site as soon as possible to complete the remaining 13-Week procedures, including PK procedures. Discuss with the participant the importance of completing these procedures and schedule the visit on a day that the participant will be available to complete all required procedures.• When Miss X returns to the study site, provided the 13-Week visit window has not elapsed, perform an interval medical/menstrual history and pregnancy test, and all remaining 13-Week visit procedures, including PK procedures.• Take care to document the actual date of all procedures performed in visit chart notes, on visit checklists, and all other documents and forms.• Confirm and reinforce the scheduling of Miss X's 14-Week visit. <p>Why? Since Miss X could not complete all protocol-specified procedures in a single visit, her 13-Week visit is considered a split visit. PK procedures can be done since procedures were not started on 28 June; therefore these were not split.</p>	

Section Appendix 6-2
Sample Participant Visit Tracking Sheet for MTN 001

Participant ID Number	
Participant Enrollment Date	

***Instructions:** The Participant Enrollment Date is defined as the date upon which an MTN 001 Randomization Envelope or an MTN 001 Replacement Randomization Document (for replacement participants) is assigned to the participant. Once the enrollment/randomization date is determined, enter target visit dates and allowable visit windows below. File this sheet with the participant's study chart and update it with scheduled and actual visit information at each visit.*

Follow-up Timepoint	Target Visit Date	Allowable Visit Window	Scheduled Visit Date	Actual Visit Date	Physical / Pelvic Exam Performed?	HIV Testing Performed?
Enrollment						
3-Week						
6-Week						
7-Week						
10-Week						
13-Week						
14-Week						
17-Week						
20-Week						
21-Week						

***Note:** This tracking sheet is not a source document. Information on this sheet is based on other source documents contained in the participant study chart.*

Section Appendix 6-3
MTN 001 Study Product Prescriptions

**MTN 001
ORAL TDF 300 MG TABLETS
PRESCRIPTION**

Instructions: All entries must be made in blue or black ink. Press firmly when completing this form. Corrections may be made by drawing a line through incorrect entries, recording correct information, and initialing and dating the correction.

Site Name:		Site Number:	
Site Location:			

Participant ID: -

Study Period: (check one) Sequence: ____

- Study Period 1
- Study Period 2
- Study Period 3

Tenofovir Disoproxil Fumarate 300 mg tablets

30

Directions: 1 tablet by mouth once each day before the longest period of rest (usually at night).

Refill/Repeat ____

Note to Pharmacist: May dispense 1 additional Tenofovir Disoproxil Fumarate 300 mg tablet if needed on day of pK visit without a new prescription.

Authorized Prescriber Name or ID (please print): _____

Authorized Prescriber Signature: _____

Date: - -
dd MMM yy

Clinic Staff Instruction: Deliver top copy to pharmacy. File bottom copy in participant study notebook.

**MTN 001
VAGINAL TENOFOVIR 1% GEL
PRESCRIPTION**

Instructions: All entries must be made in blue or black ink. Press firmly when completing this form. Corrections may be made by drawing a line through incorrect entries, recording correct information, and initialing and dating the correction.

Site Name:		Site Number:	
Site Location:			

Participant ID:

Study Period: (*check one*) Sequence: _____

- Study Period 1
- Study Period 2
- Study Period 3

**Tenofovir 1% Gel (*14 pre-filled applicators per carton*)
2 cartons**

Directions: Insert entire contents of one applicator vaginally once each day before the longest period of rest (usually at night).

Refill/Repeat _____

Note to Pharmacist: May dispense 1 additional applicator containing tenofovir 1% gel if needed on day of pK visit without a new prescription.

Authorized Prescriber Name or ID (*please print*): _____

Authorized Prescriber Signature: _____

Date:
 dd *MMM* *yy*

Clinic Staff Instruction: Deliver top copy to pharmacy. File bottom copy in participant study notebook.
--

Section Appendix 6-4
Study Product Request Slip

MTN 001 STUDY PRODUCT HOLD/RESUME/pK SUPPLY/RE-SUPPLY SLIP

Participant ID:

- -

Randomization Envelope #

Clinic Staff Instruction: Mark whether this is a product hold, resume or permanent discontinuation request. Sign and date. Deliver top copy to pharmacy. File bottom copy in participant study notebook.

<input type="checkbox"/> HOLD (Mark all products that apply)	<input type="checkbox"/> TEMPORARY	<input type="checkbox"/> PERMANENT
<input type="checkbox"/> Tenofovir 1% gel (vaginal)		
<input type="checkbox"/> TDF tablets (oral)		
<p>Pharmacy: For temporary holds, do not dispense study product marked above unless/until another Product Request Slip marked "RESUME" is received in addition to a new prescription. For permanent holds, do not dispense any further study product marked above.</p>		
<hr/>		
<input type="checkbox"/> RESUME (Mark all products that apply)		
<input type="checkbox"/> Tenofovir 1% gel (vaginal)		
<input type="checkbox"/> TDF tablets (oral)		
<p>Clinic: A new prescription must be completed for the appropriate study product and sent with this slip to pharmacy.</p>		
<hr/>		
<input type="checkbox"/> pK SUPPLY (Mark all products that apply)		
<input type="checkbox"/> Tenofovir 1% gel (vaginal) – Dispense one applicator		
<input type="checkbox"/> TDF tablets (oral) – Dispense one tablet		
<hr/>		
<input type="checkbox"/> RE-SUPPLY (Mark all products that apply)		
<input type="checkbox"/> Tenofovir 1% gel (14 pre-filled applicators per carton) Dispense 2 cartons		
<input type="checkbox"/> Tenofovir Disoproxil Fumarate 300 mg Dispense 30 tablets		
<hr/>		
Clinic Staff Name (please print): _____		
Clinic Staff Signature: _____		
Date: <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		
<p style="text-align: center;"><i>dd MMM yy</i></p>		

Section Appendix 6-5
Product Use Management Scenarios for MTN 001

6.12 **One day after receiving two cartons of study gel, a participant returns to the clinic to report that she left both cartons on the bus that she took home from the clinic. What do you do?**

Clinic Staff: Document the participant report and complete a vaginal tenofovir gel prescription for the participant. Send an official communication, per site SOP, to the pharmacy stating that the participant lost the supplies she received on the previous day and additional gel needs to be supply. Provide and document follow-up instructions and counseling to avoid further loss of gel supplies.

If the participant repeatedly reports loss of study product, or there is any other reason to suspect that she is sharing or selling her product, inform the Investigator of Record and/or other designated site supervisory staff so that appropriate follow-up action can be taken. Document the situation and action taken in signed and dated chart notes. For informational purposes, inform the MTN CORE Clinical Research Managers, SDMC Project Managers, and site Pharmacist of Record (PoR) of all cases of suspected gel sharing or selling; the PoR will inform the DAIDS Protocol Pharmacist.

Pharmacy Staff: Upon receipt of the new prescription, dispense gel per standard procedures and file the communication from the clinic explaining why additional product was dispensed.

Section Appendix 6-5
Product Use Management Scenarios for MTN 001

6.13 Suppose Miss X is randomized on 2 September 2008 and has the following sequence of follow-up visits and pregnancy tests:

<u>Study Visit</u>	<u>Visit Date</u>	<u>Pregnancy Test Result</u>
Week 3	23 September 08	POSITIVE
Week 6	14 October 08	NEGATIVE

Also suppose Miss X reports no action taken or symptoms experienced with regard to the pregnancy loss between Weeks 3 and 6. What actions are required at the Week 3 and 6 visits?

Week 3: In addition to all other routinely required procedures for Week 3 visits, initiate a Pregnancy Management Worksheet. Complete and fax a Pregnancy Report and History form and a Product Hold/Discontinuation form to SCHARP. Complete an MTN 001 Study Product Hold/Resume/PK Supply Slip marked "HOLD" and "PERMANENT" for both products to inform pharmacy staff of the product hold and that no further product will be dispensed for this participant. Arrange to retrieve all remaining product supplies from Miss X as soon as possible and within 5 days. Continue to use the Pregnancy Management Worksheet to guide and track further action.

All protocol-specified study procedures will continue except:

- Product dispensation
- Product use counseling
- PK assessment

Week 6: The negative pregnancy test at this visit is considered the outcome of the pregnancy identified at Week 3. In addition to all other routinely required procedures for Week 6 visits, complete and fax a Pregnancy Outcome form and an AE Log form to SCHARP (pregnancy outcome date = 14 October 08, AE term = spontaneous abortion). Indicate in the comments section of the Pregnancy Outcome form that the outcome date is based on a pregnancy test performed by study staff. Complete and submit an EAE form to the DAIDS Safety Office within three business days.

- NOTE: Participants who become pregnant during the course of the study will discontinue permanently all study product(s).

Section Appendix 6-5
Product Use Management Scenarios for MTN 001

6.14 Suppose Miss X is randomized in the study on 12 June 2008. During screening and enrollment, she reports that she is not breastfeeding; however, on her 3-Week study visit on 9 July she is seen breastfeeding her baby while seated in the waiting room. What you do?

- Counsel the participant about the unknown effects of tenofovir on breast milk and thoroughly document the incident and participant counseling on the chart notes.
- Complete and fax a Product Hold/Discontinuation form to SCHARP. Complete an MTN 001 Study Product Hold/Resume/PK Supply Slip marked “HOLD” and “PERMANENT” and choose both products to be permanently discontinued, to inform pharmacy staff of the product hold and that no further products will be dispensed for this participant. Arrange to retrieve all remaining product supplies from Miss X as soon as possible and within 5 days.

All protocol-specified study procedures will continue except:

- Product dispensation
- Product use counseling
- PK assessment

6.14 Suppose Miss X is randomized to sequence C (Oral + Vaginal, Oral, Vaginal) on 3 April 2008. At 10-Week study visit, her liver function test shows an elevation in ALT of Grade 3. What you do?

- Carefully assess if the elevation could be due to other reasons such as alcohol, hepatitis, or non-study medications.
- Conduct an HBsAg test and assess for signs or symptoms of clinical hepatic to determine if participant may be infected with hepatitis. If participant tests positive for Hepatitis B, all product should be permanently discontinued.
- Complete and fax a Product Hold/Discontinuation form to SCHARP. Complete an MTN 001 Study Product Hold/Resume/PK Supply Slip marked “HOLD” and “PERMANENT” to inform pharmacy staff of the product hold and that no further oral product will be dispensed for this participant. Arrange to retrieve all remaining product supplies from Miss X as soon as possible and within 5 days.
- Re-check ALT levels as soon as possible (at most within one week) and continue weekly testing until levels are Grade 1 or below. If ALT levels are Grade 1 or below prior to her 13 Week visit, product could be restarted with close follow-up and in consultation with the PSRT. If levels have not returned to Grade 1 or below within three weeks, oral product must be permanently discontinued.

Section Appendix 6-5
Product Use Management Scenarios for MTN 001

6.15 Continuing from scenario 6.14, suppose Miss X comes for follow-up testing on 8 July and her ALT level are Grade 0. What you do?

- On 8 July, the window for 14-Week study visit has opened; conduct 14-Week visit procedures.
- If participant has no other conditions that would contraindicate dispensing of study product, complete a vaginal tenofovir gel prescription and dispense two cartons of study gel, per participant's randomization sequence
- Confirm and reinforce the scheduling of Miss X's 17-Week visit.

Section Appendix 6-6
Follow-up HIV Testing Scenarios for MTN 001

6.13 Suppose Miss X's rapid HIV test is positive at Week 7. What do you do?

- Record the rapid test result on the Follow-up Laboratory Results form for the Week 7 visit.
- At the Week 7 visit, counsel Miss X that her initial HIV test indicates that she may be infected with HIV, but that an additional test (that requires N days to complete) is required to verify the result.
- Deliver Miss X's blood sample to the local lab for WB testing. Note that this testing is performed on the same sample that tested positive on the rapid test (sample 1).
- Schedule another visit to take place when Miss X's WB result will be available.
- Complete and fax a Product Hold/Discontinuation form to SCHARP. Complete an MTN 001 Study Product Hold/Resume/PK Supply Slip marked "HOLD" and "PERMANENT" to inform pharmacy staff of the product hold and that no further product will be dispensed for this participant.
- Arrange to retrieve all remaining product supplies from Miss X immediately.

6.14 Continuing from Scenario 6.18 suppose Miss X's WB is negative. What do you do?

- Record the WB result on an HIV Test Results form.
- When Miss X returns for her test result, counsel her that her test indicates that she is not infected with HIV.

If the return visit takes place before Miss X's Week 10 visit window has opened, consider the visit an interim visit. Confirm and reinforce the scheduling of Miss X's next scheduled (Week 10) visit.

OR

If the return visit takes place after Miss X's Week 10 visit window has opened, additionally conduct the Week 10 visit per protocol (if possible).

6.15 Continuing from Scenario 6.18, suppose Miss X's WB is indeterminate. What do you do?

- Record the WB result on an HIV Test Results form.
- When Miss X returns for her test result:
 - Counsel her that her tests continue to indicate that she may be infected with HIV, but the second test did not confirm her status for sure, so you must collect another blood sample for additional testing (that requires N days to complete) to confirm whether she is infected or not.
 - Collect blood (sample 2) and deliver it to the local lab for WB testing and plasma archive.
 - Schedule another visit to take place when Miss X's WB test result will be available.

If the return visit takes place before Miss X's Week 10 visit window has opened, consider the visit an interim visit. Confirm and reinforce the scheduling of Miss X's next scheduled (Week 10) visit.

OR

If the return visit takes place after Miss X's Week 10 visit window has opened, additionally conduct the Week 10 visit per protocol (if possible).

Section Appendix 6-6
Follow-up HIV Testing Scenarios for MTN 001

6.16 Continuing from Scenario 6.18, suppose Miss X's WB is positive. What do you do?

- Record the WB result on an HIV Test Results form.
- When Miss X returns for her test result:
 - Counsel her that her tests indicate that she is infected with HIV, and although you are confident that her test result is correct, you need to collect another blood sample for an additional test to be absolutely sure about the results (e.g., to rule out specimen mix-up or other errors).
 - Collect blood (sample 2) and deliver it to the local lab for WB testing and plasma archive.
 - Provide counseling and referral services for psychosocial and medical needs
 - Schedule another visit to take place when Miss X's WB test result will be available.

If the return visit takes place before Miss X's Week 10 visit window has opened, consider the visit an interim visit. Confirm and reinforce the scheduling of Miss X's next scheduled (Week 10) visit.

OR

If the return visit takes place after Miss X's Week 10 visit window has opened, additionally conduct the Week 10 visit per protocol (if possible).

6.17 Continuing from Scenario 6.20 or 6.21, suppose Miss X's sample 2 WB is either negative or indeterminate. What do you do?

- Record the WB result on the HIV Test Results form on which Miss X's sample 1 WB result has been recorded.
- Inform the MTN NL of Miss X's test results via email (copied to the MTN CORE and SDMC) and seek guidance on how best to clarify the participant's HIV status.
- When Miss X returns for her test result:
 - Counsel her that her HIV status remains unclear.
 - Collect blood (sample 3) for further testing per NL guidance.
 - Schedule another visit to take place when Miss X's test results will be available.

If the return visit takes place before Miss X's Week 10 visit window has opened, consider the visit an interim visit. Confirm and reinforce the scheduling of Miss X's next scheduled (Week 10) visit.

OR

If the return visit takes place after Miss X's Week 10 visit window has opened, additionally conduct the Week 10 visit per protocol (if possible).

Section Appendix 6-6
Follow-up HIV Testing Scenarios for MTN 001

6.18 Continuing from Scenario 6.20 or 6.21, suppose Miss X's sample 2 WB is positive. What do you do?

- Record the WB result on the HIV Test Results form on which Miss X's sample 1 WB result has been recorded.
- When Miss X returns for her test result, counsel her that the test confirmed that she is infected with HIV.
- Provide counseling and referral services for psychosocial and medical needs
- Since Week 7 is the participant's first follow-up HIV testing timepoint, test her plasma archived at enrollment for evidence of HIV infection (see Section 12 of this manual).

If the return visit takes place before Miss X's Week 10 visit window has opened, consider the visit an interim visit. Confirm and reinforce the scheduling of Miss X's next scheduled (Week 10) visit.

OR

If the return visit takes place after Miss X's Month 4 visit window has opened, conduct the Week 10 visit per protocol (if possible).

6.19 Suppose Miss X tests positive for HIV on her sample 1 rapid test and WB, but does not return to the study site to receive her WB result. What do you do?

- Make every effort to locate Miss X, provide her result and post-test counseling and obtain a second blood sample for confirmatory WB testing.

Why? From a human subjects and HIV prevention perspective, it is critical that Miss X receive her test result and post-test counseling. From a study perspective, it is critical that Miss X's HIV infection status be confirmed with a second WB, since only participants with two positive WB results will be counted in study analyses as having become HIV-infected. As such, among all participants targeted at a given time for tracing and other locator/retention efforts, participants with a positive WB result should be given highest priority.

Section Appendix 6-8
Sample Pregnancy Management Worksheet for MTN 001

PARTICIPANT ID:			
BACKGROUND INFORMATION			
First day of last menstrual period			
Date of positive pregnancy test			
Estimated week 24 and full term pregnancy dates		Week 24:	Full Term:
PREGNANCY MANAGEMENT INFORMATION		Mark ✓ When Done	Initials/Date/Comments
1	Pregnancy Report and History form completed and faxed to SCHARP		
2	Pharmacy informed of pregnancy		
3	Product supplies retrieved from participant and returned to pharmacy		
4	Product Hold/Discontinuation form completed (items 1-3) and faxed to SCHARP		
5	Pregnancy outcome and outcome date ascertained, based on: <input type="checkbox"/> medical records or other written documentation from a licensed non-study health care practitioner <input type="checkbox"/> participant self-report <input type="checkbox"/> negative pregnancy test performed by study staff <input type="checkbox"/> other (specify in comments) <i>(medical records should be obtained whenever possible)</i>		
6a	Pregnancy Outcome form completed and faxed to SCHARP		
6b	If applicable, AE Log form completed and faxed to SCHARP		
6c	If applicable, EAE Report completed and faxed to DAIDS Safety Office		

**Section Appendix 6-9
MTN 001 Study Exit Worksheet**

PTID:	Exit Visit Date:
Plan for providing participant with final study test results	
Method by which participant wishes to be contacted when study results are available	
<p>Does participant have study product remaining in her possession?</p> <input type="checkbox"/> No, per participant report, all product supplies have been used/collected/returned <input type="checkbox"/> Yes ⇒ describe plan for product collection (continue on back if needed)	
<input type="checkbox"/> Completed _____	
<p>Is participant currently pregnant?</p> <input type="checkbox"/> No <input type="checkbox"/> Yes ⇒ describe plan for ascertaining pregnancy outcome (continue on back if needed)	
IoR approval: _____ <input type="checkbox"/> Completed: _____	
<p>Does participant have any ongoing SAEs/EAEs or any AEs found to have increased in severity at this visit?</p> <input type="checkbox"/> No <input type="checkbox"/> Yes ⇒ describe plan for AE follow-up (continue on back if needed)	
IoR approval: _____ <input type="checkbox"/> Completed: _____	
<p>Is participant willing to be contacted about future studies for which she may be eligible?</p> <input type="checkbox"/> No <input type="checkbox"/> Yes	
Staff Signature and Date:	

Section Appendix 6-10 Sample Script for Study Exit Visits

Before we finish your visit today, I would like to take some time to sincerely thank you for taking part in this study. By taking part, you have made an important contribution to the fight against HIV/AIDS. In recognition of this contribution, I would like to present you with this certificate of completion which you can take with you today.

I also would like to review a few more details with you:

- *If applicable, reinforce plans to collect remaining product supplies.*
- Your appointment to receive your final exam and test results is scheduled for [date]. This appointment will take place [here at the clinic / other specify]. If you need to change this appointment for any reason, please contact us to let us know.
- Although your scheduled study visits have now been completed, the study is planned to be ongoing for another [X] months. After that, we expect it will take about 9 months to have the results of the study available to share with all study participants. In order for us to share this information with you, we need to be able to keep in touch with you. Therefore we ask you to please inform us if you move to a new home, change your phone number, or have any other new details that would help us keep in touch with you. [Give contact card.]
- As you know, [project name] is involved in many different types of research studies. We would like to be able to contact you in the future about other studies that you may be eligible for. Are you willing to give us your permission to do that? [Record response on study exit worksheet; if permission is granted, explain that information recorded on the participant's locator form would be used for this purpose and enter participant on future contact permission log.]
- *If applicable, reinforce plans to determine pregnancy outcome.*
- *If applicable, reinforce plans for AE follow-up.*
- Lastly, we would like to give you some information on places where you can go for different types of services now that you will not be coming here for regular study visits [give referral sheet]:
 - For HIV counseling and testing
 - For family planning and other reproductive health care
 - For other types of health care
 - Other
- *If applicable, replace above bullet with a discussion of plans for ongoing participation in MTN 015.*
- Please feel free to contact us if you have any questions about the study that we have not answered today, or if you encounter any problems related to your participation in the study. Once again, we sincerely thank you for your contributions to the study and we look forward to sharing the results with you when they become available.

Section 7. Visit Checklists

This section contains examples of checklists detailing the protocol-specified procedures that must be completed at MTN 001 study visits. The checklists also specify the data collection forms that must be completed at each visit. Detailed procedural guidance for performing clinical and laboratory procedures is provided in Sections 10 and 12, respectively. Detailed forms completion instructions are provided in Section 13.

7.1 Use of Checklists

The visit checklists included in this section are designed to guide site staff in proper study procedures as well as to serve as source documentation of procedures performed at study visits. Note, however, that checklists alone may not be sufficient for documenting all procedures. For example, chart notes may be required to:

- Explain why procedures in addition to those listed on a checklist were performed
- Explain why procedures listed on a checklist were not performed
- Document procedures performed at interim visits
- Document the content of counseling sessions and/or other in-depth discussions with participants (e.g., related to adherence to protocol requirements)

See Section 3 for detailed information on source documentation requirements. Tips for completing visit checklists in accordance with these requirements are as follows:

- Enter the participant identification number (PTID) and visit date in the top section of each checklist. If information is written on the front and back of the checklist, enter the PTID and visit date on both sides.
- For follow-up visits, mark the applicable visit in the top section of each checklist
- Enter your initials only beside the procedures that you perform. Do not enter your initials beside procedures performed by other staff members. If other staff members are not available to initial checklist items themselves, enter, initial, and date a note on the checklist documenting who completed the procedure, e.g., “done by {name}” or “done by lab staff.”
- If all procedures listed on a checklist are performed on the date entered in the top section of the form, the date need not be entered beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item.
- If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why on the checklist (if not self-explanatory); initial and date this entry.

7.2 Sequence of Procedures

The sequence of procedures presented on the visit checklists is a suggested ordering. In consultation with the MTN (FHI) CORE, site staff may modify the checklists included in this section to maximize the efficiency of site-specific study operations. Sites may alter the sequence of procedures to suit local staffing and logistical requirements, with the following exceptions:

- Informed consent for screening must be obtained before any screening procedures are performed.
- Informed consent for enrollment must be obtained before conduct of any study enrollment or follow-up procedures are performed. Enrollment procedures are listed in the Enrollment sub-sections of protocol Section 7
- Behavioral assessments must be administered prior to HIV/STI risk reduction, male condom counseling and study product adherence counseling.
- Pelvic procedures must be performed in the sequence shown on the pelvic exam checklists.

Screening Visit: Page 1 of 3

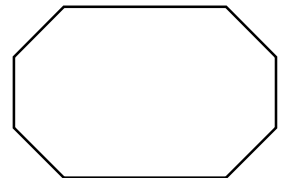
PTID:	Visit Date:
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1. _____ Confirm participant identity. Cross-check with the MTN 001 Participant Name-PTID Link Log to determine whether a MTN 001 Participant ID number has previously been assigned to the participant.
2. _____ Confirm whether the participant is between the ages of 18 and 45 (inclusive) per site SOP.
3. _____ Explain the two-step (screening and enrollment) informed consent process.
4. _____ Explain the content and sequence of procedures for the remainder of the visit.
5. _____ Administer and obtain screening informed consent with participant according to site SOPs. Complete Consent Process Worksheet.

➤ *If the participant does not consent to screening, STOP. Do not fax any forms to SCHARP.*

6. _____ Complete the **Screening Consent** form.

Based on the 30-day screening and enrollment window, beginning on the day informed consent is obtained for screening; enter the participant's last possible enrollment date for this screening attempt



7. _____ Assign an MTN 001 PTID (if not done during a previous screening attempt) by completing a new row in the MTN 001 Name-PTID Link Log.
8. _____ Collect approximately ~ 20 mL urine and:
 - 8a. _____ Aliquot approximately 5-10 mL and perform qualitative pregnancy test.
 - 8b. _____ Complete testing logs and record result on the **Screening Eligibility** form (non-DataFax).

*If the participant is pregnant, STOP. Inform the participant that she is ineligible. Retain documentation completed thus far, and complete the **Screening Summary** form, but do not fax any forms to SCHARP.*

- 8c. _____ Prepare urine for SDA for Gonorrhea and Chlamydia.

Screening Visit: Page 2 of 3

PTID:	Visit Date:
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- 8d. _____ Complete dipstick urinalysis using same aliquot as pregnancy test; record results for protein, nitrites and leukocytes on the **Safety Laboratory Results** form. Document results (e.g. blood, glucose), if any, in chart notes or other designated site specific document, if applicable. If dipstick urinalysis is positive for leukocytes or nitrites, provide treatment and/or additional UTI work-up per site SOP. Document treatment and/or additional work-up on the Concomitant Medications Log and in chart notes.
9. _____ Assess behavioral eligibility on the **Screening Eligibility and Clinical Eligibility** (non-DataFax) forms
10. _____ Provide HIV pre-test, HIV/STI risk reduction and condom counseling. Provide male condoms. *(Sites may chose to provide condoms at the end of the visit)*
11. _____ Collect blood: *(Sites to specify their site-specific volume for each tube)*
- Plain tube (no additive)
 - EDTA
12. _____ Perform HIV test
13. _____ Complete testing logs and transcribe rapid HIV test results onto the **Screening and Enrollment STI Laboratory Results** form. Before disclosing results to participant, obtain independent review, verification, and sign-off of both results.
14. _____ Provide rapid HIV test results in the context of post-test counseling. Provide referrals if needed/requested. Explain the participant's current study eligibility status.
- *If both rapid tests are negative, the participant is considered HIV-uninfected. Continue with remainder of this checklist.*
 - *If one rapid test is positive and one is one negative, WB testing is required to clarify the participant's HIV status. Continue with remainder of this checklist OR defer further screening procedures until status is clarified.*
 - *If both rapid tests are positive, the participant is considered HIV-infected. STOP. Inform the participant that she is ineligible. Retain documentation completed thus far, and complete the **Screening Summary** form, but do not fax any forms to SCHARP.*
15. _____ Prepare remaining blood for testing at the local lab:
- Syphilis serology
 - CBC (hemoglobin, hematocrit, WBC, PLT)
 - HIV-1 Western Blot (if indicated)
 - Serum Chemistries (Phosphorous, Creatinine)
 - Liver Function Tests (AST, ALT)

Screening Visit: Page 3 of 3

PTID:	Visit Date:
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Hepatitis B Surface Antigen

16. _____ Obtain contact information and record on site specific form.
 - *If the participant does not provide adequate contact information, per site-specific definition of adequate contact information, and is determined not to be a good candidate for the study (investigator decision) STOP. Inform the participant that she is ineligible. Retain documentation completed thus far, and complete the form, but do not fax any forms to SCHARP.*
17. _____ Administer the **Demographics** DataFax CRF.
18. _____ Conduct the Physical Exam and record results on the **Physical Exam** non-Data Fax form.
19. _____ Obtain medical, menstrual, and genitourinary history with documentation of current medications. Record on **Baseline Medical and Menstrual History** form (non-Data Fax) and **Concomitant Medications Log** Data Fax CRF.
20. _____ Perform and document pelvic exam using the Pelvic Exam checklist. Complete the Pelvic Exam Diagrams (non-Data Fax), **Screening and Enrollment Pelvic Exam** and **Pelvic Laboratory Results** DataFax CRFs. Treat or refer for treatment, if applicable.
21. _____ Provide contraceptive counseling. Provide and/ or refer for contraception, if applicable.
22. _____ Provide study informational material. Provide site contact information and instructions to contact the site for additional information and/or HIV/STI counseling, if needed, prior to the next visit.
23. _____ Schedule the Enrollment visit, taking into account the timing for receipt of lab results, the participant's menstrual cycle, and the 30-day screening period.
24. _____ Provide reimbursement.
25. _____ Document the visit in signed and dated chart notes. Complete the **Screening Summary** form and review all other participant chart contents for the visit, but do not fax any forms to SCHARP.

Screening Visit: Page 3 of 3

PTID:	Visit Date:
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- *Note: The **Screening and Enrollment STI Laboratory Results, Pelvic Laboratory Results, Safety Laboratory Results** forms (and **HIV Test Results** form, when applicable) should be completed when all required test results are available, prior to the Enrollment Visit. Do not fax any forms to SCHARP until the participant is randomized. If the participant's lab results indicate that she is HIV-positive per protocol Appendix II or has an active RTI and/or UTI – with the exception of asymptomatic BV and asymptomatic vulvovaginal candidiasis —she is ineligible for enrollment; retain all of these DataFax forms on site but do not fax any of them to SCHARP.*

Enrollment Visit: Page 1 of 5

PTID:	Visit Date:
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1. _____ Complete participant registration, confirm the participant's identity, and verify her PTID.
2. _____ Review/update locator information
3. _____ Confirm that the 30-day window has not been exceeded for the current screening attempt.
4. _____ Review chart notes and other relevant documentation from previous visit(s). Confirm the participant's current eligibility status based on all screening documentation.
5. _____ Confirm behavioral eligibility and record results on **Enrollment Eligibility** form
6. _____ Explain again the two-step informed consent process and obtain written informed consent for the study. Document the informed consent process in a chart note and on any other documents per site SOP.
*☞ If the participant does not consent to the study, complete the **Screening Summary** form and then STOP. Retain documentation completed thus far, but do not fax any forms to SCHARP.*
7. _____ Obtain written informed consent for specimen storage and possible future research testing. Document the informed consent process in a chart note and on any other documents per site SOP. Complete Consent Process Worksheet.
☞ Consent for specimen storage and possible future research testing is optional. If the participant does not consent, she may still take part in the study.
8. _____ Administer assessment of informed consent comprehension, utilizing comprehension checklist, according to local SOPs.
9. _____ Complete the **Screening Summary** form and items 1-2 of the **Enrollment** form.
10. _____ Collect ~20 mL first void urine and:
 - 10a. _____ Aliquot ~5 mL and perform pregnancy test.
 - 10b. _____ Complete testing logs and transcribe result here:
 negative positive
*☞ If the participant is pregnant, STOP. Inform the participant that she is ineligible. Retain documentation completed thus far, record results in the participant's chart notes, and complete the **Screening Summary** form. Do not fax any forms to SCHARP.*

Enrollment Visit: Page 2 of 5

PTID:	Visit Date:
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- 10c. ____ If clinically indicated, prepare urine for SDA for Gonorrhea and Chlamydia
11. ____ Administer the **Baseline Genital Symptoms** form.
12. ____ Review/update the **Baseline Medical and Menstrual History** and **Concomitant Medications Log**. Document review with a signed and dated note on each document reviewed. Initial and date updated entries.
13. ____ Complete the **Family Planning Methods** form by transcribing from the Baseline Medical and Menstrual History form the participants current contraceptive/family planning method (s).
14. ____ Provide contraceptive counseling. Provide or refer for contraception if applicable.
15. ____ If indicated, complete dipstick urinalysis using same aliquot as pregnancy test; record results for protein, nitrites and leukocytes on the Safety Laboratory Results form. Document results (e.g. blood, glucose), if any, in chart notes or other designated site specific document, if applicable. If dipstick urinalysis is positive for leukocytes or nitrites, provide treatment and/or additional UTI work-up per site SOP. Document treatment and/or additional work-up on the Concomitant Medications Log and in chart notes.
16. ____ Conduct physical exam as per Protocol Appendix III. Complete the **Physical Exam** (non-DataFax) form.
17. ____ Perform and document pelvic exam and CVL using the Pelvic Exam checklist. Complete the Pelvic Exam Diagrams (non-Data Fax), **Pelvic Exam and Pelvic Laboratory Results** datafax forms.
18. ____ Complete the **Clinical Eligibility** form
19. ____ If determined by site SOP, provide HIV pre-test counseling.
20. ____ Collect blood: (*Sites to include site-specific blood volume*)
 Plain tube (no additive)
 EDTA
21. ____ As determined by site SOP, perform HIV test
22. ____ If applicable, complete testing logs and transcribe rapid HIV test results onto the **Screening and Enrollment STI Laboratory Results** form. Before disclosing results to participant, obtain independent review, verification, and sign-off of both results.

Enrollment Visit: Page 3 of 5

PTID:	Visit Date:
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23. _____ If applicable, provide rapid HIV test results and post-test counseling. Provide referrals if needed/requested. Explain the participant's current study eligibility status.
- *If both rapid tests are negative, the participant is considered HIV-uninfected. Continue with remainder of this checklist.*
 - *If one rapid test is positive and one is one negative, WB testing is required to clarify the participant's HIV status. Continue with remainder of this checklist OR defer further screening procedures until status is clarified.*
 - *If both rapid tests are positive, the participant is considered HIV-infected. STOP. Inform the participant that she is ineligible. Retain documentation completed thus far, and complete the **Screening Summary** form, but do not fax any forms to SCHARP.*
24. _____ Prepare blood for testing at the local lab:
- CBC (hemoglobin, hematocrit, WBC, PLT)
 - Serum Chemistries (Phosphorous, Creatinine)
 - Liver Function Tests (AST, ALT)
 - Plasma storage
 - Syphilis serology, if indicated
 - HIV-1 Western Blot, if indicated
25. _____ Complete an **LDMS Specimen Tracking Sheet** for stored samples.
26. _____ Administer the **Enrollment Behavior Assessment**
☞ *This form must be administered prior to random assignment.*
27. _____ Provide HIV/STI risk reduction and condom counseling.
28. _____ **For non-replacement participants only:** obtain the next sequential Randomization Envelope and assign it to the participant by completing the row of the MTN 001 Randomization Envelope Tracking Record that corresponds to the next sequential envelope.
29. _____ **For non-replacement participants only:** open the assigned envelope and confirm that the envelope number printed on the MTN 001 Randomization Document contained inside the envelope corresponds with the envelope number on the outside of the envelope (envelope label). Complete the Randomization Document.
30. _____ **For replacement participants only:** obtain a blank Replacement Randomization Document and the completed Randomization Document (yellow copy) of the participant being replaced. Transcribe all of the randomization information from the Randomization Document of the participant being replaced

Enrollment Visit: Page 4 of 5

PTID:	Visit Date:
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onto the Replacement Randomization Document. Complete the remainder of the Replacement Randomization Document.

31. _____ Complete the MTN 001 prescription(s) that correspond to the participant's first study period (vaginal, oral, or dual use) per her study randomization. Deliver the Randomization Document (or Replacement Randomization Document, for replacement participants) and prescription(s) to the pharmacy according to Option A or B below. While waiting for product supplies to be delivered, continue with the remainder of this checklist.

OPTION A:

_____ Give the completed white original Randomization Document (or Replacement Randomization Document) and prescription(s) to the participant to deliver to the pharmacy (where she will obtain product supplies herself). Retain the envelope (for non-replacement participants) and the yellow clinic copy of both the Randomization Document (or Replacement Randomization Document) and the prescription(s) in the participant's study notebook.

_____ Document the amount of product the participant received here ⇒
[or in chart notes].

OPTION B:

_____ Optional: Fax a copy of the Randomization Document (or Replacement Randomization Document) and prescription(s) to the pharmacy.

_____ Deliver the completed white original Randomization Document (or Replacement Randomization Document) and prescription(s) to the pharmacy. Retain the envelope (for non-replacement participants) and the yellow clinic copy of both the Randomization Document (or Replacement Randomization Document) and the prescription(s) in the participant's study notebook.

_____ Receive requested product supplies.

_____ Provide product supplies to the participant.

_____ Document the amount of product provided to the participant here ⇒
[or in chart notes]

32. _____ Provide counseling related to the importance of participant's study participation and product use. Provide demonstration of gel applicator, instructions for gel use, and adherence counseling for participants randomized to the study gel only or dual use regimen for the first study period. Emphasize the unknown effectiveness of the study products and the importance of condom use for protection against HIV.

Enrollment Visit: Page 4 of 5

PTID:	Visit Date:
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- 32a. Counsel participants to abstain from sex 24 hours prior to the End-of-the-Study Visit, if possible.
33. _____ Once product supplies arrive, complete the remainder of the **Enrollment** form.
34. _____ Reinforce the instructions to contact the site to request additional product, if needed, prior to the next visit and remind the participant that she will be asked to return unused study product that she has remaining at her next visit.
35. _____ Provide male condoms and offer panty liners.
36. _____ Provide watch device and remind participant to record (on designated site specific document) the date and time of the 3 doses of study product she takes prior to her next study visit.
37. _____ Reinforce site contact information and instructions to contact the site to report symptoms — *especially genital symptoms* — and/or to request for additional information, HIV/STI counseling, and/or condoms, if needed, prior to the next visit.
38. _____ Explain the follow-up visit schedule and schedule her Week 3 clinic visit.
39. _____ Inform the participant of tests to be performed at the next visit. Also inform the participant of availability of HIV/STI counseling, testing, and STI treatment for partners.
40. _____ Treat or refer for findings as needed
41. _____ Provide reimbursement for study visit
42. _____ Complete the **Pre-Existing Conditions** form. Record all medical conditions that are ongoing at the time of participant randomization, based on source data collected throughout the screening process. Whenever possible, record a diagnosis rather than individual signs and symptoms. When this is not possible, record each individual sign or symptom. Do not record STIs or other infections that were fully treated prior to randomization. In the "comments" box for each condition, record as much information as possible on the severity and/or frequency of the condition at the time of participant randomization.
43. _____ Document the visit in a signed and dated chart note. Complete and review all participant chart contents from both the screening and enrollment visits, including the following non-Data Fax forms:

Screening Eligibility
Enrollment Eligibility

Enrollment Visit: Page 5 of 5

PTID:	Visit Date:
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Baseline Medical and Menstrual History
Physical Exam (x2)
Pelvic Exam Diagrams (x2)
Clinical Eligibility (x2)
Screening Summary
LDMS Specimen Tracking Sheet

44. _____ Fax all required DataFax forms to SCHARP:

Screening Consent
Demographics
Screening and Enrollment Pelvic Exam (x2)
Baseline Genital Symptoms
Screening and Enrollment STI Laboratory Results
Pelvic Laboratory Results* (x2)
Safety Laboratory Results* (x2)
Concomitant Medications Log
Family Planning Methods
Enrollment
Pre-Existing Conditions
Enrollment Behavior Assessment

☞ ***Pelvic Laboratory and Safety Laboratory Results forms are required for enrolled participants and MUST be completed, reviewed, and faxed to SCHARP once enrollment visit lab results are available. If HIV and/or other STI lab testing are conducted on samples collected at this visit, complete the **Screening and Enrollment STI Laboratory Results** form and the **HIV Test Results** form, if applicable.***

Follow-up Clinic Visits, Mid-Study Period Visit: Page 1 of 5

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>3-Week: _____ 10-Week: _____ 17-Week: _____</p>	

1. _____ Complete participant registration, confirm the participant’s identity, and verify her PTID.

2. _____ Review/update locator information.

3. _____ Review chart notes and other relevant documentation from previous visit(s).

4. _____ Explain the content and sequence of procedures for today’s visit.

5. _____ Review elements of informed consent as needed.

6. _____ Collect ~20 mL urine and:
 - 6a. _____ Aliquot ~5 mL and perform pregnancy test; retain remaining urine for remainder of visit.
 - 6b. _____ Complete testing logs and transcribe result onto the form.

If the participant is pregnant:

 - 6c. _____ Inform the participant that she must discontinue product use; arrange to collect her unused study product.
 - 6d. _____ Complete a MTN 001 Pregnancy Management Worksheet.
 - 6e. _____ Complete the Product Hold/Discontinuation Tracking Sheet (s), if applicable.
 - 6f. _____ Complete a **Study Product Hold/Resume/pK Supply/Re-Supply Slip**, marked “Permanent Discontinuation.” Deliver the completed white original to the pharmacy. Retain the yellow clinic copy in the participant’s study notebook.

7. _____ Collect unused study product to return to pharmacy. Document product collection in the chart notes. If participant did not bring the unused product at this visit, remind her to bring it for her next scheduled visit or make arrangements to collect the product.

8. _____ Provide and explain available exam and lab test results. Provide post-test counseling, if appropriate. Provide treatment for RTIs/STIs if needed. Document treatment on the **Concomitant Medications Log**.

9. _____ Record/transcribe the date and time of the participant’s last 3 doses of study product onto the **Study Product Adherence and Behavior Assessment** form.

10. _____ Administer the **Study Product Adherence and Behavior Assessment** form.

Follow-up Clinic Visits, Mid-Study Period Visit: Page 2 of 5

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>3-Week: _____ 10-Week: _____ 17-Week: _____</p>	

11. _____ Administer the **Follow-up Genital Symptoms** form.

12. _____ Perform interval medical/menstrual history; record findings on the **Follow-up Medical History Log** form. Record interval contraceptive/family planning method use and menstrual history in a visit chart note.
 - 12a. _____ Complete a **Genital Bleeding Assessment** form for unexpected genital bleeding.

13. _____ Review and update the **Concomitant Medications Log**, if applicable.

14. _____ Complete the **Family Planning Methods** form by transcribing (from the visit chart note) the participant's current contraceptive/family planning methods.

15. _____ Provide contraceptive counseling. Provide and/or refer for contraception, if applicable.

16. _____ Collect blood as follows and complete a **Pharmacokinetics –Non-Intensive** form: : (*Sites to include site-specific blood volume*)
 - Plain tube (no additive)
 - EDTA

17. _____ Complete an **LDMS Specimen Tracking Sheet** for stored samples.

18. _____ Prepare blood for testing/storage at the local lab.
 - Serum Chemistries (Phosphorous, Creatinine)
 - Liver Function Tests (AST, ALT)
 - Tenofovir levels

19. _____ Perform physical exam per Protocol Appendix III and record on the Physical Exam (non-DataFax) form.

20. _____ Perform pelvic exam using the Pelvic Exam Checklist and complete the Pelvic Exam Diagrams, **Follow-up Pelvic Exam** and **Pelvic Laboratory Results** (if indicated) forms.
 - 20a. _____ During exam, if applicable, assess genital symptoms reported during administration of the **Follow-up Genital Symptoms** form. Provide or refer for follow-up care as needed. Document follow-up in chart notes.

Follow-up Clinic Visits, Mid-Study Period Visit: Page 2 of 5

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>3-Week: _____ 10-Week: _____ 17-Week: _____</p> <p><i>Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit.</i></p>	

21. _____ If applicable, assess any non-genital symptoms reported in the participant’s interval medical/menstrual history. Provide or refer for follow-up care as needed. Document follow-up in chart notes.
22. _____ Complete/update **Adverse Experience Log** form(s) if required based on interval medical/menstrual history, clinical exams/assessments, and lab tests when available.
23. _____ If product use is held/discontinued or resumed at this visit, document the rationale for the hold/discontinuation or resumption in chart notes and/or on other applicable source documents, and on the Product Hold/Discontinuation Tracking Sheet(s), if applicable. Inform the site’s study pharmacist of the product hold/discontinuation or resumption by completing a **Study Product Hold/Resume/pK Supply/Re-Supply Slip** and delivering the white original to him/her. Retain the yellow clinic copy in the participant’s study notebook. If the hold, discontinuation, or resumption affects product use in the CURRENT study period, complete/update the **Product Hold/Discontinuation Log** form (for holds/discontinuations, complete one form per reason). Refer to Protocol Section 9.4 and the SSP Manual, Section 10, for guidelines on holding, discontinuing or continuing with study product. Contact PSRT if there are any questions about study product or clinical management.
24. _____ For all participants (unless product is held):
- 24a. _____ Complete a **Prescription** or a **Study Product Hold/Resume/pK Supply/Re-Supply Slip**.
 - 24b. _____ Follow your site-specific procedure for product re-supply.
 - 24c. _____ After product supplies are received, document the number of product provided here →
25. _____ Provide HIV/STI risk reduction, protocol and product use adherence, and male condom counseling. Provide condoms and panty liners.
26. _____ Schedule the next visit and inform the participant of what to expect. Remind the participant to abstain from having sex 24 hours prior to the next visit.
27. _____ Inform the participant of availability of HIV/STI counseling, testing, and STI treatment for partners.

Follow-up Clinic Visits, Mid-Study Period Visit: Page 4 of 5

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>3-Week: _____ 10-Week: _____ 17-Week: _____</p>	

- 28. _____ Reinforce the instructions to contact the site to request additional product, if needed, prior to the next visit and remind the participant that she will be asked to return all unused study product at her next visit.

- 29. _____ Reinforce site contact information and instructions to contact the site to report symptoms — especially genital symptoms — and/or to request for additional information, HIV/STI counseling, contraceptive counseling, and/or condoms, if needed, prior to the next visit.

- 30. _____ Provide study reimbursement

- 31. _____ Remind participant to record on her appointment card (or other designated site-specific document) the date and time of the last three doses of study product she takes prior to her next study visit.

Additionally Only If Clinically Indicated (C1-C4):

- C1. _____ Perform dipstick urinalysis on aliquot of used for pregnancy testing. Complete testing logs and transcribe protein, leukocyte, and nitrites results onto the **Safety Laboratory Results** form. Document other results (e.g., blood, glucose), if any, in visit chart note, or in other designated site-specific document, if applicable.

- C2. _____ Perform culture if positive for leukocyte esterase or nitrites; may omit if culture not standard of care for UTI diagnosis. Document additional work-up in visit chart note. If applicable, provide treatment and record on the **Concomitant Medications Log** form.

- C3. _____ Prepare urine for SDA for Gonorrhea and Chlamydia. Transcribe results onto the **STI Laboratory Results** form.

- C4. _____ Collect blood for Syphilis Serology and/or HBsAg. Transcribe results onto the **STI Laboratory Results** form.

- 32. _____ Complete the **Follow-up Visit** form.

- 33. _____ Complete and review all participant chart contents for the visit, including the following non-Data Fax forms:

Physical Exam
Pelvic Exam Diagram

Follow-up Clinic Visits, Mid-Study Period Visit: Page 5 of 5

PTID:	Visit Date:
Please indicate to which follow-up visit this checklist applies: 3-Week: _____ 10-Week: _____ 17-Week: _____	

LDMS Tracking Sheet

34. _____ Complete and fax all required Data Fax forms to SCHARP:

Follow-up Visit
Follow-up Genital Symptoms
Follow-up Pelvic Exam
Family Planning Methods
Safety Laboratory Results (when all results available)
Study Product Adherence and Behavior Assessment
Pharmacokinetics – Non-Intensive

As Needed:

Follow-up Medical History Log (update/add entries as applicable)
Pelvic Laboratory Results
HIV Test Results
Genital Bleeding Assessment
Concomitant Medications Log (required for updated or new pages)
Adverse Experience Log (required if any AEs identified or updated at this visit)
Product Hold/Discontinuation Log (required if product use in current study period is held/discontinued or resumed at this visit)
Pregnancy Report and History (required if pregnancy identified at this visit)
Pregnancy Outcome (required if pregnancy outcome ascertained at this visit)
STI Laboratory Results

Early Termination:

Termination
End of Study Inventory

Follow-up Clinic Visits, End of Study Period Visit: Page 2 of 5

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>6-Week: _____ 13-Week: _____ 20-Week: _____</p>	

1. _____ Complete participant registration, confirm the participant's identity, and verify her PTID.
2. _____ Review/update locator information.
3. _____ Review chart notes and other relevant documentation from previous visit(s).
4. _____ Review elements of informed consent as needed.
5. _____ Explain the content and sequence of procedures for today's visit.
6. _____ Collect ~20 mL urine and:
 - 6a. _____ Aliquot ~5 mL and perform pregnancy test; retain remaining urine for remainder of visit.
 - 6b. _____ Complete testing logs and transcribe result onto the form.

If the participant is pregnant:

 - 6c. _____ Inform the participant that she must discontinue product use; arrange to collect her unused study product.
 - 6d. _____ Complete a MTN 001 Pregnancy Management Worksheet (but do not complete a Product Hold/Discontinuation Log form at this time).
 - 6e. _____ Complete the Product Hold/Discontinuation Tracking Sheet(s), if applicable.
 - 6f. _____ Complete a **Study Product Hold/Resume/pK Supply/Re-Supply Slip**, marked "Permanent Discontinuation." Deliver the completed white original to the pharmacy. Retain the yellow clinic copy in the participant's study notebook.
7. _____ Collect unused study product. If participant did not bring unused product at this visit, remind her to bring it at her next scheduled visit or make arrangements to collect product.
8. _____ Provide and explain available exam and lab test results. Provide post-test counseling, if appropriate. Provide treatment for RTIs/STIs if needed. Document treatment on the **Concomitant Medications Log**.
9. _____ Observe a single AM dose of the study drug. If participant does not bring sufficient unused study product to visit for use as observed dose, study product will be dispensed to participant during study visit.

Follow-up Clinic Visits, End of Study Period Visit: Page 1 of 5

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>6-Week: _____ 13-Week: _____ 20-Week: _____</p>	

10. _____ Administer the **Follow-up Genital Symptoms** form.
11. _____ Perform interval medical/menstrual history; record findings on the **Follow-up Medical History Log** form. Record interval contraceptive/family planning method use and menstrual history in visit chart note.
 - 11a. _____ If genital blood/bleeding is reported, complete a **Genital Bleeding Assessment** form for unexpected genital bleeding.
12. _____ Review and update the **Concomitant Medications Log**.
13. _____ Complete the **Family Planning Methods** form by transcribing (from the visit chart note) the participant's current contraceptive/family planning methods.
14. _____ Provide contraceptive counseling. Provide and/or refer for contraception, if applicable.
15. _____ Perform physical exam as per Protocol Appendix III and record on the **Physical Exam** (non-DataFax) form.
16. _____ Confirm participant abstained from sex for at least 24 hours prior to the study visit.
17. _____ If applicable, assess any non-genital symptoms reported in the participant's interval medical/menstrual history. Provide or refer for follow-up care as needed. Document follow-up in chart notes.
18. _____ Collect blood as follows: (*Sites to include site-specific blood volume*)
 - Plain tube(s) (no additive)
 - EDTA
19. _____ Complete an **LDMS Specimen Tracking Sheet** for stored samples.
20. _____ Prepare blood for testing/storage at the local lab.
 - Pre-dose:
 - Complete Blood Count with differential (lymphocyte) for flow cytometry calculations
 - Serum Chemistries (Phosphorous, Creatinine)
 - Liver Function Tests (AST, ALT)
 - Tenofovir
 - Plasma for storage

Follow-up Clinic Visits, End of Study Period Visit: Page 2 of 5

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>6-Week: _____ 13-Week: _____ 20-Week: _____</p> <p><i>Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit.</i></p>	

- PBMC for intracellular tenofovir (at sites with capacity)
- Plasma for flow cytometry (at sites with capacity)
- Cell lysate (at sites with capacity)

- Post-dose blood collection per randomization assignment:
 - Tenofovir
 - PBMC for intracellular tenofovir (at sites with capacity)

21. _____ Perform pelvic exam using the Pelvic Exam Checklist and complete the Pelvic Exam Diagrams, **Follow-up Pelvic Exam, Pelvic Laboratory Results and Pharmacokinetics – Non-Intensive** forms.
- 21a. _____ During exam, if applicable, assess genital symptoms reported during administration of the **Follow-up Genital Symptoms** form. Provide or refer for follow-up care as needed. Document follow-up in chart notes.
- 21b. _____ Collect genital PK specimens at the assigned time point and record collection times on the **Pharmacokinetics – Non-Intensive** Form.
- NOTE: Pelvic exam should be timed such that the genital specimens may be collected at the randomly assigned time point. Make sure that CVL samples are collected within 15 minutes of blood collection.
22. _____ Complete/update **Adverse Experience Log** form(s) if required based on interval medical/menstrual history, clinical exams/assessments, and lab tests.
23. _____ If product use is held/discontinued or resumed at this visit, document the rationale for the hold/discontinuation or resumption in chart notes and/or on other applicable source documents, and on the Product Hold/Discontinuation Tracking Sheet(s), if applicable. Inform the site’s study pharmacist of the product hold/discontinuation or resumption by completing a **Study Product Hold/Resume/pK Supply/Re-Supply Slip** and delivering the white original to him/her. Retain the yellow copy in the participant’s study notebook. Refer to Protocol Section 9.4 and the SSP Manual, Section 10, for guidelines on holding, discontinuing or continuing with study product. Contact PSRT if there are any questions about study product or clinical management.
24. _____ Record/transcribe the date and time of the participant’s last 3 doses of study product onto the **Study Product Adherence and Behavior Assessment** form.

Follow-up Clinic Visits, End of Study Period Visit: Page 3 of 5

PTID:	Visit Date:
Please indicate to which follow-up visit this checklist applies: 6-Week: _____ 13-Week: _____ 20-Week: _____	

25. _____ Administer the **Acceptability Assessment** form (Weeks 6 and 13 only), the **Final Acceptability Assessment** form (Week 20 only), and the **Product Sharing Assessment** form
26. _____ Provide HIV/STI risk education, protocol and product use adherence, and male condom and contraceptive counseling.
27. _____ Provide condoms, panty liners, and/or referrals if needed/requested.
28. _____ Schedule the next visit and inform the participant of what to expect. Also inform the participant of availability of HIV/STI counseling, testing, and STI treatment for partners.
29. _____ Reinforce site contact information and instructions to contact the site to report symptoms — especially genital symptoms — and/or to request for additional information, HIV/STI counseling, and/or condoms, if needed, prior to the next visit.

Additionally Only If Clinically Indicated (C1-C4):

- C1. _____ Perform dipstick urinalysis on aliquot of urine used for pregnancy testing. Complete testing logs and transcribe protein, leukocyte, and nitrites results onto the **Safety Laboratory Results** form. Document other results (e.g., blood, glucose), if any, in visit chart note, or in other designated site-specific document, if applicable.
- C2. _____ Perform culture if positive for leukocyte esterase or nitrites; may omit if culture not standard of care for UTI diagnosis. Document additional work-up in visit chart note. If applicable, provide and record treatment on the **Concomitant Medications Log** form.
- C3. _____ Prepare urine for SDA for Gonorrhea and Chlamydia. Transcribe results onto the **STI Laboratory Results** form.
- C4. _____ Collect blood for Syphilis Serology and/or HBsAg. Transcribe results onto the **STI Laboratory Results** form.

30. _____ Provide study reimbursement.

Follow-up Clinic Visits, End of Study Period Visit: Page 5 of 5

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>6-Week: _____ 13-Week: _____ 20-Week: _____</p>	

31. _____ Document the visit in a signed and dated chart note. Complete and review all participant chart contents for the visit, including Follow-up Medical History

32. _____ Complete **Follow-up Visit** form

33. _____ Complete and review all participant chart contents for the visit, including the following non-Data Fax forms:

- Physical Exam Form
- Pelvic Exam Diagram
- LDMS Specimen Tracking Sheet

34. _____ Fax all required Data Fax forms to SCHARP:

- Follow-up Visit
- Follow-up Genital Symptoms
- Family Planning Methods
- Follow-up Pelvic Exam
- Pelvic Laboratory Results
- Safety Laboratory Results (when all results available)
- Study Product Adherence and Behavior Assessment
- Product Sharing Assessment
- Acceptability Assessment (Week 6 and 13 only)
- Final Acceptability Assessment (Week 20 only)
- Acceptability Assessment
- Pharmacokinetics – Non-Intensive
- Flow Cytometry

As Needed:

- Follow-up Medical History Log (update/add entries as needed)
- Concomitant Medications Log (required for updated or new pages)
- Adverse Experience Log (required if any AEs identified or updated at this visit)
- Pregnancy Report and History (required if pregnancy identified at this visit)
- Pregnancy Outcome (required if pregnancy outcome ascertained at this visit)
- STI Laboratory Results

Early Termination:

Follow-up Clinic Visits, End of Study Period Visit: Page 5 of 5

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>6-Week: _____ 13-Week: _____ 20-Week: _____</p>	

Termination
End of Study Inventory

Follow-up Clinic Visits, Study Period 2 and 3 Start: Page 1 of 5

PTID: _____	Visit Date: _____
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>7-Week: _____ 14-Week: _____</p>	

1. _____ Complete participant registration, confirm the participant’s identity, and verify her PTID.
2. _____ Review/update locator information.
3. _____ Review chart notes and other relevant documentation from previous visit(s).
4. _____ If indicated, collect unused study product. If participant did not bring unused product at this visit, remind her to bring it at her next scheduled visit or make arrangements to collect product.
5. _____ Review elements of informed consent as needed.
6. _____ Explain the content and sequence of procedures for today’s visit.
7. _____ Collect ~20 mL urine and:
 - 7a. _____ Aliquot ~5 mL and perform pregnancy test; retain remaining urine for remainder of visit.
 - 7b. _____ Complete testing logs and transcribe result onto the form.

If the participant is pregnant:

 - 7c. _____ Inform the participant that she must discontinue product use; arrange to collect her unused study product.
 - 7d. _____ Complete a MTN 001 Pregnancy Management Worksheet
 - 7e. _____ Complete/update the Product Hold/Discontinuation Log Tracking Sheet(s), if applicable.
 - 7f. _____ Complete a **Study Product Hold/Resume/pK Supply/Re-Supply Slip**, marked “Permanent Discontinuation.” Deliver the completed white original copy to the pharmacy. Retain the yellow clinic copy in the participant’s study notebook.
8. _____ Provide and explain available exam and lab test results. Provide post-test counseling, if appropriate. Provide treatment for RTIs/STIs if needed. Document treatment on the **Concomitant Medications Log**.
9. _____ Administer the **Follow-up Genital Symptoms** form
10. _____ Perform interval medical/menstrual history; record findings on the **Follow-up Medical History Log** form. Record interval contraceptive/family planning method use and menstrual history in the visit chart note
 - 10a. _____ Complete a **Genital Bleeding Assessment** form for unexpected

Follow-up Clinic Visits, Study Period 2 and 3 Start: Page 2 of 5

PTID:	Visit Date:
Please indicate to which follow-up visit this checklist applies: 7-Week: _____ 14-Week: _____	

genital bleeding.

11. _____ Review and update the **Concomitant Medications Log**.
12. _____ Complete the **Family Planning Methods** form by transcribing (from the visit chart note) the participant's current contraceptive/family planning methods.
13. _____ Provide contraceptive counseling. Provide or refer for contraception, if applicable.
14. _____ Provide HIV pre-test counseling
15. _____ Collect blood as follows: (*Sites to include site-specific blood volume*)
 - Plain tube(s) (no additive)
 - EDTA
15. _____ Perform HIV test
16. _____ Complete testing logs and transcribe rapid HIV test results onto the **STI Laboratory Results** form. Before disclosing results to participant, obtain independent review, verification, and sign-off of both results.
17. _____ Provide rapid HIV test results in the context of post-test counseling. Provide HIV/STI risk reduction and condom counseling. Provide referrals if needed/requested.
 - *If both rapid tests are negative, the participant is considered HIV-uninfected. Continue with remainder of this checklist.*
 - *If one rapid test is positive and one is one negative, WB testing is required to clarify the participant's HIV status. Continue with remainder of this checklist OR defer further procedures until status is clarified.*
 - *If both rapid tests are positive, the participant is considered HIV-infected.*
18. _____ Prepare blood for testing at the local lab.
 - CBC (hemoglobin, hematocrit, WBC, PLT)
 - Serum Chemistries (Phosphorous, Creatinine)
 - Liver Function Tests (AST, ALT)
 - HIV-1 Western Blot (if indicated)

Follow-up Clinic Visits, Study Period 2 and 3 Start: Page 3 of 5

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>7-Week: _____ 14-Week: _____</p>	

19. _____ For all participants (unless product is held):
- 19a. _____ Complete a **Prescription**.
- 19b. _____ Follow your site-specific procedures for product re-supply. The white original prescription will be taken to the pharmacy. Retain the yellow clinic copy in the participant's study notebook.
- 19c. _____ After product supplies are received, provide the supplies to the participant and document the amount of product provided here
- ↳
20. _____ Perform physical exam and record on the **Physical Exam** form. _____
21. _____ Perform pelvic exam using the Follow-Up Pelvic Exam Checklist and complete the Pelvic Exam Diagrams, **Follow-up Pelvic Exam** and **Pelvic Laboratory Results** (if indicated) forms.
- 21a. _____ During exam, if applicable, assess genital symptoms reported during administration of the **Follow-up Genital Symptoms** form. Provide or refer for follow-up care as needed. Document follow-up in chart notes.
22. _____ If applicable, assess any non-genital symptoms reported in the participant's interval medical/menstrual history. Provide or refer for follow-up care as needed. Document follow-up in chart notes.
23. _____ Complete/update **Adverse Experience Log** form(s) if required based on interval medical/menstrual history, clinical exams/assessments, and lab tests.
24. _____ If product use is held/discontinued or resumed at this visit, document the rationale for the hold/discontinuation or resumption in chart notes and/or on other applicable source documents, and on the Product Hold/Discontinuation Tracking Sheet(s), if applicable. Inform the site's study pharmacist of the product hold/discontinuation by completing a **Study Product Hold/Resume/PK Supply/Re-Supply Slip** and delivering the white original to him/her. Retain the yellow clinic copy in the participant's study notebook. If the hold, discontinuation, or resumption affects product use in the CURRENT study period, complete/update the Product Hold/Discontinuation Log form (for holds/discontinuations, complete one form per reason). Refer to Protocol Section 9.4 and the SSP Manual, Section 10, for guidelines on holding, discontinuing or continuing with study product. Contact PSRT if there are any questions about study product or clinical management.

Follow-up Clinic Visits, Study Period 2 and 3 Start: Page 4 of 5

PTID:	Visit Date:
Please indicate to which follow-up visit this checklist applies: 7-Week: _____ 14-Week: _____	

25. _____ Provide protocol and product use adherence counseling.
26. _____ Provide condoms, panty liners, and/or referrals if needed/requested.
27. _____ Schedule the next visit and inform the participant of what to expect at that visit. Also inform the participant of availability of HIV/STI counseling, testing, and STI treatment for partners.
28. _____ Reinforce site contact information and instructions to contact the site to report symptoms — especially genital symptoms — and/or to request for additional information, HIV/STI counseling, and/or condoms, if needed, prior to the next visit.
29. _____ Provide study reimbursement.
30. _____ Remind participant to record on her appointment card (or other designated site-specific document) the date and time of the last three doses of study product she takes prior to next study visit. Also, remind participant to bring in unused product at next study visit
31. _____ Complete **Follow-up Visit** form

Follow-up Clinic Visits, Study Period 2 and 3 Start: Page 5 of 5

PTID:	Visit Date:
Please indicate to which follow-up visit this checklist applies: 7-Week: _____ 14-Week: _____	

Additionally Only If Clinically Indicated (C1-C4):

- C1. _____ Perform dipstick urinalysis on aliquot of urine used for pregnancy testing. Complete testing logs and transcribe protein, leukocyte, and nitrites onto the **Safety Laboratory Results** form. Document other results (e.g., blood, glucose), if any, in visit chart note, or in other designated site-specific document, if applicable.
- C2. _____ Perform culture if positive for leukocyte esterase or nitrites; may omit if culture not standard of care for UTI diagnosis. Document additional work-up in visit chart note. If applicable, provide treatment and record treatment on the **Concomitant Medications Log**.
- C3. _____ Prepare urine for SDA for Gonorrhea and Chlamydia. Transcribe results onto the STI Laboratory Results form.
- C4. _____ Collect blood for Syphilis Serology and/or HBsAg. Transcribe results onto the **STI Laboratory Results** form.

32. _____ Document the visit in a signed and dated chart note. Complete and review all participant chart contents for the visit, including the following non-Data Fax forms:

Physical Exam
Pelvic Exam Diagrams

33. _____ Fax all required Data Fax forms to SCHARP:

Follow-up Visit
Follow-up Genital Symptoms
Follow-up Pelvic Exam
Family Planning Methods
Safety Laboratory Results (when all results available)
STI Laboratory Results (when all results are available)

As Needed:

Follow-up Medical History Log (update/add entries as needed)

Follow-up Clinic Visits, Study Period 2 and 3 Start: Page 5 of 5

PTID:	Visit Date:
Please indicate to which follow-up visit this checklist applies: 7-Week: _____ 14-Week: _____	

Pelvic Laboratory Results

Concomitant Medications Log (required for updated or new pages)

Adverse Experience Log (required if any AEs identified or updated at this visit)

Product Hold/Discontinuation Log (required if product use *in current study period* is held/discontinued or resumed at this visit)

Pregnancy Report and History (required if pregnancy identified at this visit)

Pregnancy Outcome (required if pregnancy outcome ascertained at this visit)

Early Termination:

Termination

End of Study Inventory

Follow-up Clinic Visit, Study Termination Visit: Page 1 of 4

PTID:	Visit Date:
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1. _____ Complete participant registration, confirm the participant's identity, and verify her PTID.
2. _____ Review/update locator information.
3. _____ Review chart notes and other relevant documentation from previous visit(s).
4. _____ Review elements of informed consent as needed.
5. _____ Explain the content and sequence of procedures for today's visit.
6. _____ Collect ~20 mL urine and:
 - 6a. _____ Aliquot ~5 mL and perform pregnancy test; retain remaining urine for remainder of visit.
 - 6b. _____ Complete testing logs and transcribe result onto the form.

If the participant is pregnant:

 - 6c. _____ Complete a **Pregnancy Report and History** form.
 - 6d. _____ Explain to the participant that a post-study contact will be required to ascertain the outcome of her pregnancy.
7. _____ Collect any unused study product to return to pharmacy.
8. _____ Provide and explain available exam and lab test results from previous visit. Provide post-test counseling, if appropriate. Provide treatment for RTIs/STIs if needed. Document treatment on the **Concomitant Medications Log**.
9. _____ Administer the **Follow-up Genital Symptoms** form
10. _____ Perform interval medical/menstrual history; record findings on the **Follow-up Medical History** form. Record interval contraceptive/family planning method use and menstrual history in visit chart note
 - 10a. _____ If genital blood/bleeding is reported, conduct a pelvic exam. Complete a **Genital Bleeding Assessment** form for unexpected genital bleeding.
11. _____ Review and update the **Concomitant Medications Log**.
12. _____ Complete the **Family Planning Methods** form by transcribing (from the visit chart note) the participant's current contraceptive/family planning methods.
13. _____ Provide contraceptive counseling. Provide/refer for contraception, if applicable
14. _____ If applicable, assess any non-genital symptoms reported in the participant's interval medical/menstrual history. Provide or refer for follow-up care as needed. Document follow-up in chart notes.

Follow-up Clinic Visit, Study Termination Visit: Page 1 of 4

PTID:	Visit Date:
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15. _____ Complete/update **Adverse Experience Log** form(s) if required based on interval medical/menstrual history, clinical exams/assessments, and lab tests. Contact PSRT if there are any questions about study product or clinical management.
16. _____ Review all **Adverse Experience Log** forms completed for the participant and update the forms as needed. For AEs that are “continuing” at this visit, update the status/outcome of the AE to “continuing at end of study participation.”
- ☞ Any SAEs or EAEs identified as continuing at this visit must be re-evaluated within 30 days. Any previously reported AEs found to have increased in severity at this visit also must be re-evaluated in 30 days. Consult with the IoR/designee to establish a clinically appropriate follow-up plan for the participant and document the plan on the participant’s file.*
17. _____ Provide HIV pre-test counseling; during pre-test counseling, reinforce that although this is the participant’s last scheduled study visit, additional visits and tests will be done if needed to confirm or clarify her HIV status.
18. _____ Collect blood as follows: (*Sites to include site-specific blood volume*)
- plain tube(s) (no additive)
 - EDTA
19. _____ Perform HIV test
20. _____ Complete testing logs and transcribe rapid HIV test results onto the **Laboratory Results** form. Before disclosing results to participant, obtain independent review, verification, and sign-off of both results.
21. _____ Provide rapid HIV test results in the context of post-test counseling. Provide referrals if needed/requested.
- *If both rapid tests are negative, the participant is considered HIV-uninfected. Continue with remainder of this checklist.*
 - *If one rapid test is positive and one is one negative, WB testing is required to clarify the participant’s HIV status. Continue with remainder of this checklist.*
 - *If both rapid tests are positive, the participant is considered HIV-infected.*
22. _____ Complete an **LDMS Specimen Tracking Sheet** for stored samples.
23. _____ Prepare blood for testing/storage at the local lab. .
- CBC (hemoglobin, hematocrit, WBC, PLT)
 - Serum Chemistries (Phosphorous, Creatinine)
 - Liver Function Tests (AST, ALT)
 - HIV-1 Western Blot (if indicated)
 - Plasma for storage

Follow-up Clinic Visit, Study Termination Visit: Page 3 of 4

PTID:	Visit Date:
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24. _____ If participant has been randomized to or selected for the In-Depth interview, is evaluable (i.e., does not meet criteria for replacement), and has given consent for participation, conduct the recorded in-depth interview.
25. _____ Provide HIV/STI risk reduction and male condom counseling. Also inform the participant of availability of HIV/STI counseling, testing, and STI treatment for partners.
26. _____ Provide condoms and/or referrals if needed/requested.
27. _____ Complete **Follow-up Visit** form.
28. _____ Completion **Termination** form.
29. _____ Complete **End of Study Inventory** form.
30. _____ Reinforce site contact information.
31. _____ Provide study reimbursement.

Additionally Only If Clinically Indicated (C1-C6):

- C1. _____ Perform dipstick urinalysis on aliquot of urine used for pregnancy testing. Complete testing logs and transcribe protein, leukocyte, and nitrites results onto the **Safety Laboratory Results** form. Document other results (e.g., blood, glucose), if any, in visit chart note, or in other designated site-specific document, if applicable.
- C2. _____ Perform if positive for leukocyte esterase or nitrites; may omit if culture not standard of care for UTI diagnosis. Document additional work-up in visit chart note. If applicable, provide treatment and record on the **Concomitant Medications Log** form.
- C3. _____ Prepare urine for SDA for Gonorrhea and Chlamydia. Transcribe results onto the **STI Laboratory Results** form.
- C4. _____ Collect blood for Syphilis Serology and/or HBsAg. Transcribe results onto the **STI Laboratory Results** form.
- C5. _____ Perform physical exam and complete non-DataFax **Physical Exam** form.
- C6. _____ Perform pelvic exam. Complete the **Follow-up Pelvic Exam** form and, if applicable, the Pelvic **Laboratory Results** form.

Follow-up Clinic Visit, Study Termination Visit: Page 3 of 4

PTID:	Visit Date:
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32. _____ Schedule next visit to provide the participant with any remaining lab test results, to provide counseling if indicated, and to follow-up on any AEs, if indicated.
33. _____ If indicated, treat or refer any findings. .
34. _____ Document the visit in a signed and dated chart note. Complete and review all participant chart contents for the visit, including the following non-Data Fax form:
LDMS Specimen Tracking Sheet
35. _____ Fax all required Data Fax forms to SCHARP Data Fax:

Follow-up Visit
Termination
Family Planning Methods
STI Laboratory Results
End of Study Inventory
Follow-up Genital Symptoms
Safety Laboratory Results (when all results available)

As Needed:

Follow-up Medical History Log (update/add new entries as needed)
Concomitant Medications Log (required for updated or new pages)
Adverse Experience Log (required if any AEs identified or updated at this visit)
Pregnancy Report and History (required if pregnancy identified at visit)
Pregnancy Outcome (required if pregnancy outcome ascertained at visit)

- *Note: Once the Study Termination Visit is completed, complete the MTN 001 Study Exit worksheet.*

**Pelvic Exam
Screening, Enrollment, 6-week, 13-week, 20-week
Page 1 of 2**

PTID: _____	Visit Date: _____
Please indicate to which visit this checklist applies:	
Screening : _____ Enrollment: _____ 6-week: _____ 13-week: _____ 20-week: _____	

1. _____ Explain the exam procedures to the participant and answer any participant questions.
2. _____ Using a pencil, write the PTID and specimen collection date on the frosted side of two microscope slides for vaginal wet mount. Then affix a SCHARP-provided PTID label to the other side of each slide (under the pencil markings) and write the specimen collection date in ink on each label.
3. _____ Affix a SCHARP-provided PTID label to a glass or plastic tube containing approximately six drops (100 µL) of saline. Write the specimen collection date in ink on the label.
4. _____ Position and drape the participant comfortably.
5. _____ Palpate inguinal lymph nodes. Document abnormal findings on the **Screening and Enrollment Pelvic Exam** form or the **Follow-up Pelvic Exam** form at follow-up visits.
6. _____ Inspect external genitalia: Note all findings on the Pelvic Exam Diagrams form. Document abnormal findings in items on the **Screening and Enrollment Pelvic Exam** form or the **Follow-up Pelvic Exam** form at follow-up visits.
7. _____ Insert speculum, using warm water as lubricant if needed. Observe general state and note the position of the cervix.
8. _____ Assess for homogenous discharge. Record observation on the **Pelvic Laboratory Results** form.
9. _____ Inspect cervix and vagina: Note all findings on the Pelvic Exam Diagrams form. Document abnormal findings in items on the **Screening and Enrollment Pelvic Exam** form or the **Follow-up Pelvic Exam** form at follow-up visits.
10. _____ **Screening Visit only:** If indicated, perform Pap smear per site SOP.
11. _____ **Screening Visit only:** Record the size of speculum used and position of the participant's cervix on the **Pelvic Exam Diagrams** form.
12. _____ Collect vaginal fluids from the lateral vaginal wall via swab and swab fluids onto the pH strip. Record pH on the **Pelvic Laboratory Results** form.

Pelvic Exam
Screening, Enrollment, 6-week, 13-week, 20-week
Page 2 of 2

PTID: _____	Visit Date: _____
Please indicate to which visit this checklist applies:	
Screening : _____ Enrollment: _____ 6-week: _____ 13-week: _____ 20-week: _____	

13. _____ Swab vaginal fluids from the lateral vaginal wall for wet prep; proceed immediately to Step 13a or place the swab in a labeled glass or plastic tube containing approximately six drops (100 µL) of saline to allow for non-immediate slide preparation and evaluation, as follows (see also SSP Section 12):
- 13a. _____ Smear vaginal fluids from the swab onto two labeled slides.
- 13b. _____ Apply KOH to one slide, perform whiff test, then apply cover slip.
- 13c. _____ Apply saline to the second slide, emulsifies, then apply cover slip. Immediately evaluate for trichomonads, yeast buds, pseudohyphae, and clue cells.
- 13d. _____ Evaluate KOH slide for yeast buds and pseudohyphae.
- 13e. _____ If slides are read in-clinic by clinical staff, record results directly onto the **Pelvic Laboratory Results** form. If slides are read by lab staff (either in the local lab or a designated in-clinic lab area) complete testing logs and then transcribe results onto the **Pelvic Laboratory Results** form.

For screening and enrollment visits: If lab results are positive for trichomonads, yeast buds, pseudohyphae and/or clue cells, the participant is ineligible, with the exception of asymptomatic BV and asymptomatic vulvovaginal candidiasis. STOP. Inform the participant that she is ineligible. Otherwise eligible participants diagnosed with RTI and/or UTI may be enrolled after completing treatment and all symptoms have resolved. Retain documentation completed thus far, and complete the form, but do not fax any forms to SCHARP.

14. _____ Perform bimanual exam, if indicated. Document abnormal findings on the **Screening and Enrollment Pelvic Exam** form or the **Follow-up Pelvic Exam** form at follow-up visits.
15. _____ **Enrollment visit only:** Collect CVL sample. *NOTE: CVL must be performed following all other pelvic exam/lab procedures. CVL samples need to be placed on ice immediately and then frozen*
16. _____ **6- week, 13-week and 20-week visits only:** Collect CVL sample within 15 minutes of blood collection for pK procedures. *NOTE: Blood may be collected following the CVL procedure. CVL must be performed following all other pelvic exam/lab procedures. CVL samples need to be placed on ice immediately and then frozen.*

Pelvic Exam
3-week, 7-week, 10-week, 14-week, 17-week
Page 1 of 1

PTID:	Visit Date:
Please indicate to which visit this checklist applies:	
3-Week : _____ 7-Week: _____ 10-week: _____ 14-week: _____ 17-week: _____	

1. _____ Explain the exam procedures to the participant and answer any participant questions.
2. _____ Position and drape the participant comfortably.
3. _____ Palpate inguinal lymph nodes. Document abnormal findings on the **Follow-up Pelvic Exam** form
4. _____ Inspect external genitalia: Note all findings on the **Pelvic Exam Diagrams** form. Document abnormal findings on the **Follow-up Pelvic Exam** form.
5. _____ Insert speculum, using warm water as lubricant if needed. Observe general state and note the position of the cervix.
6. _____ Assess for homogenous discharge. If indicated, perform wet mount and complete the **Pelvic Laboratory Results** form.
7. _____ Inspect cervix and vagina: Note all findings on the **Pelvic Exam Diagrams** form. Document abnormal findings in items on the **Follow-up Pelvic Exam** form.
8. _____ If indicated, perform Herpes Culture (at sites where standard of care for diagnosis)
9. _____ Perform bimanual exam, if indicated. Document abnormal findings on the **Follow-up Pelvic Exam** form.

Section 7. Visit Checklists

This section contains examples of checklists detailing the protocol-specified procedures that must be completed at MTN 001 study visits. The checklists also specify the data collection forms that must be completed at each visit. Detailed procedural guidance for performing clinical and laboratory procedures is provided in Sections 10 and 12, respectively. Detailed forms completion instructions are provided in Section 13.

7.1 Use of Checklists

The visit checklists included in this section are designed to guide site staff in proper study procedures as well as to serve as source documentation of procedures performed at study visits. Note, however, that checklists alone may not be sufficient for documenting all procedures. For example, chart notes may be required to:

- Explain why procedures in addition to those listed on a checklist were performed
- Explain why procedures listed on a checklist were not performed
- Document procedures performed at interim visits
- Document the content of counseling sessions and/or other in-depth discussions with participants (e.g., related to adherence to protocol requirements)

See Section 3 for detailed information on source documentation requirements. Tips for completing visit checklists in accordance with these requirements are as follows:

- Enter the participant identification number (PTID) and visit date in the top section of each checklist. If information is written on the front and back of the checklist, enter the PTID and visit date on both sides.
- For follow-up visits, mark the applicable visit in the top section of each checklist
- Enter your initials only beside the procedures that you perform. Do not enter your initials beside procedures performed by other staff members. If other staff members are not available to initial checklist items themselves, enter, initial, and date a note on the checklist documenting who completed the procedure, e.g., “done by {name}” or “done by lab staff.”
- If all procedures listed on a checklist are performed on the date entered in the top section of the form, the date need not be entered beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item.
- If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why on the checklist (if not self-explanatory); initial and date this entry.

7.2 Sequence of Procedures

The sequence of procedures presented on the visit checklists is a suggested ordering. In consultation with the MTN (FHI) CORE, site staff may modify the checklists included in this section to maximize the efficiency of site-specific study operations. Sites may alter the sequence of procedures to suit local staffing and logistical requirements, with the following exceptions:

- Informed consent for screening must be obtained before any screening procedures are performed.
- Informed consent for enrollment must be obtained before conduct of any study enrollment or follow-up procedures are performed. Enrollment procedures are listed in the Enrollment sub-sections of protocol Section 7.
- Behavioral assessments must be administered prior to HIV/STI risk reduction, male condom counseling and study product adherence counseling.
- Pelvic procedures must be performed in the sequence shown on the pelvic exam checklists.

Screening Visit: Page 1 of 3

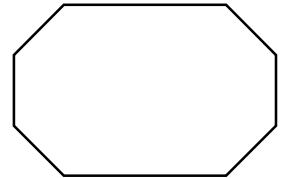
PTID:	Visit Date:
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1. _____ Confirm participant identity. Cross-check with the MTN 001 Participant Name-PTID Link Log to determine whether a MTN 001 Participant ID number has previously been assigned to the participant.
2. _____ Confirm whether the participant is between the ages of 18 and 45 (inclusive) per site SOP.
3. _____ Explain the two-step (screening and enrollment) informed consent process.
4. _____ Explain the content and sequence of procedures for the remainder of the visit.
5. _____ Administer and obtain screening informed consent with participant according to site SOPs. Complete Consent Process Worksheet.

➤ *If the participant does not consent to screening, STOP. Do not fax any forms to SCHARP.*

6. _____ Complete the **Screening Consent** form.

Based on the 30-day screening and enrollment window, beginning on the day informed consent is obtained for screening; enter the participant's last possible enrollment date for this screening attempt



7. _____ Assign an MTN 001 PTID (if not done during a previous screening attempt) by completing a new row in the MTN 001 Name-PTID Link Log.
8. _____ Collect approximately 20-60 mL urine and:
 - 8a. _____ Aliquot approximately 5-10 mL and perform qualitative pregnancy test.
 - 8b. _____ Complete testing logs and record result on the **Screening Eligibility** form (non-DataFax).

*If the participant is pregnant, STOP. Inform the participant that she is ineligible. Retain documentation completed thus far, and complete the **Screening Summary** form, but do not fax any forms to SCHARP.*

- 8c. _____ Prepare urine for SDA for Gonorrhea and Chlamydia.

Screening Visit: Page 2 of 3

PTID:	Visit Date:
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- 8d. _____ Complete dipstick urinalysis using same aliquot as pregnancy test; record results for protein, leukocytes, and nitrites on the **Safety Laboratory Results** form. Document other results (e.g., blood, glucose), if any, in visit chart note, or in other designated site-specific document, if applicable. If dipstick urinalysis is positive for leukocytes or nitrites, provide treatment and/or additional UTI work-up per site SOP. Document additional work-up in chart notes. Document treatment on the **Concomitant Medications Log**.
9. _____ Assess behavioral eligibility on the **Screening Eligibility and Clinical Eligibility** (non- DataFax) forms.
10. _____ Provide HIV pre-test, HIV/STI risk reduction and condom counseling. Provide male condoms. *(Sites may chose to provide condoms at the end of the visit)*
11. _____ Collect blood: *(Sites to specify their site-specific volume for each tube)*
- Plain tube (no additive)
 - EDTA
12. _____ Explain to study participant that eligibility is based on results as determined by the study HIV algorithm (Protocol Appendix II).
13. _____ Prepare blood for testing at the local lab:
- HIV serology
 - Syphilis serology
 - CBC (hemoglobin, hematocrit, WBC, PLT)
 - Serum Chemistries (Phosphorous, Creatinine)
 - Liver Function Tests (AST, ALT)
 - Hepatitis B Surface Antigen
14. _____ Obtain contact information and record on site specific form.
- *If the participant does not provide adequate contact information, per site-specific definition of adequate contact information and is determined not to be a good candidate for the study (investigator decision) STOP. Inform the participant that she is ineligible. Retain documentation completed thus far, and complete the form, but do not fax any forms to SCHARP.*
15. _____ Administer the **Demographics** DataFax CRF.
16. _____ Conduct the Physical Exam and record results on the **Physical Exam** non-Data Fax form.

Screening Visit: Page 3 of 3

PTID:	Visit Date:
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17. _____ Obtain medical, menstrual, and genitourinary history with documentation of current medications. Record on **Baseline Medical and Menstrual History** form (non-Data Fax) and **Concomitant Medications Log** Data Fax CRF.
18. _____ Perform and document pelvic exam using Pelvic Exam Checklist. Complete the Pelvic Exam Diagrams (non-Data Fax), **Screening and Enrollment Pelvic Exam** and **Pelvic Laboratory Results** DataFax CRFs. Treat or refer for treatment, if applicable.
19. _____ Provide contraceptive counseling. Provide and/or refer for contraception, if applicable.
20. _____ Provide study informational material. Provide site contact information and instructions to contact the site for additional information and/or HIV/STI counseling, if needed, prior to the next visit.
21. _____ Schedule the Enrollment visit, taking into account the timing for receipt of lab results, the participant's menstrual cycle, and the 30-day screening period.
22. _____ Provide reimbursement.
23. _____ Document the visit in signed and dated chart notes. Complete the **Screening Summary** form and review all other participant chart contents for the visit, but do not fax any forms to SCHARP.

➤ *Note: The **Screening and Enrollment STI Laboratory Results, Pelvic Laboratory Results, Safety Laboratory Results** forms (and **HIV Test Results** form, when applicable) should be completed when all required test results are available, prior to the Enrollment Visit. Do not fax any forms to SCHARP until the participant is randomized. If the participant's lab results indicate that she is HIV-positive per protocol Appendix II, or has an active RTI and/or UTI – with the exception of asymptomatic BV and asymptomatic vulvovaginal candidiasis — she is ineligible for enrollment; retain all of these DataFax forms on site but do not fax any of them to SCHARP.*

Enrollment Visit: Page 1 of 6

PTID:	Visit Date:
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1. _____ Complete participant registration, confirm the participant's identity, and verify her PTID.
2. _____ Review/update locator information
3. _____ Confirm that the 30-day window has not been exceeded for the current screening attempt.
4. _____ Review chart notes and other relevant documentation from previous visit(s). Confirm the participant's current eligibility status based on all screening documentation.
5. _____ Confirm behavioral eligibility and record results on **Enrollment Eligibility** form
6. _____ Explain again the two-step informed consent process and obtain written informed consent for the study. Document the informed consent process in a chart note and on any other documents per site SOP.
*☞ If the participant does not consent to the study, complete the **Screening Summary** form and then STOP. Retain documentation completed thus far, but do not fax any forms to SCHARP.*
7. _____ Obtain written informed consent for specimen storage and possible future research testing. Document the informed consent process in a chart note and on any other documents per site SOP. Complete Consent Process Worksheet.
☞ Consent for specimen storage and possible future research testing is optional. If the participant does not consent, she may still take part in the study.
8. _____ Administer assessment of informed consent comprehension, utilizing comprehension checklist, according to local SOPs.
9. _____ Complete the **Screening Summary** form and items 1-2 of the **Enrollment** form.
10. _____ Provide HIV test results in the context of post-test counseling. [Before disclosing result(s) to participant, obtain independent review, verification, and sign-off of results(s)]. Provide referrals if needed/requested. Explain the participant's current study eligibility status.
☞ If the participant is HIV-positive per protocol Appendix II, STOP. Retain documentation completed thus far, but do not fax any forms to SCHARP.

Enrollment Visit: Page 2 of 6

PTID:	Visit Date:
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☞ *If the participant requires Sample 2 collection for WB testing: _____*

10a. _____ Provide pre-test counseling, if applicable.

10b. _____ Collect blood (plain tube or EDTA).

10c. _____ Schedule Enrollment Visit when WB test result is available, up to 30-days after written consent for screening was obtained for the current screening attempt.

11. _____ Collect 20-60 mL first void urine and:

11a. _____ Aliquot ~5 mL and perform pregnancy test.

11b. _____ Complete testing logs and transcribe result here:

negative

positive

☞ *If the participant is pregnant, STOP. Inform the participant that she is ineligible. Retain documentation completed thus far, record results in the participant's chart notes, and complete the **Screening Summary** form. Do not fax any forms to SCHARP.*

11c. _____ If clinically indicated, prepare urine for SDA for Gonorrhea and Chlamydia

12. _____ Administer the **Baseline Genital Symptoms** form.

13. _____ Review/update the **Baseline Medical and Menstrual History and Concomitant Medications Log**. Document review with a signed and dated note on each document reviewed. Initial and date updated entries.

14. _____ Complete the **Family Planning Methods** form by transcribing (from the Baseline Medical and Menstrual History form) the participant's current contraceptive/family planning methods.

15. _____ Provide contraceptive counseling. Provide and/or refer for contraception, if applicable.

16. _____ If indicated, complete dipstick urinalysis using same aliquot as pregnancy test; record results for protein, leukocytes, and nitrites on **Safety Laboratory Results** form. Document other results (e.g., blood, glucose), if any, in visit chart note, or in other designated site-specific document, if applicable. If dipstick urinalysis is positive for leukocytes or nitrites, provide/refer for treatment and/or additional UTI work-up per site SOP. Document additional work-up in chart notes. Provide treatment and document on the **Concomitant Medications Log**.

17. _____ Conduct physical exam as per Protocol Appendix III. Complete the **Physical Exam** (non-DataFax) form.

Enrollment Visit: Page 3 of 6

PTID:	Visit Date:
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18. _____ Perform and document pelvic exam and CVL using Pelvic Exam checklist. Complete the Pelvic Exam Diagrams (non-Data Fax), **Screening and Enrollment Pelvic Exam and Pelvic Laboratory Results** Data Fax forms.
19. _____ Complete the **Clinical Eligibility** form
20. _____ Collect blood: : (*Sites to include site-specific blood volume*)
- Plain tube (no additive)
 - EDTA
21. _____ Prepare blood for testing at the local lab:
- CBC (hemoglobin, hematocrit, WBC, PLT)
 - Serum Chemistries (Phosphorous, Creatinine)
 - Liver Function Tests (AST, ALT)
 - Plasma storage
 - Syphilis serology, if indicated
 - HIV serology if determined by site SOP
 - HIV-1 Western Blot, if indicated and determined by site SOP
22. _____ Complete an **LDMS Specimen Tracking Sheet** for stored samples.
23. _____ Administer the **Enrollment Behavior Assessment**
☞ This form must be administered prior to random assignment.
24. _____ Provide HIV/STI risk reduction and male condom counseling.
25. _____ **For non-replacement participants only:** obtain the next sequential Randomization Envelope and assign it to the participant by completing the row of the MTN 001 Randomization Envelope Tracking Record that corresponds to the next sequential envelope.
26. _____ **For non-replacement participants only:** open the assigned envelope and confirm that the envelope number printed on the MTN 001 Randomization Document contained inside the envelope corresponds with the envelope number on the outside of the envelope (envelope label). Complete the Randomization Document.
27. _____ **For replacement participants only:** obtain a blank Replacement Randomization Document and the completed Randomization Document (yellow copy) of the participant being replaced. Transcribe all of the randomization information from the Randomization Document of the participant being replaced onto the Replacement Randomization Document. Complete the remainder of the Replacement Randomization Document.

Enrollment Visit: Page 4 of 6

PTID:	Visit Date:
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28. _____ Complete the MTN 001 prescription(s) that correspond to the participant's first study period (vaginal, oral, or dual use) per her study randomization. Deliver the Randomization Document (or Replacement Randomization Document, for replacement participants) and prescription(s) to the pharmacy according to Option A or B below. While waiting for product supplies to be delivered, continue with the remainder of this checklist.

OPTION A:

- _____ Give the completed white original Randomization Document (or Replacement Randomization Document) and prescription(s) to the participant to deliver to the pharmacy (where she will obtain product supplies herself). Retain the envelope (for non-replacement participants) and the yellow clinic copy of both the Randomization Document (or Replacement Randomization Document) and the prescription(s) in the participant's study notebook.
- _____ Document the amount of product the participant received here ⇒
[or in chart notes].

OPTION B:

- _____ Optional: Fax a copy of the Randomization Document (or Replacement Randomization Document) and prescription(s) to the pharmacy
- _____ Deliver the completed white original Randomization Document (or Replacement Randomization Document) and prescription(s) to the pharmacy. Retain the envelope (for non-replacement participants) and the yellow clinic copy of both the Randomization Document (or Replacement Randomization Document) and the prescription(s) in the participant's study notebook.
- _____ Receive requested product supplies.
- _____ Provide product supplies to the participant.
- _____ Document the amount of product provided to the participant here ⇒
[or in chart notes]

29. _____ Provide counseling related to the importance of participant's study participation and product use. For participants randomized to the study gel only or dual use regimen for the first study period, provide demonstration of gel applicator, instructions for gel use, and adherence counseling. Emphasize the unknown effectiveness of the study products and the importance of condom use for protection against HIV.

- 29a. _____ Counsel participants to abstain from sex 24 hours prior to the End-of-the-Study Visit, if possible.

Enrollment Visit: Page 5 of 6

PTID:	Visit Date:
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30. _____ Once product supplies arrive, complete the remainder of the **Enrollment** form.
31. _____ Reinforce the instructions to contact the site to request additional product, if needed, prior to the next visit and remind the participant that she will be asked to return unused study product that she has remaining at her next visit.
32. _____ Provide male condoms and offer panty liners.
33. _____ Provide watch device and remind participant to record on her appointment card (or other designated site-specific document) the date and time of the last 3 doses of study product she takes prior to her next study visit.
34. _____ Reinforce site contact information and instructions to contact the site to report symptoms — *especially genital symptoms* — and/or to request for additional information, HIV/STI counseling, and/or condoms, if needed, prior to the next visit.
35. _____ Explain the follow-up visit schedule to the participant and schedule her Week 3 Clinic Visit.
36. _____ Inform the participant of tests to be performed at the next visit. Also inform the participant of availability of HIV/STI counseling, testing, and STI treatment for partners.
37. _____ Treat or refer for findings as needed.
38. _____ Provide reimbursement for study visit.
39. _____ Complete the **Pre-Existing Conditions** form. Record all medical conditions that are ongoing at the time of participant randomization, based on source data collected throughout the screening process. Whenever possible, record a diagnosis rather than individual signs and symptoms. When this is not possible, record each individual sign or symptom. Do not record STIs or other infections that were fully treated prior to randomization. In the "comments" box for each condition, record as much information as possible on the severity and/or frequency of the condition at the time of participant randomization.
40. _____ Document the visit in a signed and dated chart note. Complete and review all participant chart contents from both the screening and enrollment visits.

Enrollment Visit: Page 6 of 6

PTID:	Visit Date:
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41. _____ Non-Data Fax forms:
- Screening Eligibility
 - Enrollment Eligibility
 - Baseline Medical and Menstrual History
 - Physical Exam (x2)
 - Pelvic Exam Diagrams (x2)
 - Clinical Eligibility (x2)
 - Screening Summary
 - LDMS Specimen Tracking Sheet
42. _____ Complete and fax all required DataFax forms to SCHARP:
- Screening Consent
 - Demographics
 - Screening and Enrollment Pelvic Exam (x2)
 - Baseline Genital Symptoms
 - Screening and Enrollment STI Laboratory Results
 - Pelvic Laboratory Results* (x2)
 - Safety Laboratory Results* (x2)
 - Concomitant Medications Log
 - Family Planning Methods
 - Enrollment
 - Pre-Existing Conditions
 - Enrollment Behavior Assessment

☞ ***Pelvic Laboratory and Safety Laboratory Results forms are required for enrolled participants and MUST be completed, reviewed, and faxed to SCHARP once enrollment visit lab results are available. If HIV and/or other STI lab testing are conducted on samples collected at this visit, complete the **Screening and Enrollment STI Laboratory Results** form and the **HIV Test Results** form, if applicable.***

Follow-up Clinic Visits, Mid-Study Period Visit: Page 1 of 5

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>3-Week: _____ 10-Week: _____ 17-Week: _____</p>	

1. _____ Complete participant registration, confirm the participant’s identity, and verify her PTID.

2. _____ Review/update locator information.

3. _____ Review chart notes and other relevant documentation from previous visit(s).

4. _____ Explain the content and sequence of procedures for today’s visit.

5. _____ Review elements of informed consent as needed.

6. _____ Collect 20-60 mL urine and:
 - 6a. _____ Aliquot ~5 mL and perform pregnancy test; retain remaining urine for remainder of visit.
 - 6b. _____ Complete testing logs and transcribe result onto the form.

If the participant is pregnant:

 - 6c. _____ Inform the participant that she must discontinue product use; arrange to collect her unused study product.
 - 6d. _____ Complete an MTN 001 Pregnancy Management Worksheet.
 - 6e. _____ Complete Product Hold/Discontinuation Tracking Sheet(s), if applicable.
 - 6f. _____ Complete a **Study Product Hold/Resume/pK Supply/Re-Supply Slip**, marked “Permanent Discontinuation.” Deliver the completed white original to the pharmacy. Retain the yellow clinic copy in the participant’s study notebook.

7. _____ Collect unused study product to return to pharmacy. Document product collection in the chart notes. If participant did not bring the unused product at this visit, remind her to bring it for her next scheduled visit or make arrangements to collect the product.

8. _____ Provide and explain available exam and lab test results. Before disclosing HIV test results to participant, obtain independent review, verification, and sign-off of both results. Provide post-test counseling. Provide referrals if needed/requested. Provide treatment for RTIs/STIs if needed. Document treatment on the **Concomitant Medications Log**.

9. _____ Record/transcribe the date and time of the participant’s last 3 doses of study product onto the **Study Product Adherence and Behavior Assessment** form.

Follow-up Clinic Visits, Mid-Study Period Visit: Page 2 of 5

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>3-Week: _____ 10-Week: _____ 17-Week: _____</p> <p><i>Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit.</i></p>	

10. _____ Administer the **Study Product Adherence and Behavior Assessment** form.
11. _____ Administer the **Follow-up Genital Symptoms** form
12. _____ Perform interval medical/menstrual history; record findings on the **Follow-up Medical History Log** form. Record interval contraceptive/family planning method use and menstrual history in the visit chart note.
 - 12a. _____ Complete a **Genital Bleeding Assessment** form for unexpected genital bleeding.
13. _____ Review and update the **Concomitant Medications Log** form.
14. _____ Complete the **Family Planning Methods** form by transcribing (from the visit chart note) the participant's current contraceptive/family planning methods.
15. _____ Provide contraceptive counseling. Provide and/or refer for contraception, if applicable.
16. _____ Collect blood as follows. Complete a **Pharmacokinetics – Intensive** form. (*Sites to include site-specific blood volume*)
 - Plain tube (no additive)
 - EDTA
17. _____ Complete an **LDMS Specimen Tracking Sheet** for stored samples.
18. _____ Prepare blood for testing/storage at the local lab.
 - Serum Chemistries (Phosphorous, Creatinine)
 - Liver Function Tests (AST, ALT)
 - Tenofovir levels
19. _____ Perform physical exam per Protocol Appendix III and record on the **Physical Exam** (non-DataFax) form.
20. _____ Perform pelvic exam using the Pelvic Exam Checklist and complete the Pelvic Exam Diagrams, **Follow-up Pelvic Exam** and **Pelvic Laboratory Results** (if indicated) forms.
 - 20a. _____ During the exam, if applicable, assess genital symptoms reported during administration of the **Follow-up Genital Symptoms** form. Provide or refer for follow-up care as needed. Document follow-up in chart notes.

Follow-up Clinic Visits, Mid-Study Period Visit: Page 3 of 5

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>3-Week: _____ 10-Week: _____ 17-Week: _____</p> <p><i>Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit.</i></p>	

21. _____ If applicable, assess any non-genital symptoms reported in the participant’s interval medical/menstrual history. Provide or refer for follow-up care as needed. Document follow-up in chart notes.
22. _____ If applicable, complete/update **Adverse Experience Log** form(s) if required based on interval medical/menstrual history, clinical exams/assessments, and lab tests when available.
23. _____ If product use is held/discontinued or resumed at this visit, document the rationale for the hold/discontinuation or resumption in chart notes and/or on other applicable source documents, and on the Product Hold/Discontinuation Tracking Sheet(s), if applicable. Inform the site’s study pharmacist of the product hold/discontinuation or resumption by completing a **Study Product Hold/Resume/pK Supply/Re-Supply Slip** and delivering the white original to the pharmacy. Retain the yellow clinic copy in the participant’s study notebook. If the hold, discontinuation, or resumption affects product use in the CURRENT study period, complete/update the **Product Hold/Discontinuation Log** form (for holds/discontinuations, complete one form per reason). Refer to Protocol Section 9.4 and the SSP Manual, Section 10, for guidelines on holding, discontinuing or continuing with study product. Contact PSRT if there are any questions about study product or clinical management.
24. _____ For all participants (unless product is held):
- 24a. _____ Complete a **Prescription or Study Product Hold/Resume/pK Supply/Re-Supply Slip**.
- 24b. _____ Follow your site-specific procedure for product re-supply.
- 24c. _____ Provide panty liners and watch device as needed
- 24d. _____ After product supplies are received, document the number of product provided here →
25. _____ Provide HIV/STI risk reduction, protocol and product use adherence, and male condom counseling. Provide condoms and offer panty liners.
26. _____ Schedule the next visit and inform the participant of what to expect. Remind the participant to abstain from having sex 24 hours prior to the next visit.
27. _____ Inform the participant of availability of HIV/STI counseling, testing, and STI treatment for partners.

Follow-up Clinic Visits, Mid-Study Period Visit: Page 4 of 5

PTID:	Visit Date:
Please indicate to which follow-up visit this checklist applies: 3-Week: _____ 10-Week: _____ 17-Week: _____ <i>Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit.</i>	

28. _____ Reinforce the instructions to contact the site to request additional product, if needed, prior to the next visit and remind the participant that she will be asked to return all unused study product at her next visit.
29. _____ Reinforce site contact information and instructions to contact the site to report symptoms — especially genital symptoms — and/or to request for additional information, HIV/STI counseling, contraceptive counseling, and/or condoms, if needed, prior to the next visit.
30. _____ Provide study reimbursement

Additionally and Only If Clinically Indicated (C1-C4):

- C1. _____ Perform dipstick urinalysis on aliquot of used for pregnancy testing. Complete testing logs and transcribe protein, leukocyte, and nitrites results onto the **Safety Laboratory Results** form. Document other results (e.g., blood, glucose), if any, in visit chart note, or in other designated site-specific document, if applicable.
- C2. _____ Perform culture if positive for leukocyte esterase or nitrites; may omit if culture not standard of care for UTI diagnosis. Document additional work-up in visit chart note. If applicable, provide treatment and record on the **Concomitant Medications Log** form.
- C3. _____ Prepare urine for SDA for Gonorrhea and Chlamydia. Transcribe results onto the **STI Laboratory Results** form.
- C4. _____ Collect blood for Syphilis Serology, and/or HBsAg. Transcribe results onto the **STI Laboratory Results** form.

31. _____ Remind participant to record on her appointment card (or other designated site-specific document) the date and time of the last three doses of study product she takes prior to her next study visit.
32. _____ Complete the **Follow-up Visit** form.

Follow-up Clinic Visits, Mid-Study Period Visit: Page 5 of 5

PTID:	Visit Date:
Please indicate to which follow-up visit this checklist applies: 3-Week: _____ 10-Week: _____ 17-Week: _____	

33. _____ Complete and review all participant chart contents for the visit, including the following non-Data Fax forms:

Physical Exam Form
Pelvic Exam Diagram
LDMS Tracking Sheet

34. _____ Complete and fax all required Data Fax forms to SCHARP:

Follow-up Visit
Follow-up Genital Symptoms
Follow-up Pelvic Exam
Family Planning Methods
Safety Laboratory Results (when all results available)
Study Product Adherence and Behavior Assessment
Pharmacokinetics - Intensive

As Needed:

Follow-up Medical History Log (update/add entries as applicable)
Pelvic Laboratory Results
HIV Test Results
Genital Bleeding Assessment
Concomitant Medications Log (required for updated or new pages)
Adverse Experience Log (required if any AEs identified or updated at this visit)
Product Hold/Discontinuation Log (required if product use *in current study period* is held/discontinued or resumed at this visit)
Pregnancy Report and History (required if pregnancy identified at this visit)
Pregnancy Outcome (required if pregnancy outcome ascertained at this visit)
STI Laboratory Results

Early Termination:

Termination
End of Study Inventory

Follow-up Clinic Visits, End of Study Period Visit: Page 1 of 5

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>6-Week: _____ 13-Week: _____ 20-Week: _____</p> <p><i>Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit.</i></p>	

1. _____ Complete participant registration, confirm the participant's identity, and verify her PTID.
2. _____ Review/update locator information.
3. _____ Review chart notes and other relevant documentation from previous visit(s).
4. _____ Review elements of informed consent as needed.
5. _____ Explain the content and sequence of procedures for today's visit.
6. _____ Collect 20-60 mL urine and:
 - 6a. _____ Aliquot ~5 mL and perform pregnancy test; retain remaining urine for remainder of visit.
 - 6b. _____ Complete testing logs and transcribe result onto the form.

If the participant is pregnant:

 - 6c. _____ Inform the participant that she must discontinue product use; arrange to collect her unused study product.
 - 6d. _____ Complete a MTN 001 Pregnancy Management Worksheet (but do not complete a Product Hold/Discontinuation Log form at this time).
 - 6e. _____ Complete the Product Hold/Discontinuation Tracking Sheet(s), if applicable.
 - 6f. _____ Complete a **Study Product Hold/Resume/pK Supply/Re-Supply Slip**. Deliver the original to the pharmacy. Retain a copy in the participant's study notebook.
7. _____ Collect unused study product. If participant did not bring unused product at this visit, remind her to bring it at her next scheduled visit or make arrangements to collect product.
8. _____ Provide and explain available exam and lab test results. Provide post-test counseling, if appropriate. Provide treatment for RTIs/STIs if needed. Document treatment on the **Concomitant Medications Log**.
9. _____ Observe a single dose of the study drug. If participant does not bring sufficient unused study product to visit for use as observed dose, study product will be dispensed to participant during study visit.

Follow-up Clinic Visits, End of Study Period Visit: Page 2 of 6

PTID:	Visit Date:
Please indicate to which follow-up visit this checklist applies: 6-Week: _____ 13-Week: _____ 20-Week: _____ <i>Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit.</i>	

10. _____ Administer the **Follow-up Genital Symptoms** form.
11. _____ Perform interval medical/menstrual history; record findings on the **Follow-up Medical History Log** form. Record interval contraceptive/family planning method use and menstrual history in visit chart note.
 - 11a. _____ If genital blood/bleeding is reported, complete a **Genital Bleeding Assessment** form for unexpected genital bleeding.
12. _____ Review and update the **Concomitant Medications Log**.
13. _____ Complete the **Family Planning Methods** form by transcribing (from the visit chart note) the participant's current contraceptive/family planning methods.
14. _____ Provide contraceptive counseling. Provide and/or refer for contraception, if applicable.
15. _____ Perform physical exam as per Protocol Appendix III and record on the **Physical Exam** (non-DataFax) form.
16. _____ Confirm participant abstained from sex for at least 24 hours prior to the study visit.
17. _____ If applicable, assess any non-genital symptoms reported in the participant's interval medical/menstrual history. Provide or refer for follow-up care as needed. Document follow-up in chart notes.
18. _____ Collect blood as follows:
 - Plain tube(s) (no additive)
 - EDTA
 - CPT Tube with Sodium Citrate
19. _____ Complete an **LDMS Specimen Tracking Sheet** for stored samples

Follow-up Clinic Visits, End of Study Period Visit: Page 4 of 6

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>6-Week: _____ 13-Week: _____ 20-Week: _____</p> <p><i>Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit.</i></p>	

20. _____ Prepare blood for testing/storage at the local lab. Insert lock for specimen collection:
- Pre-dose:
 - Complete Blood Count with differential (lymphocyte) for flow cytometry calculations
 - Serum Chemistries (Phosphorous, Creatinine)
 - Liver Function Tests (AST, ALT)
 - Tenofovir
 - Plasma for storage
 - PBMC for intracellular tenofovir
 - Plasma for flow cytometry
 - Post-dose blood collection at 1, 2, 4, 6, and 8 hours:
 - Tenofovir
 - PBMC for intracellular tenofovir
21. _____ Perform pelvic exam using the Pelvic Exam Checklist and complete the Pelvic Exam Diagrams, **Follow-up Pelvic Exam** and **Pelvic Laboratory Results** forms.
- 21a. _____ During the exam, if applicable, assess genital symptoms reported during administration of the **Follow-up Genital Symptoms** form. Provide or refer for follow-up care as needed. Document follow-up in chart notes.
- 21b. _____ Collect genital PK specimens at the assigned time point and record collection times on the **Pharmacokinetics -- Intensive** form.
NOTE: Pelvic exam should be timed such that the genital specimens may be collected at the randomly assigned time point. Make sure that genital PK specimens are collected within 15 minutes of blood collection for the assigned collection time point.
- 21c. _____ **For Bronx site only:** collect rectal PK specimens within 15 AFTER collection of the vaginal PK specimens. Complete the **Rectal PK** form.

Follow-up Clinic Visits, End of Study Period Visit: Page 4 of 6

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>6-Week: _____ 13-Week: _____ 20-Week: _____</p> <p><i>Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit.</i></p>	

22. _____ Complete/update **Adverse Experience Log** form(s) if required based on interval medical/menstrual history, clinical exams/assessments, and lab tests.
23. _____ If product use is held/discontinued or resumed at this visit, document the rationale for the hold/discontinuation or resumption in chart notes and/or on other applicable source documents, and on the Product Hold/Discontinuation Tracking Sheet(s), if applicable. Inform the site's study pharmacist of the product hold/discontinuation or resumption by completing a **Study Product Hold/Resume/pK Supply/Re-Supply Slip** and delivering the white original to the pharmacy. Retain the yellow copy in the participant's study notebook. Refer to Protocol Section 9.4 and the SSP Manual, Section 10, for guidelines on holding, discontinuing or continuing with study product. Contact PSRT if there are any questions about study product or clinical management.
24. _____ Record/transcribe the date and time of the participant's last 3 doses of study product onto the **Study Product Adherence and Behavior Assessment** form.
25. _____ Administer the **Study Product Adherence and Behavior Assessment** form, the **Acceptability Assessment** form (Weeks 6 and 13 only), the **Final Acceptability Assessment** form (Week 20 only), and the **Product Sharing Assessment** form.
26. _____ Provide HIV/STI risk reduction, protocol and product use adherence, and male condom counseling.
27. _____ Provide condoms, offer panty liners, and provide referrals if needed/requested.
28. _____ Schedule the next visit and inform the participant of what to expect. Also inform the participant of availability of HIV/STI counseling, testing, and STI treatment for partners.
29. _____ Reinforce site contact information and instructions to contact the site to report symptoms — especially genital symptoms — and/or to request for additional information, HIV/STI counseling, and/or condoms, if needed, prior to the next visit.
30. _____ Provide study reimbursement.

Follow-up Clinic Visits, End of Study Period Visit: Page 5 of 6

PTID:	Visit Date:
Please indicate to which follow-up visit this checklist applies: 6-Week: _____ 13-Week: _____ 20-Week: _____	

Additionally Only If Clinically Indicated (C1-C4):

C1. _____ Perform dipstick urinalysis on aliquot of urine used for pregnancy testing. Complete testing logs and transcribe protein, leukocyte, and nitrites results onto the **Safety Laboratory Results** form. Document other results (e.g., blood, glucose), if any, in visit chart note, or in other designated site-specific document, if applicable.

C2. _____ Perform culture if positive for leukocyte esterase or nitrites; may omit if culture not standard of care for UTI diagnosis. Document additional work-up in visit chart note. If applicable, provide and record treatment on the **Concomitant Medications Log** form.

C3. _____ Prepare urine for SDA for Gonorrhea and Chlamydia. Transcribe results onto the **STI Laboratory Results** form.

C4. _____ Collect blood for Syphilis Serology and/or HBsAg. Transcribe results onto the **STI Laboratory Results** form.

31. _____ Document the visit in a signed and dated chart note. Complete and review all participant chart contents for the visit, including Follow-up Medical History
32. _____ Complete **Follow-up Visit** form
33. _____ Complete and review all participant chart contents for the visit, including the following non-Data Fax forms:
- Physical Exam Form
 - Pelvic Exam Diagram
 - LDMS Specimen Tracking Sheet

Follow-up Clinic Visits, End of Study Period Visit: Page 6 of 6

PTID:	Visit Date:
Please indicate to which follow-up visit this checklist applies: 6-Week: _____ 13-Week: _____ 20-Week: _____	

34. _____ Complete and fax all required Data Fax forms to SCHARP:

- Follow-up Visit
- Follow-up Genital Symptoms
- Family Planning Methods
- Follow-up Pelvic Exam
- Pelvic Laboratory Results
- Safety Laboratory Results (when all results available)
- Study Product Adherence and Behavior Assessment
- Product Sharing Assessment
- Acceptability Assessment (Week 6 and 13 only)
- Final Acceptability Assessment (Week 20 only)
- Pharmacokinetics – Intensive
- Rectal PK (if applicable)
- Flow Cytometry

As Needed:

- Follow-up Medical History Log (update/add entries as needed)
- Concomitant Medications Log (required for updated or new pages)
- Adverse Experience Log (required if any AEs identified or updated at this visit)
- Pregnancy Report and History (required if pregnancy identified at this visit)
- Pregnancy Outcome (required if pregnancy outcome ascertained at this visit)
- STI Laboratory Results

Early Termination:

- Termination
- End of Study Inventory

Follow-up Clinic Visits, Study Period 2 and 3 Start: Page 1 of 5

PTID: _____	Visit Date: _____
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>7-Week: _____ 14-Week: _____</p>	

1. _____ Complete participant registration, confirm the participant's identity, and verify her PTID.
2. _____ Review/update locator information.
3. _____ Review chart notes and other relevant documentation from previous visit(s).
4. _____ If indicated, collect unused study product. If participant did not bring unused product at this visit, remind her to bring it at her next scheduled visit or make arrangements to collect product.
5. _____ Review elements of informed consent as needed.
6. _____ Explain the content and sequence of procedures for today's visit.
7. _____ Collect 20-60 mL urine and:
 - 7a. _____ Aliquot ~5 mL and perform pregnancy test; retain remaining urine for remainder of visit.
 - 7b. _____ Complete testing logs and transcribe result onto the form.

If the participant is pregnant:

 - 7c. _____ Inform the participant that she must discontinue product use; arrange to collect her unused study product.
 - 7d. _____ Complete a MTN 001 Pregnancy Management Worksheet
 - 7e. _____ Complete/update the Product Hold/Discontinuation Log Tracking Sheet(s), if applicable.
 - 7f. _____ Complete a **Study Product Hold/Resume/PK Supply/Re-Supply Slip**. Deliver the original copy to the pharmacy. Retain a copy in the participant's study notebook.
8. _____ Provide and explain available exam and lab test results. Provide post-test counseling, if appropriate. Provide treatment for RTIs/STIs if needed. Document treatment on the **Concomitant Medications Log**.
9. _____ Administer the **Follow-up Genital Symptoms** form
10. _____ Perform interval medical/menstrual history; record findings on the **Follow-up Medical History Log** form. Record interval contraceptive/family planning method use and menstrual history in the visit chart note.
 - 10a. _____ Complete a **Genital Bleeding Assessment** form for unexpected genital bleeding.

Follow-up Clinic Visits, Study Period 2 and 3 Start: Page 2 of 5

PTID: _____	Visit Date: _____
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>7-Week: _____ 14-Week: _____</p>	

11. _____ Review and update the **Concomitant Medications Log**.

12. _____ Complete the **Family Planning Methods** form by transcribing (from the visit chart note) the participant's current contraceptive/family planning methods.

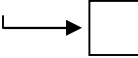
13. _____ Provide contraceptive counseling. Provide or refer for contraception, if applicable.

14. _____ Collect blood as follows:
 - Plain tube(s) (no additive)
 - EDTA

15. _____ Provide HIV pre-test, HIV/STI risk reduction and condom counseling.

16. _____ Prepare blood for testing at the local lab.
 - HIV Serology
 - CBC (hemoglobin, hematocrit, WBC, PLT)
 - Serum Chemistries (Phosphorous, Creatinine)
 - Liver Function Tests (AST, ALT)

17. _____ For all participants (unless product is held):
 - 17a. _____ Complete a **Prescription**.
 - 17b. _____ Follow your site-specific procedures for product re-supply. The white original prescription will be taken to the pharmacy. Retain the yellow clinic copy in the participant's study notebook.
 - 17c. _____ After product supplies are received, provide the supplies to the participant and document the amount of product provided here



18. _____ Perform physical exam and record on the **Physical Exam** form.

19. _____ Perform pelvic exam using the Follow-Up Pelvic Exam Checklist and complete the Pelvic Exam Diagrams, **Follow-up Pelvic Exam** and **Pelvic Laboratory Results** (if indicated) forms.
 - 19a. _____ During exam, if applicable, assess genital symptoms reported during administration of the **Follow-up Genital Symptoms** form. Provide or refer for follow-up care as needed. Document follow-up in chart notes.

Follow-up Clinic Visits, Study Period 2 and 3 Start: Page 3 of 5

PTID: _____	Visit Date: _____
Please indicate to which follow-up visit this checklist applies: 7-Week: _____ 14-Week: _____	

20. _____ If applicable, assess any non-genital symptoms reported in the participant's interval medical/menstrual history. Provide or refer for follow-up care as needed. Document follow-up in chart notes.
21. _____ Complete/update **Adverse Experience Log** form(s) if required based on interval medical/menstrual history, clinical exams/assessments, and lab tests.
22. _____ If product use is held/discontinued or resumed at this visit, document the rationale for the hold/discontinuation or resumption in chart notes and/or on other applicable source documents, and on the Product Hold/Discontinuation Tracking Sheet(s), if applicable. Inform the site's study pharmacist of the product hold/discontinuation by completing a **Study Product Hold/Resume/PK Supply/Re-Supply Slip** and delivering the white original to him/her. Retain the yellow clinic copy in the participant's study notebook. If the hold, discontinuation, or resumption affects product use in the CURRENT study period, complete/update the Product Hold/Discontinuation Log form (for holds/discontinuations, complete one form per reason). Refer to Protocol Section 9.4 and the SSP Manual, Section 10, for guidelines on holding, discontinuing or continuing with study product. Contact PSRT if there are any questions about study product or clinical management
23. _____ Provide condoms, offer panty liners, and provide referrals if needed/requested.
24. _____ Schedule the next visit and inform the participant of what to expect at that visit. Also inform the participant of availability of HIV/STI counseling, testing, and STI treatment for partners.
25. _____ Reinforce site contact information and instructions to contact the site to report symptoms — especially genital symptoms — and/or to request for additional information, HIV/STI counseling, and/or condoms, if needed, prior to the next visit.
26. _____ Provide study reimbursement.
27. _____ Remind participant to record on her appointment card (or other designated site-specific document) the date and time of the last three doses of study product she takes prior to next study visit. Also, remind participant to bring in unused product at next study visit.
28. _____ Complete **Follow-up Visit** form

Follow-up Clinic Visits, Study Period 2 and 3 Start: Page 5 of 5

PTID:	Visit Date:
Please indicate to which follow-up visit this checklist applies: 7-Week: _____ 14-Week: _____	

Additionally Only If Clinically Indicated (C1-C4):

- C1. _____ Perform dipstick urinalysis on aliquot of urine used for pregnancy testing. Complete testing logs and transcribe protein, leukocyte, and nitrites onto the **Safety Laboratory Results** form. Document other results (e.g., blood, glucose), if any, in visit chart note, or in other designated site-specific document, if applicable.
- C2. _____ Perform culture if positive for leukocyte esterase or nitrites; may omit if culture not standard of care for UTI diagnosis. Document additional work-up in visit chart note. If applicable, provide treatment and record treatment on the **Concomitant Medications Log**.
- C3. _____ Prepare urine for SDA for Gonorrhea and Chlamydia. Transcribe results onto the STI Laboratory Results form.
- C4. _____ Collect blood for Syphilis Serology and/or HBsAg. Transcribe results onto the **STI Laboratory Results** form.

29. _____ Document the visit in a signed and dated chart note. Complete and review all participant chart contents for the visit, including the following non-Data Fax forms:

Physical Exam
Pelvic Exam Diagrams

30. _____ Complete and fax all required Data Fax forms to SCHARP Data Fax:

Follow-up Visit
Follow-up Genital Symptoms
Follow-up Pelvic Exam
Family Planning Methods
Safety Laboratory Results (when all results available)
STI Laboratory Results (when all results are available)

As Needed:

Follow-up Clinic Visits, Study Period 2 and 3 Start: Page 5 of 5

PTID:	Visit Date:
Please indicate to which follow-up visit this checklist applies: 7-Week: _____ 14-Week: _____	

Follow-up Medical History Log (update/add entries as needed)
Pelvic Laboratory Results
Concomitant Medications Log (required for updated or new pages)

Adverse Experience Log (required if any AEs identified or updated at this visit)
Product Hold/Discontinuation Log (required if product use *in current study period* is held/discontinued or resumed at this visit)
Pregnancy Report and History (required if pregnancy identified at this visit)
Pregnancy Outcome (required if pregnancy outcome ascertained at this visit)

Early Termination:

Termination
End of Study Inventory

Follow-up Clinic Visit, Study Termination Visit: Page 1 of 4

PTID: _____	Visit Date: _____
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1. _____ Complete participant registration, confirm the participant's identity, and verify her PTID.
2. _____ Review/update locator information.
3. _____ Review chart notes and other relevant documentation from previous visit(s).
4. _____ Review elements of informed consent as needed.
5. _____ Explain the content and sequence of procedures for today's visit.
6. _____ Collect 20-60 mL urine and:
 - 6a. _____ Aliquot ~5 mL and perform pregnancy test; retain remaining urine for remainder of visit.
 - 6b. _____ Complete testing logs and transcribe result onto the form.

If the participant is pregnant:

 - 6e. _____ Complete a **Pregnancy Report and History** form.
 - 6f. _____ Explain to the participant that a post-study contact will be required to ascertain the outcome of her pregnancy.
7. _____ Collect any unused study product to return to pharmacy.
8. _____ Provide and explain available exam and lab test results from previous visit. Provide post-test counseling, if appropriate. Provide treatment for RTIs/STIs if needed. Document treatment on the **Concomitant Medications Log**.
9. _____ Administer the **Follow-up Genital Symptoms** form
10. _____ Perform interval medical/menstrual history; record findings on the **Follow-up Medical History** form. Record interval contraceptive/family planning method use and menstrual history in visit chart note.
 - 9a. _____ If genital blood/bleeding is reported, conduct a pelvic exam. Complete a **Genital Bleeding Assessment** form for unexpected genital bleeding.
11. _____ Review and update the **Concomitant Medications Log**.
12. _____ Complete the **Family Planning Methods** form by transcribing (from the visit chart note) the participant's current contraceptive/family planning methods.
13. _____ Provide contraceptive counseling. Provide/refer for contraception, if applicable.

Follow-up Clinic Visit, Study Termination Visit: Page 2 of 4

PTID: _____	Visit Date: _____
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14. _____ If applicable, assess any non-genital symptoms reported in the participant's interval medical/menstrual history. Provide or refer for follow-up care as needed. Document follow-up in chart notes.
15. _____ Complete/update **Adverse Experience Log** form(s) if required based on interval medical/menstrual history, clinical exams/assessments, and lab tests. Contact PSRT if there are any questions about management.
16. _____ Review all **Adverse Experience Log** forms completed for the participant and update the forms as needed. For AEs that are "continuing" at this visit, update the status/outcome of the AE to "continuing at end of study participation."
- ☞ Any SAEs or EAEs identified as continuing at this visit must be re-evaluated within 30 days. Any previously reported AEs found to have increased in severity at this visit also must be re-evaluated in 30 days. Consult with the IoR/designee to establish a clinically appropriate follow-up plan for the participant and document the plan on the participant's file.*
17. _____ Provide HIV pre-test counseling; during pre-test counseling, reinforce that although this is the participant's last scheduled study visit, additional visits and tests will be done if needed to confirm or clarify her HIV status.
18. _____ Collect blood as follows:
 plain tube(s) (no additive)
 EDTA
19. _____ Complete an **LDMS Specimen Tracking Sheet** for stored samples.
20. _____ Prepare blood for testing/storage at the local lab.
 HIV Serology
 CBC (hemoglobin, hematocrit, WBC, PLT)
 Serum Chemistries (Phosphorous, Creatinine)
 Liver Function Tests (AST, ALT)
 Plasma for storage
21. _____ If participant has been randomized to or selected for the In-Depth interview, is evaluable (i.e., does not meet criteria for replacement), and has given consent for participation, conduct the recorded in-depth interview.
22. _____ Provide HIV/STI risk reduction and male condom counseling. Also inform the participant of availability of HIV/STI counseling, testing, and STI treatment for partners.
23. _____ Provide condoms, and/or referrals if needed/requested.
24. _____ Complete **Follow-up Visit** form.

Follow-up Clinic Visit, Study Termination Visit: Page 3 of 4

PTID:	Visit Date:
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25. _____ Completion **Termination** form.
26. _____ Complete **End of Study Inventory** form.
27. _____ Reinforce site contact information.
28. _____ Provide study reimbursement.

Additionally Only If Clinically Indicated (C1-C6):

- C1. _____ Perform dipstick urinalysis on aliquot of urine used for pregnancy testing. Complete testing logs and transcribe protein, leukocyte, and nitrites results onto the **Safety Laboratory Results** form. Document other results (e.g., blood, glucose), if any, in visit chart note, or in other designated site-specific document, if applicable.
- C2. _____ Perform if positive for leukocyte esterase or nitrites; may omit if culture not standard of care for UTI diagnosis. Document additional work-up in visit chart note. If applicable, provide treatment and record on the **Concomitant Medications Log** form.
- C3. _____ Prepare urine for SDA for Gonorrhea and Chlamydia. Transcribe results onto the **STI Laboratory Results** form.
- C4. _____ Collect blood for Syphilis Serology and/or HBsAg. Transcribe results onto the **STI Laboratory Results** form.
- C5. _____ Perform physical exam and complete non-DataFax **Physical Exam** form.
- C6. _____ Perform pelvic exam. Complete the **Follow-up Pelvic Exam** form and, if applicable, the Pelvic **Laboratory Results** form.

29. _____ If indicated, treat or refer any findings.
30. _____ Schedule next visit to provide the participant with any remaining lab test results, to provide counseling if indicated, and to follow-up on any AEs, if indicated.
31. _____ Document the visit in a signed and dated chart note. Complete and review all participant chart contents for the visit, including the following non-Data Fax form:

LDMS Specimen Tracking Sheet

Follow-up Clinic Visit, Study Termination Visit: Page 4 of 4

PTID:	Visit Date:
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32. _____ Complete and fax all required Data Fax forms to SCHARP Data Fax:

Termination
Follow-up Visit
Family Planning Methods
STI Laboratory Results
End of Study Inventory
Follow-up Genital Symptoms
Safety Laboratory Results (when all results available)

As Needed:

Follow-up Medical History Log (update/add new entries as needed)
Concomitant Medications Log (required for updated or new pages)
Adverse Experience Log (required if any AEs identified or updated at this visit)
Pregnancy Report and History (required if pregnancy identified at this visit)
Pregnancy Outcome (required if pregnancy outcome ascertained at this visit)

➤ *Note: Once the Study Termination Visit is completed, complete the MTN 001 Study Exit worksheet.*

Pelvic Exam

Screening, Enrollment, 6-week, 13-week, 20-week

Page 1 of 2

PTID:	Visit Date:
Please indicate to which visit this checklist applies:	
Screening : _____ Enrollment: _____ 6-week: _____ 13-week: _____ 20-week: _____	

1. _____ Explain the exam procedures to the participant and answer any participant questions.
2. _____ Using a pencil, write the PTID and specimen collection date on the frosted side of two microscope slides for vaginal wet mount. Then affix a SCHARP-provided PTID label to the other side of each slide (under the pencil markings) and write the specimen collection date in ink on each label.
3. _____ Affix a SCHARP-provided PTID label to a glass or plastic tube containing approximately six drops (100 µL) of saline. Write the specimen collection date in ink on the label.
4. _____ Position and drape the participant comfortably.
5. _____ Palpate inguinal lymph nodes. Document abnormal findings on the **Screening and Enrollment Pelvic Exam** form or the **Follow-up Pelvic Exam** form at follow-up visits.
6. _____ Inspect external genitalia: Note all findings on the Pelvic Exam Diagrams. Document abnormal findings on the **Screening and Enrollment Pelvic Exam** form or the **Follow-up Pelvic Exam** form at follow-up visits.
7. _____ Insert speculum, using warm water as lubricant if needed. Observe general state and note the position of the cervix.
8. _____ Assess for homogenous discharge. Record observation on the **Pelvic Laboratory Results** form.
9. _____ Inspect cervix and vagina: Note all findings on the **Pelvic Exam Diagrams** form. Document abnormal findings on the **Screening and Enrollment Pelvic Exam** form or the **Follow-up Pelvic Exam** form at follow-up visits.
10. _____ **Screening Visit only:** If indicated, perform Pap smear per site SOP.
11. _____ **Screening Visit only:** Record the size of speculum used and position of the participant's cervix on the **Pelvic Exam Diagrams** (non-DataFax) form.
12. _____ Collect vaginal fluids from the lateral vaginal wall via swab and swab fluids onto the pH strip. Record pH on the **Pelvic Laboratory Results** form.

Pelvic Exam
Screening, Enrollment, 6-week, 13-week, 20-week
Page 2 of 2

PTID:	Visit Date:
Please indicate to which visit this checklist applies:	
Screening : _____ Enrollment: _____ 6-week: _____ 13-week: _____ 20-week: _____	

13. _____ Swab vaginal fluids from the lateral vaginal wall for wet prep; proceed immediately to Step 13a or place the swab in a labeled glass or plastic tube containing approximately six drops (100 µL) of saline to allow for non-immediate slide preparation and evaluation, as follows (see also SSP Section 12):
- 13a. _____ Smear vaginal fluids from the swab onto two labeled slides.
- 13b. _____ Apply KOH to one slide, perform whiff test, then apply cover slip.
- 13c. _____ Apply saline to the second slide, emulsify, then apply cover slip. Immediately evaluate for trichomonads, yeast buds, pseudohyphae, and clue cells.
- 13d. _____ Evaluate KOH slide for yeast buds and pseudohyphae.
- 13e. _____ If slides are read in-clinic by clinical staff, record results directly onto the **Pelvic Laboratory Results** form. If slides are read by lab staff (either in the local lab or a designated in-clinic lab area) complete testing logs and then transcribe results onto the **Pelvic Laboratory Results** form.

For screening and enrollment visits: If lab results are positive for trichomonads, yeast buds, pseudohyphae and/or clue cells, the participant is ineligible, with the exception of asymptomatic BV and asymptomatic vulvovaginal candidiasis. STOP. Inform the participant that she is ineligible. Otherwise eligible participants diagnosed with RTI and/or UTI may be enrolled after completing treatment and all symptoms have resolved. Retain documentation completed thus far, and complete the form, but do not fax any forms to SCHARP.

14. _____ Perform bimanual exam, if indicated. Document abnormal findings on the **Screening and Enrollment Pelvic Exam** form or the **Follow-up Pelvic Exam** form at follow-up visits.
15. _____ **6- week, 13-week and 20-week visits only:**
- 15a. _____ Collect CVL sample, cytologic brush specimens, and vaginal biopsies for pK analysis. Genital samples should be collected within 15 minutes of blood collection for pK analysis.
- NOTE: Blood may be collected prior to or following genital sample collection; genital sample collection must follow all other pelvic exam/lab procedures. CVL samples need to be placed on ice immediately and then frozen.*
16. _____ **For Bronx site only at 6- week, 13-week and 20-week visits only:**
- 16a. _____ Collect rectal samples for pK analysis within 15 minutes *after* vaginal pK sample collection; put on ice for up to 4 hours, then freeze.
17. _____ At **Enrollment visit only**: collect CVL sample.

Pelvic Exam
3-week, 7-week, 10-week, 14-week, 17-week
Page 1 of 1

PTID:	Visit Date:
Please indicate to which visit this checklist applies:	
3-Week : _____ 7-Week: _____ 10-week: _____ 14-week: _____ 17-week: _____	

1. _____ Explain the exam procedures to the participant and answer any participant questions.
2. _____ Position and drape the participant comfortably.
3. _____ Palpate inguinal lymph nodes. Document abnormal findings on the **Follow-up Pelvic Exam** form.
4. _____ Inspect external genitalia: Note all findings on the **Pelvic Exam Diagrams** form. Document abnormal findings on the **Follow-up Pelvic Exam** form.
5. _____ Insert speculum, using warm water as lubricant if needed. Observe general state and note the position of the cervix.
6. _____ Assess for homogenous discharge. If indicated, perform wet mount and complete the **Pelvic Laboratory Results** form.
7. _____ Inspect cervix and vagina: Note all findings on the **Pelvic Exam Diagrams** (non-DataFax) **form**. Document abnormal findings on the **Follow-up Pelvic Exam** form.
8. _____ If indicated, perform Herpes culture (at sites where standard of care for diagnosis)
9. _____ Perform bimanual exam, if indicated. Document abnormal findings on the **Follow-up Pelvic Exam** form.

Section 8. Participant Retention

This section presents information related to definitions, requirements, and procedures for participant retention in MTN 001.

8.1 Retention Definitions

The term “retention” generally refers to completion of follow-up visits and procedures as specified in a study protocol. This definition must be operationalized for any study, and operational definitions usually reflect the primary objectives and endpoints of a study. For MTN 001, two retention measures are planned to be used, one during the study and one at the end of the study. Additional retention measures may be defined and used during the study if desired by the Protocol Chair and/or Protocol Statisticians.

- During the study, retention for scheduled (required) follow-up visits will be defined based on whether participants complete some part of the required scheduled visits within the allowable visit window. Participants who complete all or part of their scheduled visits within the allowable visit window will be considered “retained” for those visits.
- Overall retention is calculated as the percentage of the total number of visits completed by all participants (within their allowable visit window) divided by the number of visits expected for all participants. A visit is considered expected for a participant once the allowable window closes, regardless of whether or not a participant is lost to follow-up or terminated early from the study.

As indicated above, participants who do not complete a particular scheduled visit within the allowable window, but then complete the next scheduled visit, will not be considered retained for the missed visit, but will be considered retained for the next scheduled visit. Thus retention rates can fluctuate over time and across visits. Importantly, retention shortfalls can be made up by ensuring that participants return for their next scheduled visit after missing a visit.

The MTN Statistical and Data Management Center (SDMC) will generate reports during the study presenting retention rates for key study visits designated by the Protocol Team. The SDMC also will generate a final end-of-study retention rate for each site after the study is completed.

8.2 Retention Requirements

Each study site will target retention of at least 95 percent of enrolled study participants for each scheduled follow-up visit. The purpose of the 95 percent retention target is to ensure the accuracy of study results. The pharmacokinetics and adherence measures tested in MTN 001 will be estimated by comparing these measures observed in each participant in all three study product periods to other participants assigned to various sequence groups. Low retention rates can have serious impacts on the accuracy of the study results because we cannot know if participants who do not return for scheduled study visits have varying levels of study drug absorbed into their bodies or have varying levels of adherence. In each sequence group, the observed levels of absorbed vaginal and oral tenofovir could be higher or lower than the true amount, but it is not possible to determine the direction of the error. Furthermore, because this is a crossover study, it is important to obtain complete data for each participant as she will be assigned to each of the three study periods. To avoid these problems, and thereby avoid bias in the study results, high participant retention rates must be maintained throughout the study.

8.3 Retention SOPs

Site staff is responsible for establishing a standard operating procedure (SOP) for participant retention to meet the study retention goal of 95 percent. The SOP should minimally contain the following elements:

- Site-specific retention goals
- Methods for tracking actual retention versus retention goals
- Procedures for completing and updating participant locator information
- Site-specific definition of “adequate” locator information (for purposes of determining participant eligibility)
- Visit reminder methods and timeframes
- Methods and timeframes for identifying when a visit has been missed
- Planned retention methods, including what outreach/locator efforts are taken within 24 hours, 1-3 days, 1 week, and 2 weeks after a missed visit
- Methods for timely evaluation of the utility of retention methods
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements (if not specified elsewhere)
- QC/QA procedures related to the above (if not specified elsewhere)

8.4 Obtaining and Updating Locator Information

Successful retention begins with collection of exhaustive locator information from each study participant. All study participants will be asked to provide locator information during the study screening process, and to continually review/update this information during follow-up. Provision of "adequate" locator information during screening is a study eligibility requirement and each site must specify its definition of adequate locator information in its retention SOP.

Each study site is encouraged to develop an exhaustive locator form to maximize contact effectiveness and participant retention. Sites also may wish to consider having outreach workers accompany participants to their homes or other community based locations to verify or further clarify their locator details. Potential locator items include:

- Participant's full name, alias, and/or nickname; government-issued identification number; home address; home phone number; mobile phone number; pager number; work address; work phone number; fax number; e-mail address; daytime and nighttime locations, meeting places, hangouts.
- Walking/driving/public transport directions and/or pictorial map to the participant's home, workplace, etc.
- Name, address, telephone number, and/or other contact information for stable community contacts (i.e., participant family members and friends) who typically know the whereabouts of the participant.

Note: Although contact information for a participant's current primary partner will likely be useful, contact information for other contacts also should be collected, since the participant's relationship with this partner could change during the course of the study.

- Name, address, telephone number, and/or other contact information for the participant's health care provider, school or training program; church or other place of worship; social service case worker; counselor, rehabilitation provider, etc.; participant's child's school and health care provider.
- Name, address, telephone number, and/or other contact information for support groups, shelters, food pantries, and other social service organizations used by the participant.

During the informed consent process and when collecting locator information, study participants must be informed that their locator sources will be contacted if study staff are unable to locate the participant directly. Study staff will negotiate with the participant how they will identify themselves when locator sources are contacted. Arrangements agreed upon with the participant should be documented on the locator form.

Study staff should view every participant contact as an opportunity to update the participant's locator information. When updating locator information, actively review each item on the locator form to determine whether the information is still current (i.e., rather than simply asking "Has any of your information changed since your last visit?"). Staff should also, probe for additional information that the participant was not able or willing to provide at previous visits.

8.5 Retention Tips

Some general strategies for maximizing participant retention are as follows:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at each study visit. When participants complete scheduled visits, acknowledge and comment on their commitment, time, and effort devoted to the study.

- Thorough explanation of the importance of completing all study periods to the overall success of the study.
- Collection of detailed locator information at the study screening visit, and active review and updating of this information at each subsequent visit.
- Use of mapping techniques to establish the location of participant residences and other locator venues.
- Mobilization of trained outreach workers or “tracers” to complete in-person contact with participants at their homes and/or other community locations.
- Dedicate adequate staff time and effort to retention efforts.
- Work with community members to identify the most applicable contact and retention strategies for the local study population, including the type and amount of participant incentives.
- Keep participants and community members up-to-date on study progress to foster a sense of partnership and ownership of the study (through the use of participant newsletters, for example).
- Inform local service providers who interact with the local study population about the study, so that they also can express their support for the study.
- Host gatherings, parties and/or other social events for participants.
- Host social, educational, and/or other “male involvement” events for participants’ partners.
- Use the visit calendar created for the participant to identify when participants’ scheduled visits are due and/or overdue. Establish routine mechanisms to remind both study staff and participants of upcoming scheduled visits.
- Schedule all follow-up visits at the participant’s Enrollment Visit. Thereafter, at each follow-up visit, confirm the scheduling of the next visit and give the participant an appointment card with the scheduled visit date and time noted.
- Prepare a calendar of scheduled visits for each enrolled participant, based on her enrollment date, or offer a planner/calendar as an incentive and note all study appointments in the planner/calendar. Note the dates of all scheduled visits in the participant’s file for easy reference.
- For participants who demonstrate a pattern of late or missed appointments, schedule follow-up visits for the beginning of the allowable visit window (i.e., up to one week before the actual target date) to allow maximum time for re-contact and re-scheduling if needed.
- Pay close attention to the allowable visit window and prioritize retention efforts for participants nearing the end of the window. Organize daily caseloads and work assignments based on these priorities.

- Follow-up on missed appointments with an attempt to re-contact/re-schedule within 24 hours (preferably on the same day). Continue these efforts per the local retention SOP until contact is made.
- Keep locator information up-to-date and maintain thorough documentation of all efforts to contact the participant. Keep all this information in an organized manner, so that different staff members can easily review the information and contribute to re-contact efforts when necessary.
- Make use of all information collected on the participant's locator form. Even if a locator source is not useful/successful on one occasion, try it again later.
- Make use of all available contact methods (e.g. phone, mail, home visits, street outreach, newspapers, e-mail/internet). Also make use of other available locator information sources, such as phone and postal directories and other public registries.
- Post outreach workers at other local service organizations utilized by the study population.
- Attempt contact with the participant at different times during the day and the week, including evenings and weekends.
- If a participant reports that she wishes to discontinue participation in the study, explain that she is always welcome to come back if she wishes.
- If a participant reports that she wishes to discontinue her participation in the study, ask if she would be willing to complete an early Study Exit Visit, or at least a final blood draw (for safety labs and HIV testing) and urine collection for pregnancy testing. Please document her response in her chart notes. If the participant is willing to complete an early Study Exit Visit, complete all Week 21 Visit procedures and CRFs. If the participant is only willing to give blood and urine for safety labs, HIV, and pregnancy testing, complete the following CRFs: Interim Visit, Safety Laboratory Results, Termination, and End of Study Inventory. If the participant is unwilling to complete any additional study procedures, reinforce site contact information and explain that she is always welcome to return to the clinic if she wishes. Then complete a Termination form and End of Study Inventory form for her, and fax these forms to SCHARP.

If a participant wishes to discontinue participation in the study, her wishes must be respected. At the time when the participant states that she wishes to discontinue participation, study staff must document the participant's stated wishes in a detailed chart note that includes the following information:

- Why the participant wishes to leave the study.
- Whether the participant is willing to have any further contact with study staff in the future and, if so, for what purpose, at what frequency, and through what methods.
- If the participant has any pending laboratory test results, whether and how she is willing to be contacted for purposes of receiving her results.

- Whether and how the participant wishes to be contacted for purposes of learning the results of the study (when results are available).
- Please remember that for MTN 001, home visits are not allowed except to collect remaining unused study product, if necessary.

Section 9. Study Product Considerations for Non-Pharmacy Staff

This section provides information and instructions for non-pharmacy staff related to the request, transport, and delivery of MTN 001 study products for study participants. Record keeping requirements for non-pharmacy staff also are provided. Associated instructions for pharmacy staff are provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*, which will be made available to each study site Pharmacist of Record (PoR) by the DAIDS PAB Protocol Pharmacist. Please also refer to related information in Sections 4 and 6 of this manual.

9.1 Gel Use Instructions

During the 6-week gel only period, or dual use period, participants will be instructed to insert the gel — the entire contents of one applicator — into the vagina, once daily.

Vaginal administration of the study gel should occur before bedtime, or the longest period of rest. If a participant misses a dose, she must insert vaginally the missed dose as soon as possible, unless the next dose is estimated to be due within six hours. If the next dose is estimated to be due within six hours, the missed dose must be skipped. The next dose will be inserted vaginally as originally scheduled.

Detailed instructions for application of gel are listed in Figure 9-1 below. A listing of frequently asked gel use questions, and answers to these questions, is provided in Section Appendix 9-1.

Figure 9-1
Gel Use Instructions for MTN 001

Removing the Applicator: <ul style="list-style-type: none">• Tear open the opaque, plastic wrapper• Remove applicator from wrapper
Inserting the Applicator: <ul style="list-style-type: none">• Choose a comfortable position to insert the applicator, for example lying on your back with your knees bent or standing up with one leg raised and resting on an object• Hold the filled applicator about half-way along the barrel• Gently insert the filled applicator into the vagina as far as it will comfortably go• Slowly press the plunger until it stops to deposit the gel into the vagina• Withdraw the applicator from the vagina <p><i>* Note: Study Staff should inform participants that they may experience some minor gel leakage from the vagina, when inserting the filled applicator into the vagina</i></p>
Follow up Information: <ul style="list-style-type: none">• Dispose of the <i>used</i> applicator and plastic wrapper. If you can not dispose of your study supplies at your home or off site, you can bring your used applicators to the study clinic for disposal in accordance with applicable biowaste requirements (See SSP Section 9.5.2)• Bring all of your <i>unused</i> study gel tubes to your next visit

9.2 Tablet Use Instructions

During the 6-week tablet only period or dual use period, participants will be instructed to take one tenofovir disoproxil fumarate 300 mg tablet, by mouth, once daily for the six-week tablet only period and the six-week dual use period.

If a participant misses a dose, she must take the missed dose as soon as possible, unless the next dose is estimated to be due within 6 hours. If the next dose is estimated to be due within six hours, the missed dose must be skipped. The next dose will be taken orally as originally scheduled.

In the dual use period, both the pill and gel should be administered at approximately the same time, before the longest period of rest.

9.3 Observed dose of study product at End of Study Period Visits

Study staff will observe a single dose of study gel, tablet, or both gel and tablet, for participants at their End of Study Period Visits, to assess Pharmacokinetic measures. Each clinic will determine the appropriate method for the observation of the gel insertion. It is acceptable if the participant is given some privacy by placing a curtain between the study staff and the participant during gel insertion. When privacy is given, the study staff needs to ensure that the gel has been vaginally inserted. Please also refer additional information in Sections 6 and 7 of this manual. Study staff may permit participants to administer the gel dose behind a curtain while they remain in the exam room with the participant. Following the gel dose insertion, participants will be instructed to ambulate prior to conducting PK procedures, but taking into consideration the required timeframe between product use and PK procedures.

9.4 Distributing Study Product During Visits

Upon receipt of a completed and signed MTN 001 Prescription, or a completed and signed MTN 001 Study Product Re-Supply Slip (during mid-period visits), pharmacy staff will dispense product supplies for study participants as per the DAIDS Pharmacy Guidelines. Study gel cartons will be sealed with tamper-evident tape and labeled by the PoR in accordance with local requirements. In all cases, labeling will include the PTID of the participant for whom the supplies have been prepared and to whom they should be dispensed/delivered.

Participant-specific study product supplies may be dispensed to participants in one of three ways:

- From the pharmacy directly to the participant
- From the pharmacy to authorized clinic staff who will then deliver the study product to the participant
- From the pharmacy to authorized transport staff (or “runners”) who will transfer the study product to authorized clinic staff who will then deliver the study product to the participant

Each study site must designate its dispensing method in MTN 001 standard operating procedures (SOPs) for participant randomization and product re-supply during follow-up. These SOPs should be developed with input from both pharmacy and clinic staff. Further information is provided in Sections 9.4.1-9.4.3 below.

9.4.1 Dispensing from the Pharmacy Directly to Participants

At sites choosing to dispense study product directly from the pharmacy to participants, prescriptions and study product re-supply slips are expected to be delivered to the pharmacy by the participants themselves, although this may be done by clinic staff or a runner. Upon receipt of a completed and signed prescription or study product re-supply slip, the PoR will prepare either two cartons of study gel (14 pre-filled applicators per carton) and/or one bottle of 30 tenofovir disoproxil fumarate tablets entered on the prescription or study product re-supply slip. Study product supplies may be prepared based on either original documents or faxed copies, but product will not be released to participants until the original prescription or request slip is received.

9.4.2 Dispensing from the Pharmacy to Clinic Staff

At sites choosing to dispense study product to clinic staff who will then deliver the product to participants, prescriptions and study product re-supply slips are expected to be delivered to the pharmacy by clinic staff or a runner. Upon receipt of a completed and signed prescription or study product re-supply slips, the PoR will prepare the study product entered on the prescription or re-supply slip. Study product may be prepared based on either original documents or faxed copies, but product will not be released to clinic staff until the original prescription or re-supply slip is received.

The MTN 001 Record of Receipt of Participant-Specific Study Product for Clinic Staff (see Section Appendix 9-2) must be used to document dispensing of participant-specific study product to clinic staff. Pharmacy staff will complete the top section (site name and site number,) and the first five columns on the Record of Receipt. When receiving study product from the pharmacy, clinic staff will verify the PTIDs, confirm the amount of product received for each PTID, and complete the remaining three columns on the Record of Receipt for each PTID. Comments may be recorded in the designated column and, if additional space is needed, on the back of the record. All Records of Receipt will be retained in the pharmacy.

Clinic staff are responsible for controlling access to the study product dispensed into their custody and ensuring that the product is delivered to the participants for whom they were dispensed. Clinic staff also must document delivery of the study product to designated participants in the participants' study charts. Delivery may be documented in chart notes, on visit checklists, or on other source documents designated for this purpose by clinic staff. In the event that study product dispensed for a participant is not delivered to the participant, clinic staff will document this in the participant's study chart and return the remaining product to the pharmacy as soon as the participant's visit is completed.

9.4.3 Dispensing from the Pharmacy to Runners for Further Transfer to Clinic Staff

At sites choosing to dispense study product to runners who will transfer the product to clinic staff for subsequent delivery to participants, prescriptions and study product re-supply slips are expected to be delivered to the pharmacy by a runner. Upon receipt of a completed and signed prescription or product request slip, the PoR will prepare the number of participant-specific study product entered on the prescription or study product re-supply slip. Study product may be prepared based on either original documents or faxed copies, but product will not be released to a runner until the original prescription or study product re-supply slip is received.

The MTN 001 Record of Receipt of Participant-Specific Study Product for Runners (see Section Appendix 9-3) must be used to document dispensing of participant-specific study product to runners and transfers of the product to the clinic staff.

Pharmacy staff will complete the top section (site name and site number) and the first five columns on the Record of Receipt. When receiving study product from the pharmacy, runners will verify the PTIDs, confirm the amount of study product received for each PTID, and complete the remaining three columns on the Record of Receipt for each PTID. Comments may be recorded in the designated column and, if additional space is needed, on the back of the record. All Records of Receipt will be retained in the pharmacy.

At the beginning of each work day, runners will complete the top section (site name, site number, clinic name, date) of their Daily Runner Logs. When receiving study product from the pharmacy, in addition to completing the Record of Receipt for each PTID, runners will complete the first four columns on the Daily Runner Log for each PTID.

Runners are expected to deliver participant-specific study product to authorized clinic staff directly after collecting the product from the pharmacy. Runners must control access to the product dispensed into their custody and deliver the product only to authorized clinic staff. Runners also must retain and control access to their Daily Runner Logs until the logs are returned to the pharmacy, at which time pharmacy staff assume responsibility for the logs. If completed logs are not returned to the pharmacy by the end of each work day, the PoR will notify appropriate clinic or pharmacy supervisory staff (per site SOPs) to ensure timely recovery of the logs. If completed logs are not recovered and delivered to the pharmacy within five calendar days, the PoR will notify the DAIDS PAB Protocol Pharmacist.

When receiving study product from runners, clinic staff will verify the PTIDs, confirm the amount of product received for each PTID, and complete the remaining two columns on the Daily Runner Log for each PTID. Comments may be recorded in the designated column and, if additional space is needed, on the back of the log.

Clinic staff are responsible for controlling access to the study product transferred into their custody, ensuring that the product is stored appropriately while in their custody, and ensuring that the product is delivered to the participants for whom they were dispensed. Clinic staff also must document delivery of study product to designated participants in the participants' study charts. Delivery may be documented in chart notes, on visit checklists, or on other source documents designated for this purpose by clinic staff. In the event that study product dispensed for a participant is not delivered to the participant, clinic staff will document this in the participant's study chart and return the remaining product to the pharmacy as soon as possible after the participant's visit is completed.

9.5 Return of Study Product Supplies

Study participants will be instructed to return all unused study products to the site at each scheduled study visit. Study staff will be required to collect unused product at the Mid-Study Period and End of Study Period Visits. The unused study product collected at these scheduled visits will not be reissued to the participants. New prescriptions must be completed and additional study product will be dispensed. As indicated, study staff will collect unused products at all other unscheduled visits. If the participant is going to continue the study, the study product may be returned to the participant at the unscheduled visit. In the event that unused study products are not returned at the end of each study period visit, study staff members will make every effort to encourage participants to return study product as soon as possible.

9.5.1 Unused Product Supplies

Participants who are permanently discontinued from study product use will be instructed to return all unused study product to the site. The PoR will store returned unused study products in designated areas within the study pharmacy

In the event that a participant becomes infected with HIV, or has a severe (Grade 3 or higher) renal or hepatic toxicity, every effort should be made to collect unused applicators or tablets remaining in her possession within 24 hours. In the event that a participant becomes pregnant, infected with Hepatitis B, or experiences an adverse event that requires permanent discontinuation of gel or tablet use (per protocol Section 9), any unused pre-filled applicators or tablets remaining in her possession should be collected from her as soon as possible, within five working days, and returned to the pharmacy on the day of collection. It is not necessary to collect remaining study product from participants for whom product use is temporarily held. However, study product must be collected from such participants within five working days, to protect their safety, if it is suspected that the participant may not comply with clinic staff instructions to refrain from product use for the duration of the temporary hold.

In the event that an issue or problem is identified that would necessitate collection of unused product from all participants, detailed instructions for collection and handling of the study product, and documentation thereof, will be provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* and from the DAIDS PAB Protocol Pharmacist. Other associated operational and/or data collection instructions also may be provided by the MTN CORE and/or MTN SDMC. Clinic and pharmacy staff will follow all such instructions.

Finally, any unused product remaining in a participant's possession at the time of study exit must be collected from the participant and returned to the pharmacy on the day of collection. When planning and scheduling study exit visits, clinic staff should instruct participants to bring all remaining unused product to their exit visits. For participants who do not bring their remaining product to their exit visits, arrangements should be made to collect the product as soon as possible and document all such efforts in the participants' study charts. For participants for whom all reasonable efforts fail, guidance should be sought from the MTN 001 PSRT.

Unused study product collected from participants for any reason should be returned to the pharmacy on the day of collection. When study product is collected by clinic staff, the staff may return the collected applicators or tablets to the pharmacy themselves or, if product runners are utilized at the site, clinic staff may transfer the collected product to a runner for return to the pharmacy. In such cases, the MTN 001 Daily Runner Log should be used to document transfer of the collected study product into the custody of the runners and subsequent return to the pharmacy, with notations in the “comments” column of the log indicating that the study product is being returned by, rather than received by, clinic staff.

9.5.2 Used Gel Supplies

Participants will be instructed to dispose of used applicators off-site (e.g., at their homes) whenever possible and allowed per local biowaste requirements. When this is not possible or allowed, participants may return their used applicators to the study clinic for disposal in accordance with applicable biowaste requirements. Clinic staff should provide participants with plastic bags or other suitable containers in which to store their used applicators between visits. Clinic staff also may wish to consider installing easily accessible biowaste containers near the clinic doorway and/or in other common areas within the clinic. Clinic staff should not return used applicators to the pharmacy.

Section Appendix 9-1
Frequently Asked Gel Use Questions

Q1: What is the best position to insert the gel?

A: Any position that is comfortable can be used to insert the gel. The positions that are recommended include sitting, standing, and lying down.

Q2: What should I do if it hurts when I use the applicator to insert the gel?

A: Inserting the gel should not be painful. If you have pain when inserting the gel, try another position (sitting, standing, or lying down). If you still have pain in the new position, perhaps you need to change the angle of the applicator. The applicator should be angled slightly upward, towards your back, when you insert it. If you try to change the angle, and you still feel pain on insertion, please contact the study clinic.

Q3: Where does the gel go to after I put it inside?

A: The gel will come out of the vagina (through the same opening where it was inserted) over the next day. Sometimes when the gel comes out it looks clear. Sometimes it has a white color, and sometimes it has white clumps. This has been seen in other studies of the gels and it is normal. It is not normal to see a yellow or green discharge from the vagina, or a discharge with a bad odor, or with pain or itching. If this happens, it could mean you have an infection, in which case you should contact the study clinic.

Q4: Can the applicator get lost inside me?

A: No, the applicator cannot get lost inside you. When you use the applicator, hold it with your fingers about half-way along the barrel, and insert it until your fingers touch your body. Half of the barrel of the applicator should go inside your body. The other half should stay outside the body.

Q5: What should I do if I have trouble applying the gel with the applicator?

A: The applicators should be easy to use. If you have difficulty using the applicators, please contact the study clinic, as the clinic staff may be able to show you different ways that you can insert the gel, which might make it easier.

Q6: What should I do if I think there is something wrong with an applicator or its gel?

A: If an applicator does not seem to be working properly (for example, you find it difficult to push the gel out of the applicator, or if gel has leaked out, or you think there is some other problem), do not use the applicator. Use another applicator instead. Keep the applicator that had something wrong and bring it to the study pharmacy at your next study visit. If you think that something is wrong with all of your applicators, contact the study staff as soon as possible (i.e., do not wait until your next visit) so the staff can make sure you have enough working applicators to use for the study period.

Q7: What happens if I press the plunger too early and most of the gel comes out on my outside? Can I put more in?

A: Yes. If most of the gel comes out on your outside, discard that applicator and use a new applicator to insert another dose of gel.

Q8: If I have my period, should I use the gel?

A: Yes. You should use the gel daily, even during your period.

Q9: Can I use tampons at the same time as the gel?

A: You can use tampons while taking part in this study. If you use tampons, you should take out the tampon when you insert the gel, and put another tampon in an hour after you inserted the gel.

Q10: What if I have bleeding between periods?

A: Please contact the study clinic.

Q11: How do I store the gel?

A: Store the gel in a cool, dry place.

Q12: What happens if the applicators get wet before I use them?

A: If only the wrapper gets wet, the applicator can still be used. Dry the wrapper off before taking out the applicator. If the applicator itself gets wet, it should not be used, but this might only happen if the wrapper is already open.

Q13: What should I do if the wrapper is already open when I want to use the gel?

A: You should only use applicators with sealed wrappers, so you should always open the wrapper right before inserting the gel. If you notice an applicator with a wrapper that is not sealed, do not use that applicator. Use a different applicator with a sealed wrapper instead. Discard the applicator with the open wrapper. When they return for the next scheduled visit and they should inform the study staff of any applicators they had to discard because they were not sealed.

Q14: What should I do if I forget to use the gel?

A: If you miss a dose (gel or tablet), you should insert the missed dose as soon as possible, unless the next dose is estimated to be due within 6 hours. If the next dose is estimated to be due within six hours, you should skip the missed dose. The next dose will be inserted as originally scheduled.

Q15: Is the gel contraceptive?

A: The study gel is not a way to prevent pregnancy. If you wish to avoid pregnancy, you should use known reliable methods of contraception (such as tablets, and injections) while you are in this study.

Q16: Will the gel affect my partner's ability to father children?

A: No. The ingredients in the gel are not known to have any effect on male fertility.

Q17: What should I do if my partner has a reaction to the gel?

A: Contact the study clinic and ask their advice. They might ask your partner to go to the clinic to be assessed and receive treatment if needed.

Q18: What should I do if I have a reaction to the gel (e.g., unusual itching, stinging)?

A: Contact the study clinic.

Q19: What should I do if I think I am pregnant?

A: Contact the study clinic immediately. The clinic staff will give you a pregnancy test to find out if you are pregnant or not.

Q20: Can I have sex straight away after inserting gel, or do I need to wait?

A: You don't need to wait to have sex after inserting gel.

Q21: Does it matter what brand condoms we use?

A: Ideally, you should use the condoms given to you by the study clinic staff. However, if you do not have one of those condoms, and you have a different condom, use that condom. Condoms are the only known way to protect against HIV and other sexually transmitted diseases (STDs), so it is always better to use any condom (even if it was not given to you by the study) than to use no condom.

Q22: What should I do if the gel leaks out?

A: It is likely that some gel will leak out. This is normal and you don't need to do anything about it. You should always apply the full amount in the applicator. It may be helpful to wipe yourself on the outside with a dry cloth/tissue if you have been standing for a minute or two after you applied the gel, if you find that a small amount leaks out. The study staff will give you panty liners to help catch the gel if it leaks out.

Q23: Can I use herbs or other substances for tight or dry sex while I am using the gel?

A: Herbs or other substances could damage the inside of the vagina. These substances also could interfere with the study gels. Therefore we recommend that you do not use herbs or other substances in the vagina. If you feel you must use these substances, please do not use them from one hour before you insert the gel. This will help make sure the substances do not interfere with the gel.

Q24: Can my partner insert the gel for me?

A: It is preferable that you insert the gel yourself, but if you are happy that your partner knows how to do it in a way that won't cause you discomfort, then this is acceptable. It is better for your partner to insert the gel for you than to not use the gel at all.

Q25: Will I have access to the gel if it is shown to be effective?

A: If the gel is shown to be safe and effective, it will take some time for the gel to be allowed to be sold in the shops, but we will try to make sure this happens as quickly as possible.

Q26: What happens if I spill my tablets accidentally?

A: If any of the tablets become lost or unusable before the next scheduled visit, inform the clinic staff immediately so that they make arrangements for replacement tablets to be dispensed.

Q27: Do I need to eat before taking my tablets?

A: No, you may take the tablet with or without a meal.

Q28: What if I throw up immediately after taking a tablet?

A: If you throw up immediately after taking your tablet, wait approximately 30 minutes and take another tablet. If you throw up again, skip the dose until the next scheduled does.

Q29: What if I have trouble swallowing the tablet?

A: If you have trouble swallowing the pill, take a sip of water and relax. Place the pill on the back of your tongue and swallow with water. You may try drinking the water with a straw as this may help to swallow the tablet.

Q30: What if I forget to take the tablet?

A: If you forget to take your tablet, take the missed dose as soon as possible unless the next dose is due within 6 hours. If the next dose is due within 6 hours, the missed dose will be skipped and the next dose will be administered as originally scheduled.

Q31: What if I am taking oral contraception?

A: You may continue your oral contraception.

Q32: What are the side effects?

A: The most common side effects are: diarrhea, nausea, vomiting and intestinal gas. Other side effects that have been reported include: weakness, low phosphate, dizziness, shortness of breath, and rash.

Section Appendix 9-2
 *MTN 001 Record of Receipt of Participant-Specific Study Product (For Clinic Staff)

Site Name:

Site Number:

PHARMACY STAFF					CLINIC STAFF			COMMENTS
Date Dispensed by Pharmacy dd-MMM-yy	*PTID	No. of Study gel cartons Dispensed by Pharmacy	No. of Study tablet containers Dispensed by Pharmacy	Pharmacist Initials	PTID <i>*(Verify PTID transcribed from box matches PTID recorded by Pharmacist in Pharmacy Staff Section)</i>	Date and Time Received in Clinic (dd MMM yy, 00:00 AM/PM)	Clinic Staff Initials	

Instructions: Complete one row each time participant-specific study product is dispensed to non-pharmacy staff for delivery to a study participant. All entries must be made in dark ink. Corrections may be made by drawing a single line through incorrect entries, entering correct information, and initialing and dating the correction.

*** Form must be returned to the pharmacy at the end of every business day**

Section 10. Clinical Considerations

This section presents information on the clinical procedures performed in MTN 001. Further clinical considerations related to participant safety monitoring and adverse event reporting are provided in Section 11. Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in Section 12. Instructions for completing data collection forms associated with clinical procedures are provided in Section 13.

10.1 Baseline Medical/Menstrual/Genitourinary History and Ascertainment of Concomitant Medications

A focused baseline medical/menstrual/genitourinary history is obtained from potential study participants at the Screening and Enrollment Visits. Medications used by the participant are also ascertained and documented at this time. Any updated information is obtained at all follow-up visits. The purpose for obtaining this information during screening and enrollment is to:

- Assess and document participant eligibility for the study
- Assess and document the participants' baseline medical conditions and symptoms, for comparison with signs, symptoms, and conditions that may be identified or reported during follow-up
- Monitor any potential AEs associated with the use of the product during the course of the study

10.1.1 Focused Baseline Medical/Menstrual/Genitourinary/Genitourinary History

The non-DataFax MTN 001 Baseline Medical and Menstrual History form is a recommended source document for collecting pertinent baseline medical/menstrual history data. This form will be available to sites via Word format upon request. Sites may adapt the form for local use, taking into consideration local methods of capturing medical and menstrual history information. Alternative site-specific history forms also may be used.

The Baseline Medical and Menstrual History form is initially completed at the Screening Visit. It is reviewed and updated at the participant's Enrollment Visit in order to capture any medical events occurring between the Screening and Enrollment visits. In addition, at the Enrollment Visit, the Baseline Genital Symptoms form is administered to the participant. This form is used to collect data on genitourinary symptoms, including intermenstrual bleeding/spotting, that the participant reports experiencing since her last Screening Visit.

For enrolled participants, all baseline conditions identified as ongoing at the time of the Enrollment Visit are documented on the (DataFax) Pre-existing Conditions form. This includes ongoing medical conditions captured in Section E of the Baseline Medical and Menstrual History form as well as any ongoing genital symptoms recorded on the Baseline Genital Symptoms form. Recurring and/or chronic conditions are considered ongoing whether or not they are present/active at baseline (e.g. headaches, asthma).

When obtaining a focused baseline medical/menstrual history for MTN 001, it is not necessary to document the participant's lifetime medical history. Rather, focus on conditions and symptoms that were experienced since the participant became sexually active. Probe for the most accurate information available on the participant's current health and reproductive status vis-à-vis the reported history. Several additional guidelines are presented below:

- Use the list of questions in Section D of the MTN 001 Baseline Medical and Menstrual History form to probe for conditions/symptoms the participant may have experienced.
- Record symptoms, illnesses, allergies, and medical procedures (this is included as item "t" in Section D of the MTN 001 Baseline Medical and Menstrual History form).
- Record both chronic and acute conditions, as well as both ongoing and resolved conditions.
- For menstrual history, document the details of the participant's usual menstrual cycle and flow. Also enter the first and last day of the participant's last menstrual period, and the average number of bleeding days (e.g., 3-5 days) she experiences during her regular menses. Note the participant's age of menarche and any menstrual problems she may have, such as irregular menses, amenorrhea, menorrhagia, etc. Document the type and severity of any usual menstrual symptoms. See Section A of the MTN 001 Baseline Medical and Menstrual History form.
- Document any usual or typical non-menstrual genital bleeding patterns experienced by the participant. This includes any breakthrough genital bleeding/spotting associated with the participant's contraceptive use. Include the frequency of bleeding, the average duration, type of flow (e.g. light, moderate, or heavy) and any associated symptoms (this is included as item "s" in Section D of the MTN 001 Baseline Medical and Menstrual History form).
- Explore whether the participant has experienced (or continues to experience) any type of sexual trauma (item "v" in Section D of MTN 001 Baseline Medical and Menstrual History form).
- For reproductive history, record the number, date, and outcome of each of the participant's pregnancies, (see Section B of the MTN 001 Baseline Medical and Menstrual History form) as well as any gynecologic and obstetrical procedures/surgeries (item "t" in Section D of MTN 001 Baseline Medical and Menstrual History form).
- At the Screening Visit, record the participant's history of contraceptive use (see Section C of the MTN 001 Baseline Medical and Menstrual History form). Review and update this section at the Enrollment Visit, and transcribe the participant's current family planning methods onto the Family Planning Methods case report form. If applicable, enter details of the participant's current contraceptive method on the Concomitant Medications Log form. Per Section 5 of the study protocol, spermicides, diaphragms, sponges, and contraceptive vaginal rings should not be used during participation in MTN 001. Participants who report current use of these contraceptive products and devices during screening are ineligible for participation in the study. If the participant reports use of any of these contraceptive products at the Enrollment Visit, she is not eligible for the study. If the participant is interested, refer the participant to family planning services for provision of alternative methods prior to enrollment in the study.

- Document medications currently taken for all ongoing conditions, including usual menstrual symptoms, on the Concomitant Medications Log form, as described in Section 10.1.2.

Site clinicians are encouraged to use their clinical experience and judgment — together with any advice available from Community Advisory Board members or others — to determine the best phrasing in the local language to elicit complete and accurate history information from study participants.

10.1.2 Initial Ascertainment of Concomitant Medications

The MTN 001 protocol requires documentation of all medications taken by study participants beginning at the Screening Visit and continuing throughout follow-up. For purposes of this study, medications include all of the following, regardless of route of administration:

- Prescription and “over-the counter” medications and preparations
- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations
- Recreational drugs

The Concomitant Medications Log form may be used as a source document for collecting information on participants’ use of medications. When recording the route of medications/preparations that are applied intravaginally, mark the box labeled “VAG”. When recording the route of medications/preparations that are applied rectally, mark the box “REC.”

It is recommended that study clinicians ascertain participants’ baseline medication information in the context of obtaining the baseline medical/menstrual history. In addition to asking open-ended questions to elicit participant report of current medications, use the information obtained in the medical/menstrual history to probe for additional medications that the participant may forget to report. For example, if the participant reports recurrent headaches as part of her medical history, but does not spontaneously list any medications taken for headaches; ask her if she takes any medications for the headaches. Similarly, if a participant reports taking a medication for a condition that she inadvertently did not report when providing medical history information, add the condition to the Baseline Medical History form and Pre-existing Conditions form as appropriate.

10.1.3 Pre-existing Conditions

As noted above, a key purpose of conducting the baseline medical/menstrual history — as well as the physical exam and screening pelvic exam described below — is to document participants’ baseline medical conditions, for comparison with signs, symptoms, and conditions that may be identified or reported at subsequent scheduled or interval study visits. For MTN 001, all ongoing medical conditions, problems, signs, symptoms, and (abnormal) findings that are observed and/or reported *at enrollment* are considered pre-existing conditions. Such conditions should be documented per the screening and enrollment visit guidance provided in Sections 4 and 7 of this manual, as well as in the remainder of this section.

For participants who enroll in the study, all ongoing medical/laboratory conditions observed and/or reported at the Enrollment Visit should be reported on the Pre-existing Conditions form. This case report form is completed at the Enrollment Visit, based on all other screening and enrollment source documents, including the Baseline Medical and Menstrual History form, Baseline Genital Symptoms form, Physical Exam form, Screening and Enrollment Pelvic Exam form, all screening laboratory results, chart notes, and any other site-specific source documents. Once the participant is enrolled in the study, any ongoing symptoms at the time of enrollment will be recorded in the Follow-up Medical History Log. This log will facilitate the review of participant's symptom(s) during follow-up.

As is described in greater detail in Section 11, the Pre-existing Conditions form serves as the “starting point” from which study clinicians must determine whether medical conditions, problems, signs, symptoms, and other abnormal findings identified or reported during follow-up are adverse events (AEs). By definition, pre-existing conditions are present at the time of randomization/enrollment in the study and are therefore not considered AEs. However, if a pre-existing condition resolves after randomization, but then recurs at a later date, the recurrence is considered an AE. New conditions identified during follow-up that were not present at the time of enrollment/randomization, and any pre-existing conditions that increase in severity or frequency during follow-up, are also considered AEs. With this in mind, when completing the source documents listed above, as well as the Pre-existing Conditions form, study clinicians should document as much detail as possible about the severity and frequency of each pre-existing condition. When completing the Pre-existing Conditions case report form, it is recommended that this information be recorded in the “Comments” section for each condition.

10.2 Interval Medical/Menstrual/Genitourinary History and Updating of Concomitant Medications

For enrolled participants, an interval medical/menstrual/genitourinary history and update of concomitant medications is obtained at each scheduled follow-up visit. This procedure also is performed at interim visits. The purpose of these procedures is to determine whether participants have experienced any new illnesses, symptoms, etc., since the last study visit. An interval medical/menstrual/genitourinary history also should be performed at interim visits to obtain updated information on previously reported adverse events when applicable.

10.2.1 Interval Medical/Menstrual/Genitourinary History

The non-DataFax Follow-up Medical History Log form is a recommended source document for collecting interval medical/menstrual history data. This form is used to track any symptom reported by the participant that are ongoing at the Enrollment Visit through follow-up.

At each follow-up visit, site staff should actively review the Follow-up Medical History Log and review any conditions that are ongoing (that is, conditions that do not have an “outcome date” recorded on the form). If the condition has resolved, record the outcome date. If the condition has not resolved, leave the outcome date blank and inquire about the condition the next time an interval medical history is performed. Once all ongoing conditions on the Follow-up Medical History form have been reviewed, ask the participant an open-ended question such as “What, if any, other symptoms or health problems have you had since your last visit?” to complete the history. Add new conditions to the log form as needed. Additionally, the interviewer-administered Follow-up Genital Symptoms form, a source document, will be used to document in the study database any genitourinary symptoms experienced by the participant since her last interval medical history.

See Section 10.5 below for more information on assessing participant reports of genital bleeding.

Site clinicians are encouraged to use their clinical experience and judgment — together with any advice available from Community Advisory Board members or others — to determine the best phrasing in the local language to elicit complete and accurate follow-up information from study participants.

10.2.2 Updating of Concomitant Medications Information

At each visit retrieve the participant's Concomitant Medications Log, record any new medications taken by the participant, and actively inquire as to whether the participant is still taking medications listed previously, at the same dose and frequency. Also actively inquire as to whether the participant has begun taking any new medications since her last visit, including medications obtained outside the study (not provided by the study staff). To further probe for updates, if the participant reports any intercurrent illnesses, symptoms, etc., since her last visit, inquire as to whether she took any medications for these. Add all new information to the form in log fashion, using additional form pages as needed. Similarly, if a participant reports taking a new medication for a condition that she inadvertently did not report when providing interval medical/menstrual history information, add the condition to the Follow-up Medical History log, and Pre-existing Conditions form (if present at enrollment).

10.3 Physical Exams

A physical exam is required at the Screening, Enrollment, and all Follow-up Clinic Visits with the exception of the Week 21 visit. Site clinicians may use their discretion to determine whether or not to conduct a more complete physical exam, in response to reported symptoms or illnesses present at the time of the exam. Following is a list of the required physical exam components.

- Height (may be omitted after the Enrollment Visit)
- Weight
- Vital signs
 - Temperature
 - Pulse
 - Blood pressure
- General appearance
- Abdomen

The non-DataFax Physical Exam form is a recommended source document for recording physical exam findings. For participants who enroll in the study, abnormal physical exam findings identified at the Enrollment Visit also are recorded on the Pre-existing Conditions form.

Physical exams may identify additional baseline medical history information that participants inadvertently do not report in their baseline medical/menstrual history. For example, the clinician may identify a skin condition during the physical exam and upon further inquiry learn that the participant has had the condition since age 15. In such situations, the clinician should add the newly identified information to the Baseline Medical History form, and the Pre-existing Conditions form as well, since the condition was present at the time of enrollment.

10.4 Pelvic Exams

Pelvic exams are performed in MTN 001 for purposes of determining eligibility and identifying study safety information. As such, they are critical to ensure the ongoing safety of study participants. Pelvic exams are performed at Screening, Enrollment and all scheduled Follow-up Clinic Visits with the exception of the Week 21 Visit, per the schedule in protocol Section 7. Pelvic exams also are performed when clinically indicated to evaluate genital symptoms.

Pelvic exams are performed, and findings classified, according to the CONRAD/World Health Organization (WHO) Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004 (available at www.conrad.org), and the remainder of this section. Exam procedures must be performed in the order shown on the exam checklists in Section 7 of this manual. All procedures listed on the exam checklists should be performed during routinely scheduled exams. When additional exams are performed to assess genital symptoms, only clinically indicated procedures should be performed. As indicated in greater detail below, exam findings are reported on the following forms provided by the MTN SDMC:

- Screening and Enrollment Pelvic Exam (SPE-1)
- Follow-up Pelvic Exam (FPE-1)
- Pelvic Exam Diagrams (non Datafax form)
- Pelvic Laboratory Results (PLR-1)
- Follow-up Medical History Log

For participants who enroll in the study, abnormal exam findings identified at the Enrollment Visit (that are not exclusionary per the study eligibility criteria) also are recorded on the Pre-existing Conditions form.

10.4.1 Overview

General Technique: Maximize the comfort and privacy of the participant. Position the examination table away from the door or hang a curtain to ensure privacy. Explain what you are doing as you do it. Take as much time as needed to assure participant comfort and accurate documentation of exam findings.

Use clean hand/dirty hand technique, and/or assistants, to avoid contamination. Keep extra gloves available as two hands may be needed to adjust equipment.

For each area examined, i.e., the external genitalia, cervix, and vagina, first perform a naked eye exam.

Use a speculum of appropriate type and size to permit adequate visualization of the vagina and cervix. For most participants, a Graves speculum is preferred to enable visualization of all anatomic areas and tissues. Prior to insertion, ensure that the speculum functions properly and has no rough edges. The speculum may be lubricated with warm water if needed. No other lubricant may be used.

Record the length and axis of the vagina, position of the cervix, and type and size of speculum during the participant's first pelvic examination (e.g., on the exam checklist or Pelvic Exam Diagrams form). This information can then be reviewed prior to subsequent exams to reduce the risk of iatrogenic injury.

Lavage and Removal of Visual Obstruction: During the pelvic exams at the Screening Visit, Mid-Study-Period Visits (3, 10, and 17 Week), and Study Period 2 and 3 Start Visits (7 and 14 Week), after assessment of vaginal pH and collection of vaginal swabs, if necessary remove any obstruction (e.g., mucus, cellular debris) by lavage with sterile, isotonic, non-bacteriostatic saline. Avoid contact between the pipette and the epithelium. The lateral fornices may be lavaged without manipulation by directing the stream into them. Aspirate the fluid with the tip of the pipette against the inner surface of the posterior blade of the speculum. Do not lavage prior to assessing pH and collecting swabs for wet prep.

If lavage does not adequately remove the obstruction, use a large saline-moistened swab (scopette) in a gentle dabbing fashion to remove the obstruction. Avoid twisting or rolling the swab over the surface of epithelium. Do not use a dry swab to remove any obstruction at any time, as this may cause trauma to the epithelium.

The lavage for removal of visual obstruction will not be conducted during the pelvic exams performed at the Enrollment Visit and at End of Study Period Visits (6, 13, and 20 Week). At these visits, participants will undergo PK procedures (see Protocol section 7), where cervicovaginal lavage (CVL) will be collected to evaluate vaginal flora proteomics, markers of inflammation, and tenofovir levels. Procedures for collection of PK samples are described in Section 10.8. Do not collect CVL samples prior to assessing pH and collecting swabs for wet prep.

Specimen Collection: Perform specimen collection during each exam in the sequence specified on the pelvic exam checklists (see Section 7 of this manual).

Documentation of Findings: Document all exam findings — both normal and abnormal — on the Pelvic Exam Diagrams form. Document abnormal findings only on the appropriate pelvic exam form case report form. Both the Screening Pelvic Exam form and the Follow-up Pelvic Exam forms are recommended source documents for recording relevant descriptors and details of abnormal findings. However, supplemental information may be recorded on the Pelvic Exam Diagrams form, in chart notes, and/or on other source documents. For participants who enroll in the study, abnormal exam findings identified at the Screening Visit (that are not exclusionary per the study eligibility criteria) also are recorded on the Pre-existing Conditions form. See Section 10.4.3 for detailed instructions on classifying and documenting exam findings.

10.4.2 Detailed Procedural Instructions

***Note:** As much as possible, study-specific pelvic exams should not be performed during menses, since the presence of menstrual blood will likely interfere with visualization of the vagina and cervix, elevate the vaginal pH, and complicate interpretation of wet prep findings. Site staff should make every effort to schedule participants for study visits when the participant is not menstruating. This is especially important during the “end of study period” visits when PK procedures are required. If the participant is on her menses and the visit cannot be rescheduled, all PK procedures will be conducted, including collection of CVL samples, and cytobrush and vaginal biopsy where applicable. If a participant is menstruating when she presents for an interim visit complaining of genital symptoms, every effort should be made to perform a pelvic exam to evaluate her symptoms at that time. However, if this is not possible the participant should be instructed to return for a pelvic exam as soon as possible after menses.*

***Note:** See Section 6 of this manual for procedural modifications to be followed with pregnant participants.*

Prior to the Exam: Prepare all required equipment, supplies, and paperwork. Verify that all equipment is in good working order. Review documentation of prior exams (if any) and other relevant documentation from the current visit and prior visits. While the participant is clothed, explain the procedure and equipment to her and answer any questions she may have.

Position the Participant: Establish a comfortable examination position for the participant that allows for the perineum and vulva to be inspected. Adjust stirrups and back elevation as needed. Provide socks if the room is cold; provide a fan for the participant’s face if the room is warm. Drape the participant and point out distractions such as photos on the ceiling or music if available.

Examine the External Genitalia:

- Do not insert the speculum prior to examining the external genitalia.
- Spread the participant’s knees as far apart as is comfortable for her.
- Palpate the inguinal lymph nodes to assess for enlargement and/or tenderness.
- Perform naked eye examination of the external genitalia including the perineum, perianal area, and the epithelial lining of the introitus.
- Note all findings on the Pelvic Exam Diagrams form. Further document abnormal findings on the appropriate pelvic exam case report form.

Examine the Cervix:

- The speculum may be lubricated with warm water if needed. No other lubricant may be used. Gently insert the speculum and open it once past the pelvic floor muscles, using gentle downward pressure, so as to avoid trauma while enabling visualization of the cervical face and upper vagina.
- If the cervix is poorly visualized, to avoid iatrogenic injury, remove the speculum and use a gloved finger (lubricated with warm water if needed) to establish the position of the cervix. Then re-insert the speculum.

- Perform naked eye exam without manipulation, observing the general state of the cervix, the size and shape of the cervical os, and any other findings.
- Assess cervical ectopy.
- Assess for homogeneous discharge. Record outcome on the Pelvic Laboratory Results form. If any abnormal vaginal or cervical discharge and/or blood-tinged discharge are also present, document the discharge on the Pelvic Exam Diagrams and on the appropriate pelvic exam form (Screening and Enrollment Pelvic Exam form or the Follow-up Pelvic Exam form).
- Vaginal fluids are collected via swab and then swabbed onto the pH strip (instead of inserting the pH strip into the vagina). Avoid contact with cervical mucus, which has a high pH. Match the resulting color of the pH strip to the color scale provided with the strips to determine the pH value. Record the pH on the Pelvic Laboratory Results form.
- Collect vaginal fluids via (dry) swab for wet prep as required by the visit. Collect fluids from the lateral vaginal wall, away from any apparent abnormalities. See Section 12 of this manual for detailed wet prep slide preparation and assessment procedures.

Wet prep slides are to be read by local laboratory or site research staff, and results should be recorded on the Pelvic Laboratory Results form.

- If needed, lavage the cervix and vagina as described in Section 10.4.1 and complete naked eye exam (except for visits requiring PK sample collection).
- Note all findings (variants of normal and abnormal) on the non-DataFax Pelvic Exam Diagrams form. See the variants of normal in section 10.4.3 below. Further document abnormal findings on the appropriate pelvic exam case report form.

Examine the Vagina: To examine the rest of the vagina, slowly withdraw the speculum with the blades moderately open, re-focusing as needed. Alternatively, the speculum may be rotated ninety degrees to allow visualization of the anterior and posterior vaginal walls; retract the speculum away from the cervix and close the blades to rotate. Note all findings on the Pelvic Exam Diagrams form. Further document abnormal findings on the appropriate pelvic exam case report form.

Collect Genital Ulcer Swabs: If local standard of care, if any genital ulcers are observed during follow-up, swab the base of the ulcer for HSV-2 culture per local laboratory specifications. Document specimen collection on the Follow-up Pelvic Exam form. See Section 12 of this manual for further instructions for proper swab handling and storage prior to testing at the MTN Network Laboratory.

Collect Pap Smear: A Pap smear is required at the Screening Visit if there is no documentation of a normal result in the form of a written report within the 12 calendar months prior to screening. If no such documentation exists, collect ecto- and endo-cervical cytobrush specimens after completing all naked eye examinations. Document specimen collection on the Pelvic Laboratory Results form and transcribe results, once they become available, to that same form. Participants with abnormal results will not be eligible for the study. Pap smears will be reported as per the 2001 Bethesda System and will be presumed normal in the absence of intra-epithelial lesion or malignancy.

Perform Bimanual Exam (if clinically indicated): After completing all tissue examinations and specimen collection, close the speculum blades, gently remove the speculum, and perform bimanual exam for adnexal or fundal masses and/or tenderness.

NOTE: At the End of Study Period, the bimanual exam will be done after all PK samples have been collected.

10.4.3 Documentation of Findings

Document all exam findings, both variants of normal and abnormal, on the Pelvic Exam Diagrams form.

The following findings are considered normal:

- anatomic variants
- gland openings
- Nabothian cysts
- mucus retention cysts
- Gartner's duct cysts
- atrophic changes
- blood vessel changes other than disruption
- skin tags
- scars

Per the CONRAD/WHO Manual, abnormal findings will be classified according to the state of the epithelium and blood vessels associated with the finding, as follows:

Epithelium

Integrity:

- Intact
- Disrupted:
 - Superficial
 - Deep (complete disruption is considered deep and exposes stroma and possibly blood vessels; a bleeding area is considered deep)

Color:

- Normal
- Slightly red
- Red
- White
- Other (includes “pale”)

Blood Vessels

Integrity:

- Intact
- Disrupted

Figure 10-1 provides information to guide and standardize terminology used to describe abnormal pelvic exam findings. Examining clinicians also are encouraged to consult the Photo Atlas for Microbicide Evaluation developed by Bollen, Kilmarx, and Wiwatwongwana (MOPH-US CDC Collaboration, 2007) for further examples of terminology applied to pelvic exam findings in microbicide studies.

The Screening and Enrollment Pelvic Exam form, and the Follow-up Pelvic Exam form are recommended source documents for recording relevant descriptors and details of abnormal findings; however supplemental information may be recorded on the Pelvic Exam Diagrams form, in chart notes, and/or on other source documents. Iatrogenic findings such as those caused by speculum trauma should be included among the “abnormal” findings documented for the exam, with notations added to source documents and case report forms to specify the cause of the finding.

Figure 10-1
CONRAD/WHO Terminology for Pelvic Exam Findings

Term	Status of Epithelium	Status of Blood Vessels	Comments	
Erythema	Intact	Intact	Distinguished by color (erythema being redder than normal, edema either normal or paler than normal, and grossly white findings being white). Grossly white findings are sharply demarcated whereas edema and erythema may be sharp or diffuse.	
Edema	Intact	Intact		
Grossly white finding	Intact	Intact		
Petechiae	Intact	Disrupted	≤ 3 mm	Color of finding is red or purple.
Ecchymosis	Intact	Disrupted	> 3 mm	
Peeling	Disrupted, superficial	Intact	Fragment of disrupted epithelium may remain attached to the area from which it has peeled off. Generally has well demarcated outline. Underlying epithelium looks normal	
Ulcer	Disrupted, superficial or deep	Intact or disrupted	May include sloughing at base. Generally round or oval with sharply demarcated outline. Superficial ulcers are more accurately called erosions.	
Abrasion	Disrupted, superficial or deep	Intact or disrupted	Distinguished from other findings in this class by diffuse or poorly demarcated outline.	
Laceration	Disrupted, superficial or deep	Intact or disrupted	Sharply demarcated linear finding. Includes fissures. Lacerations appear to be the result of trauma. Fissures appear to be linear “pulling apart” or wearing away of tissue.	

Note: Superficial epithelial disruption does not penetrate into subepithelial tissue. Deep epithelial disruption penetrates into and exposes the subepithelial tissue and possibly blood vessels. If bleeding from the finding is present, the disruption is considered deep.

10.5 Genital Bleeding Assessment

Genital bleeding other than menstrual bleeding, often referred to as “intermenstrual bleeding” or “IMB” is a common occurrence among reproductive age women, and often is of physiologic or benign etiology. Some women normally experience mid-cycle bleeding or pre-menstrual bleeding. IMB is common in oral contraceptive users, particularly new and/or inconsistent users. Use of intrauterine contraceptive devices, smoking, and chlamydia infection have been identified as risk factors for IMB, and IMB may be associated with genital tract pathology such as cancer or polyps. IMB also may be associated with traumatic injury to the cervicovaginal epithelium (e.g., due to speculum insertion, product applicator insertion, sexual activity).

Background rates of IMB in the general population are not known with precision. In a recent survey of HIV-negative and HIV-positive women, 12 percent and 11 percent respectively reported IMB in the last six months. In clinical trials of oral contraceptives, IMB rates have ranged from five percent to over 50 percent. The high variability in IMB rates seen in these studies is likely due to different methods of data collection and reporting as well as cultural factors. Regardless, since oral contraceptive trials generally are not placebo controlled, it is difficult to assess how rates reported in those trials compare to background rates in the general population.

Similar to observations in contraceptive trials, variable rates of IMB have been observed in Phase I microbicide trials, many of which have not included a control group. While IMB has been reported in microbicide trials, IMB has not been associated with anemia or hemodynamic instability in those trials. The main concern raised by observation of IMB in microbicide trials is that candidate microbicides that are associated with increased rates of IMB may increase, rather than decrease, the user’s risk of HIV infection, presumably by disrupting the cervicovaginal epithelium and blood vessels. Increased rates of IMB also might affect the microbicide’s acceptability.

The MTN 001 Protocol Team has carefully considered the potential risks that may be associated with IMB and has developed procedures to evaluate, monitor, and report on genital bleeding throughout the course of the study. These procedures are described below and several possible genital bleeding assessment scenarios are presented in Appendix 10-1.

10.5.1 Genital Bleeding Assessment for Pregnant Participants

The remainder of this section provides procedural instructions and guidance for assessment of genital bleeding among non-pregnant participants. If a pregnant participant reports genital bleeding, study staff will clinically manage the participant per local practice standards for pregnancy. In particular, study staff will refer the participant to a qualified clinician for further evaluation, care, and treatment; pelvic exams may be performed by qualified clinicians unless contraindicated. Study staff will document the bleeding event and all follow-up actions in the participant's study records.

When reporting the event as an AE, it is not expected that a term such as “intermenstrual bleeding” or “metrorrhagia” will be used to describe the AE. Rather clinically appropriate terminology reflecting the cause or source of the bleeding (e.g., “threatened abortion”) should be used, if possible, and the bleeding itself should be graded according to the “First trimester bleeding”, “Second/third trimester bleeding”, or “Postpartum hemorrhage” row of the Female Genital Toxicity Table as appropriate. Any questions related to genital bleeding assessment or AE reporting for pregnant participants should be submitted to the MTN 001 PSRT as described in Section 11.

10.5.2 Participant Reports of Genital Bleeding

As part of the MTN 001 informed consent and enrollment process, study participants will be counseled to report all occurrences of genital bleeding — other than usual menstrual bleeding — to the study site as soon as possible after identification of the bleeding. Study staff will provide site contact information to each participant upon enrollment. Thereafter, at each study follow-up visit, contact information will be reiterated and active reporting of genital symptoms including unexpected menstrual bleeding and unexpected non-menstrual genital bleeding will be emphasized.

As described in Section 10.2, at each study visit, clinicians will obtain interval medical/menstrual history information from participants, including active ascertainment of whether any genitourinary symptoms including genital bleeding were experienced since the last study visit. Any changes in participants' use of concomitant medications, including contraceptives and topical and intravaginal medications/preparations, also will be actively ascertained. Reports of genital bleeding should be recorded on the Baseline Genital Symptoms form (at enrollment) or on the Follow-up Genital Symptoms form (for follow-up visits).

10.5.3 Clinician Assessment of Genital Bleeding

Study participants will undergo pelvic exams at the Screening Visit, Enrollment and at every Follow-up Visit, with the exception of the 21-Week Visit, thereafter. Pelvic exams also will be performed to evaluate any participant report of unexpected menstrual bleeding and/or unexpected non-menstrual genital bleeding. Pelvic examinations will be performed and documented as described in Section 10.4.

Figures 10-2a and 10-2b outline the genital bleeding assessment and reporting procedures that will be followed at all sites during follow-up. As shown in the figures, the sequence of procedures will differ depending on whether genital bleeding is first reported by the participant or first observed on pelvic exam. The Genital Bleeding Assessment form (see Section 13) will be used at all sites to guide and document clinicians' assessment of both participant-reported genital bleeding and clinician-observed genital bleeding when applicable (see more below). The Genital Bleeding Assessment form guides clinicians to collect and consider information on the many factors that may contribute to the observation of genital bleeding, to help determine whether the bleeding may be related to product use, or whether it may be more likely attributable to another cause. These factors include:

- Early onset of menses
- Use of hormonal contraceptive methods
- Use of intrauterine contraceptive devices
- Missed oral contraceptive pills or injections
- Sexual activity/trauma
- Trauma associated with insertion of study product or other vaginal preparations
- Trauma associated with pelvic exam procedures
- Sexually transmitted or reproductive tract infections/outbreaks
- Epithelial and/or blood vessel disruption observed on pelvic exam
- Other pathology observed on pelvic exam (e.g., polyps, carcinoma)

Assessment of genital bleeding should begin by determining whether the bleeding is *expected* or *unexpected*, and then proceed to determining whether the bleeding is *menstrual* or *non-menstrual*. Expectedness will be determined based on the participant's baseline medical/menstrual history (e.g., whether she reports genital bleeding as a pre-existing condition) as well as any other relevant factors such as hormonal contraceptive use. If a participant reports bleeding consistent in amount and duration with her baseline menstrual history, or that is consistent with use of her hormonal contraceptive method, the bleeding will be considered *expected*. In particular, intermenstrual genital bleeding occurring within the first three months of initiating a hormonal contraceptive method will be considered expected, unless the study clinician determines that the bleeding is inconsistent with bleeding patterns usually associated with that method. Lochia also will be considered expected.

A pelvic exam must be performed to evaluate all episodes of unexpected genital bleeding. Pelvic exams are not required to evaluate expected bleeding events; however, such exams may be performed at the discretion of the IoR or designee.

During follow-up, the Genital Bleeding Assessment form must be completed for participants who:

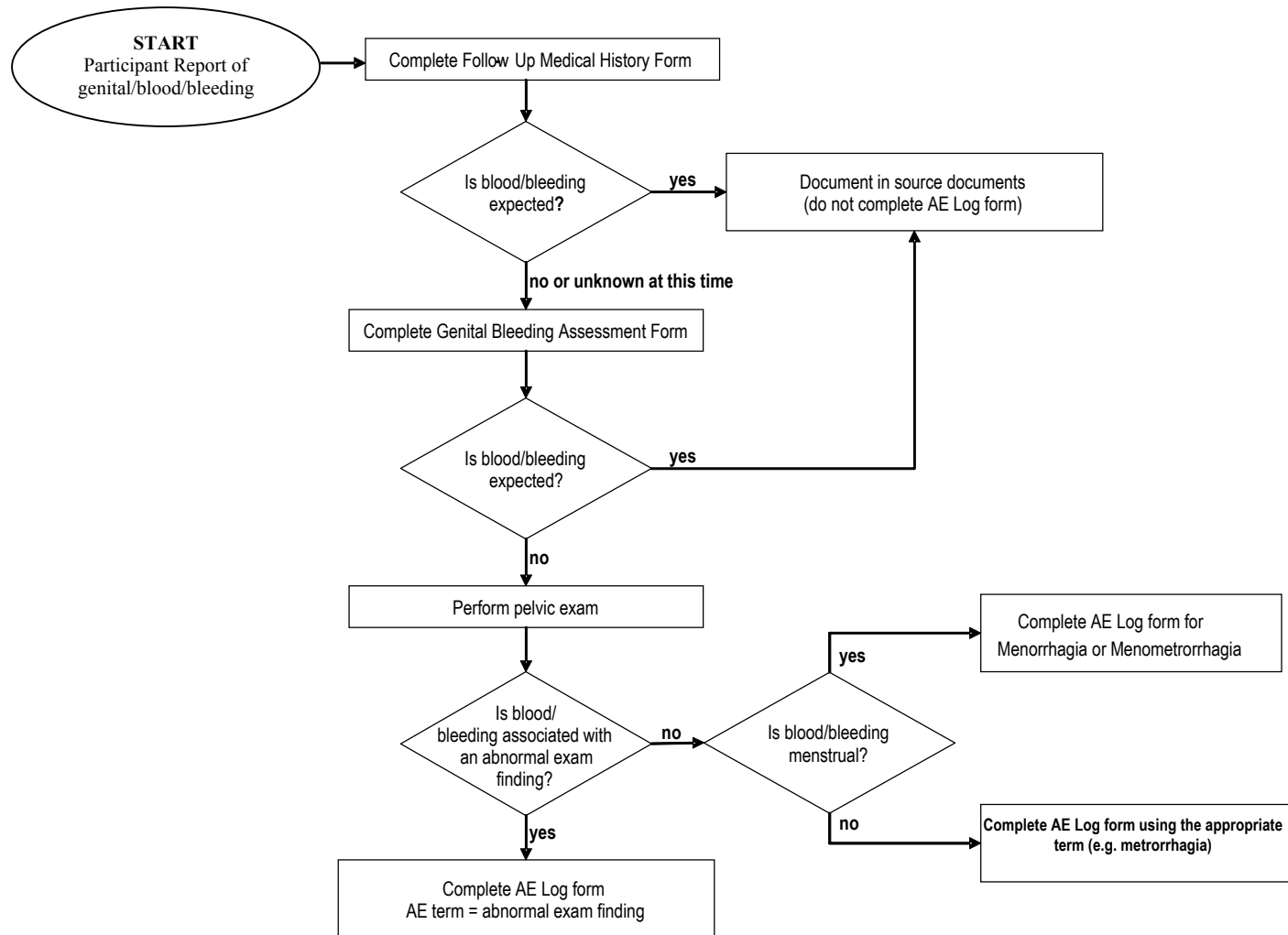
- Self-report genital bleeding other than their normal menses, unless the bleeding is determined to be expected before completing the form
- Do not self-report genital bleeding, but have genital blood/bleeding observed on pelvic exam that is not associated with an abnormal exam finding (e.g., laceration).

The Genital Bleeding Assessment form is not required to be completed for participants who:

- Self-report genital bleeding that is determined to be expected prior to completion of the form

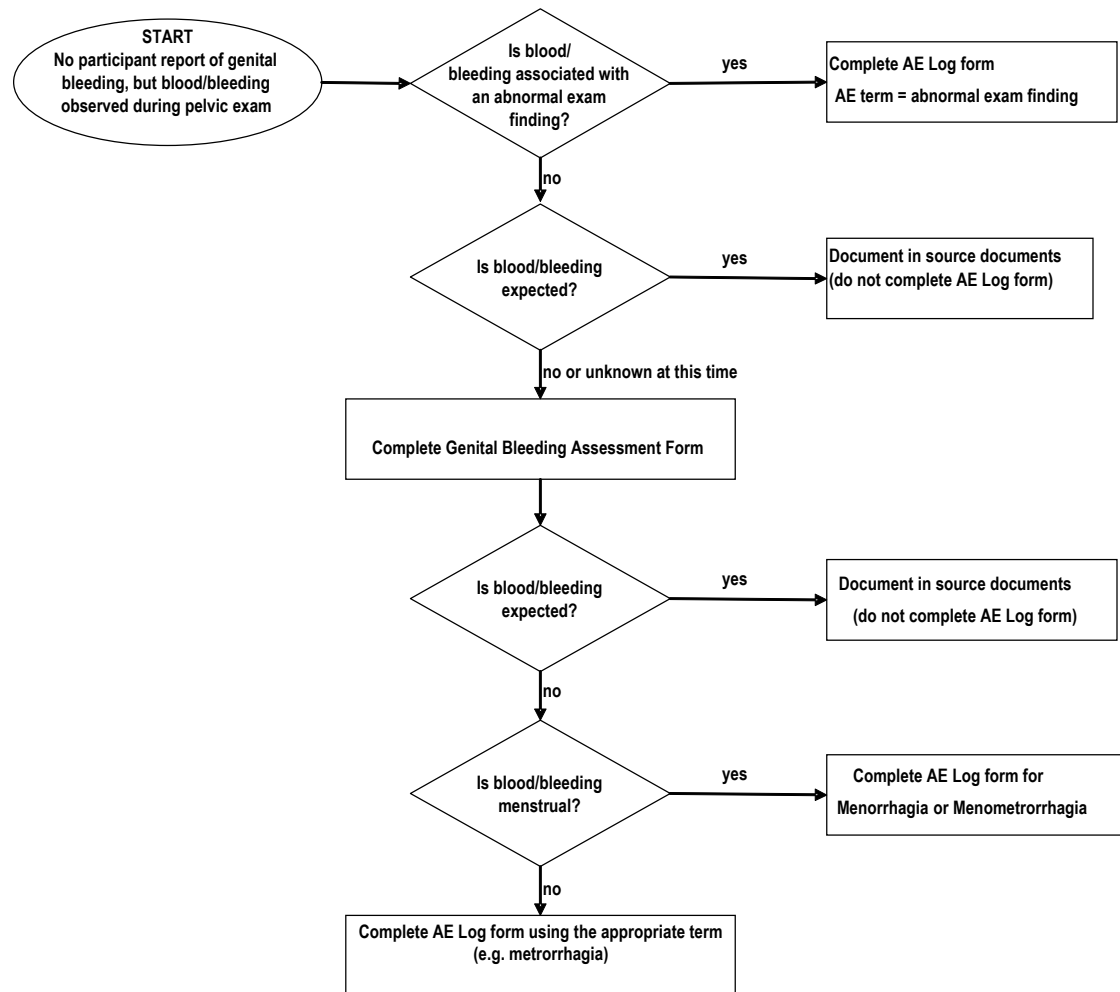
- Do not self-report genital bleeding but have genital blood/bleeding observed on pelvic exam that is associated with an abnormal exam finding.
- Do not self-report genital bleeding but have genital blood/bleeding observed on pelvic exam that is determined to be menstrual bleeding before completing the form.

Figure 10-2a
Overview of Assessment and Reporting Procedures for Genital Bleeding in MTN 001 — Beginning with Participant Report of Bleeding



Note: This algorithm is followed for non-pregnant participants only (see Section 10.5) and does not apply to genital hemorrhage. See Section 10.5.4 for more information on terminology and severity grading for adverse events (AEs) involving genital bleeding.

Figure 10-2b
Overview of Assessment and Reporting Procedures for Genital Bleeding in MTN 001 — Beginning with Clinical Observation of Blood/Bleeding



Note: This algorithm is followed for non-pregnant participants only (see Section 10.5) and does not apply to genital hemorrhage. See Section 10.5.4 for more information on terminology and severity grading for adverse events (AEs) involving genital bleeding.

10.5.4 Documentation of Genital Bleeding

Participants' prior history of menstrual and non-menstrual genital bleeding will be documented on the non-DataFax Baseline Medical History form and on the Pre-existing Conditions case report form, if applicable.

All cases of participant-reported genital bleeding occurring between usual menstrual periods will be documented on the Baseline Genital Symptoms form (at enrollment) or the Follow-up Genital Symptoms form (at follow-up visits). The non-DataFax Pelvic Exam Diagrams form is used to record all pelvic exam findings, both normal and abnormal. This means that all clinically observed genital blood/bleeding, whether expected, unexpected, menstrual, or non-menstrual, should be documented on the non-DataFax Pelvic Exam Diagrams form. In contrast, the Screening and Enrollment Pelvic Exam form and Follow-up Pelvic Exam form are used to record only abnormal pelvic exam findings. This means that only unexpected menstrual bleeding (excluding early menses) and unexpected non-menstrual bleeding should be recorded on these forms. In addition, certain episodes of genital bleeding will be documented on the Genital Bleeding Assessment form, as specified in Section 10.5.3 above.

All episodes of unexpected menstrual bleeding and unexpected non-menstrual genital bleeding — whether participant-reported or clinician-observed or both — will be considered adverse events (AEs) that must be documented on Adverse Experience Log case report forms.

Detailed information on AE reporting is provided in Section 11, however when reporting genital bleeding events, reference also should be made to the nine points below, which standardize the terminology that should be used at all sites when reporting AEs involving genital bleeding.

- Expected menstrual bleeding should not be reported as an AE. “Early menses” also should not be reported as an AE. Although clinical judgment will be required to determine whether any genital bleeding event may be due to early menses, as a general guideline, menses occurring more than two days prior to the participant’s usual menstrual cycle should be considered early menses. It is recognized, however, that it may not be possible to make a real-time diagnosis of early menses, based on the information available when first documenting a genital bleeding event. For example, the event could be reported on the first day of bleeding and it may not be known at that time whether a full menstrual period will follow. When information needed for a real time diagnosis of early menses is not available, study clinicians should initially report the event using a term other than “early menses” and then review the event after its final outcome has been ascertained and to determine whether it should be re-categorized as “early menses.”
- Unexpected menstrual bleeding (i.e., menstrual bleeding that is heavier in volume or of longer duration than the participant’s usual menses), should be reported as an AE using the following AE terms:
 - Menorrhagia: prolonged (more than seven days) or excessive (more than 80 mL) uterine bleeding
 - Menometrorrhagia: prolonged uterine bleeding occurring at irregular intervals

Grade these AEs per the “Menorrhagia” row of the Female Genital Toxicity Table.

- Expected non-menstrual bleeding should not be reported as an AE. This may include a small amount of cervical bleeding that can occur with speculum insertion or specimen collection, provided the IoR or designee deems the amount of bleeding to be within the range of normal. If the cervical bleeding observed with speculum insertion or specimen collection exceeds that which is expected, in the opinion of the IoR or designee, then the cervical bleeding should be recorded as an AE of “cervical friability”, and graded according to the “Cervical edema and friability” row of the Female Genital Toxicity Table.
- Unexpected non-menstrual bleeding that is associated with an observed abnormal pelvic exam finding should be reported as an AE using the term associated with the exam finding, with the anatomical location noted. For example, if a laceration is observed on exam, with blood emanating from the finding, the term “laceration” should be used to describe the AE. The fact that blood or bleeding was present also will be documented on the Pelvic Exam Diagrams form and the Pelvic Exam case report form, and may be noted in the Comments section of the Adverse Experience Log form, but the term “metrorrhagia” (“intermenstrual bleeding”) should not be used to describe the AE.
- Unexpected non-menstrual bleeding that is not associated with an observed pelvic exam finding, i.e., for which no abnormal source of blood or bleeding is observed on exam, should be reported as an AE using the term “metrorrhagia.” This term refers to bleeding of variable amounts occurring between regular menstrual periods and should be used to report all types of unexpected non-menstrual bleeding such as prolonged or excessive uterine bleeding, spotting between menses, ovulation bleeding, vaginal spotting, and breakthrough bleeding. This term also should be used to report blood-tinged discharge and blood observed in the vagina with no identified source. Grade these AEs per the “Metrorrhagia” row in the Female Genital Toxicity Table.
- In cases with bleeding that qualifies as both menorrhagia and metrorrhagia, it should be labeled menometrorrhagia, but will be graded based on the menorrhagia component. For example, if a participant experiences genital bleeding at irregular intervals that is heavier than her usual menses, you will report the event as “menometrorrhagia” and grade per the “Menorrhagia” row in the Female Genital Toxicity Table.
- If a participant reports genital bleeding after sexual intercourse, you will report this event as “postcoital bleeding” and grade it per the “Postcoital Bleeding” row of the Female Genital Toxicity Table.

- Genital Hemorrhage should be reported as an AE; however, the term genital hemorrhage should not be used to describe the AE. When reporting genital hemorrhage, a specific location must be specified. To report uterine hemorrhage, the term “uterine hemorrhage” will be used to describe the AE and graded per the menorrhagia row in the Female Genital Toxicity Table. In the event that a participant experiences a non uterine genital hemorrhage, the specific location of the hemorrhage needs to be included and the term to be used to describe the AE should be the underlying cause of the condition. For example, if the hemorrhage is caused by trauma in the vagina, then it should be graded per the "Vaginal abrasions or lacerations" row, which is graded by extent of laceration not by degree of bleeding.

10.6 STI/RTI Management

Clinical and laboratory evaluations are performed throughout the course of MTN 001 to diagnose the following sexually transmitted diseases and other reproductive tract infections (STIs/RTIs):

- Bacterial vaginosis (BV)
- Candidiasis (any species)
- Chlamydia infection
- Genital ulcer disease
- Gonorrhea infection
- Syphilis infection
- Trichomoniasis

Signs and symptoms commonly associated with the above-listed infections are presented in Figure 10-3. Infections should be considered “symptomatic” when a participant self-reports or complains of symptoms associated with the infection. Symptoms should not be confused with “signs” of infection that may be observed during clinical evaluations performed by study staff.

Figure 10-3
Signs and Symptoms Commonly Associated with STIs/RTIs

STI/RTI	Common Signs and Symptoms
Bacterial vaginosis	Excessive or malodorous discharge is a common finding. Other signs and symptoms include erythema, edema, and pruritis of the external genitalia.
Candidiasis	Clinical presentation varies from no signs or symptoms to erythema, edema, and pruritis of the external genitalia. Symptoms and signs alone do not distinguish the microbial etiology.
Chancroid	The combination of painful ulcer and tender inguinal adenopathy, symptoms occurring in one third patients, suggests a diagnosis of chancroid; when accompanied by suppurative inguinal adenopathy, these signs are almost pathognomonic.
Chlamydia infection	Many infections are asymptomatic and probably chronic. Mucopurulent discharge may not be recognized by the patient or may not be perceived as abnormal.
Genital herpes	Single or multiple vesicles, which usually are pruritic can appear anywhere on the genitalia. Vesicles spontaneously rupture to form shallow ulcers that may be very painful. Lesions spontaneously resolve with minimal scarring.
Gonorrhea infection	Women may have abnormal vaginal discharge, abnormal menses, or dysuria, or most commonly are asymptomatic. Pharyngeal gonorrhea can produce symptoms of pharyngitis.
Syphilis infection — primary	The classical chancre is a painless indurated ulcer located at the site of exposure.
Syphilis infection — secondary	Patients may have a highly variable skin rash, mucous patches, condylomatalata (fleshy, moist tissue growths), lymphadenopathy, alopecia, or other signs.
Syphilis infection — latent	Patients are without clinical signs of infection.

Figure 10-3
Signs and Symptoms Commonly Associated with STIs/RTIs

STI/RTI	Common Signs and Symptoms
Trichomoniasis	Excessive, frothy, diffuse, yellow-green discharge is common, although clinical presentation varies from no signs or symptoms to erythema, edema, and pruritis of the external genitalia. Dysuria and dyspareunia are also frequent. The type of symptoms or signs alone do not distinguish the microbial etiology.
Pelvic Inflammatory Disease (PID)	Patients must meet three criteria for PID: symptoms and exam findings of lower abdominal pain and tenderness, cervical motion tenderness, and adnexal tenderness. Additionally patients may present with fever, abnormal cervical or vaginal discharge, and cervicitis.
Cervical or Vaginal Warts	Patients usually present with a painless cauliflower lesion(s), sessile or on a stalk. Patients usually present with a painless cauliflower lesion(s), sessile or on a stalk.

Adapted from: *Contraceptive Technology* (18th Revised Edition, 2004); Chapter 8: Reproductive Tract Infections; Alphabetic Catalog of Reproductive Tract Infections; pages 201-218.

10.6.1 STI/RTI Treatment

STIs/RTIs will be treated in accordance with current WHO Guidelines for the Management of Sexually Transmitted Infections. WHO guidelines can be found at:

http://www.who.int/reproductive-health/publications/mngt_stis/guidelines_mngt_stis.pdf.

Should updated guidelines be issued by the WHO during the study, the updated guidelines will then be followed.

Note: Neither asymptomatic bacterial vaginosis nor asymptomatic vaginal candidiasis require treatment per WHO guidelines. These conditions will not be reported as an AE for this protocol

Figure 10-4 summarizes the WHO treatment guidelines for each of the conditions listed above. In day-to-day practice, the WHO guidelines — or local site treatment guidelines based on the WHO guidelines — should be referenced to obtain complete information on treatment regimens, contraindications, etc. To optimize cure rates, and thereby optimize the validity of study endpoint data, directly observed single dose treatment regimens should be provided whenever possible.

Figure 10-4
(2003) WHO Guidelines for the Management of Sexually Transmitted Infections
for STI/RTI Diagnosed in MTN 001

STI/RTI	WHO Sexually Transmitted Infections Treatment Guidelines
Bacterial vaginosis	<p><u>For symptomatic patients only.</u> Recommended:</p> <ul style="list-style-type: none"> • Metronidazole, 400 mg or 500 mg orally, twice daily for 7 days <p>Alternative:</p> <ul style="list-style-type: none"> • Metronidazole, 2 g orally, as a single dose • Clindamycin 2% vaginal cream, 5 g intravaginally, at bedtime for 7 days • Metronidazole 0.75% gel, 5 g intravaginally, twice daily for 5 days • Clindamycin, 300 mg orally, twice daily for 7 days
Candidiasis	<p><u>For symptomatic patients only.</u> Recommended:</p> <ul style="list-style-type: none"> • Miconazole or clotrimazole, 200 mg intravaginally, daily for 3 days • Clotrimazole, 500 mg intravaginally, as a single dose • Fluconazole, 150 mg orally, as a single dose <p>Alternative:</p> <ul style="list-style-type: none"> • Nystatin, 100 000 IU intravaginally, daily for 14 days
Chlamydia infection (uncomplicated anogenital infection)	<p>Recommended:</p> <ul style="list-style-type: none"> • Doxycycline, 100 mg orally, twice daily for 7 days • Azithromycin, 1 g orally, in a single dose <p>Alternative:</p> <ul style="list-style-type: none"> • Amoxicillin, 500 mg orally, 3 times a day for 7 days • Erythromycin, 500 mg orally, 4 times a day for 7 days • Ofloxacin, 300 mg orally, twice a day for 7 days • Tetracycline, 500 mg orally, 4 times a day for 7 days
Genital herpes (first clinical episode)	<p>Recommended:</p> <ul style="list-style-type: none"> • Acyclovir, 200 mg orally, 5 times daily for 7 days • Acyclovir, 400 mg orally, 3 times daily for 7 days • Valaciclovir, 1 g orally, twice daily for 7 days • Famciclovir, 250 mg orally, 3 times daily for 7 days <p><i>NOTE: Famciclovir should be used preferentially for genital herpes in the absence of contraindications</i></p>

Figure 10-4
(2003) WHO Guidelines for the Management of Sexually Transmitted Infections
for STI/RTI Diagnosed in MTN 001

STI/RTI	WHO Sexually Transmitted Infections Treatment Guidelines
Genital herpes (recurrent episodes of genital lesions)	<p>Recommended:</p> <ul style="list-style-type: none"> • Acyclovir, 200 mg orally, 5 times daily for 5 days • Acyclovir, 400 mg orally, 3 times daily for 5 days • Acyclovir, 800 mg orally, twice daily for 5 days • Valaciclovir, 500 mg orally, twice daily for 5 days • Valaciclovir, 1000 mg orally, once daily for 5 days • Famciclovir, 125 mg orally, twice daily for 5 days <p><i>NOTE: Famciclovir should be used preferentially for genital herpes in the absence of contraindications</i></p>
Gonorrhea infection (uncomplicated anogenital infection)	<p>Recommended:</p> <ul style="list-style-type: none"> • Ciprofloxacin, 500 mg orally, as a single dose • Ceftriaxone, 125 mg by intramuscular injection, as a single dose • Cefixime, 400 mg orally, as a single dose • Spectinomycin, 2 g by intramuscular injection, as a single dose
Syphilis infection (early infection)	<p>Recommended:</p> <ul style="list-style-type: none"> • Benzathine benzylpenicillin, 2.4 million IU, IM injection, at a single session (usually two injections at separate sites) <p>Alternative:</p> <ul style="list-style-type: none"> • Procaine benzylpenicillin, 1.2 million IU, IM injection, daily for 10 consecutive days <p>Alternative for penicillin-allergic non-pregnant patients:</p> <ul style="list-style-type: none"> • Doxycycline, 100 mg orally, twice daily for 14 days • Tetracycline, 500 mg orally, four times daily for 14 days
Trichomoniasis	<p>Recommended:</p> <ul style="list-style-type: none"> • Metronidazole, 2 g orally, as a single dose • Tinidazole, 2 g orally, as a single dose <p>Alternative:</p> <ul style="list-style-type: none"> • Metronidazole, 400 mg or 500 mg orally, twice daily for 7 days • Tinidazole, 500 mg orally, twice daily for 5 days

STI/RTI tests of cure are not required in MTN 001; however clinical management of syphilis infections should include repeat serology (RPR) following diagnosis of a new infection to confirm treatment effectiveness. If syphilis is diagnosed during screening, the participant will be eligible for enrollment when treatment is complete and the participant is asymptomatic. In some cases this may occur on the same day that the screening results are available. Please contact the MTN NL with any questions related to quarterly testing to confirm treatment effectiveness and/or interpretation of unusual syphilis test results.

10.6.2 Screening and Enrollment Considerations

Potential study participants diagnosed during screening with an STI/RTI per WHO guidelines via laboratory tests will be excluded from enrollment. The only exceptions to this are women with clinical evidence or laboratory evidence of BV or vulvovaginal candidiasis but who are asymptomatic. If the participant is otherwise eligible, she may be enrolled after completing treatment and all symptoms have resolved within 30 days after screening. If symptoms resolve after 30 days, she may be re-screened.

At some study sites, Pap smear results may include notations of findings associated with certain STIs (e.g., trichomoniasis). Because Pap smear methods are not adequately sensitive and specific for STIs, Pap smear findings associated with STIs should not be considered diagnostic of any infections. Rather, such findings should be handled as follows:

- Do not consider STI-related notations on Pap smear result reports when assessing participant eligibility for the study. Use only the results of protocol-specified STI tests for purposes of eligibility determination.
- If protocol-specified STI testing was performed on other specimens (i.e., blood, urine, vaginal fluids) collected on the same day as specimen collection for Pap smear, the results of the protocol-specified testing overrule STI-related findings noted on the Pap smear result report. Provide treatment as needed based on the results of the protocol-specified tests.
- If protocol-specified testing was not performed on other specimens (i.e., blood, urine, vaginal fluids) collected on the same day as specimen collection for the Pap smear, collect specimens for indicated protocol-specified STI testing at the participant's next study visit after receipt of the Pap test result report. Provide treatment as needed based on the results of the protocol-specified tests.

10.6.3 Adverse Event Reporting Considerations

Per the MTN 001 eligibility criteria, no participant may enter the study with an active STI/RTI diagnosed per WHO guidelines via laboratory tests. Since no treatable STI or RTI should be recorded as a pre-existing condition for an enrolled participant, any curable STI/RTI identified during follow-up in MTN 001 is considered an AE that must be documented on an Adverse Experience Log case report form. Detailed information on AE reporting is provided in Section 11. When reporting STI/RTI AEs, the severity of the event should be graded according to the "Genitourinary Infections" section of the Female Genital Toxicity Table (with the exception of asymptomatic bacterial vaginosis and vulvovaginal candidiasis).

Genital herpes and genital warts are considered non-curable STIs and are handled differently from the curable STIs. Genital herpes and genital warts are associated with chronic viral infections — HSV-2 and HPV — and periodic symptomatic outbreaks — genital ulcers and genital warts. Reporting of these conditions as pre-existing conditions and/or AEs should be handled as follows:

- If infection with HSV-2 or HPV is known to have occurred before randomization, the infection is considered a pre-existing condition: report on the Pre-existing Conditions form.
- For HPV, genital warts present before randomization are considered a pre-existing condition: report on the Pre-existing Conditions form.
- Any outbreaks that occur after randomization are considered AEs, regardless of whether the viral infection was pre-existing before randomization: report on an Adverse Experience Log form.

10.7 Urinary Tract Infections

Dipstick urinalyses will be performed at Screening, and when clinically indicated during follow up, to diagnose urinary tract infections (UTI). See Section 12 for details on the required laboratory procedures. Record results on applicable testing log sheets and then transcribe results onto the STI Laboratory Results form.

The following symptoms are considered indicative of a possible UTI:

- Frequent urge to urinate
- Passage of only a small volume of urine
- Pain and burning during urination
- Lower abdominal pain and/or uncomfortable pressure above the pubic bone
- Milky/cloudy, reddish, or bloody urine

When clinically indicated, a urine culture and sensitivity should be performed, and the culture should be documented on the STI Laboratory Results form. The sensitivity test results should be documented in the participant's chart notes only. Once a diagnosis has been made, treatment will be provided per site standards of care and applicable site standard operating procedures (SOPs).

10.8 Management of Laboratory Abnormalities

Clinical management strategies for specific toxicities are detailed in Protocol Section 9.5.

10.8.1 ALT/AST Elevation

Oral Product

Participants with Grade 1 or Grade 2 AST/ALT elevation identified on a single blood draw should have confirmatory laboratory testing as soon as possible (at most within 1 week). Study product may be continued during this time, at the discretion of the investigator, provided the participant is asymptomatic.

Participants that have a Grade 3 AST/ALT elevation should have a repeated laboratory testing as soon as possible (at most within 1 week), and product should be held. Participants should be followed weekly until levels are Grade ≤ 1 at which point study medication may be restarted with close follow-up and in consultation with the PSRT. If lab documentation is not available that levels have returned to Grade ≤ 1 within three weeks, study products must be permanently discontinued. For participants who are restarted on study product, any return to a level of Grade 3 or above should result in permanent discontinuation of study product.

For participants that have a Grade 4 AST/ALT elevation, product should be permanently discontinued. Participants should be followed weekly until levels are Grade ≤ 1 .

Vaginal Product

For participants with Grade 1 or 2 AST/ALT elevation, product may be continued at the discretion of the investigator.

Participants that have a Grade 3 AST/ALT elevation assessed to be possible, probably, or definitely related to study product should be held product in consultation with the PSRT. Participants should be re-evaluated at least weekly up to 2 weeks. If documentation is not available within 2 weeks to show an AST/ALT reduction to ≤ 2 , the product must be permanently discontinued. For participants who are restarted on study product, any return to a level of Grade 3 or above should result in permanent discontinuation of study product.

For participants that have a Grade 4 AST/ALT elevation, product should be held. If the investigator determines that elevation is definitely not related to the study product, the investigator will consult the PSRT for consultation about restarting study product. Participants should be re-evaluated at least weekly up to 2 weeks. If documentation is not available within 2 weeks to show an AST/ALT reduction to ≤ 2 , the product must be permanently discontinued. For participants who are restarted on study product, any return to a level of Grade 3 or above should result in permanent discontinuation of study product.

10.8.2 Hypophosphatemia

Participants with an initial laboratory abnormality of Grade 1 or 2 hypophosphatemia should have the phosphate level repeated as soon as possible (at most within 2 weeks). Participants can be encouraged to consume phosphate rich foods during this time. Participants with confirmed Grade 1 and 2 hypophosphatemia, should be encouraged to increase consumption of phosphate rich foods; in addition, supplemental phosphate in the form of neutral phosphate solution can be prescribed to the participant at the discretion of the investigator.

For participants with a Grade 3 hypophosphatemia assessed to be possible, probably, or definitely related to study product should be held product in consultation with the PSRT and the phosphate level repeated as soon as possible (at most within 1 week). During this time, supplemental phosphate with phosphate rich foods should be encouraged, neutral phosphate solution can be prescribed to the participants at the investigator's discretion, and other causes of low phosphate should be investigated.

Product should be held for participants with a Grade 4 hypophosphatemia, regardless of the relationship to study product. During this time, supplemental phosphate with phosphate rich foods should be encouraged, neutral phosphate solution can be prescribed to the participants at the investigator's discretion, and other causes of low phosphate should be investigated.

Oral Product

For Grade 1 and 2, participants may continue product use per the discretion of the investigator.

Participant with Grade 3 and 4 hypophosphatemia should be evaluated within a week to show response to supplementation. If documentation is not available within one week to show resolution to \leq Grade 2, oral study product must be permanently discontinued.

Vaginal Product

For Grade 1 and 2, participants may continue product use per the discretion of the investigator.

Participants that have a Grade 3 hypophosphatemia assessed to be possible, probably, or definitely related to study product should be held product in consultation with the PSRT. Participants should be re-evaluated at least weekly up to 2 weeks. If documentation is not available within 2 weeks to show hypophosphatemia resolution to ≤ 2 , product must be permanently discontinued. For participants who are restarted on study product, any return to a level of Grade 3 or above should result in permanent discontinuation of study product.

For participants that have a Grade 4 hypophosphatemia elevation, product should be held. If the investigator determines that elevation is definitely not related to the study product, the investigator will consult the PSRT for consultation about restarting study product. Participants should be re-evaluated at least weekly up to 2 weeks. If documentation is not available within 2 weeks to show a hypophosphatemia reduction to ≤ 2 , product must be permanently discontinued. For participants who are restarted on study product, any return to a level of Grade 3 or above should result in permanent discontinuation of study product.

10.8.3 Creatinine Clearance

For participants with a creatinine clearance laboratory value of $<50\text{mL}/\text{min}$, laboratory testing should be repeated within 1 weeks of the receipt of the results in consultation with the PSRT. If the creatinine clearance is confirmed to be $<50\text{mL}/\text{min}$, the oral study product must be permanently discontinued. For participants who fail to have a confirmatory test, the oral study product will be permanently discontinued. Vaginal study product may be continued at the discretion of the investigator.

10.9 Pharmacokinetic Procedures

During the “Mid-Study” and “End of Study Visits” at all three periods (oral, vaginal, and dual use), samples will be collected for PK measures. All PK results will be documented on the Pharmacokinetics – Non-intensive form (Non-US sites) or the Pharmacokinetics – Intensive form (US sites). Participants will be asked to record the three doses (hour: minute) of tenofovir taken prior to the study visit. To ensure that time will be recorded correctly, at enrollment, all participants will be provided a watch device. When providing the watch device to participants, site staff need to counsel participants on how to use the watch, how and where to record the time, and remind participants of the importance of bringing these records to these visits. Sites are encouraged to develop strategies to ensure participants are reminded to record the timing of their last three doses prior to their visits as well as bring this record to the clinic. These strategies may include phone calls, letters, and appointment calendars.

NOTE: If participants forget to bring documentation of the time of the last three doses, site staff should make every effort to work with the participant to obtain the best estimates of timing of previous product use. When completing the appropriate CRF, sites need to write a note in the white space next to the times that these are estimates.

10.9.1 Mid-Study Period

At 3-Week, 10-Week, and 17-Week study visits (Mid-Study-Period Visits) all participants will provide blood samples to be tested for tenofovir levels. At these visits, participants will not take an observed dose of product.

10.9.2 End of Study Period

At 6-Week, 13-Week, and 20-Week study visits (End of Study Period Visits) all participants will provide a blood sample within 15-30 minutes prior to taking an observed dose of product(s). Participants will be asked to bring one dose of product(s) to these visits and take this dose in the presence of study staff. For the observation of the vaginal product, each site will determine the most culturally appropriate method for observing the dose. For example, a site may choose to directly observe the product insertion or they may choose to allow the participant to insert the product behind a privacy curtain. Regardless of the method chosen, site staff need to ensure that the product has been inserted. Following insertion of the vaginal dose, it is recommended that participants ambulate between 10-15 minutes to increase the gel distribution.

PK procedures may not be split over multiple days, meaning that all PK procedures must be completed on the same day (see Section 6.3.3). In addition, every effort should be made to schedule these visits when the participant is not experiencing her menses. However, if the participant is on her menses at the time of the visit, all PK procedures will be conducted, including collection of CVL, cervical cytology brush, and vaginal biopsies if applicable.

Prior to the End of the Study Period visit, study participants will be asked to abstain from sex, if possible, at least 24 hours prior to their study visit. If participants are not able to abstain from sex, participants should be reminded to negotiate male condom use.

Sites participating in the Non-intensive PK procedures (Non-US sites), will follow the guidelines described in Section 10.9.2.1. Sites participating in the Intensive PK procedures (US sites) will follow the procedures described in Section 10.9.2.1.

10.9.2.1 Non-Intensive PK

At the Non-US sites, participants will be assigned to a sampling window based on their sequence randomization assignment:

- 1-3 hours, Sequence E and F
- 3-5 hours, Sequence A and B
- 5-7 hours, Sequence C and D

These participants will have one blood sampling time pre-dose, and only one sampling time post-dose that will include blood sample and CVL sample (see Figure 10-5).

**Figure 10-5
Non-Intensive PK Procedures**

	PRE-DOSE	POST-DOSE TIMING		
		1-3 HOURS	3-5 HOURS	5-7 HOURS
Blood: <ul style="list-style-type: none"> Flow cytometry (at sites with capacity) 	Study Regimen Sequences A, B, C, D, E, and F			
Blood: <ul style="list-style-type: none"> PBMC cell lysate (intracellular tenofovir diphosphate) (at sites with capacity) Tenofovir 	Study Regimen Sequences A, B, C, D, E, and F	Study Regimen Sequences E and F	Study Regimen Sequences A and B	Study Regimen Sequences C and D
CVL <ul style="list-style-type: none"> Tenofovir Proteomics and markers of inflammation 		Study Regimen Sequences E and F	Study Regimen Sequences A and B	Study Regimen Sequences C and D

Post-dose samples must be collected within 15-30 minutes of each other and either sample may be taken first. Site staff need to record the time that each sample is collected with hour:minute accuracy in the Pharmacokinetics – Non-Intensive form.

During the pelvic exam, procedures will be done in the following order:

- Vaginal pH
- Wet mount
- CVL
- Bi-manual examination

Cervicovaginal Lavage (CVL)

CVL samples will be taken after pelvic exam procedures such as examination of the external genitalia, vagina, and cervix, assessment of pH and collection of swabs for wet prep. Lavage will be performed by rinsing the cervix with 10 ml of sterile saline with a syringe and then collecting the pooled fluid in the vaginal fornix with the same device.

10.9.2.2 Intensive PK

The US sites will participate in the Intensive PK measures. These participants will provide cervical cells and vaginal tissue which will be used for measurement of tenofovir levels. All 72 participants will be randomized into groups (see Figure 10-6) to provide collection of pelvic exam specimens pre-dose, 2, 4, or 6 hours after dosing.

During the pelvic exam, procedures will be done in the following order:

- Vaginal pH
- Wet mount
- CVL
- Cervical brush
- Vaginal biopsy
- Bi-manual examination (if clinically indicated)

All participants in this group will have blood collected pre-dose, and 1, 2, 4, 6, and 8 hours following dosing.

**Figure 10-6
Intensive PK Procedures**

SPECIMEN	PRE-DOSE	1 HOUR	2 HOURS	4 HOURS	6 HOURS	8 HOURS
Blood draw <ul style="list-style-type: none"> • PBMC cell lysate (intracellular tenofovir diphosphate) (at sites with capacity) • Tenofovir 	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)
Blood draw <ul style="list-style-type: none"> • Flow cytometry 	Groups M, N, O, and P)					
Cervical cytology brush <ul style="list-style-type: none"> • Cell lysates (intracellular tenofovir diphosphate) • Tenofovir 	12 ppts (Group M)		12 ppts (Group N)	12 ppts (Group O)	12 ppts (Group P)	
CVL <ul style="list-style-type: none"> • Tenofovir • Proteomics and markers of inflammation 	Group M		Group N	Group O	Group P	
Vaginal biopsies <ul style="list-style-type: none"> • Cell lysates (intracellular tenofovir diphosphate) • Tenofovir 	Group M		Group N	Group O	Group P	
Rectal Fluid (Bronx-Lebanon Hospital Center CRS only)	Group M		Group N	Group O	Group P	

Cervicovaginal Lavage (CVL)

CVL samples will be taken after the following pelvic exam procedures; examination of the external genitalia, vagina, and cervix, assessment of pH and collection of swabs for wet prep, and before the cytology collection, vaginal biopsy and, if clinically indicated, bimanual examination. Lavage will be performed by rinsing the cervix with 10 ml of sterile saline with a syringe and then collecting the pooled fluid in the vaginal fornix with the same device.

Cervical Cytology Brush

The cervix must be visualized with the speculum in-situ under adequate lighting. A lubricant should not be used for insertion of the speculum. If bimanual examination is indicated, it should be carried out only after sampling to prevent lubricant contamination, trauma or dislodgment of diagnostic cells.

The cytobrush should be applied to with some degree of firmness to ensure maximal contact. Place the cytobrush in the cervical os and rotated around the full circumference (360° turns) at least two times. The cytobrush should be vigorously stirred in the solution for collection (see Section 12.7.3) so that an adequate sample is deposited into the solution. Slight bleeding at the cervix may occur and a small amount of blood in the sample will not interfere with interpretation. Similarly, a small amount of mucus in the sample does not affect interpretation.

Vaginal Biopsy

The vaginal biopsy will always be the last sample collected. After the cytobrush sample has been obtained, the vagina should be cleansed with a bacteriostatic solution. Using forceps, approximately 2-4 mm samples will be taken from two different areas of the vagina. Usually, biopsy of the vagina does not require an anesthetic, although this procedure typically feels like a sharp pinch or a cramp. Taking a nonsteroidal anti-inflammatory drug (NSAID), such as ibuprofen, 20 minutes before the procedure may help relieve any discomfort during the procedure.

Rectal Fluid

Participants at the Bronx-Lebanon Hospital Center CRS who opt to have rectal fluid samples taken, will have these samples taken after (within 15 minutes) the vaginal specimens are taken. A short (approximately 3 ½ inch length) and narrow (approximately 1 ½ inch diameter) hollow plastic tube called an anoscope will be used to help collect the rectal fluid samples. The anoscope will be placed gently into the participants' rectum, and two special swabs used to collect fluid will be placed in the anoscope. The swabs and anoscope will remain in the rectum for about 5 minutes.

10.10 Product Use Management

For this study, product use management may involve temporarily holding or permanently discontinuing either gel or pill use for individual study participants, to protect their safety and well-being while in the study. A participant may be temporarily or permanently discontinued from one study product and be eligible to use the other product; however, if a participant is temporarily or permanently discontinued from either study product, she cannot use any product during the dual period. Product use management in this study will not involve modification of the dose (one applicator or one pill) or route (intravaginal or oral) of product administration by any participant.

If a participant is permanently or temporary discontinued from oral study product, and if the Tenofovir 1% Gel Period has not yet begun for this participant, the investigator in consultation with the PSRT may decide that she may participate per protocol in the Tenofovir 1% Gel Period as scheduled according to her sequence randomization. If a participant is permanently or temporary discontinued from gel study product, and if the TDF 300 mg Oral Tablet Period has not yet begun for this participant, the investigator in consultation with the PSRT may decide that she may participate per protocol in the TDF 300 mg Oral Tablet Period as scheduled according to her sequence randomization. However, a participant who has been permanently or temporary discontinued from either type of study product will not take any study product during the Dual Formulation Period (if this study period has not yet begun for an individual participant), but will be followed according to regularly scheduled evaluations of safety, according to Protocol section 7.4.5.

It is the responsibility and obligation of the IoR and other authorized study clinicians to assess participants' eligibility for continued product use throughout their participation in the study.

Certain product use management decisions and actions must be undertaken, per protocol, under the direction of the study site IoR. Other product use management decisions and actions are undertaken, under the direction of the IoR/PI, in consultation with the MTN 001 PSRT as described in Section 11.

10.10.1 Circumstances In Which Product Use Must Be Either Temporarily Held or Permanently Discontinued

Product use must be temporarily held in the following circumstances:

- Evidence of vaginal biopsy may be apparent in follow-up examinations. Vaginal product use should not be held if the biopsy sites are healing normally with intact epithelium or healthy granulation tissue. Vaginal product use should be temporarily held if the investigator deems the biopsy site to be inappropriately healing with evidence of infection or other epithelial disruption. In these instances, the site must consult the PSRT.

With respect to documentation of vaginal biopsy sites, any biopsy site which is visible to the naked eye should be documented on the Follow-Up Pelvic Exam Form. While the majority of vaginal biopsy sites will be completely healed within four weeks after biopsy, it is not unusual to see evidence of a vaginal biopsy for up to 6 weeks. Evidence of a normally healing biopsy site within 6 weeks of biopsy is considered expected and therefore does not meet the requirement for adverse event reporting. Normally healing biopsy sites should show evidence of re-epithelialization. Abnormally healing biopsy sites, which should prompt adverse event reporting, include biopsy sites with evidence of infection at any time, evidence of bleeding after one week, or any other characteristics which the IoR deems to be abnormal and reason for concern.

- Vaginal product may be held if the participant has signs or symptoms of Grade 2 STI(s)/RTI(s) requiring treatment according to the discretion of the investigator and in consultation with the PSRT. Once treatment is complete and any symptoms have resolved, vaginal product use can be resumed. In cases in which the participant is in the dual study product period, if treatment is completed in a single dose and that participant is asymptomatic, study gel need not be held. If at the discretion of the IoR a participant is temporarily or permanently held from one study product, she will be eligible to use the other product; however, if a participant is discontinued from either study product, she cannot use any product during the dual period.

- The participant experiences a Grade 3 AE that is judged by the IoR or designee to be possibly, probably, or definitely related to product use. In general, and unless otherwise decided in consultation with the PSRT, the investigator should re-evaluate the participant at least weekly up to 2 weeks. If documentation is not available within two weeks to show that the adverse event is \leq Grade 2, the current study product must be permanently discontinued. To obtain approval for resumption of product use from the PSRT, the IoR or designee should submit a query to the PSRT, via the MTN 001 Protocol Safety Physicians, using the MTN 001 PSRT query form as described in Section Appendix 11-3. The PSRT will consider the query and provide a written response (or request more information) via email within three business days.

If the same Grade 3 adverse event recurs after reintroduction of study product, the current study product must be permanently discontinued if the investigator considers the adverse event possibly, probably, or definitely related to study product. However if the investigator determines that the toxicity is definitely not related to study product, participants may continue the study product and the PSRT must be notified.

- The participant experiences a Grade 4 adverse event, regardless of relationship to study product. If the investigator determines that the toxicity is definitely not related to study product(s), the IoR or designee will consult the PSRT to consider restarting study product(s), and product cannot be restarted until approval from the PSRT is obtained. The participant should be re-evaluated at least weekly up to 2 weeks. If documentation is not available within two week to show that the adverse even is \leq Grade 2, the current study product must be permanently discontinued.
 - *NOTE: The above product management guidelines are applicable to any adverse event experienced by the participant in addition to any genital conditions such as deep epithelial disruption, intermenstrual bleeding, and pelvic exam finding of generalized erythema or severe edema.*
- If a participant experiences Grade \geq 3 nausea and/or vomiting, oral study product must be held until the toxicity grade returns to Grade \leq 2 and be treated symptomatically.
- If a participant experiences new onset Grade \geq 3 diarrhea that is unresponsive to antimotility agents and for which an alternative etiology (e.g., infectious diarrhea) is not established, oral study product must be held until the toxicity grade returns to Grade \leq 2 or to baseline and be treated symptomatically.
 - *NOTE: Unless other product hold guidelines apply, vaginal study product need not be held for diarrhea or vomiting unless the investigator has compelling evidence that the toxicity is possibly, probably, or definitely related to vaginal study product.*
- If a participant experiences AST or ALT elevations \geq 3 ULN, oral study product must be held up to 2 weeks until the toxicity returns to Grade \leq 1 (with repeat measures done according to the clinical judgment of the investigator).

Product use must be permanently discontinued in the following circumstances:

- Study product-related toxicity requiring permanent discontinuation of study product(s) per Section 9 of the protocol
- Completion of regimen as defined in the protocol
- Request by participant to terminate study product(s)
- Clinical reasons determined by the physician
- HIV infection

NOTE: Study product should be held immediately after the first reactive rapid test or ELISA pending confirmatory WB testing. If participant is confirmed to be HIV uninfected per WB testing, product may resume. If HIV infection is confirmed, product must be permanently discontinued.

- Hepatitis B infection
- Pregnancy or breastfeeding
- Use of the following medications: acyclovir, valacyclovir, and tenofovir disoproxil fumarate/emtricitabine
- If documentation is not available within 2 weeks to show that a Grade 3 AE is \leq Grade 2, the current study product must be permanently discontinued.
- If documentation is not available within 2 weeks to show that a Grade 4 AE is \leq Grade 2, the study product(s) must be permanently discontinued. If the same Grade 4 adverse event recurs at either grade 3 or 4 level within 4 weeks of reintroduction of study product(s), study product(s) must be permanently discontinued.
- If Grade 4 elevation in AST or ALT, oral study product must be permanently discontinued. ALT/AST must be followed weekly until levels have returned to a Grade ≤ 1 .
- If documentation is not available within 3 weeks to show that a Grade 3 elevation in AST or ALT has not returned to Grade ≤ 1 , oral study product must be permanently discontinued.
- If documentation is not available within 1 week to show response to supplementation (resolution to ≤ 2) for a Grade 3 or 4 hypophosphatemia, the oral product must be permanently discontinued.
- If creatinine clearance is confirmed to be $<50\text{mL}/\text{min}$, the oral study product must be permanently discontinued.

10.10.2 Circumstances In Which Product Use May Be Either Temporarily Held or Permanently Discontinued

Product use may be either temporarily held or permanently discontinued, at the discretion of the IoR, under the following circumstances and in consultation with the PSRT:

- The participant is unable or unwilling to comply with required study procedures
- The participant might otherwise be put at undue risk to her safety and well-being by continuing product use

10.10.3 Documentation of Product Use Management

All product use management decisions must be thoroughly documented in participants' study charts. It is expected that signed and dated chart notes, together with correspondence to and from the PSRT, when applicable, will serve as the primary source documentation for these decisions; however other site-specific source documents also may be used. In addition to this documentation, product holds should be communicated to study pharmacy staff using the MTN 001 Study Product Hold/Resume/pK Supply/Re-supply Slip, as described in Section 6 and a Product Hold/Discontinuation case report form should be completed and faxed to the MTN SDMC, as described in Section 13.

10.10.4 Participant Follow-Up During Periods of Product Use Discontinuation

Participants who either temporarily or permanently discontinue product use will not routinely be withdrawn from the study. Rather, every effort will be made to complete all protocol-specified follow-up visits and procedures with these participants (with the exception of product-related procedures that are not applicable during the period of product use discontinuation).

10.10.5 Collection of Product Supplies During Periods of Product Use Discontinuation

If a participant becomes pregnant or experiences an adverse event that requires permanent discontinuation of product use, any unused applicators and/or pills remaining in her possession should be collected from her as soon as possible per the guidance provided in Figure 10-7 and returned to the pharmacy on the day of collection.

Figure 10-7: Retrieval of Study Product after discontinuation

Permanent discontinuation due to HIV seroconversion	Retrieve within 24 hours
Permanent discontinuation due to severe (Grade 3 or higher) renal or hepatic toxicity	Retrieve within 24 hours
Permanent discontinuation for any other reason	Retrieve within 5 working days
Temporary hold for any reason if there are safety concerns	Retrieve within 5 working days

For all product holds requiring collection of unused applicators and/or pills, if the applicators and/or pills are not collected within the timeframe specified in Figure 10-7, the MTN 001 PSRT must be informed, using the PSRT Query Form as described in Section Appendix 11-3. When informing the PSRT, please describe the reason for the product hold, actions taken to try to collect the unused applicators and/or pills, and plans and timelines for further action to collect the study product.

10.11 Pregnancy Management

Please refer to the Section 6 of this manual for procedural instructions for management of participant pregnancies that may occur during follow-up.

Section Appendix 10-1
Scenarios for AE Grading using Female Genital Toxicity Table

10-1.1 During the Screening/Enrollment Visit, Ms. X reports that her menses usually occur every four weeks and lasts for five to seven days. She gives no previous history of intermenstrual or prolonged/heavy bleeding. When she returns for her 6-Week Clinic Visit, she reports that her menses started that day, approximately one week earlier than expected. What procedures should be followed?

- Depends on the clinician’s judgment. If the clinician considers this event to be early onset menses, this event should not be reported as an AE. However, if the clinician considers this event to be unexpected bleeding, then report this genital bleeding as an AE using the term metrorrhagia and grade according to the Female Genital Toxicity Table under “Abnormal Uterine Bleeding Unrelated to Pregnancy”. The Clinician should perform a pelvic exam for further evaluation.

Why? This event is considered metrorrhagia if it is unexpected (i.e. her baseline history does not have any previous history of intermenstrual bleeding).

10-1.2 Continuing from the scenario above, suppose the clinician judged the genital bleeding to be unexpected and decided to conduct a safety visit to follow up on the AE of metrorrhagia. At the Follow up Clinic Visit, seven days later the participant is still bleeding. What would you do?

- Update item 1 of the metrorrhagia AE log form to “menometrorrhagia”, and grade according to menorrhagia row in the Female Genital Toxicity Table under “Abnormal Uterine Bleeding Unrelated to Pregnancy”. The clinician should perform a pelvic exam for further evaluation. The clinician should attempt to follow this AE until resolution.

Why? The prolonged menses is part of the same bleeding event reported on the previous visit; therefore the term used to describe this event needs to be updated to reflect the participant’s current bleeding symptoms. Grade this event per the Female Genital Toxicity table.

10-1.3 Ms. Y reports at her 10-Week Clinic Visit that she had menstrual cramps during her last period that were so painful that she stayed home from work, in bed, for two days. Generally this participant has very mild menstrual symptoms, if any. What would you do?

- Report this event as an AE using the term dysmenorrhea and grade according to the Female Genital Toxicity Table under “General”. The Clinician should perform a pelvic exam for further evaluation.

Why? The reported menstrual cramps are a change from this participant’s baseline menstrual symptoms. It is important that the clinician evaluates if there is an anatomical reason why the participant is having pain.

Section Appendix 10-1
Scenarios for AE Grading using Female Genital Toxicity Table

10-1.4 Suppose instead, Ms. Y reports to the Clinic at her 10-Week Clinic Visit and reports that two days ago, she experienced some vaginal spotting after having sex with her partner. What would you do?

- Report this event as an AE of Postcoital Bleeding, and grade according to the Postcoital Bleeding Row in the Female Genital Toxicity Table. Clinician should perform a pelvic exam for further evaluation (e.g. anatomical location of bleed).
- If the clinician identifies the anatomical source of bleeding, the adverse event should be reported using the anatomical site (e.g., cervical friability)

Why? Postcoital bleeding is considered unexpected non-menstrual bleeding, and should be considered an AE. The term “metrorrhagia” (intermenstrual bleeding) *should not* be used to describe this AE.

10-1.5 Ms. Z reported at baseline that her usual menstrual cycle is about 29 days and that she usually has 8 menstrual bleeding days per cycle. At her last weekly visit, Ms. Z reported that her last menses lasted 9 days. Should this be reported as an AE?

- If the reported length of bleeding is greater than baseline, you must grade according to the “Menorrhagia” row under “Abnormal Uterine Bleeding Unrelated to Pregnancy” in the Female Genital Toxicity Table and determine whether an increase in severity has occurred. If there is an increase in severity you would need to report the occurrence of menorrhagia at the higher severity grade as an AE.

Why? Ms. Z should be considered to have menorrhagia as a pre-existing condition (menses lasting longer than 7 days). At baseline you will need to grade the pre-existing menorrhagia based on the guidance provided in the Female Genital Toxicity Table under “Abnormal Uterine Bleeding Unrelated to Pregnancy” and record the grade on the Baseline Medical History form and Pre-Existing Conditions form. By having this information recorded on the Baseline Medical History form and Pre-Existing Conditions form, you will be able to assess whether or not an AE has occurred and the grade of the AE.

Section Appendix 10-1
Scenarios for AE Grading using Female Genital Toxicity Table

10-1.6 At her 10-Week Clinic Visit, Ms. P has a positive pregnancy test. She discontinues study product use per protocol, but she agrees to stay in the study for follow up. At her 13-Week Clinic Visit, she reports genital bleeding. What should you do?

- Take a detailed history and determine whether the bleeding, and possible abortion, was induced or spontaneous.
- Report this AE using clinically appropriate terminology reflecting the cause or source of the bleeding. If this is a spontaneous abortion, use the correct terminology including the term spontaneous. Grade this AE according to the *Complications of Pregnancy* row of the Female Genital Toxicity Table. The participant should be referred to a qualified clinician for further evaluation, care and treatment.
- If this is an elective abortion (e.g. the patient took an herbal inducement) this would not be an adverse event and should only be reported if the bleeding is unexpected.

Why? The term “metrorrhagia” (intermenstrual bleeding) should not be used in this case because the participant is pregnant, and the bleeding may be associated with complication in pregnancy.

10-1.7 Suppose Ms. W reports at her 3-Week Clinic Visit she had vaginal itching, rash, and vaginal discharge two days before the clinic visit. On the day of the visit, the clinician performs a pelvic exam and notices an area with erythema and another area with an edema. What do you do?

- Determine if all these signs and symptoms could be grouped together as one condition. Since all these symptoms/signs are related, report this event as an AE and grade according to the Female Genital Toxicity Table under “Composite Signs/Symptom.”

Why? Whenever possible and particularly if two or more signs/symptoms are present, you will use a diagnosis for reporting instead of individual categories.

10-1.8 At her 3-Week Clinic visit, Ms. T reports vaginal discharge. During the pelvic exam, a wet prep is collected for Wet Mount testing. When the wet prep slide is read, yeast is observed. What do you do?

- Complete an AE log for vaginal candida or yeast vaginitis and grade according to the Genitourinary Infection section of the Female Genital Toxicity Table. Treat this participant in accordance with current WHO Sexually Transmitted Infections Treatment Guidelines. Product may be temporarily discontinued for this participant, based on the judgment of the investigator.

Why? Product may be temporarily held for this participant at the judgment of the investigator, per the MTN 001 protocol, Section 9.5.6.

Section 11. Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN 001. Please also refer to Section 8 of the MTN 001 protocol and the Manual for Expedited Reporting of Adverse Events to DAIDS in Appendix V of the protocol.

11.1 Definitions and General Reporting Guidance

11.1.1 Adverse Event (AE)

The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (ICH-E6) defines an AE as any untoward medical occurrence in a clinical research participant administered an investigational product and that does not necessarily have a causal relationship with the investigational product. As such, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

The MTN 001 protocol specifies that any untoward medical occurrence experienced by a study participant after randomization is considered an AE, regardless of the study group to which the participant is assigned. Therefore AEs must be identified and reported for MTN 001 participants in all of the six sequence groups.

The Adverse Experience Log case report form (see Section 13) is used to report all AEs that occur among MTN 001 study participants to the MTN Statistical and Data Management Center (SDMC) via DataFax. Each site's SOP for source documentation should define the extent to which this form will be used as a source document. Site-specific delegation of duties documentation should designate study staff authorized by the Investigator or Record (IoR) to complete Adverse Experience Log forms. Regardless of who initially completes these forms, a clinician listed on the site's FDA Form 1572 should review them to ensure the accuracy of the data reported and to help maintain consistency of reporting across clinicians.

Medical conditions, problems, signs, symptoms, and findings identified prior to randomization are considered pre-existing conditions. Such conditions should be documented per the screening and enrollment visit guidance provided in Sections 4, 7, and 10 of this manual, and reported on the Pre-Existing Conditions case report form (see Section 13). If a pre-existing condition worsens (increases in severity or frequency) after randomization, the worsened condition is considered an AE.

11.1.2 Serious Adverse Event (SAE)

ICH-E6 defines a serious adverse event (SAE) as any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongs an existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

ICH guidance (E2A) also states that medical and scientific judgment should be exercised in deciding whether other adverse events not listed above should be considered serious and that “important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed in the definition above” should also usually be considered serious.

SAEs are a subset of all AEs. For each AE identified in MTN 001, an authorized study clinician must determine whether the AE meets the definition of SAE. The Adverse Experience Log case report form includes an item (item 8) to record this determination.

11.1.3 Expedited Adverse Event (EAE)

Expedited adverse events (EAEs) are AEs that meet criteria specified in the study protocol as requiring additional reporting for rapid review and assessment by DAIDS. In some cases, DAIDS may be required to report the EAE to the US Food and Drug Administration (FDA). All EAEs must be reported to the DAIDS Safety Office within three business days of site awareness of the EAE.

Although seriousness (defined in Section 11.1.2) is a consideration in determining whether an AE meets the definition of EAE, the terms SAE and EAE are not synonymous. The two terms refer to two different, but overlapping, subsets of AEs. For MTN 001, the subset of AEs that are considered EAEs includes some AEs that are serious and some that are not serious.

The Manual for Expedited Reporting of Adverse Events to DAIDS, which can be found at http://rcc.tech-res.com/DAIDS%20RCC%20Forms/EAE_ManualFinal_1.0_6May2004.pdf, defines levels of EAE reporting that may be used in DAIDS-sponsored studies. For MTN 001 the “standard” reporting level will be followed.

EAE reporting is undertaken for all participants assigned to the six sequence groups. For each participant, EAE reporting is undertaken through completion of the participant’s study exit visit. Thereafter, only pregnancy outcomes that meet criteria for expedited reporting (e.g., fetal losses) occurring among participants known to be pregnant at study exit will be reported.

All EAEs must be reported on a DAIDS Expedited Adverse Event (EAE) Form. Copies of the form and form completion instructions are available at <http://rcc.tech-res-intl.com>.

A study physician listed on the site's FDA Form 1572 must review and verify all data recorded on the DAIDS EAE Form for accuracy and completeness. This physician also must make the final assessment of the relationship between the EAE and study product and sign the completed form. If necessary to meet required reporting timeframes, an EAE Form may be submitted to the DAIDS Safety Office without a completed signature page. However, the completed signature page, and any necessary corrections or additions, must be submitted to the DAIDS Safety office within the next three business days.

As noted above, EAE Forms must be submitted to the DAIDS Safety Office within three business days of site awareness of the EAE. The DAIDS Safety Office fax number is shown on the first page of the EAE Form. Completed forms also may be digitally scanned and submitted to the DAIDS Safety Office via email. Contact details are as follows:

Website:	http://rcc.tech-res-intl.com
Phone:	301-897-1709 or toll free in the US: 800-537-9979
Fax:	301-897-1710 or toll free in the US: 800-275-7619
Email:	RCCSafetyOffice@tech-res.com
Office Hours:	Monday through Friday, 8:30 AM to 5:00 PM ET

All EAEs must also be reported on Adverse Experience Log case report forms. When completing Adverse Experience Log case report forms and EAE Forms, study clinicians should carefully review all documentation of the event to ensure accuracy, completeness, and consistency. All AE descriptions and details (e.g., onset date, severity grade, relationship to study product) must be recorded consistently across all documents. All EAE Forms received at the DAIDS Safety Office will be compared with Adverse Experience Log forms received at the MTN SDMC to ensure that all reports that should have been received by both the DAIDS Safety Office and the SDMC have been received and that the details recorded on each form are consistent.

11.1.3.1 EAEs Reporting Requirements

Type of Adverse Event	Standard EAE Reporting
Results in death	Report as EAE regardless of relationship to study product
Is a congenital anomaly or birth defect or fetal loss	Report as EAE regardless of relationship to study product
Results in persistent or significant disabilities or incapacities	Report as EAE regardless of relationship to study product
Requires or prolongs hospitalization or requires intervention to prevent significant/permanent disability or death	Report as EAE if relationship to study product is: <ul style="list-style-type: none"> • Definitely related • Probably related • Possibly related • Probably not related
Is life-threatening (includes all Grade 4 AEs)	Report as EAE if relationship to study product is: <ul style="list-style-type: none"> • Definitely related • Probably related • Possibly related • Probably not related
Other Grade 1, 2 and 3 AEs	Do not report as EAE

In addition to the events listed above, the following also should be reported as EAEs:

- AEs that may be related to study product (i.e., definitely, probably, possibly, or probably not related) that the IoR believes are of sufficient concern to be reported on an expedited basis to DAIDS. This includes AEs that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent a serious AE.
- Serious AEs that are not related to study product but could be associated with study participation or procedures.
- Unexpected serious AEs that may be related to study product (i.e., definitely, probably, possibly, or probably not related) that occur after the participant's study exit visit.

11.2 Adverse Event Terminology

Both the Adverse Experience Log case report form and the DAIDS EAE Form require site staff to assign a term or description to each AE. Whenever possible, a diagnosis should be reported, rather than a cluster of signs and/or symptoms. When relevant, an anatomical location should be included in the term or description. This is especially important in MTN 001 for distinguishing pelvic exam findings that may be observed on the vulva, in the vagina, or on the cervix.

When it is not possible to identify a single diagnosis to describe a cluster of signs and/or symptoms, each individual sign and symptom must be reported as an individual AE.

If an abnormal laboratory test result is reported as an AE, separate from any clinical diagnosis associated with the result, the type of test performed and the direction of the abnormality should be reported (e.g., decreased hematocrit, elevated ALT). The severity grade of the result should not be reported as part of the AE description since the grade is captured elsewhere (item 3) on the form.

11.3 Adverse Event Severity

The term severity is used to describe the intensity of an AE. The severity of each AE identified in MTN 001 must be graded on a five-point scale:

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe
- Grade 4 = Potentially life-threatening
- Grade 5 = Death

Severity is not the same as seriousness, which is based on the outcome or action associated with an event, as described in Section 11.1.2.

Protocol version 2.0, dated 3 September 2008, specifies that severity grading for MTN 001 will be based on the DAIDS Table for Grading Adult and Pediatric Adverse Events, dated 28 December 2004, which can be found in Section Appendix 11.1 and at the following web site: <http://rcc.tech-res-intl.com>.

The Female Genital Grading Table for Use in Microbicide Studies (included in Section Appendix 11-1) will be the primary tool for grading adverse events for this protocol, with the exception of asymptomatic bacterial vaginosis which will not be a reportable AE. Adverse events not included in that table will be graded by the DAIDS AE Grading Table Version 1.0, December 2004. In cases where an AE is covered in both tables, the Female Genital Grading Table for Use in Microbicide Studies will be the grading scale utilized.

11.4 Adverse Event Relationship to Study Product

For each AE identified in MTN 001, an authorized study clinician must assess the relationship of the AE to study product, based on the temporal relationship of the AE to administration of product, product pharmacology and other information provided in the Investigator's Brochures, and clinical judgment. One of the following relationship categories must be assigned to each AE:

- **Definitely Related:** The AE and administration of study product are related in time, and a direct association can be demonstrated.
- **Probably Related:** The AE and administration of study product are reasonably related in time, and the AE is more likely explained by study product than other causes.
- **Possibly Related:** The AE and administration of study product are reasonably related in time, and the AE can be explained equally well by causes other than study product.
- **Probably Not Related:** A potential relationship between the AE and study product could exist (i.e., the possibility cannot be excluded), but the AE is most likely explained by causes other than study product.
- **Not Related.** The AE is clearly explained by another cause not related to study product.

***Note:** For AEs with an onset date during the oral period or the washout period following the oral period, the tenofovir tablets only are considered the MTN 001 study product for which AE relatedness should be assessed. For AEs with an onset date during the vaginal period or the washout period following the vaginal period, the tenofovir gel only (including the applicator) is considered the MTN 001 study product for which AE relatedness should be assessed. For AEs with an onset date during the dual period or the washout period following the dual period, both the tenofovir tablets and the tenofovir gel (including the applicator) together are considered the MTN 001 study product for which AE relatedness should be assessed. Any AEs thought to be related to a tenofovir gel applicator should be documented as such by choosing one of the "related" categories and using descriptive text, comments, or other notations to indicate that the presumed relationship is to the applicator.*

In addition to the relationship categories listed above, DAIDS allows a relationship of "pending" to be temporarily assigned to AEs that result in death, if additional time and information are needed to determine the relationship of the AE to study product. However, a final relationship assessment must be submitted to DAIDS (via the EAE Form) within three business days after first reporting the death. If a final assessment is not made within three business days, the AE will be considered possibly related to study product.

11.5 Adverse Event Outcomes and Follow-Up Information

Each AE identified in MTN 001 must be followed clinically until the AE resolves (returns to baseline) or stabilizes. In addition to performing other protocol-specified procedures, at each follow-up visit an authorized study clinician should review all previously reported ongoing AEs to evaluate their current status. To assist study sites in following unresolved AEs, the MTN SDMC will generate listings of such AEs throughout the period of study implementation (see also Section 15 of this manual).

In many cases the final outcome of an AE will not be available when the Adverse Experience Log case report form is first completed and faxed to DataFax. In such cases, the form should be updated when the final outcome becomes available and re-faxed to DataFax at that time.

If an AE increases in severity or frequency (worsens) after it has been reported on an Adverse Experience Log case report form, it must be reported as a new AE, at the increased severity or frequency, on a new Adverse Experience Log case report form. In this case, the outcome of the first AE will be documented as “severity/frequency increased.” The outcome date of the first AE and the onset date of the new (worsened) AE will both be the date upon which the severity or frequency increased.

Site staff are not required to report the outcome of EAEs to the DAIDS Safety Office, unless outcome information is specifically requested by DAIDS. However, if an EAE increases in severity to a higher grade than previously reported, it must be reported to the DAIDS Safety Office as a new EAE on a new EAE Form.

EAE follow-up information also must be reported to the DAIDS Safety Office under the following circumstances:

- Requests from DAIDS for additional information
- A change in the relationship between the AE and study product by the study physician
- Additional significant information that becomes available for a previously reported adverse event (this is particularly important for new information addressing cause of death if the initial assignment was “pending”)
- Results of re-challenge with the study product, if performed

In these circumstances, the required follow-up information should be reported on a new EAE Form as a Follow-Up Report. See also Section 5.1 of the Manual for Expedited Reporting of Adverse Events to DAIDS.

11.6 Reporting Recurrent Adverse Events

If an AE that was previously reported on an Adverse Experience Log case report form resolves and then recurs at a later date, the second occurrence must be reported as a new AE on a new Adverse Experience Log case report form.

An important clarification of this guidance for MTN 001 relates to genital herpes and genital warts. Both of these conditions are associated with chronic viral infections — HSV-2 and HPV — and periodic symptomatic outbreaks — herpetic ulcers and genital warts.

- If infection with HSV-2 or HPV occurred before randomization, the infection is considered a pre-existing condition: report on the Pre-Existing Conditions form.
- For HPV, genital warts present before randomization also are considered a pre-existing condition: report on the Pre-Existing Conditions form.
- If infection with HSV-2 or HPV is newly diagnosed after randomization, the infection is considered an AE: report on an Adverse Experience Log form. Since HSV-2 and HPV infections cannot be cured, they should be reported as AEs only once per participant.

- If any new symptomatic outbreaks occur after randomization, each outbreak is considered an AE: report on an Adverse Experience Log form.

If an EAE that was previously reported to the DAIDS Safety Office resolves and then later recurs at a level requiring expedited reporting, the second occurrence must be reported to the DAIDS Safety Office as a new EAE on a new EAE Form.

11.7 Social Harms

In addition to medical AEs, participants in MTN 001 may experience social harms — non-medical adverse consequences — as a result of their participation in the study. For example, participants could experience difficulties in their personal relationships with partners, family members, and friends. They also could experience stigma or discrimination from family members and members of their community. In the event that any social harms occur, study staff should fully document the issues or problems and make every effort to facilitate their resolution as described in this section.

Prior to study initiation, study staff teams at each site should discuss as a group, and with community representatives, what issues and problems are most likely to be encountered by participants at their site, and should agree upon how these issues and problems should be handled if reported. Roles and responsibilities should be defined for all staff members, such that each staff member is aware of what actions he/she can appropriately take, and what actions should be referred to other members of the team. During study implementation, staff teams at each site should continue to discuss actual participant experiences, successful and unsuccessful response strategies, and other lessons learned among themselves and with community representatives. Based on these discussions and lessons learned, procedures for responding to issues and problems should be reassessed and updated as needed throughout the study.

The following are suggested strategies for responding to social harms that may be adapted and tailored to best meet participant needs at each site:

- When first responding to an issue or problem, actively listen to the participant's description of the problem and ask questions to elicit as much detail as possible about the problem, including the participant's perception of the severity of the problem. Record all pertinent details in signed and dated chart notes. If the issue or problem meets criteria for expedited reporting to the DAIDS Safety Office, report it as described in Section 11.1.3 above. Also report the issue or problem to all responsible IRBs/ECs, if required per IRB/EC guidelines.
- Ask the participant to articulate her thoughts on what can/should be done to address the problem, including what she would like study staff to do in response to the problem (if anything).
- Discuss with the participant any additional or alternative strategies that you might suggest to address the problem and collaborate with her to develop a plan to try to address the problem. Document the plan in signed and dated chart notes.

- Take all possible action to try to address the problem, per the plan agreed upon with the participant. Document all action taken, and outcomes thereof, in signed and dated chart notes.
- As with medical AEs, follow all problems to resolution or stabilization.
- Provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem.
- Consult the MTN 001 Protocol Safety Review Team (PSRT) for further input and guidance as needed.

As is the case with medical AEs, data collected on social harms will be monitored by the MTN 001 PSRT, as described below.

11.8 MTN 001 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN 001 protocol and Section Appendix 11-3 for a complete description of the participant safety monitoring procedures in place for MTN 001. Also refer to Section 15 of this manual for a description of the reports prepared by the MTN SDMC in support of MTN 001 safety monitoring procedures.

Participant safety is of paramount importance in MTN 001. Primary safety monitoring and safeguarding of individual study participants is the responsibility of study site staff, under the direction of the IoR. The IoR and designated site staff also are responsible for submitting case report forms to the MTN SDMC and EAE Forms to the DAIDS Safety Office, such that relevant safety data are available in a timely manner for other study-specific safety monitoring procedures, as follows:

- Clinical Affairs staff at the MTN SDMC will review clinic and laboratory data received at the SDMC and apply clinical data quality control notes (queries) to data requiring confirmation, clarification, or further follow-up by site staff. These queries will be issued to site staff for resolution on an ongoing basis throughout the period of study implementation.
- The DAIDS Safety Office, DAIDS RAB Safety Specialist, and DAIDS PSB Medical Officer will review all EAE Forms received for MTN 001 and follow up on these reports with site staff, the MTN 001 Protocol Team, and drug regulatory authorities when indicated.
- The MTN 001 Protocol Safety Review Team (PSRT) will routinely review safety data reports prepared for MTN 001 by the MTN SDMC. As described further in Section Appendix 11-3, the PSRT will meet via conference call to discuss the accumulating study safety data and any potential safety concerns.

In the event that the protocol team or PSRT has serious safety concerns, the protocol team or PSRT will request a review of the data by the MTN Study Monitoring Committee (SMC). While site staff are not typically involved in these reviews, site staff should be aware that the SMC may make recommendations to DAIDS and/or the MTN leadership that could affect the study and study sites in significant ways. These decisions are based on detailed review of the available study data and careful consideration of ongoing participant safety and study viability.

11.9 Safety Distributions from DAIDS

As noted in Section 1 of this manual, study sites will receive product- and safety-related information throughout the period of study implementation. This information will be distributed by DAIDS, through its Regulatory Compliance Center and/or the MTN Coordinating and Operations Center, and may include:

- Updated Investigator's Brochures
- IND Safety Reports
- Other safety memoranda and updates

Each distribution will include a cover memo providing instructions on how the document is to be handled. In all cases, a copy of the distribution must be filed in the study site Essential Document files for MTN 001. Also in all cases, study staff responsible for clinical oversight of study participants should be made aware of any newly available safety information. In many cases, the distribution will need to be submitted to all study site IRBs/ECs. Safety distributions do not require IRB/EC approval; however acknowledgement of receipt is desirable. Submission letters/memos for IRB/EC submissions should specify the name and date of all documents submitted.

Section Appendix 11-1
DAIDS Female Genital Table for Use in Microbicide Studies

Section Appendix 11-2
DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

Section Appendix 11-3
DRAFT MTN 001 Protocol Safety Review Team Plan

Roles and Responsibilities of the PSRT

Per the MTN 001 protocol, the roles and responsibilities of the MTN 001 Protocol Safety Review Team (PSRT) are to:

1. Conduct regular reviews of standardized study safety data reports (protocol Section 8). Once the SDMC begins receiving study follow-up safety data, the PSRT will convene via regularly scheduled monthly conference calls (for example, on the first Thursday of each month). The frequency of calls may be adjusted throughout the period of study implementation as agreed upon by the PSRT. Should any safety concerns be identified by the PSRT, these will be referred to the MTN Study Monitoring Committee (SMC).
2. Respond to Investigator queries regarding temporary or permanent discontinuation of product use (protocol Section 9.4). The protocol specifies criteria for permanent discontinuation of further study product use of one or both study products. These situations include:
 - (a) Study product-related toxicity requiring permanent discontinuation of study product(s) per Section 9 of the MTN 001 protocol.
 - (b) Completion of regimen as defined in the protocol
 - (c) Request by participant to terminate study product(s)
 - (d) Clinical reasons determined by the physician
 - (e) HIV infection
 - (f) Hepatitis B infection
 - (g) Pregnancy or breastfeeding

When the IoR holds study product(s) due to study product-related toxicity, or any other clinical reason that it's not specified in the protocol as criteria for permanent discontinuation, the PSRT should be notified immediately.

There are other situations when the IoR would hold product and then submit a PSRT query form to notify the PSRT of product discontinuation and obtain further product use management guidance, such as:

- (a) Study product-related toxicity per Sections 9.3 and 9.5 of the MTN 001 protocol.
 - (b) Use of a prohibited medication
 - (c) Participants are unable or unwilling to comply with required study procedures;
 - (d) Otherwise might put participant at risk or the safety and well-being of the participant may be compromised by continuing product use.
3. Respond to Investigator queries regarding product resumption following occurrence of a grade 3 or grade 4 AE (protocol Section 9.3).
4. Respond to Investigator queries regarding study eligibility and general AE management and reporting (not necessarily related to product use; protocol Section 8.3).
5. Respond to Investigator requests for participant withdrawal from the study (protocol Section 9.8).

PSRT Composition

The following individuals currently comprise the MTN 001 PSRT:

- Craig Hendrix, Protocol Chair
- Lydia E. Soto-Torres, DAIDS PSB Medical Officer
- Katherine Bunge, MTN Safety Physician, PSRT Co-Chair
- Nancy Connolly, MTN Safety Physician, PSRT Co-Chair
- Ross D. Cranston, MTN Safety Physician, PSRT Co-Chair
- SDMC Clinical Affairs Research Nurse
- Barbara Richardson, Protocol Statistician

Ideally all of the above-listed PSRT members will take part in routine PSRT conference calls; however a quorum of at least three members must take part in all calls. The quorum must consist of:

- The DAIDS PSB Medical Officer (or designee) and
- One of the Safety Physicians

If a quorum is not present, the call may be deferred until the next scheduled call time unless a quorum member requests a more immediate call.

The MTN CORE (FHI) Clinical Research Managers, SDMC (SCHARP) Project Managers, SDMC (SCHARP) Statistical Research Associates, and SDMC (SCHARP) Clinical Affairs staff also will participate in and facilitate PSRT calls and reviews. The DAIDS PSB Program Officer(s), DAIDS PAB Protocol Pharmacist, MTN CORE Pharmacist and Co-Sponsors also may attend calls as observers.

Routine Safety Data Summary Reports: Content, Format and Frequency

The SDMC will generate and distribute standard safety data reports to the PSRT via e-mail within a week prior to each PSRT conference call. Tabulations will be generated for all study participants combined (i.e., across all study regimen groups). Pending final confirmation from the PSRT, the following events will be included in the standard safety data reports, regardless of relationship to study product:

- All new or modified Adverse Events (AEs) by study regimen (since the last report distribution)
- Cumulative listing of all study expedited adverse events (EAEs) and serious adverse events (SAEs) by study regimen
- Summary of adverse event coding progress
- Summary of pregnancies and pregnancy outcomes
- Summary of “Definitely Related” and “Probably Related” AEs by body system and severity
- Summary of Grade 3-5 AEs by body system and relationship to study product

Reports will include summary information regarding the number and frequency of events that meet the criteria above organized by body system (using MedDRA terms) and severity, and will include information on relatedness to study product.

During PSRT conference calls, the DAIDS PSB Medical Officer will summarize any additional EAE Forms received at the DAIDS Safety Office after the cut-off date for inclusion in the SDMC PSRT report.

PSRT Communications

An email alias (mtn001psrt@mtnstopshiv.org) will be used to facilitate communication with the PSRT. All safety data summary reports from the SDMC, all PSRT queries from study sites, and all query responses from the PSRT will be distributed via this alias. A standard PSRT query form (below) will be used to elicit sufficient information to allow the PSRT to respond to each query. To ensure a timely PSRT response, the MTN Safety Physicians have ultimate responsibility for providing a final response to the query (via email) within three business days after receipt of the query. All members of the PSRT are encouraged to review the information provided by the site and to offer their advice; however final determination rests with the MTN Safety Physicians.

MTN 001 Protocol Safety Review Team Query Form
Page 1 of 2

Instructions: Email completed form to MTN Safety Physicians to cranstonr@dom.pitt.edu, kbunge@mail.magee.edu and nancycsc@gmail.com.

IMPORTANT: Complete all required fields so the PSRT has all information needed to respond to your query.

Site: _____ **Query Date (dd-MMM-yy):** _____

Completed by: _____ **Email address:** _____

PTID: _____ **Participant Age (in years):** _____

- Reason for query:**
- Product use consultation:
 - Should use of study product be temporarily discontinued?
 - Should use of study product be permanently discontinued?
 - Should use of study product be resumed?
 - Request for consultation on AE management
 - Request to withdraw participant from the study
 - Other, specify: _____

Is this query a request for the PSRT to consult on an adverse event (AE)?

- Yes → continue completing this page
- No → skip to Comments on page 2

Primary AE of concern: _____

AE onset date (dd-MMM-yy): _____

AE severity grade at onset: _____

Relatedness to study product:

- Definitely related
- Probably related
- Possibly related
- Probably not related
- Definitely not related

Current study product administration:

- No change
- On hold
- Permanently discontinued
- Not applicable

Has this AE been reported on a SCHARP AE Log form?

- Yes
- No

Has this AE been reported as an EAE?

- Yes
- No

Has this AE been assessed more than once?

- Yes
- No → skip to Comments on page 2

Date of most recent assessment (dd-MMM-yy): _____

Status of AE at most recent assessment:

- Continuing, stabilized (severity grade unchanged)
- Continuing, improving → severity grade decreased to
- Continuing, worsening → severity grade increased to
- Resolved

Comments: Provide additional details relevant to this query. If product use has been held, include date of last reported product use prior to the hold (per participant report).

End of Form for Site Staff. Email completed form to the MTN 001 Protocol Safety Physicians cranstonr@dom.pitt.edu, kbunge@mail.magee.edu and nancycsc@gmail.com. If an email response is not received from the PSRT within 3 business days, re-contact the Protocol Safety Physicians and/or the MTN CORE (kgomez@fhi.org, sjohnson@fhi.org) for assistance as soon as possible.

FOR PSRT USE ONLY — PROVIDE RESPONSE TO QUERY HERE

PSRT Responding Member:

PSRT Response Date (dd-MMM-yy):

Query Outcome:

- Approved
- Not approved
- Not applicable

PSRT Comments:

Section 12. Laboratory Considerations

12.1 Overview and General Guidance

This section contains information on the laboratory procedures performed in MTN 001.

As transmission of HIV and other infectious agents can occur through contact with contaminated needles, blood, blood products, and vaginal secretions, all study staff must take appropriate precautions when collecting and handling biological specimens. Sites must have appropriate written safety procedures in place before study initiation. Guidance on universal precautions available from the US Centers for Disease Control can be found at the following websites:

- http://www.cdc.gov/ncidod/dhqp/bp_universal_precautions.html

Some laboratory procedures will be performed in study site clinics or laboratories and others in the MTN Network Laboratory (NL) Johns Hopkins Laboratories or University of Washington. **Table 12-1 lists for each test the testing location, specimen type, specimen container and kit/method (if specified). Appendix 12-4 summarizes information for specimen requirements.**

Regardless of whether tests are performed in clinic or laboratory settings, study staff that performs the tests must be trained in associated QC procedures prior to performing the tests for study purposes; training documentation should be available for inspection at any time.

All site laboratories will be monitored by the MTN NL which will utilize information from DAIDS monitoring groups (PNL, IQA, VQA, etc...) to monitor and certify laboratories for testing. US Laboratories that are certified by CLIA (Clinical Laboratory Improvement Amendment) will be able to substitute this for some of the documentation requirements required of other labs. Valid CLIA certificates must be provided in these cases.

Only the U.S. sites will perform the Intensive PK sub study. Certain procedures in this section are limited to the intensive PK sub study and do not apply to the non-U.S. sites: Vaginal Biopsies and Cervical Cytobrushes. Some procedures for MTN 001 will be performed only at sites that have capacity: Flow Cytometry and PBMC for Intracellular tenofovir. Refer to section 7 of the protocol for details of laboratory testing for intensive PK and non-intensive PK sites.

**Table 12-1
Overview of Laboratory Testing Locations, Specimens,
and Methods for MTN 001**

Assay	Testing Location	Specimen Type	Tube/Container	Kit/Method
Urine pregnancy test	In clinic	Urine	Plastic screw top cup	Quidel Quick Vue
Urine SDA for gonorrhea and Chlamydia (neat method)	MTN Network Lab Regional or site lab	Urine	Plastic screw top Cup-Urine Preservative Tube for shipping	BD Probetec
Dipstick Urinalysis ¹	In Clinic	Urine	Plastic screw top cup	Bayer Multistix® 10 SG or Bayer Uristix 4
HIV antibody screen and Western Blot	Clinic/Local Lab	Plasma or whole blood (<i>serum acceptable</i>)	EDTA or plain tube	FDA approved tests ²
Complete blood count	Local Lab	Whole Blood	EDTA tube	Not specified
Chemistries (AST, ALT, Creatinine, Phosphorus)	Local Lab	Serum	Plain or serum separator	Not specified
Hepatitis B Surface Antigen	Local Lab	Serum	Plain or serum separator	Not specified
Flow Cytometry (CD38, CD3, CD4 and HLA-DR) ³	Local Lab	EDTA Whole Blood	EDTA Tube	Not Specified
Blood tenofovir level	Network Lab	Serum	Plain Tube	JHU method
Pap Smear	Local Lab	Ecto- and Endocervical cells	Slides	Not specified
Vaginal pH	In clinic	N/A	N/A	S/P pH Indicator Strips
Vaginal wet preparation	In clinic	Vaginal fluid swab	N/A	N/A
Syphilis Serology	Local Lab	Serum or Plasma	EDTA tube, plain or serum separator	Not specified
PBMC Isolation for Intracellular Tenofovir ³	Isolation and storage at local labs; testing at network lab	Whole Blood	CPT Tubes	JHU Protocol
Herpes Culture ⁴	Local Lab	Swab	Swab	Not Specified
Cervicovaginal Lavage (CVL) for vaginal flora proteomics, markers of inflammation and tenofovir level	Collected Locally, sent to network lab	Fluid recovered from CVL (saline used)	Conical Vial	Network Lab to provide SOP template
Cervical Cell lysate for intracellular tenofovir	Network Lab	Cervical Cytobrush	Screw top vial or test tube	JHU method
Vaginal Biopsy for tenofovir	Network Lab	Vaginal Biopsy	Cryovial	JHU method
Rectal Tenofovir Level ⁵	Network Lab	Rectal Sponge	5 ml cryovial	JHU Method

1 Perform Urine Culture as indicated if local standard of care. Dipstick tests are glucose, protein, leukocytes and nitrites.

2 If performing 2 rapid tests as part of the HIV algorithm, sites may use one non-FDA approved test with one FDA-approved test

3 To be performed only at sites with capacity

4 Only if local standard of care

5 Bronx Site only

**Table 12-2
Overview of Specimens for Storage and Shipment**

Specimen	Additive	Use LDMS?	Ship to:	Shipping schedule
PBMC for Intracellular Tenofovir ¹	CPT With Sodium Citrate	Yes	MTN Network Lab	Store at site until notified by MTN ²
CVL	Saline	Yes	MTN Network Lab	Store at site until notified by MTN ²
Plasma for storage	EDTA	Yes	MTN Network Lab	Store at site until notified by MTN ²
Serum for storage	None	Yes	MTN Network Lab	Store at site until notified by MTN
Urine for GC/CT testing (Only sites that do not have a validated Probetec)	BD Urine Preservation Tubes	No	MTN Network Lab or Regional Network lab	1-2 times per week, depending on volume
Cytology Brush ³	PBS	Yes	MTN Network Lab	Store at site until notified by MTN ²
Vaginal Biopsy ³	None	Yes	MTN Network Lab	Store at site until notified by MTN ²
Rectal Sponge ⁴	PBS	Yes	MTN Network Lab	Store at site until notified by MTN ²

1 To be performed only at sites with capacity

2 At the time of shipment, the MTN NL will furnish shipping instructions and addresses.

3 Intensive PK sub study sites only

4 Bronx Site only

Sites are responsible to ensure that specimen volumes collected do not exceed what is described in the informed consent process. The MTN NL may request details of collection containers and volumes for this purpose. These blood draws will vary by site. Ideally, one method, type of test kit, and/or combination of test kits will be used for each protocol specified test throughout the duration of the study. If for any reason a new or alternative method or kit must be used after study initiation, site laboratory staff must perform a validation study of the new method or test prior to changing methods. The MTN NL must be notified before the change (for non-CLIA certified labs) and can provide further guidance on validation requirements. Similarly, all labs (including CLIA certified labs) must contact the MTN NL in cases of changes to normal ranges.

Provided in the remainder of this section is information intended to standardize laboratory procedures across sites. Adherence to the specifications of this section is essential to ensure that data derived from laboratory testing will be considered acceptable to all regulatory authorities across study sites.

This section of the MTN 001 SSP manual gives basic guidance to the sites but is not an exhaustive procedure manual for all laboratory testing. This section must be supplemented with Standard Operating Procedures. SOP's will be provided by the MTN for local adaptation for PBMC for Intracellular Tenofovir and Cervicovaginal Lavage.

12.2 Specimen Labeling

All containers into which specimens are initially collected (e.g., urine collection cups, blood collection tubes) will be labeled with SCHARP-provided Participant ID (PTID) labels. Study sites will be provided with pre-printed labels or a template that can be used to generate labels. The date the specimens are collected should also be included on the label. If the date is handwritten, it should be in indelible ink (such as a Sharpie pen).

Microscope slides used for evaluation of vaginal/cervical fluids also will be labeled with SCHARP designed PTID labels. PTIDs are pre-printed on these labels; however study staff must write the specimen collection date on each label. The visit code also may be written on the label.

When specimens are tested at the local lab, any additional labeling required for on-site specimen management and chain of custody will be performed in accordance with site SOPs. The following specimens will be entered into LDMS and labeled with LDMS-generated labels: stored plasma specimens, stored serum specimens, PMBC, and cervical lavage specimens.

Specimen Labeling for PK specimens

In addition to standard specimen labels, there will be special labels for PK specimens. These will be for visit codes 4.0, 7.0 and 10.0. There will be specific labels for each time point to be drawn. On each PK specimen label, write in the specimen collection time and the date.

Non Intensive PK Sites Only (Uganda and South Africa):

Use the following conventions for labeling the Post dosing PK Time points (see Table 10 Page 57 in the MTN 001 Protocol)

- 1-3 Hours label as 1 hour timepoint
- 3-5 Hours label as 3 hour timepoint
- 5-7 Hours label as 5 hour timepoint

12.3 Procedures for Specimens that can not be evaluated

Specimens will be redrawn or recollected if it is found that they can not be evaluated per site SOP's. Sites will monitor specimen management problems as part of ongoing Quality Assurance. In cases where additional specimens need to be recollected either due to a laboratory error (lost or broken specimen or clerical error) or clinic error (clerical error), a protocol event form may be required.

12.4 Use of LDMS

The Laboratory Data and Management System (LDMS) is a program used for the storage and shipping of laboratory specimens. It is supported by the Frontier Science Foundation (FSTRF). LDMS must be used at all sites to track the collection, storage, and shipment of seven types of specimens in MTN 001: plasma, serum, PMBC, vaginal biopsies, cervical cytobrushes, rectal sponges and CVL.

Detailed instructions for use of LDMS are provided at: <https://www.fstrf.org/ldms> (may require a password).

All sites will be required to maintain the current version of LDMS and monitor updates relating to use of the LDMS. It is crucial to be aware of proper label formats to ensure that specimens are correctly labeled. Sites will be responsible to back up their LDMS data (frequency determined by site) locally and to export their data to FSTRF (at least weekly).

Questions related to use of LDMS in MTN 001 may be directed to Edward Livant or LDMS Technical (User) Support. Usual business hours for LDMS User Support are 7:30 am - 6:00 pm (ET) on Monday and Fridays and 7:30 am - 8:00 pm (ET) on Tuesdays, Wednesdays, and Thursdays. During business hours, please contact LDMS User Support as follows:

Email: ldmshelp@fstrf.org

Phone: +716-834-0900, ext 7311

Fax: +716-898-7711

LDMS User Support can be paged during off business hours if you are locked out of LDMS or experience errors that prevent you from completing LDMS lab work. To page LDMS User Support, email LDMS pager 1 (address shown in table below) and include the following information in the body of your email:

- LDMS lab number (this is a three-digit number that is different from your network assigned clinical site number)
- The full telephone number at which you can be reached, including the country code and city code if you are outside the United States
- A short description of the problem

If a response is not received within 15 minutes after emailing LDMS 1, try emailing LDMS 2, then finally, LDMS 3. The pagers also can be reached via telephone. When paging via telephone, after dialing you will hear a voice greeting followed by three quick beeps that indicate you are connected to the paging service. Please include the full telephone number at which you can be reached, including the country and city codes if you are outside the United States. Please call LDMS pager 1 first (telephone number shown in table below). If you do not receive a response within 15 minutes after calling LDMS 1, please try LDMS 2, then finally, LDMS 3.

**Table 12-3
LDMS User Support Paging Details**

Pager	Email Address	Telephone Number
LDMS 1	ldmspager1@fstrf.org	716-556-0583
LDMS 2	ldmspager2@fstrf.org	716-556-0584
LDMS 3	ldmspager3@fstrf.org	716-556-0585

Each site must export its LDMS data to Frontier Science (FSTRF) on a weekly basis. Exported data are used by the MTN SDMC to generate a monthly specimen repository report and to reconcile data entered in LDMS with data entered on study case report forms. Any discrepancies identified during the reconciliation are included in a monthly discrepancy report for each site. Sites are expected to resolve all discrepancies within two weeks of receipt of the report. The MTN NL is responsible for reminding sites to adhere to the two week timeframe and for following up with sites that do not resolve discrepancies within two weeks. The MTN SDMC reviews the discrepancy reports for critical samples (e.g., plasma needed for confirmatory HIV testing) that appear to be missing, and works with the NL and site staff to undertake appropriate corrective action. All corrective action should be documented in paper-based clinic and/or laboratory records as appropriate, and entered in the details section of LDMS. The NL and SDMC will discuss and document any items that, although resolved, appear 'irresolvable' in LDMS.

**Table 12-4
LDMS Specimen Management Guide to Logging in MTN 001 Specimens**

Test	Primary	Additive	Derivative	Sub Add/Derv	Primary Volume	Aliquot Volume	Units
Vaginal Biopsies	VGL	NON	TIS	N/A	Variable	1	N/A
PBMC for Intracellular Tenofovir	BLD	CPS	CEL	MET	Variable	1	ml
Cervicovaginal Lavage	CVL	NSL	CVL	N/A	Variable	1	ml
Plasma for storage	BLD	EDT	PL1/2	N/A	Variable	1-2	ml
Serum for Tenofovir	BLD	NON	SER	N/A	Variable	1-2	ml
Cytology Brushes	CER	PBS	CTB	N/A	Variable	1	N/A
Rectal sponge for PK (Bronx Site only)	REC	PBS	SPG	N/A	Variable	1	Ea

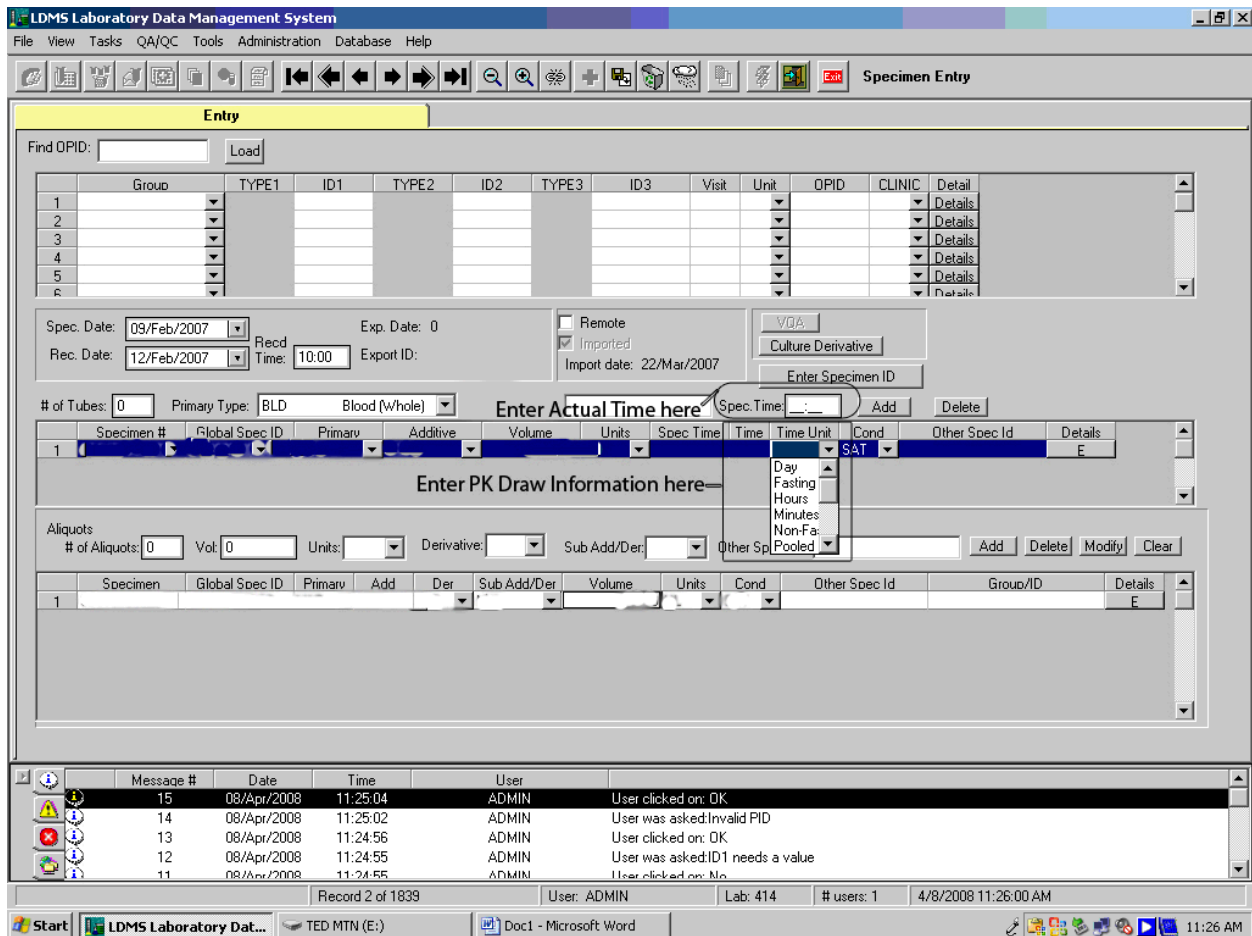
The table above should be used as a guide when logging in MTN 001 specimens. Please use the LDMS codes listed above when logging in specimens for each test

listed. Tests that are listed as local do not require that a sample be logged into the LDMS. See Appendix 12-1 for a copy of the LDMS tracking sheet.

Logging in PK Samples

- Enter the actual time in the Specimen Time area (See Image 1)
- Enter the PK timepoint information in Time and Time Unit area (See Image 1)
 - For Pre dose samples
 - The time should be 0:00
 - Select “Pre-dose” from the drop menu for units
 - For Post dose samples
 - Enter the number that corresponds to the PK timepoint (“1” for 1-Hour, “2” for 2-Hour, etc...)
 - Select “Hours” from the drop menu for units

IMAGE 1: LDMS Entry Screen



12.5 Urine Testing for Pregnancy, Dipstick, Chlamydia, and Gonorrhea

The urine tests performed at each study visit will depend on the time point of the visit and the clinical presentation of the participant. In general, at study visits when urine testing is required, a single specimen will be collected and then aliquots will be made for each test when possible. When doing multiple tests from one specimen, the correct order is separation of urine for the Chlamydia and Gonorrhea first, pregnancy test next, then the urine dipstick last. Collect urine specimens before collecting any pelvic specimens.

12.5.1 Specimen Collection

- The participant should not have urinated within one hour prior to urine collection.
- Provide the participant with a sterile, plastic, preservative-free screw-top urine collection cup labeled with a SCHARP-provided PTID label.
- Instruct the participant not to clean the labia prior to specimen collection.
- Collect the first 15-60 ml of voided urine in a sterile collection cup. (Not mid-stream).
- Instruct the participant to screw the lid tightly onto the cup after collection.
- At visits when pregnancy testing and/or dipstick urinalysis is required, aliquot 5-10 ml for these tests and store the remaining urine at 2-8°C or introduce the urine immediately into the Urine Preservation Tube (UPT) for subsequent chlamydia and gonorrhea testing.

12.5.2 Dipstick Urinalysis

Dip the urinalysis test strip into an aliquot of urine. At visits when both pregnancy testing and dipstick urinalysis are required, the same aliquot should be used for both tests, but the urinalysis should be performed after urine has been pipetted from the aliquot for the pregnancy test.

Either the Bayer/Siemens Multistix 9, Bayer Uristix 4 urine test strips or other Bayer/Siemens dipstix with the necessary tests must be used at all sites. Perform this test according to site SOPs and the package insert. Assess and record results for protein, leukocytes and nitrites. If leukocytes or nitrites are positive, perform a urine culture (may omit if not standard of care for UTI diagnosis). To avoid overgrowth of bacteria, refrigerate specimen before and during transport to laboratory.

Inventory should be monitored closely and re-supply orders placed at least 8-12 weeks in advance of actual need (or longer if needed per site procurement policies and procedures). Notify the NL immediately if any kit inventory or quality control problems are identified, so that appropriate action can be taken.

When entering results onto a CRF, a dipstick result of 1+ or greater is considered a “positive” result.

12.5.3 Pregnancy Testing

At visits when pregnancy testing is required, aliquot approximately 5-10 ml of urine from the specimen collection cup and pipette from this aliquot for pregnancy testing. If the urine is too dark to read the pregnancy test, another urine sample will need to be collected.

Note: Protocol-specified pregnancy testing is not discontinued during pregnancy.

The Quidel QuickVue One-Step hCG urine pregnancy test must be used at all sites. Perform the test according to site SOPs and the package insert. Do not perform any other urine pregnancy tests for confirmatory purposes.

12.5.4 Chlamydia and Gonorrhea Testing

This testing will be done at the MTN NL (U.S. sites) and site laboratories using the BD Probe Tec Method. Sites that have an approved Probetec will do the testing themselves using urine collected in any sterile plastic, preservative-free screw-top urine container. Sites which have met NL validation requirements will perform the neat procedure (no Urine Preservative Pouch). When shipping is required, send samples using the BD Urine Preservation Tubes (UPT). Following are shipping instructions:

Instructions for transferring urine into the UPT

- Collect urine as noted above.
- Open the UPT kit and remove the UPT and transfer pipette. Label the UPT with the participants PTID number and date.
- Hold the UPT upright and firmly tap the bottom of the tube on a flat surface to dislodge any large drops from inside the cap.
- Uncap the UPT and use the transfer pipette to transfer enough urine to fill the tube to the level indicated on the tube between the black lines. Do not under fill or overfill the tube.
- Cap tightly and invert the tube 3-4 times to ensure that the specimen and reagent are mixed.
- The specimen can now remain at 2-30°C for 30 days.

Below are shipping instructions for urine samples to Magee-Womens Research Institute for US sites. Shipping instructions for other site laboratories will be provided as needed for non-US sites.

- Urine specimens are stable for 30 days in the UPT therefore specimens can be batched and sent once a week if your turn around time is 8-9 days.
- Fill out a shipping manifest with the information listed in the example located in appendix 12-2 (Do not use LDMS for urine specimens).
- Package the specimens according to the IATA packing instructions 650 for non-refrigerated specimens.

- Place the tubes in a biohazard zip-lock bag.
- Enclose the tubes in the small Styrofoam container without ice packs.
- Place the Styrofoam container inside the cardboard box.
- Insert the box and the shipping manifest in a FedEx Diagnostic envelope.
- Check 2 day delivery on the FedEx air bill when shipping only urines (2 day delivery will save shipping costs)
- The day of shipment, send Lorna Rabe an e-mail at rabelk@upmc.edu with the FedEx tracking number.

If sending Monday through Thursday, send to:

Lorna Rabe

Magee-Womens Research Institute

204 Craft Ave, Room 530

Pittsburgh, PA 15213

Phone # 412-641-6042

(If sending on Friday, do not check Saturday delivery)

12.6 Blood Specimens for HIV testing, Syphilis, Hematology, Chemistries, PBMC for Intracellular Tenofovir, Blood Tenofovir, Hepatitis B Surface Antigen, Flow Cytometry and Plasma Archive

The blood tests performed at each study visit vary depending on the time point of the visit and potentially the clinical presentation of the participant. Perform all tests according to site SOPs and package inserts.

12.6.1 Specimen Collection and Initial Processing

Label all required tubes with a SCHARP-provided PTID label at the time of collection.

After collection:

- Allow plain tubes (no additive or serum separator tubes) to clot, then centrifuge per site SOPs to yield serum for syphilis, liver function, renal function testing, HBsAG and tenofovir level (do not use serum separator for tenofovir).
- EDTA Tubes should be gently inverted at least eight times after specimen collection to prevent clotting. EDTA tubes are used for hematology, HIV testing and plasma archive. If whole blood for hematology testing and plasma are to be taken from the same tube, the hematology must be completed before the tube is centrifuged and aliquotted. If whole blood is to be used for multiple tests, ensure that the tube is well mixed before removing any specimen.
- Cell Preparation Tubes (CPT) with Sodium Citrate are used for PBMC for intracellular Tenofovir. These should be mixed gently after collection.

12.6.2 HIV Testing

Plasma (whole blood and serum are also acceptable) will be tested for HIV using tests that have been validated at the study site. US sites must perform testing in laboratories certified by the Clinical Laboratory Improvement Amendment (CLIA) for HIV testing. At all sites, all tests and associated QC procedures must be documented on local

laboratory log sheets or other laboratory source documents. Also for all HIV testing done in non-CLIA certified labs or clinics, a second independent clinic or laboratory staff member trained in proper HIV testing and result recording procedures must review, verify, and sign-off on test results within the timeframe of the tests and prior to disclosure of results to participants. At all sites, HIV infection status will be assessed per the MTN 001 HIV testing algorithm (see appendix 12-3 in this section of the MTN 001 SSP or appendix III in the current version of the MTN 001 protocol).

SCREENING

Sites will use either one non rapid ELISA or two rapid tests at screening. When using rapid tests, at least one of the rapid tests must be FDA approved. If the ELISA or both rapid tests are non-reactive, the participant will be considered HIV-uninfected.

If the non rapid ELISA is reactive, or one rapid test is positive and one is negative, an FDA-approved Western Blot (WB) will be performed. If additional blood must be drawn for the WB, this is still considered sample 1 per the algorithm. If the WB is negative, the participant will be considered HIV-uninfected; this situation is not anticipated-contact the MTN NL if this occurs for instruction before proceeding. If the WB is positive, the participant will be considered HIV-infected. If the WB is indeterminate, notify the MTN NL. The participant will be asked to present to the study site in approximately one month for re-testing. At that time, the testing will be repeated per algorithm from the beginning. A WB will only be performed if the EIA is reactive.

FOLLOW UP

For follow up, sites will use either one non rapid ELISA or one FDA approved rapid test. If the ELISA or rapid test is non-reactive, the participant will be considered HIV-uninfected.

If the ELISA or rapid test is positive, an FDA-approved Western Blot (WB) will be performed. (Counsel the participant per local guidelines at this point.) If additional blood must be drawn for the WB, this is still considered sample 1 per the algorithm. If the WB is negative, the participant will be considered HIV-uninfected; this situation is not anticipated-contact the MTN NL if this occurs for instruction before proceeding.

If the WB is positive, the participant will be instructed to come back for a second draw (sample 2). If this WB is positive, the participant is considered seroconverted for MTN 001. All seroconversions will be confirmed by Western Blot at a MTN Network Lab.

Contact the MTN NL in any cases of indeterminate WB results.

Plasma from the enrollment archives from all participants will be retested by the MTN NL for HIV for Quality Assurance purposes.

Kit inventories should be monitored closely and re-supply orders placed at least 8-12 weeks in advance of actual need (or longer if needed per site procurement policies and

procedures). Notify the NL immediately if any kit inventory or quality control problems are identified, so that appropriate action can be taken.

At all sites, all test results must be documented on local laboratory log sheets or other laboratory source documents. In addition to initialing or signing the testing logs to document review and verification of the results, a second staff member must also record the time at which the results were reviewed and verified.

12.6.3 Syphilis Testing

Syphilis testing will be performed using a rapid plasma reagin (RPR) screening test followed by a confirmatory microhemagglutinin assay for *Treponema pallidum* (MHA-TP) or *Treponema pallidum* haemagglutination assay (TPHA) for reactive samples. Sites may choose to eliminate the RPR and test all samples with the confirmatory assay.

Any RPR, MHA-TP, and TPHA test may be used at each study site; however titers must be obtained and reported for all positive RPR tests. RPR tests may be performed on either serum or plasma. MHA-TP and TPHA tests must be performed on serum. All testing and QC procedures must be performed and documented in accordance with study site SOPs.

For reactive RPR tests observed during screening, a confirmatory test result must be received and appropriate clinical management action taken, prior to enrollment in the study. Clinical management should include repeat RPR tests at quarterly intervals following syphilis diagnosis to confirm treatment effectiveness. If the RPR titer does not decrease four-fold or revert to sero-negative within three months after treatment, treatment should be repeated.

Please consult the MTN NL with any questions related to Syphilis testing to confirm treatment effectiveness and/or interpretation of unusual test results.

Questions related to result interpretation vis-à-vis eligibility and enrollment in the study should be directed to the MTN 001 Protocol Safety Review Team.

Sites may perform only the confirmatory microhemagglutinin assay for *Treponema pallidum* (MHA-TP) or *Treponema pallidum* haemagglutination assay (TPHA) in lieu of performing first the RPR if this is consistent with local treatment standards. This must be approved before study initiation by the MTN NL.

12.6.4 Hematology Testing

Complete blood counts will be performed at all sites, per protocol .at the Screening, Enrollment, Week 7, Week 14, and Week 21 Visits. In addition, at the intensive PK sites, CBC testing *with differential* is required at each of the end-of-study period visits (Weeks 6, 13, and 20) to obtain the lymphocyte counts needed for flow cytometry.

Each of the following must be analyzed and reported:

- Hemoglobin
- Hematocrit
- Platelets
- White blood cell count with differential (differential required only for flow cytometry calculations at the Week 6, 13, and 20 Visits)
- Red blood cell count

These tests will be performed on EDTA whole blood per local site SOP's.

12.6.5 Serum Chemistries

Liver Function

- Aspartate aminotransferase (AST)
- Alanine transaminase (ALT)

Renal Function

- Creatinine (Calculated creatinine clearance is done each time creatinine is done
Formula: mL/min = (140 - age in years) x (weight in kg) x 0.85/72 x (serum creatinine in mg/dL)

Other

- Phosphorus

These chemistry tests will be performed on serum per local SOP's.

12.6.6 Plasma archive

For plasma archive, use EDTA. These will be stored at $\leq -70^{\circ}\text{C}$ and batched onsite until the MTN 001 study team requests shipping and/or testing.

- LDMS will be used to label and track the specimens.
- If at room temp, freeze within 4 hours. If refrigerated or on ice after collection, freeze within 24 hours.
- Prepare as many 1-2 mL aliquots as available to store. If less than 5 mLs of plasma are available, store that plasma and inform the MTN NL for instruction.
- The MTN NL will send instructions to the site when shipping and/or testing is required.

12.6.8 Serum Tenofovir

Serum will be frozen at $\leq -70^{\circ}\text{C}$ onsite and tracked in LDMS for Tenofovir levels within 8 hours of collection. A minimum of 2 mls serum is required. The MTN NL will notify sites for batch shipping details.

12.6.8 Hepatitis B Surface Antigen

This testing will be done on serum per local SOP's.

12.6.9 Peripheral Blood Mononuclear Cells for Intracellular Tenofovir

To be performed at all intensive PK sites and non intensive sites with capacity. Draw 16 mLs into Cell Preparation Tubes (CPT) with Sodium Citrate (BD Cat# 362761 is recommended). Specimens must be processed within 8 hours. Refer to Johns Hopkins SOP for details.

12.6.10 Flow Cytometry for CD38 and HLA-DR

To be performed at all intensive PK sites and non intensive sites with capacity. EDTA whole blood is analyzed for CD38 and HLA-DR by methods defined in local SOP's. Report total cells, percent positive cells, and mean fluorescent intensity (MFI) results. A complete blood count to obtain absolute lymphocyte count may be required for these calculations; this is not a scheduled test in the protocol at the PK visits and should be done as part of flow cytometry testing.

12.7 Testing of Vaginal and Cervical Specimens

Refer to the Screening and Follow-up Pelvic Exam checklists in other sections of this manual for further information of the required sequence of specimen collection and diagnostic procedures to be performed during study pelvic exams.

Pelvic specimen collection sequence:

1. Collect any urine specimens before taking pelvic specimens.
2. Vaginal pH and Wetmount (Herpes Culture if indicated and local standard of care)
3. Cervicovaginal Lavage
4. Cervical Cytobrush (Pap Smear if Indicated)
5. Vaginal Biopsy

12.7.1 Vaginal pH

Vaginal pH will be assessed as part of on-site evaluations for bacterial vaginosis. pH Indicator Strips (pH range 3.6 to 6.1) from Machery-Nagel (92130), Baker (4394-01) or SP (P1119-22) must be used unless other strips are approved by the MTN NL.

- During pelvic examination, vaginal fluids are collected via swab and then swabbed onto the pH strip. Avoid contact with cervical mucus, which has a high pH. Avoid contact with cervical mucus, which has a high pH.
- Match the resulting color of the indicator strip to the color scale provided with the strips to determine the pH value.
- Record the pH value directly onto the appropriate case report form. It is not necessary to record pH values onto laboratory log sheets or other source documents prior to recording values onto case report forms.

12.7.2 Vaginal Fluid Wet Mount Testing

Wet mount procedures for this study consist of two different preparations —saline prep and potassium hydroxide (KOH) prep —for diagnosis of bacterial vaginosis, trichomoniasis, and candidiasis, as summarized in Table 12-5.

If wet prep slides are read in-clinic by clinical staff, results may be recorded directly onto appropriate case report forms. If slides are read by lab staff (either in the local laboratory or a designated in-clinic lab area), results must be recorded onto laboratory log sheets or other laboratory source documents and then transcribed onto appropriate case report form.

Prior to study initiation, the MTN NL will conduct on-site training and proficiency testing for clinic and laboratory staff designated to perform wet mounts. CLIA regulations require semi-annual proficiency testing; therefore the MTN NL will administer a web-based proficiency testing approximately every six months. The MTN NL will post wet mount slides on the MTN web pages for this purpose every 6 months; results will be entered directly on the website (contact: Lorna Rabe: rabelk@upmc.edu). The MTN NL will report results back to the Laboratory Manager and also specify any corrective action that may be needed based on the results. Contact the MTN NL for additional information and guidance on performing and documenting the proficiency testing. Also contact the MTN NL when new laboratory staff is hired, so that appropriate training can take place prior to such staff performing wet mounts for study purposes.

**Table 12-5
Summary of Wet Prep Assessments and Diagnostic Criteria**

Assessment	Saline Prep	KOH Prep
Whiff Test	Not applicable	Positive if fishy amine odor detected
Clue Cells	Individual cells rather than clusters of cells should be examined. Positive if at least 20% clue cells observed. Cells must be completely covered with bacteria (<i>Gardnerella vaginalis</i> and/or anaerobic GNR) to be counted as clue cells.	Not applicable (clue cells are lysed by KOH)

Trichomonads	Positive if at least one motile trichomonad is observed. Actively motile organisms are easily seen upon low power (10X). High power (40X) may be needed to detect less vigorously motile organisms when only the flagella may be moving.	Not applicable (organisms are lysed by KOH)
Yeast	Positive if pseudohyphae and/or budding yeast are observed. Pseudohyphae and budding yeast may be obscured by epithelial cells. These cells will be lysed by KOH, thus pseudohyphae and budding yeast not observed in saline prep may be observed in KOH prep.	Positive if pseudohyphae or budding yeast are observed.

Note: Bacterial vaginosis will be diagnosed based on the presence of any three of the following Amsel's criteria: homogenous vaginal discharge, vaginal pH greater than 4.5, positive whiff test, at least 20% clue cells

Prepare and examine wet prep slides according to study site SOPs as follows:

- Use a pencil to write the PTID and specimen collection date on one side of the frosted end of two microscope slides. Affix a SCHARP-provided PTID label to the other side of the slides (on the frosted end, under the pencil markings) and write the specimen collection date in indelible ink (e.g. Sharpie pen) on each label.
- Immediately following collection from the lateral vaginal wall via swab, smear vaginal fluid specimens onto each slide. Alternatively, the swab may be placed in a glass or plastic tube with approximately six drops (100 µL) sterile physiologic saline to allow for non-immediate slide preparation. In this case, vaginal fluid specimens should be smeared onto the two slides upon receipt from the collecting clinician.
- Apply one drop of 10% KOH to one slide and immediately perform whiff test for a “fishy” amine odor. Then apply cover slip.
- Apply one drop of sterile physiologic saline to the second slide, emulsify with the vaginal fluid specimen, and then apply coverslip. Examine immediately at 10X magnification for epithelial cells, motile trichomonads, budding yeast, and pseudohyphae. Examine at 40X magnification to determine whether observed epithelial cells are clue cells and quantitate the cells. Clue cells are irregularly bordered squamous epithelial cells that are completely covered with bacteria (*Gardnerella vaginalis*). Clue cells must comprise at least 20% of the observed epithelial cells for the saline prep to be considered positive for clue cells.
- Examine the KOH slide at both 10X and 40X magnification for yeast and pseudohyphae.

12.7.3 Cytobrush Collection and Storage

Cytobrush: use the Medscand Sample Collection Kit, reference # 02500. Company Phone Number (at the time of printing) 800-243-2974. If sites have trouble obtaining this item, contact the MTN NL.

1. Place cytobrush in the cervical os and collect sample using 2 - 360° turns.
2. Add 3.5 mL of 1x PBS to a 5 mL screw cap vial or test tube labeled with a SCHARP-provided PK specimen label. The shaft of the cytobrush can be broken off at this step to cap the sample. Keep on ice or refrigerate until processing for storage.
3. Elute the cervical mononuclear cells into the PBS by agitation and rolling against the side of the tube - pulse vortex on medium 1-2 seconds approximately 4x
4. Clip off the cytobrush head from the support and centrifuge the tube at 400xg for 10 minutes
5. Carefully remove the cytobrush head and vortex on a medium setting for 2 seconds.
6. Remove 50 µL aliquot to count cells using a hemocytometer with trypan blue exclusion.
 - a. Record the total number of cells (including squamous cells*) and percent viable.
 - b. The MTN NL will provide an excel sheet to record these results.
7. Centrifuge tube at 400xg for 10 minutes
8. Pour off supernatant
9. Add 1mL 70% ice cold methanol and lyse cells on ice for 15 minutes.
10. Centrifuge tube at 800g x 10 minutes
11. Pour off supernatant into cryovial and store at -70°C.

*Note: squamous cells are expected to be rare on this specimen and will appear similar to squamous cells in urine. They will be larger than cervical mononuclear cells and will have a “fried egg” appearance. These should be counted in the same fashion as cervical mononuclear cells.

12.7.4 Cervicovaginal Lavage (CVL)

CVL specimens are collected and processed following approved site SOP's. Saline is used for MTN 001 CVL-the speculum may be warmed with warm saline for the comfort of the participant. The MTN NL will provide the sites with an SOP template. The sites will adapt this SOP for their site; these SOP's will be approved by the MTN NL.

CVL specimens are kept on ice or refrigerated after collection until they processed. All collected liquid will be spun for 10 minutes at ~800xg. Remove the supernatant from the cell pellet and re-spin at 10 minutes at ~800xg. Store all supernatant in as many 1-2 mL aliquots as possible. Store aliquots at -70°C within 8 hours of collection and track in LDMS. The MTN NL will send instructions to the site when shipping is required. If less than 6 mls of supernatant are recovered, contact the MTN NL. Discard Cell pellets.

Study sites will schedule PK visits to avoid menses. If a participant is menstruating when CVL is scheduled, collect the CVL and include a comment on the LDMS tracking sheet and then when the sample information is entered electronically in LDMS.

12.7.5 Vaginal Biopsy

The vaginal biopsy should be the last part of the exam performed using standard procedures. Two biopsy specimens are collected from different areas of the vagina. The biopsy should be taken using cervical or vaginal forceps. The forceps may be used to apply pressure to the site of the biopsy to slow bleeding. Place the biopsy specimen into a cryovial with no additive and label. Place the cryovial on ice and freeze at -70°C until shipment is requested by the MTN. Track the specimens in LDMS. More information can be found in the MTN 001 SSP Section 10.8.2.2.

12.7.6 Herpes Culture

This testing will only be performed if it is the local standard of care. Perform as indicated per local SOP's.

12.7.7 Papanicolaou (Pap) Test

Pap smears will be performed at selected sites. At visits when Pap smears are required, ecto- and endocervical cells will be collected after all tissues have been visually inspected and all other required specimens have been collected. Specimen collection, slide preparation, slide interpretation, and QC procedures must be performed and documented in accordance with study site SOPs.

- At some study sites, Pap smear results may include notations of findings associated with certain STIs (e.g., trichomoniasis). Because Pap smear methods are not adequately sensitive and specific for STIs (including HPV), Pap smear findings associated with STIs should not be used to diagnose of any STI's during follow up.

12.8 Rectal Specimens (Bronx Site Only)

Materials

Sponge: Available at Fisher Scientific Cat # NC9830573

5ml cryovial: Fischer Scientific Cat # 10-500-27 or equivalent.

Scale able to measure to .01 Grams

Disposable Transfer Pipettes

PBS

PRE personal lubricant

Preparation of Materials (45 minutes prior to procedure):

1. Prepare insertion tube using transfer pipette by cutting off the end approximately 1 inch from the tip. Make sure the stem of the sponge will fit the pipette snugly and will not dislodge during insertion or extraction from the rectal cavity.
2. Weigh the sponge, insertion tube and 5 ml cryovial. Record the total dry weight on CRF (Item 2a). Note that the CRF does not mention the cryovial.
3. Add 50 μ L of sterile PBS to cryovial and insert the sponge into the cryovial to moisten. The PBS may be added up to 2 weeks in advance as long as the cryovials are kept tightly capped.
4. Weigh the cryovial containing 50 μ L of PBS, insertion tube and sponge for tenofovir and record the total wet weight on the CRF (Item 2b). Note that the CRF does not mention the cryovial.
5. When removing the sponge from the cryovial before insertion in the anus, expel PBS by pushing it against the inside wall of the cryovial. Recap the cryovial and ensure that no PBS is spilled.

Collection Procedure:

1. Use the PRE personal lubricant to lubricate the anoscope.
2. Introduce the 1 sponge (attached to the pipette extensions) through the anoscope into the rectum.
3. Hold (or leave) sponge in place for 5 minutes.
4. Remove the sponge.
5. Slowly remove anoscope.
6. Disengage sponge from plastic pipettes and place the sponge in the same cryovial from the initial weighings (steps 1 and 3 from preparation of materials above) and cap.
7. Weigh the cryovial, insertion tube and sponge after collection and record the total weight on CRF (Item 2c). Note that the CRF does not mention the cryovial.
8. Record the time the sponge was collected on the CRF. Use the time the sponge was removed.
9. Place on ice for transport to the study site laboratory within 4 hours.
10. The laboratory will freeze at $< -70^{\circ}\text{C}$.

Appendix 12-1 LDMS Tracking Sheets

MTN 001 Africa Sites - LDMS Specimen Tracking Sheet

For login of MTN 001 stored specimens into LDMS

Participant ID		Visit Code		Specimen Collection Date	
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Site Number	Participant Number	Chk		dd	MMM yy
SPECIMEN TYPE/ TIMEPOINT	PRIMARY SPECIMEN TYPE	TIME COLLECTED hh:mm 24-hr clock	NUMBER of TUBES or SPECIMENS COLLECTED (Primary additive)	INSTRUCTIONS FOR PROCESSING LAB	
Enrollment Visit	Cervico-vaginal Lavage (CVL)	Not applicable	<input type="checkbox"/> NSL (saline)	Keep on ice or refrigerate until specimen is frozen long term. Centrifuge and Freeze supernatant within 8 hours of collection. Store with derivative CVL.	
Plasma for Storage	Blood (BLD)	Not applicable	<input type="checkbox"/> EDT (Purple top)	Store as plasma with derivative PL 1/2.	
PK Specimens					
Mid-period Visit	Blood (BLD) Tenofovir Level		<input type="checkbox"/> Non (red top)	Transport to lab and process within eight hours. Freeze immediately after centrifugation. Store with derivative SER.	
Pre-dose	Blood (BLD) PBMC		<input type="checkbox"/> CPS (CPT Tube)	At sites with Capacity. The time from blood draw to centrifugation and lysis should be eight hours or less. Enter "pre dose" in comments field. Store with derivative CEL.	
	Blood (BLD) Tenofovir Level		<input type="checkbox"/> Non (red top)	Transport to lab and process within eight hours. Freeze immediately after centrifugation. Store with derivative SER.	
Post-dose <i>Circle correct time point</i>	Blood (BLD) PBMC		<input type="checkbox"/> CPS (CPT Tube)	At sites with Capacity. The time from blood draw to centrifugation and lysis should be eight hours or less. Store with derivative CEL.	
	1-3 Hour	Blood (BLD) Tenofovir Level	<input type="checkbox"/> Non (red top)	Transport to lab and process within eight hours. Freeze immediately after centrifugation. Store with derivative SER.	
	3-5 Hour				
	5-7 Hour	Cervico-vaginal Lavage (CVL)		<input type="checkbox"/> NSL (saline)	Keep on ice or refrigerate until specimen is frozen long term. Centrifuge and Freeze supernatant within 8 hours of collection. Store with derivative CVL.

Initials: _____ LDMS Data Entry Date: / / _____
Sending Staff Receiving Staff dd MMM yy LDMS Staff

Version 1.0, 03-SEP-08

MTN 001

US Sites - LDMS Specimen Tracking Sheet

For login of MTN 001 stored specimens into LDMS

Page 2 of 2

Participant ID		Visit Code		Specimen Collection Date	
[][]-[][][][]-[][]	[][][][][]-[][]	[][]	[][]	[][]	[][][][] [][]
Site Number	Participant Number	Chk		dd	MMM yy

SPECIMEN TYPE/VISIT	PRIMARY SPECIMEN TYPE	TIME COLLECTED hh:mm 24-hr clock	NUMBER of TUBES or SPECIMENS COLLECTED (Primary additive)	INSTRUCTIONS FOR PROCESSING LAB
4 Hour	Blood (BLD) Tenofovir Level		<input type="checkbox"/> Non (red top)	Transport to lab and process within eight hours. Freeze immediately after centrifugation. Store with derivative SER.
	Blood (BLD) PBMC		<input type="checkbox"/> CPS (CPT Tube)	The time from blood draw to centrifugation and lysis should be eight hours or less. Store with derivative CEL.
6 Hour	Blood (BLD) Tenofovir Level		<input type="checkbox"/> Non (red top)	Transport to lab and process within eight hours. Freeze immediately after centrifugation. Store with derivative SER.
	Blood (BLD) PBMC		<input type="checkbox"/> CPS (CPT Tube)	The time from blood draw to centrifugation and lysis should be eight hours or less. Store with derivative CEL.
8 Hour	Blood (BLD) Tenofovir Level		<input type="checkbox"/> Non (red top)	Transport to lab and process within eight hours. Freeze immediately after centrifugation. Store with derivative SER.
	Blood (BLD) PBMC		<input type="checkbox"/> CPS (CPT Tube)	The time from blood draw to centrifugation and lysis should be eight hours or less. Store with derivative CEL.
Circle correct time point: Pre-dose ___ Hour Enter post-dose hour, if applicable.	Cervicovaginal Lavage (CVL)		<input type="checkbox"/> NSL (saline)	Keep on ice or refrigerate until specimen is frozen long-term. Centrifuge and Freeze supernatant within 8 hours of collection. Store with derivative CVL.
	Cervical cytology brush (CER)		<input type="checkbox"/> PBS	Keep on ice or refrigerate until processing for storage. Freeze within 8 hours of collection. Store with derivative CTB.
	Vaginal tissue (VGL)		<input type="checkbox"/> NON	Keep on ice or refrigerate until specimen is frozen long-term. Freeze within 8 hours of collection. Store with derivative TIS. Enter location of biopsies in specimen comments.
	Rectal sponge for PK (REC)		<input type="checkbox"/> PBS	Keep on ice until specimen is frozen long-term. Freeze within 4 hours of collection. Store with derivative SPG.

Initials: _____ LDMS Data Entry Date: [][] / [][][][] / [][][][][]
 Sending Staff Receiving Staff dd MMM yy LDMS Staff

N:\hivnet\forms\MTN_001\forms\LDMS\MTN001_US_LDMS_v3.0_17Aug09_Page2only.rtf
 Version 3.0, 17-AUG-09

**Appendix 12-2: Sample Shipping Manifest (Shipments for Probetec GC/CT Only:
Use LDMS for all other shipments)**

MTN 001

Site:

**Contact person: (fill in)
(Fill in address)**

Phone number:

Fax number:

E-mail address:

Shipment Date _____

Specimen type: Urine for GC/CT testing

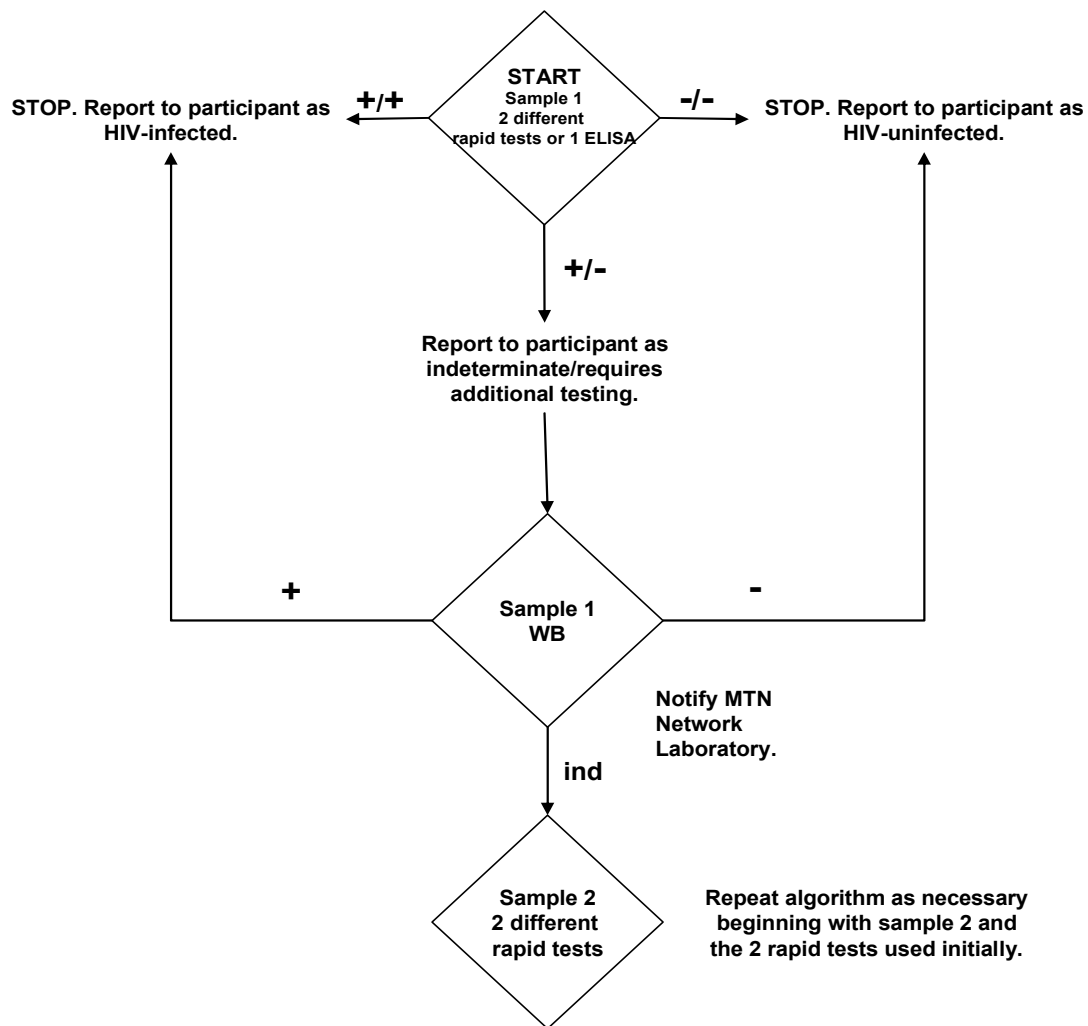
PTID	Collection Date	Visit Code

Comments _____

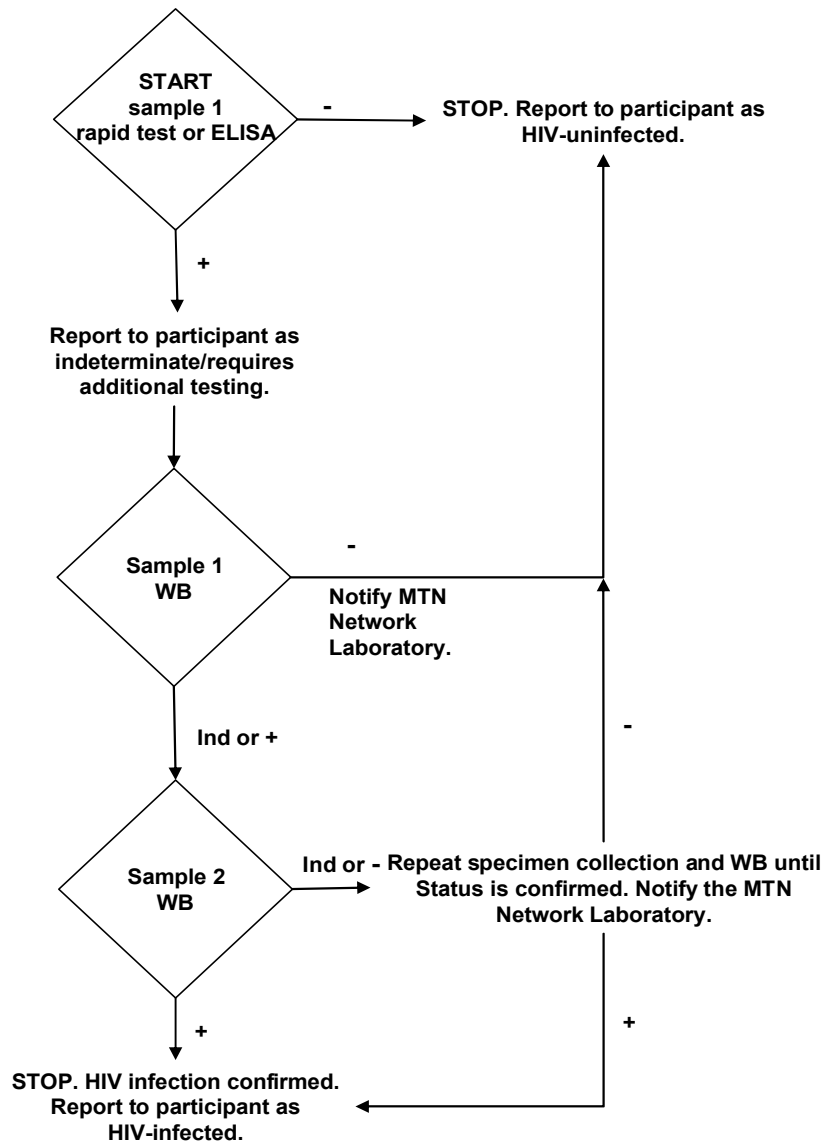
Ship to: Lorna Rabe Magee-Womens Research Institute 204 Craft Ave. Room 530 Pittsburgh, Pa. 15213 412-641-6041
--

On the day of shipment E-mail the FedEx tracking # to
rabelk@upmc.edu and cosentinola@upmc.edu

Algorithm for HIV Antibody Testing (Screening)



Algorithm for HIV Antibody Testing (Follow-up)



Appendix 12-4 Specimen Requirements Overview

MTN 001 LAB SPECIMEN PROCESSING GUIDELINES-PELVIC AND URINE SPECIMENS

Assay	Primary Specimen	Additive/Container	Minimum Volume	Testing Specifications	Handling Requirements
SDA for GC/CT	Urine	Local Testing: Urine Container- No additive	4 ml	Locally: batched 2-3 times per week	Performed Locally: 30 hours at room temp or 7 days refrigerated
		For Transport: Use Urine Preservative Tube (UPT)		Shipped: site dependent	Shipped in UPT: 30 days at room temperature
Dipstick Urinalysis	Urine	Urine Container- No additive	Enough to cover strip	Locally in real time	Room temp-analyze within 2 hours of collection
hCG	Urine	Urine Container- No additive	3 drops	Locally in real time	Room temp-test within 8 hours Refrigerate-test within 72 hours
Culture	Urine	Urine Container (Sterile) - No additive	N/A	Locally in real time	Locally Defined
Vaginal Biopsies	Vaginal Tissue	Plain Tube-No additive	N/A	Stored and shipped for analysis in batches.	Keep on ice or refrigerate until specimen is frozen long term. Freeze within 8 hours of collection.
Cytobrush	Cytobrush	PBS	N/A	Stored and shipped for analysis in batches.	Keep on ice or refrigerate until processing for storage. Vortex 1 minute, centrifuge and resuspend in buffer. Freeze within 8 hours of collection.
CVL	Saline	Conical Vial	10 cc's of saline used- recover all fluid. If less than 6 mls recovered, contact NL. Store at least 3 aliquots of 1-2 mls.	Stored and shipped for analysis in batches.	Keep on ice or refrigerate until specimen is frozen long term. Centrifuge and Freeze supernatant within 8 hours of collection.
Pap Smear	Cervical Cells	Slide	N/A	Locally in real time	Locally Defined
Herpes Culture	Swab from Lesion	Locally Defined	N/A	Locally in real time	Locally Defined
Wet Mount	Vaginal Fluid Swab	Variable	N/A	Locally in real time	Read within 30 minutes- If transported to lab: place swab in tube with 5 drops of saline
Vaginal pH	Vaginal Fluid	None-performed at bedside	N/A	Locally in real time	Done immediately at bedside

MTN 001 LAB SPECIMEN PROCESSING GUIDELINES-BLOOD SPECIMENS

Assay	Primary Specimen	Additive/Container	Minimum Volume	Testing Specifications	Handling Requirements
AST and ALT	Blood	Plain Tube-No additive or Serum separator tube (locally defined)	Locally defined	Locally in real time	Locally Defined
Phosphorus and Creatinine	Blood	Plain Tube-No additive or Serum separator tube (locally defined)	Locally defined	Locally in real time	Locally Defined
Syphilis Serology	Blood	Plain Tube-No additive or Serum separator tube (locally defined)	Locally defined	Locally in real time	Locally Defined
HBsAG	Blood	Plain Tube-No additive or Serum separator tube (locally defined)	Locally defined	Locally in real time	Locally Defined
Full Blood Count	Blood	EDTA Tube	Locally defined	Locally in real time	Locally Defined
HIV-1 Test	Blood	EDTA Tube	Locally defined	Locally in real time	Locally Defined
Flow Cytometry (CD38 and HLA-DR)	Blood	EDTA Tube	Locally defined	Locally in real time	Locally Defined
Tenofovir Level	Blood	Plain Tube-No additive	2 mls serum	Stored and shipped for analysis in batches.	Transport to lab and process within eight hours. Freeze immediately after centrifugation.
Plasma Archive	Blood	EDTA Tube	5 mls plasma	Stored and shipped for analysis in batches.	If at room temp, freeze within 4 hours. If refrigerated or on ice after collection, freeze within 24 hours.
PBMC for Intracellular Tenofovir	Blood	CPT Tube-Sodium Citrate	16 mls whole blood	Stored and shipped for analysis in batches.	The time from blood draw to centrifugation and lysis should be eight hours or less.

Section 13. Data Collection

The purpose of this document is to provide site staff with the information they need to successfully complete and submit MTN 001 case report forms. For questions about this section or about general data collection policies, procedures, or materials, please contact Karen Patterson (karen@scharp.org or karenp@scharp.org).

For this study, the SDMC (Statistical and Data Management Center) is SCHARP (the Statistical Center for HIV/AIDS Research and Prevention). SCHARP is located in Seattle, WA, USA, and is in the US Pacific Time (PT) time zone. The SCHARP MTN001 team members, along with their job roles and e-mail addresses, are listed below.

Role on MTN 001	Name	E-mail address
Protocol Statistician	Barbra Richardson	barbra@scharp.org
Project Manager	Karen Patterson	karen@scharp.org
Statistical Research Associates	Fang Gai	fang@scharp.org
	Sharavi Gandham	sharavi@scharp.org
Protocol Programmer	Jackie Fitzpatrick	jackie@scharp.org
Data Coordinator	Sara Jasinski	jasinski@scharp.org
Document Specialist	Lori Filipcic	lorif@scharp.org
Reporting Programmer	Kate Bader	kate@scharp.org
Laboratory Programmer	Laura Robins-Morris	lrobins@scharp.org
Clinical Affairs Safety Associate	Donna Robinett	donnar@scharp.org

13.1 DataFax Overview

DataFax is the data management system used by SCHARP to receive and manage data collected at study sites. The site faxes an electronic image of each case report form (CRF) to SCHARP DataFax, and the original hard copy CRF is retained by the site.

CRF Transmission

Case report forms can be transmitted to SCHARP in one of two ways: faxed using a fax machine connected to a land phone line (fax to phone number 206.667.4805); or faxed using a fax machine connected to the internet (fax to e-mail <datafax@scharp.org>).

SCHARP's Information Systems Technology (IST) group is available to consult with the site to determine the best method for data transmission. The SCHARP IST group can be contacted via e-mail at support@scharp.org. The SCHARP IST group should also be contacted anytime the site has technical questions or problems with their fax equipment.

Data Entry/Quality Control

Once a CRF image is received by SCHARP DataFax, the following occurs:

- DataFax identifies the study to which each CRF belongs using the barcode at the top of the form. It reads and enters the data into the study database and stores each CRF on a computer disk.
- Next, each CRF is reviewed by at least two members of SCHARP's Data Operations Group. Problems such as missing or potentially incorrect data are identified and marked with Quality Control notes (QCs).
- QCs are compiled into QC reports that are sent via e-mail to the study site on a regular basis. Sites are asked to correct or clarify any problems identified on the QC reports and refax the corrected CRFs to SCHARP DataFax.
- When the re-faxed pages are received, SCHARP staff review the corrected pages and resolve the QCs.

If a change is made to a CRF but the updated page is not re-faxed to SCHARP DataFax, the change will **not** be entered and the study database will continue to contain incomplete or incorrect data. Additionally, if the change was prompted by a QC, the QC will continue to appear on subsequent QC reports until the modified CRF is received at SCHARP. Therefore, it is very important that the site refax updated CRF pages to SCHARP DataFax **any time** a change is made to a CRF, regardless of whether or not the change was made in response to a QC report.

13.2 DataFax Form Completion

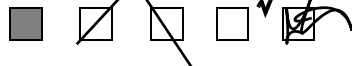
13.2.1 Guidelines

Based on the use of fax technology and Good Clinical Practices (GCPs), the following guidelines should be used for completing DataFax CRFs:

- Use a black or dark blue medium ballpoint pen. Do not use any other type of writing tool. Use only one color per form. That is, do not begin completing a form using a blue pen and then switch to a black pen during the same form completion session.
- Press firmly when recording data or writing comments.
- Print all data and comments legibly by hand. Entries that cannot be read will result in QC notes.
- Do not type data onto CRFs. Do not use cursive/script handwriting, as it can be difficult to read.
- Write numbers as large as possible while staying within the boundaries of the boxes.
- Record data on the front of CRFs only. DataFax cannot read the back of CRFs.
- Do not record data or make marks in the 0.5-inch/1.5-cm margins at the top, bottom, or sides of the CRF.
- If the lines provided for written responses are not long enough, continue in another blank area of the form (within the page margins).
- Mark only one answer except when given the instruction “Mark all that apply.”
- A response is required for every item unless instructed otherwise by a skip pattern.
- **Never** obscure, mark over, or punch holes through the barcode at the top of each CRF. DataFax requires the barcode to identify the CRF.
- **Never** use correction fluid (“white-out”) or correction tape on CRFs.
- Remove any paper clips, staples, or other attachments before faxing CRFs.
- The site staff person who initially completes the form **must** record his/her initials **and** the date in the space provided in the bottom right-hand corner of each CRF page.
- Fax forms as soon as possible after they have been completed and reviewed. Ideally, completed forms will be faxed to SCHARP within 1–2 days of completing the visit, though up to 5 days is allowed.

13.2.2 How to Mark Response Boxes

Many items on DataFax CRFs have a box or series of boxes for recording a response. Mark the box clearly with an **X**. Do not fill in the box with shading or mark it with a slash or other character.

Correct:**Incorrect:**

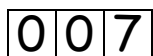
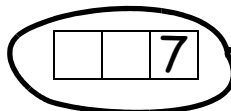
Mark only one response box for each item unless the “Mark all that apply” instruction is present.

13.2.3 How to Record Numbers

Some questions on DataFax CRFs include boxes for recording a numeric response. DataFax can only read the numbers in these boxes if they are recorded clearly. The following instructions should be followed when recording numeric responses:

- Right justify **all** numbers and fill in any blank leading boxes with zeroes. If boxes are left blank, a QC note will be applied asking for the boxes to be filled in.

The following example shows how a value of 7 is recorded when three response boxes are provided:

Correct:**Incorrect:**

→ This example would result in a QC note.

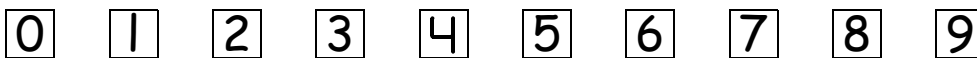
- Write the number(s) as large as possible while staying within the boundaries of the box; try not to stray outside the boundaries of the box.

In the following example, the 4 could be misinterpreted as a 7 or a 1 because DataFax can only read what is *inside* the box:

Correct:**Incorrect:**

- Write the number(s) simply, with few loops.

The following example shows the format in which numbers will be most easily read by DataFax. Also included are some commonly used formats that may be difficult for DataFax to identify.

Easily Identified:**Difficult to Identify:**

13.2.4 How to Record Dates

Dates are recorded using the “dd MMM yy” format, where “dd” represents the two-digit day, “MMM” represents the three-letter abbreviation of the month (in capital letters), and “yy” represents the last two digits of the year.

The month field must be filled in with the three-letter abbreviation *in English* for the date to be read in DataFax. Abbreviations are shown below:

Month	Abbreviation	Month	Abbreviation
January	JAN	July	JUL
February	FEB	August	AUG
March	MAR	September	SEP
April	APR	October	OCT
May	MAY	November	NOV
June	JUN	December	DEC

For example, June 6, 2008 is recorded as:

0	6	J	U	N	0	8
<i>dd</i>		<i>MMM</i>			<i>yy</i>	

Sometimes, only a month and a year are required (e.g., diagnosis date for a pre-existing condition), in which case the response boxes will look like this:

<i>MMM</i>			<i>yy</i>		

A diagnosis date of October, 2008 would be recorded as follows:

O	C	T	0	8
<i>MMM</i>			<i>yy</i>	

13.2.5 How to Record Time

Time is recorded on DataFax CRFs using the 24-hour clock (00:00-23:59), in which hours are designated from 0–23. For example, in the 24-hour clock 2:25 p.m. translates to 14:25 (2 p.m. = 14), which would be recorded as follows:

1	4	:	2	5
<i>hr</i>			<i>min</i>	

Midnight is recorded as 00:00, not 24:00.

The following chart shows equivalencies between the 12- and 24-hour clocks:

12-hour clock (a.m.)	24-hour clock	12-hour clock (p.m.)	24-hour clock
Midnight	00:00	Noon	12:00
1:00 a.m.	01:00	1:00 p.m.	13:00
2:00 a.m.	02:00	2:00 p.m.	14:00
3:00 a.m.	03:00	3:00 p.m.	15:00
4:00 a.m.	04:00	4:00 p.m.	16:00
5:00 a.m.	05:00	5:00 p.m.	17:00
6:00 a.m.	06:00	6:00 p.m.	18:00
7:00 a.m.	07:00	7:00 p.m.	19:00
8:00 a.m.	08:00	8:00 p.m.	20:00
9:00 a.m.	09:00	9:00 p.m.	21:00
10:00 a.m.	10:00	10:00 p.m.	22:00
11:00 a.m.	11:00	11:00 p.m.	23:00

13.2.6 Data Corrections and Additions

Sometimes, data on a DataFax CRF may need to be changed, clarified, or amended. There are many reasons why data may need to be changed, such as in response to a QC report or as a result of site review of the CRF before faxing.

It is important to make these changes to the original CRF—*never* copy data onto a new form. After making the change, the CRF *must* be re-faxed to SCHARP DataFax.

Note: If a correction or addition is made to one page of a multiple-page CRF, only refax the page that was changed.

Note: Never write over an entry once it is recorded. Use the standards outlined in the following paragraphs when changing, clarifying, or amending data.

Whenever an entry on a DataFax CRF is changed, do the following:

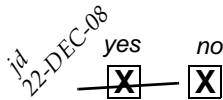
- draw a single horizontal line through the incorrect entry (do not obscure the entry or make it unreadable with multiple cross-outs),
- place the correct or clarified answer near the box, and

- initial and date the correction as shown below:



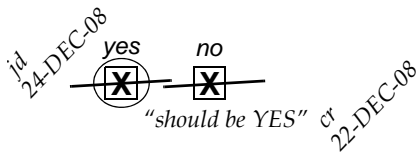
If an **X** is marked in the wrong response box, correct it by doing the following:

- draw a single horizontal line through the incorrectly marked box,
- mark the correct box, and
- initial and date the correction as shown below:



If the correct answer has previously been crossed out, do the following:

- circle the correct item,
- write an explanation in the white space near the item, and
- initial and date all corrections as shown below:

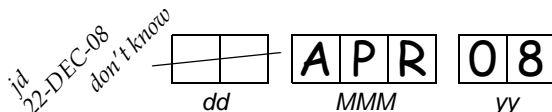


The standards above must **always** be followed whenever a CRF is changed, clarified, or amended, even if the change is made **before** the CRF is faxed to SCHARP for the first time.

13.2.7 How to Handle Missing and Unknown Data

If the answer to an item is not known, is not available, or if the participant refuses to answer, draw a single horizontal line through the blank boxes and initial and date the item. It is helpful to write “don’t know,” “refuses to answer,” “UNK” (unknown), “N/A” (not applicable), or “REF” (refused) near the blank boxes.

For example, when recording a date, if the exact day is not known, draw a single horizontal line through the “dd” boxes and write “don’t know” next to the response boxes, as shown below:



A skip pattern is the **only** valid reason to leave a response blank. Initials and date are required for any data item that is refused, missing, unknown, or not applicable, regardless of whether it is marked as such during the initial form completion, or as an update to the form.

13.3 MTN 001 Study-Specific Data Collection Information

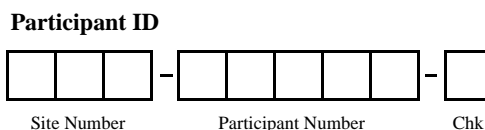
13.3.1 Participant ID numbers (PTIDs)

DataFax uses a unique participant identification number (PTID) to identify each study participant in the database. SCHARP provides each site with a list of PTIDs prior to study start-up. The site should assign one PTID to each participant enrolled in the study. The PTIDs are assigned in sequential order as participants screen for the study. The site should ensure that each PTID is assigned only once. Once a participant has received a PTID, she maintains that same PTID throughout the entire study.

PTID boxes are located near the upper left corner of each CRF page.

Site staff are responsible for maintaining a log linking PTIDs to participant names (PTID-Name Link log) in accordance with Section 3 of this manual.

The PTIDs used for this study are nine digits and formatted as “XXX-YYYYY-Z.” The PTID consists of three parts: the site number (XXX), the participant number (YYYYY), and a numerical check digit (Z). The check digit (Z) is a number generated by SCHARP with the participant number, and helps ensure that the correct PTID is recorded. Below is an example of the PTID structure used in MTN 001.



13.3.2 Study Visit Timing

Screening and Enrollment

Screening visit procedures may take place over more than one day, when needed. The initial screening visit is defined as the day the participant provided written informed consent to be screened for the study. The enrollment visit will be scheduled to take place within 30 days of the initial screening visit.

For MTN 001, a participant is considered enrolled once the participant has been assigned a MTN 001 Randomization Envelope (or MTN 001 Replacement Randomization Document, if a replacement participant). Assignment of MTN 001 randomization envelopes will be documented using the MTN 001 Randomization Envelope Tracking Record provided to each site by SCHARP.

Multiple Screening Attempts (Re-screens)

If a participant's first screening attempt is unsuccessful, she may re-screen for the study if she chooses. If she does re-screen, ALL screening procedures (except PTID assignment), evaluations, and forms must be repeated, including provision of written informed consent. Once a PTID is assigned to a participant, that PTID is used for that participant for all re-screens and enrollment into the study. If a participant re-screens, only case report forms from the successful screening and enrollment visits are faxed to SCHARP.

Follow-Up Visits

There are 9 required follow-up visits for this study. For each of the nine visits, the visit type, visit code, target visit day, and visit windows (allowable and target) are listed in table 13-1.

Table 13-1: List of MTN 001 Required Visits, Target Visit Dates, and Visit Windows

All windows are listed in days, with Enrollment = Day0						
Visit Type	Visit Code	Allowable Window Opens	Target Window Opens	Target Day	Target Window Closes	Allowable Window Closes
Week 3	3.0	1	18	21	24	31
Week 6	4.0	32	39	42	45	45
Week 7	5.0	46	46	49	52	59
Week 10	6.0	60	67	70	73	80
Week 13	7.0	81	88	91	94	94
Week 14	8.0	95	95	98	101	108
Week 17	9.0	109	116	119	122	129
Week 20	10.0	130	137	140	143	143
Week 21	11.0	144	144	147	150	150

Target Days and Visit Windows

Whenever possible, visits should be completed within the target window. Ideally, visits will be completed on the target day for the visit. Visits completed within the target window will appear on the MTN 001 Retention Report as being completed “on-time”. It is not always possible to complete the visit on the target day, or within the target window. In these cases, every effort should be made to complete the visit within the allowable window for the visit. The allowable window is, in most cases, larger than the target window. Visits completed within the allowable window will count with regard to participant retention (that is, the participant will be considered retained for the visit). However, visits completed within the allowable window will appear on the MTN 001 Retention Report as being completed “early” or “late” depending on when the visit was completed. For example, a Week 17 visit completed 124 days after Enrollment will be listed as being completed “late”.

SCHARP will provide sites with an Excel spreadsheet tool that may be used to generate individual participant follow-up visit calendars. The spreadsheet requires that the participant’s Enrollment date be entered. Once the enrollment date is entered, the target day and visit windows for each of the 9 required follow-up visits will appear in the spreadsheet, which can then be printed and added to the participant’s study notebook.

Split Visits

In cases where a participant is not able to complete all required visit evaluations on the same day, the participant may come back and complete the remaining evaluations on another day, as long as the evaluations are completed within the allowable visit window. For example, a participant comes in on her Week 3 target day and completes all required evaluations except for the pelvic exam (she is on menses).

She comes back 5 days later (once she is off menses) and completes the pelvic exam and associated procedures.

Note that end-of-study period PK procedures cannot be split across days; the end-of-period PK procedures must all be completed on the same day (see the Participant Follow-up section of this manual for more information on PK procedures). Also note that the Study Product Adherence and Behavior Assessment must be completed on the same day as the end-of-period PK procedures.

See Section 13.3.3 for information on assigning visit codes to split visits.

Missed Visits

In those cases where a participant is not able to complete any part of a required visit within the allowable visit window, the visit is considered “missed”. For example, an enrolled participant does not report to the clinic for her first follow-up visit until 32 days after enrollment. Per table 13-1, the Week 3 allowable window closes on Day 31. In this case, since the allowable visit window has “closed”, the Week 3 visit is considered missed, and is documented by completion of a Missed Visit case report form.

Interim Visits

A clinic visit is considered an Interim Visit when a participant presents at the site for additional clinical/laboratory/pharmacy assessments and/or procedures *outside* of the required evaluations for a scheduled study visit. A clinic visit is also considered an Interim Visit when the participant presents to the clinic early on in the allowable visit window and the site decides not to complete the required visit at that time (and instead wait until the participant is closer to her target visit day). The following are examples of interim visits for MTN 001:

1. A participant completes all required evaluations for a scheduled study visit within the visit window (target or allowable). She then returns to the site clinic within the same visit window (target or allowable) to request replacement study product for lost study product.
2. A participant completes all required evaluations for a scheduled study visit within the visit window. She then returns to the clinic within the same visit window (target or allowable) to request a pregnancy test.
3. A participant completes all required evaluations for the Week 3 visit within the target window. At the Week 3 visit, superficial epithelial disruption is noted during her pelvic exam. She then returns to the clinic 2 days later (still within the Week 3 allowable visit window) for clinical follow-up (another pelvic exam) of the superficial epithelial disruption.
4. A participant enrolls on 04-NOV-08. She returns to the site clinic three days later (07-NOV-08) to request replacement study product for lost study product. Since it is so early in her Week 3 window, and the participant has been shown to be reliable, the site does not want to conduct the Week 3 visit on 07-NOV-08. Instead, the site conducts an Interim Visit to resupply the participant with study product. The site then schedules the participant to come back to the clinic on her Week 3 target day to complete her Week 3 visit.

Phone contact with a participant is also considered an Interim Visit if the phone contact results in reporting of a new Adverse Experience (AE). Phone contact is also considered an Interim Visit if, during the phone contact, the participant is instructed by site staff to resume product use (after a product hold has been initiated). The following are examples of phone contacts that would need to be documented as Interim Visits on MTN 001:

1. A participant completes her Week 6 visit on the target day. The next day (still within the Week 6 window), she calls the clinic to report a new symptom, which results in the reporting of a new adverse experience. Although she is still within the Week 6 allowable window, she has already completed all

required Week 6 visit evaluations. Thus, the phone contact is considered an interim visit, and is assigned an interim visit code.

2. A participant completes her Week 3 visit on the target day. At the Week 3 visit, she is diagnosed with grade 2 sexually-transmitted infection (STI). She is given treatment to take for the STI, and per protocol, is put on study product hold. Three days later you call her to confirm she has completed the STI treatment and that she has no STI symptoms. Once confirmed, you instruct her to begin using study product. In this case, the phone contact is considered an interim visit, and is assigned an interim visit code.

Assignment of visit codes to Interim Visits is covered later in the next section, section 13.3.3.

For questions about phone contacts and assignment of visit codes to such contacts, please contact the SCHARP MTN 001 Project Managers.

13.3.3 Visit Codes and Page Numbers

Some DataFax CRFs will include boxes in the upper right corner for a visit code. DataFax uses the visit code to identify the visit at which a CRF is completed. However, not all DataFax CRFs include boxes for visit codes. If a form is only completed once during a study (for example, the Enrollment form, the Termination form), the visit code will be automatically assigned in DataFax.

MTN 001 has four scheduled study visits. When visit code boxes are provided, site staff are responsible for entering the visit code in the boxes provided in the upper right corner of each page.

The following table lists the visit codes assigned to each required study visit.

Table 13-2: Visit Code Assignments for Required Study Visits

Visit Type	Visit Code
Screening	01.0
Enrollment	02.0
Week 3	03.0
Week 6	04.0
Week 7	05.0
Week 10	06.0
Week 13	07.0
Week 14	08.0
Week 17	09.0
Week 20	10.0
Week 21	11.0

Visit Codes for Split Visits

See Section 13.3.2 for a definition of split visits. When split visits occur, the case report forms completed for the visit are all assigned the same visit (even though some forms and evaluations will have different visit dates). For example, a participant comes in on her Week 3 target day of 23-AUG-08 and completes all required evaluations except for the pelvic exam (she is on menses). She comes back on 28-AUG-08 and completes the pelvic exam and associated procedures. All case report forms completed on 23 and 28 August are assigned a visit code of 03.0 (since all evaluations are Week 3 evaluations).

Visit codes for interim visits

In addition to the scheduled, protocol-required visits listed in Table 13-1, interim visits may occur once the participant is enrolled (see Section 13.3.2 for a definition and examples of unscheduled/interim visits). Interim visit codes are assigned using the following guidelines:

- In the boxes to the left of the decimal point, record the two-digit visit code for the most recent scheduled visit (whether that visit was completed or missed).
- Use the guide below to complete the box to the right of the decimal point:
 - ##.1 = the first interim visit after the most recent scheduled visit,
 - ##.2 = the second interim visit after the most recent scheduled visit,
 - ##.3 = the third interim visit after the most recent scheduled visit, and so on.

Example: A participant returns to the site clinic two days after Enrollment in order to replace study product that she lost. Since she is early on in her Week 3 window, the site decides to wait until closer to the Week 3 target day to complete the Week 3 visit. At this time, she is only given study product, and the visit is considered an interim visit and is assigned the following interim visit code:

Visit Code for this Interim Visit:

Visit Code .

Page numbers

Other CRFs, such as log forms (e.g., Adverse Experience Log, Concomitant Medications Log, Pre-existing Conditions), include boxes in the upper right corner for recording page numbers, as shown below:

Page

Assign page numbers in sequential order, starting with 01 (or 001, for Adverse Experience Log CRFs). Assign numbers in sequential order (for example, the second Concomitant Medications Log page would be assigned page number 02, the third page would be assigned 03, and so on).

13.3.4 Staff Initials/Date

Most forms include a line in the lower-right corner for a staff member's initials and the date on which the form was completed. When more than one staff member records data on a CRF, the site should designate the staff member who has primary responsibility for the form. This individual completes the staff initials/date field. The individual not identified in the staff initials/date field writes his/her initials and date next to each data element for which he/she is responsible.

13.3.5 Case Report Form Completion Schedule

The SCHARP-provided case report forms for this study include DataFax forms (forms that are completed and faxed to SCHARP DataFax) and non-DataFax forms (forms that are completed but **not** faxed to SCHARP DataFax).

Some SCHARP-provided forms are required to be completed at each visit, while other forms are required only at one visit or only when specifically indicated. The following table (Table 13-3) lists the DataFax and non-DataFax forms that are **required** to be completed at each study visit.

Table 13-3: Case Report Form Completion Schedule

SCREENING (DAY -30)	
Form Acronym	Form Name
SC	Screening Consent
DEM	Demographics
SPE	Screening and Enrollment Pelvic Exam
PLR	Pelvic Laboratory Results
SL	Safety Laboratory Results
SSL	Screening and Enrollment STI Laboratory Results
CM	Concomitant Medications
nonDataFax	MTN 001 Baseline Medical and Menstrual History
nonDataFax	Physical Exam
nonDataFax	Pelvic Exam Diagrams
nonDataFax	Screening Eligibility
nonDataFax	Clinical Eligibility
nonDataFax	Screening Summary
ENROLLMENT (DAY 0)	
Form Acronym	Form Name
FPM	Family Planning Methods
BGS	Baseline Genital Symptoms
SPE	Screening and Enrollment Pelvic Exam
PLR	Pelvic Laboratory Results
SL	Safety Laboratory Results
PRE	Pre-existing Conditions
ENR	Enrollment
EBA	Enrollment Behavior Assessment
nonDataFax	Enrollment Eligibility
nonDataFax	Physical Exam
nonDataFax	Pelvic Exam Diagrams
nonDataFax	Clinical Eligibility
nonDataFax	LDMS Specimen Tracking Sheet – US or Africa version as applicable
Mid-study Period Visits (Weeks 3, 10, and 17)	
Form Acronym	Form Name
FV	Follow-up Visit
FPM	Family Planning Methods
FGS	Follow-up Genital Symptoms
FPE	Follow-up Pelvic Exam

SL	Safety Laboratory Results
SPA	Study Product Adherence and Behavior Assessment
PKI	Pharmacokinetics-Intensive <i>US sites only</i>
PKN	Pharmacokinetics-Non-intensive <i>Africa sites only</i>
nonDataFax	Physical Exam
nonDataFax	Pelvic Exam Diagrams
nonDataFax	LDMS Specimen Tracking Sheet – US or Africa version as applicable
Week 7 and 14 Visits	
Form Acronym	Form Name
FV	Follow-up Visit
FPM	Family Planning Methods
FGS	Follow-up Genital Symptoms
FPE	Follow-up Pelvic Exam
SL	Safety Laboratory Results
SLR	STI Laboratory Results
nonDataFax	Physical Exam
nonDataFax	Pelvic Exam Diagrams
End-of Study Period Visits (Weeks 6, 13, and 20)	
Form Acronym	Form Name
FV	Follow-up Visit
FPM	Family Planning Methods
FGS	Follow-up Genital Symptoms
FPE	Follow-up Pelvic Exam
PLR	Pelvic Laboratory Results
SL	Safety Laboratory Results
SPA	Study Product Adherence and Behavior Assessment
PSA	Product Sharing Assessment
AA	Acceptability Assessment <i>Weeks 6 and 13 only</i>
FAA-	Final Acceptability Assessment <i>Week 20 only</i>
PKI	Pharmacokinetics-Intensive <i>US sites only</i>
PKN	Pharmacokinetics-Non-intensive <i>Africa sites only</i>
FC	Flow Cytometry
nonDataFax	Physical Exam
nonDataFax	Pelvic Exam Diagrams
nonDataFax	LDMS Specimen Tracking Sheet – US or Africa version as applicable
Week 21/Study Exit	
Form Acronym	Form Name
FV	Follow-up Visit
FPM	Family Planning Methods
FGS	Follow-up Genital Symptoms
SL	Safety Laboratory Results
SLR	STI Laboratory Results
TM	Termination

ESI	End of Study Inventory
nonDataFax	LDMS Specimen Tracking Sheet – US or Africa version as applicable

13.3.6 Site Review of DataFax Forms

Each form must be reviewed for completeness and legibility before being faxed to SCHARP DataFax. As part of the review, the site should check the following:

- Other than the participant ID number (PTID), there is no information on the form that could identify the participant (e.g., name, phone number, national identification number, or any other personal identifiers).
- A response has been recorded for each item, unless the item was skipped as instructed by a skip pattern or the item was marked as missing or unknown as described in 13.2.7.
- All text responses are clearly recorded.
- There are no marks on or above the DataFax barcode at the top of each DataFax page.
- There are no:
 - missing dates,
 - missing visit codes,
 - incorrect PTIDs,
 - incorrect visit codes,
 - missing data for items beginning a series of skip patterns, and/or
 - inconsistent or discrepant data.

While CRFs are being reviewed, it is important that they are stored and tracked systematically. It is also necessary to have a system to identify whether a CRF has been faxed to SCHARP DataFax. Such a system may include using a stamp to date the back of the CRF, or utilizing the SCHARP CRF Tracking System (see SSP Section 13.3.7 for more information).

Important: If a date stamp is used to document when the form is faxed, stamp *only* the back of the CRF, *never* the front. Be sure to date stamp the back of the CRF each time it is faxed, including refaxes.

13.3.7 Faxing DataFax Forms

To streamline the submission of DataFax forms, the site should identify which staff members will be responsible for faxing forms to SCHARP DataFax and receiving and responding to QC reports.

It is important that the sites fax completed DataFax CRFs to SCHARP within the time period specified in the site's MTN 001 Data Management SOP, and that they respond promptly to requests for clarifications and corrections included in QC reports. Early detection of recurrent problems provides an opportunity to reduce errors and improve data quality.

For sites wishing to confirm the receipt of faxed forms at SCHARP, the CRF Tracking System (CTS) is available. This system generates two types of e-mails listings: 1) the number of form pages received at SCHARP; and 2) which specific forms were received at SCHARP for a given PTID and visit. Please

contact the MTN 001 Project Manager if you would like to use the CRF Tracking System or for more information about the CRF Tracking System.

13.3.8 Non-DataFax Forms

MTN 001 sites will receive non-DataFax forms from SCHARP. These forms will be easily identifiable because there will not be a DataFax barcode along the top of the CRF. In place of the barcode, the following text will appear: “NOT A DATAFAX FORM. DO NOT FAX TO DATAFAX.”

These forms should **not** be faxed to SCHARP DataFax. Instead, they should be kept in the participant’s file as a record of the activities recorded on the form. The form completion guidelines described in sections 13.3.1 through 13.3.4 should be applied when completing non-DataFax CRFs.

13.4 Form Supply and Storage

13.4.1 Form and Specimen Label Supply

All case report forms needed for the study will be provided by SCHARP. Forms will be supplied using form visit packets, where the packet contains all of the required CRFs for the visit. For example, the Screening Visit packet will include all of the CRFs listed for this visit in the Case Report Form Completion Schedule table (table 13-3). In addition for form packets for each visit listed in Table 13-3, bulk supplies of “as needed” CRFs will be provided to the site (for example, Pregnancy Report and History, Pregnancy Outcome, Genital Bleeding Assessment, etc.).

SCHARP will also ensure sites have access to specimen labels (either printed on-site or printed by SCHARP). Specimen labels should be used for all primary specimen collection containers. Customized PK labels for use on PK specimen primary collection containers will also be provided. Please refer to the Laboratory section of the manual for more information on laboratory specimen collection and labeling.

13.4.2 Form Storage

Specifications for form storage will be detailed in the site’s MTN 001 Data Management SOP. It is recommended that for each participant, study CRFs be stored in a hard-cover notebook. SCHARP can provide a template for use in creating notebook cover labels and spine labels. SCHARP can also provide a template that can be used to create tab dividers.

It is suggested that Concomitant Medications Log forms, Adverse Experience Log forms, and Product Hold/Discontinuation forms be kept in their own tabbed sections within the participant study notebook. This makes page numbering and updating of these forms easier than if these forms are stored by visit within the participant’s study notebook.

13.5 How to Complete Interviewer-administered Forms

In order to standardize interviewer-administered data collection from site to site and to maximize quality, it is critical that participant interviews be conducted with a non-biased, non-judgmental approach. Study staff should help a participant feel comfortable sharing personal information and opinions while asking the study questions in a consistent manner from participant to participant.

Interviewing Techniques

An interviewer uses both verbal and non-verbal techniques to obtain the most honest, accurate, and thorough responses from participants. These techniques are discussed in the sections below.

Welcoming the Participant

- When a new participant arrives at the clinic, everything about the study is new. Help make the participant feel comfortable.
- Perhaps offer the participant a glass of water or other beverage.
- Introduce yourself, and try to create rapport (connection) between yourself and the participant to help her feel comfortable during the interview.
- Some DataFax forms include introduction statements before certain items to help prepare the participant for sensitive questions. Read each of these introductions as they appear on the forms.

Asking Sensitive Questions

This study is about a very sensitive subject: HIV. Gaining an understanding of sexual behavior patterns can affect the transmission of HIV and the development of prevention methods.

Your level of comfort with asking sensitive questions will affect the participant's comfort and answers. If you ask the questions in a confident and supportive manner, the participant will feel more confident and comfortable answering the questions. Make eye contact with the participant to let her know that you are listening to her and aware that she is being asked difficult questions. Avoid apologizing for questions or making facial gestures that might show you feel any way but neutral about a question or the participant's response. If the participant feels judged for her behavior, she will be less likely to share honestly with you.

Recording Participants' Responses Verbatim

Often, interviewer-administered questions will have a list of response categories provided to capture the participant's response. Almost always, an "other, specify" box is included as one of the response categories in order to capture participant responses that do not fit into one of the categories already listed. When a participant's response does not match or fit into one of the listed response categories, record the participant's verbatim (word-for-word) response on the line labeled "Local Language" (even if the participant's response is in English). Record the participant's response in the language spoken by the participant. Once the interview is over, go back and translate the text recorded on the "Local Language" line into English, and record the English translation of the response on the "English" line. If the participant's response was in English originally, leave the "English" line blank.

Pacing the Interview

Every participant is different. Some will know or say the answer to questions very quickly. Others may have to think longer to come up with answers, or may change their answers after giving more thought to the subject. Always account for this variety when doing and interview. Read items slowly. Let the participant finish thinking before you record her response and go on to the next item.

Reading Items Aloud

Read all items to the participant **word-for-word**, and speak clearly. Avoid re-phrasing items because this can change the meaning of the item, making it inconsistent with another participant's interview. Provide explanation or interpretation if necessary only after reading the item word-for-word. Avoid tangential—though related—counseling and educational discussions during data collection. When applicable, acknowledge

questions and concerns raised by the participant during the interview, and state that the subject can be discussed after the end of the interview.

Vary your tone of voice, so that you don't sound automated. Emphasize the important words in an item, so that the meaning of the question comes through.

When given the option, choose “clinical” versus “street” or “vernacular” language based on participant preferences/cues.

For items with multiple sub-items, read all sub-items to the participant and mark the appropriate response for each, based on participant report.

Probing

One of the major goals of the study's interviews is to obtain accurate information on many HIV related behaviors. These interviews ask participants to recall many aspects of personal behaviors. However, participants may not remember or know the answer to every question. The technique for helping a participant remember an answer, clarify a response, decide between two similar but different answers, or report something more precisely is called “probing.”

Effective probing helps a participant think more about a question or refine an answer that is too general, however, probing must not bias or otherwise direct participant responses. As the interviewer, you cannot offer the participant an answer. Therefore, all probes must be neutral.

The following are some probing strategies to use when a participant initially answers “don't know” to an item or cannot refine her response enough for the item to be adequately recorded.

- **Repeat Probe:** The repeat probe is used by repeating the item or response categories (if the response categories are part of the question). Although the participant might hear you the first time you ask a question, she may need to hear the question more than once to provide an answer. Instead of rephrasing a question if you notice the participant is confused, always first repeat the item as it is written. Sometimes hearing the question a second time is all that is needed.
- **Echo Probe:** The echo probe involves repeating the participant's exact response. Sometimes hearing the answer with a different voice will help her be more precise. The echo should always be repeated in a neutral, non-judgmental style.
- **Silent Probe:** The silent probe is used by pausing briefly after a participant gives what seems to be an uncertain answer. Although silence can feel awkward, sometimes it is helpful when a participant is trying to determine the most accurate answer to a question. Use a silent probe when the participant sounds unsure of her answer and may need some extra time to think more carefully about the question.
- **Non-verbal Probe:** The non-verbal probe is used by giving hand or facial gestures that may help the participant to come up with an answer. Remember that all such gestures must be neutral and non-judgmental.
- **Specification Probe:** The specification probe is used by asking the participant to give a more precise answer. Although a participant may give an answer that he or she considers accurate, it may not be specific enough. For example, if an item asks how many times the participant did something and she answers with a range (“5 to 10”). Ranges are not acceptable for this type of interviewing. In this case, the probe, “Can you be more specific?” is often enough to help the participant choose the most accurate response.
- **Historical Probe:** The historical probe is used by asking whether the event in question occurred anytime around major holidays or personal events such as a birthday or other life event. Some items require the participant to recall dates, and initially she may be unable to recall a date. Referencing a calendar can also help the participant remember dates.

Watching for Non-verbal Cues

A participant may give you one answer verbally, but express something else using body language or facial expressions. Although you should not question a participant so as to make her feel like you don't trust her answers, be aware of whether she is giving you non-verbal cues that indicate she is not feeling comfortable, not taking the interview seriously, or not answering honestly.

Checking Your Work

During the interview it is important to use the forms instructions (those on the front and back of each page) to guide the interview. Also, make sure the participant is understanding and responding to you, and record all reported information on the forms. **After the interview and while the participant is still there**, review the forms for accuracy and completeness so you can complete an item that might have accidentally been missed. **Once the participant has left, any items identified as missed must remain as is and will be considered “missing data”**. Because all interviewer-administered CRFs are source documents (with the participant being the source of the data), missing items cannot be completed once the participant has left the clinic. For items identified as “missed”, please line through the item and write “item missed in error” in the white space next to the item, and initial and date.

13.6 Form Completion Instructions

Detailed form completion instructions for each form are provided on the back of each form page. These instructions include the purpose of each form as well as how each form should be completed. Some items on forms are straightforward and do not require specific instructions. Therefore, you will not see all form items listed in the form-specific completion instructions, but rather, only those items needing detailed explanation.

Below are some additional instructions for the **Pre-existing Conditions, Concomitant Medications Log, and Adverse Experience Log** case report forms.

Pre-existing Conditions and Concomitant Medication Log

- For the Pre-existing Conditions and Concomitant Medication Log forms, note that you should fax each page to SCHARP any time a new entry is added or modified, even if the page is not complete. You should **not** wait to complete all entries on a page before faxing to SCHARP.

Adverse Experience Log (AE Log)

- For the Adverse Experience Log form, do **not** wait until the AE resolves before faxing the form page to SCHARP. In most cases, when you first report the AE on an AE Log form, the AE will have a “continuing” status (form item 6). Once the AE has an outcome (the AE resolves, the AE is grade 5 - death, or the AE increases in severity/frequency), update item 6 and 6a of the **original** AE Log form page. Initial and date all additions, and any other changes made to the form page, and refax the page to SCHARP.
- Always make changes, corrections, and updates to the **originally-completed** Adverse Experience Log form page. Once an AE Log form page has been started and faxed to SCHARP, the data from that page should **never** be transcribed onto another AE Log form page. All updates and corrections should be made to the originally-completed form page (regardless of how messy or crowded the form page becomes).
- For item 1, note that planned procedures or surgeries are **not** AEs. For example, a tonsillectomy is not an AE and should not be reported as an AE. Any adverse experiences associated with the planned procedure or surgery are AEs and should be reported on an AE Log form. For example, a throat infection that resulted from the tonsillectomy is a reportable AE.

- Note that for **item 3**, the Female Genital Grading Table for Use in Microbicide Studies (Female Genital Tox Table) is used to assign severity grades to AEs (in addition to the DAIDS “Tox Table”). The Female Genital Tox Table is in Section Appendix 11-1 of this SSP Manual.
- For **item 4**, note that if “not related” is marked, you need to record the reason the AE is determined to be “not related” in the Comments section of the form. For example, for an AE of headache that is judged “not related”, the Comments entry may be something like “#4 - not related in time to this AE onset”.
- For **item 5**, mark “no change” if the AE does not result in a product hold or discontinuation. This includes AEs that are reported during the washout weeks (Weeks 6, 13, and 20).
- For **item 7**, note that if the AE results in a new or prolonged hospitalization, the AE meets the criteria for “serious” and item 8 of the AE Log form should be marked “yes”.
- There may be a situation where an AE reported on an Adverse Experience Log form needs to be deleted (for example, in the case where the AE is later found to actually be a pre-existing condition). To indicate an AE Log page should be deleted, draw a diagonal line across the entire form page, write “delete due to _____” (include the reason the AE is being deleted), and initial and date. Refax the form to SCHARP. Do **not** reassign the page number assigned to the deleted AE to another AE, and do not renumber the other AE Log pages present for the participant. Do not renumber AE Log pages after faxing unless specifically instructed to do so by SCHARP.
- For **item 10**, note that the Visit Code recorded in item 10 is the visit code assigned to the visit date in the “Date Reported to Site” field
- For AEs of gradable laboratory results (e.g., “Increased ALT”), the date the laboratory report is received should be recorded as the “Date Reported to Site” on the AE Log. The date of specimen collection should be recorded as **item 2** “Onset Date”. The **item 6a** “Status/Outcome Date” should be the collection date of the follow-up specimen that yields a result within normal range (non-gradable), or a result of increased severity (thus requiring completion of a new AE Log).

13.7 Case Report Forms

This section contains each MTN 001 case report form developed for the study. Detailed form completion instructions for each form are provided on the back of each form page.

Refer to the Visit Checklist of a given visit for a suggested order in which the forms should be completed at that visit.

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Demographics (DEM-1)

This interviewer-administered form is used to collect participants' demographic and socioeconomic information.

This form is faxed to SCHARP DataFax only if the participant enrolls in the study, and only after completion of her Enrollment visit.

Note: *If a participant is being re-screened, a new Demographics form must be completed as part of the subsequent screening attempt. Refer to the Study-Specific Procedures (SSP) Manual for more instructions regarding re-screening form completion and transmission procedures.*

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write "refused" or "don't know," and initial and date the note in the white space next to the item.

Item-specific Instructions:

- **Item 1:** If any portion of the date of birth is unknown, record age at time of enrollment. If age is unknown, record the participant's best estimate of her age. Do not complete both answers. **Note:** *Participant must be between the ages of 18 and 45 years at the time of screening, as verified per site standard operating procedures (SOP), to be eligible for study participation.*
- **Item 5:** Record the **average** monthly income for the household (record in local currency). The participant should include all sources of income. Right justify the response and use leading zeros.

For example, if the income is 2,145 record:

0	0	0	0	2	1	4	5
---	---	---	---	---	---	---	---

If the household's average monthly income is greater than 99,999,999 write "99999999" in the boxes provided, and record the actual value in the white space near the item.

- **Item 6:** This item must be self-identified by the participant. This item asks about race. Read each category aloud and mark the response(s) that apply based on the participant's response. If the participant feels that an appropriate choice is not listed mark the "other, specify" box and record her response on the line provided.

SAMPLE. Do NOT FAX
TO DATAFAX



MTN 001 (146)

DEM-2 (002)

Participant ID

Site Number			Participant Number						Chk		

Demographics

8. What is your highest level of education?

- no schooling
- primary school, not complete
- primary school, complete
- secondary, not complete
- secondary, complete
- attended college or university

Demographics (DEM-2)

No instructions necessary.

SAMPLE. DO NOT FAX
TO DATAFAX



MTN 001 (146)

SC-1 (005)

Participant ID

--	--	--	--	--	--	--	--	--	--	--

Site Number Participant Number Chk

Screening Consent

Visit Date

--	--	--	--	--	--

dd *MMM* *yy*

1. Is the participant between the ages of 18 and 45 years old? *yes* *no* **→ If no, participant is ineligible. End of form.**

2. Was the participant able and willing to provide written informed consent for screening per local regulations and guidelines? *yes* *no* **→ If no, participant is ineligible. End of form.**

2a. Date the informed consent form for screening was marked or signed:

dd *MMM* *yy*

Comments: _____

Screening Consent (SC-1)

This form is used to document that a participant provided written informed consent for screening for this study. This form must be completed for each participant who is assigned an MTN 001 Participant ID (PTID).

This form is faxed to SCHARP DataFax only if the participant enrolls in the study, and only after completion of her Enrollment visit.

***Note:** If a participant is being re-screened, a new Screening Consent form must be completed as part of the subsequent screening attempt. See the Study-Specific Procedures (SSP) Manual for more instructions regarding re-screening form completion and transmission procedures.*

Item-specific Instructions:

- **Item 1:** Per protocol, a participant must be between the ages of 18 and 45 years-old at the time of screening (inclusive), as verified per site standard operating procedures (SOPs) in order to be eligible for the study. Participants who are under 18 years or over 45 years of age should not be screened for the study.

SAMPLE *Do NOT FAX*
TO DATAFAX



Note: Number pages sequentially (01, 02, 03) for each participant.

Page

MTN 001 (146)

PRE-1 (012)

Participant ID

- -
Site Number Participant Number Chk

Pre-existing Conditions

No pre-existing conditions reported or observed. _____ → **End of form. Fax to SCHARP DataFax.**
Staff Initials / Date

1.	Description	<i>MMM</i>	<i>yy</i>	Date of Diagnosis/ Surgery	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
	Comments	Is condition ongoing?		yes <input type="checkbox"/>	no <input type="checkbox"/>
				_____ Staff Initials / Date	
2.	Description	<i>MMM</i>	<i>yy</i>	Date of Diagnosis/ Surgery	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
	Comments	Is condition ongoing?		yes <input type="checkbox"/>	no <input type="checkbox"/>
				_____ Staff Initials / Date	
3.	Description	<i>MMM</i>	<i>yy</i>	Date of Diagnosis/ Surgery	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
	Comments	Is condition ongoing?		yes <input type="checkbox"/>	no <input type="checkbox"/>
				_____ Staff Initials / Date	
4.	Description	<i>MMM</i>	<i>yy</i>	Date of Diagnosis/ Surgery	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
	Comments	Is condition ongoing?		yes <input type="checkbox"/>	no <input type="checkbox"/>
				_____ Staff Initials / Date	
5.	Description	<i>MMM</i>	<i>yy</i>	Date of Diagnosis/ Surgery	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
	Comments	Is condition ongoing?		yes <input type="checkbox"/>	no <input type="checkbox"/>
				_____ Staff Initials / Date	
6.	Description	<i>MMM</i>	<i>yy</i>	Date of Diagnosis/ Surgery	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
	Comments	Is condition ongoing?		yes <input type="checkbox"/>	no <input type="checkbox"/>
				_____ Staff Initials / Date	

Pre-existing Conditions (PRE-1)

Purpose: This form is used to document the participant's pre-existing medical conditions.

General Information/Instructions: Only medical conditions experienced up to study product initiation should be recorded unless otherwise specified in the protocol or Study Specific Procedures (SSPs). Include current medical conditions and any ongoing conditions such as mental illness, alcoholism, drug abuse, and chronic conditions (controlled or not controlled by medication).

Item-specific Instructions:

- **Page:** Number pages sequentially throughout the study, starting with 01. Do not repeat page numbers. Do not renumber any Pre-existing Conditions pages after faxing, unless instructed by SCHARP.
- **Description:** Whenever possible, provide a diagnosis instead of listing a cluster of symptoms. If no diagnosis is identified, each symptom must be recorded as a separate entry on the Pre-existing Conditions form. If an abnormal lab value is reported, record the lab assay with the direction (i.e., increased or decreased) of the abnormality. For example, "decreased hematocrit" or "increased ALT."
- **Date of Diagnosis/Surgery:** If the participant is unable to recall the date, obtain participant's best estimate. At a minimum, the year is required. If the date is within the same year as study enrollment, the month and year are both required. If the condition is diagnosed due to an abnormal lab result, record the date on which the specimen was collected. If a diagnosis is not available, record the date of onset of condition.
- **Comments:** This field is optional. Use it to record any additional relevant information about the condition.
- **Is condition ongoing?:** Mark "yes" if condition is ongoing at enrollment.
- **Pre-existing Conditions Revisions and Updates:**
 - If a participant recalls a pre-existing condition at a later date, update the form at that time. Refax updated page(s).

SAMPLE Do NOT FAX TO DATAFAX



MTN 001 (146)

BGS-1 (030)

Participant ID

Site Number - Participant Number - Chk

Baseline Genital Symptoms

Visit Date

dd MMM yy

1. Since your last study visit, have you experienced any of the following symptoms:

If yes: Are you currently experiencing this symptom?

1a. genital sores? 1b. genital/vaginal itching? 1c. genital/vaginal burning? 1d. genital/vaginal pain (other than during sex)? 1e. pain during sex? 1f. difficulty when urinating? 1g. burning when urinating? 1h. abnormal or unusual genital/vaginal discharge? 1i. unusual genital/vaginal odor? 1j. menstrual symptoms worse than your usual menstrual symptoms? 1k. lower abdominal pain? 1l. other genital symptoms? 11. If yes, specify below.

Local Language: _____

English: _____

1m. vaginal bleeding or spotting between your usual menstrual periods? 1n. blood-tinged discharge?

Comments: _____

Baseline Genital Symptoms (BGS-1)

This form is interviewer-administered and is used to document genital symptoms reported by the participant at the Enrollment Visit.

Note: *If a participant is being re-screened, a new Baseline Genital Symptoms form must be completed as part of the subsequent screening attempt. Refer to the Study-Specific Procedures (SSP) Manual for more instructions regarding re-screening form completion and transmission procedures.*

Interview tips:

Refer to the Study-Specific Procedures (SSP) Manual for detailed interviewing techniques.

- It is important for you to review this form for accuracy and completeness once the interview is complete. By reviewing the form briefly while the participant is still there, you can go back to an item that may have accidentally been skipped.

Note: *Responses to all of the items on this form are based on participant recall at the time of the Enrollment Visit. When administering this form, do **not** refer back to previous documentation completed at screening. Any clarifications and/or updates to this form should be made during the Enrollment Visit only, unless requested otherwise by SCHARP. Once the participant has completed the Enrollment Visit, do **not** make any further updates or changes to the responses recorded on this form. Record symptoms that are ongoing at the time of enrollment on the Pre-existing Conditions form.*

Item-specific Instructions:

Note: *There is no visit code field on this form since this form is only administered during enrollment.*

- **Item 1:** This item refers to any genitourinary symptoms the participant may have experienced since her last Screening Visit. This may include symptoms that were reported as ongoing at the last Screening Visit. Read each item 1a–1n aloud. For each item marked “yes,” complete the adjacent item, “If yes: Are you currently experiencing this symptom?” For items marked “no,” leave the adjacent item “If yes: Are you currently experiencing this symptom?” blank. For any item 1a–1l marked “yes,” evaluate the participant for a UTI or STIs/RTIs per the protocol and SSP. If the participant is diagnosed with a UTI/STI/RTI that is exclusionary per protocol, do **not** enroll the participant. Provide treatment as necessary (per WHO guidelines).
 - **If yes: Are you currently experiencing this symptom?:** For any item 1a–1n marked “yes” (meaning the condition is ongoing), record the symptom on the Pre-existing Conditions form.
 - **Item 1j:** This item is intended to capture dysmenorrhea reported at baseline.
 - **Item 1l:** If “yes” is marked, record the participant’s verbatim response on the “Local Language” line. If the response is given in a language other than English, provide the English translation on the “English” line.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “refused” or “don’t know” in the white space next to the response boxes, and initial and date.

SAMPLE. Do NOT FAX
TO DATAFAX

Visit Code

. 0

1

MTN 001 (146)

SPE-1 (041)

Participant ID

- -

Site Number Participant Number Chk

Screening and Enrollment Pelvic Exam

Exam Date

/ /

dd MMM yy

1. Naked eye, speculum, and bimanual exam assessments:

If no abnormal findings, go to item 3.

no abnormal findings

abnormal findings

If abnormal findings are noted, consult protocol to determine participant eligibility.

1a. Abnormal findings: *Mark all that apply.*

- enlarged/tender inguinal lymph nodes
- abnormal vaginal discharge
- abnormal cervical discharge
- blood-tinged discharge
- blood in vagina—no identified source
- blood from cervical os
- bleeding from site of epithelial disruption
- erythema

- ulceration
- laceration
- abrasion
- peeling
- petechia
- ecchymosis
- vesicles
- edema
- abnormal cysts

- grossly white finding
- mass
- warts—on and/or interior to labia minora
- warts—exterior to labia minora
- adnexal tenderness
- cervical motion tenderness
- uterine tenderness
- other abnormal findings, specify: _____

If finding is present at Enrollment, record on Pre-existing Conditions form.

2. Do any of these exam findings involve Grade 2 or above genital lesions, erythema, and/or edema?

yes no

If yes, participant is ineligible at this time.

3. Cervical Ectopy: Percentage of cervical surface area.

0% 1–25% 26–50% 51–75% > 75%

not required stored not stored Reason:

4. Cervicovaginal lavage (CVL) fluid:

→ _____

Comments: _____

Screening and Enrollment Pelvic Exam (SPE-1)

This form, along with the non-DataFax Pelvic Exam Diagrams, is used to document the pelvic exams conducted during the Screening and Enrollment Visits.

This form is faxed to SCHARP DataFax only if the participant enrolls in the study, and only after completion of her Enrollment Visit.

Note: *If a participant screens more than once for the study (i.e., has multiple screening attempts), and eventually enrolls in the study, only the Screening and Enrollment Pelvic Exam form from the successful screening attempt that led to enrollment should be faxed to SCHARP. For each enrolled participant, only one Screening and Enrollment Pelvic Exam form for the Screening Visit (assigned visit code 01.0), and one Screening and Enrollment Pelvic Exam form for the Enrollment Visit (assigned visit code 02.0) should be faxed to SCHARP DataFax.*

Item-specific Instructions:

- **Item 1:** Document abnormal findings observed during the naked eye, speculum, and/or bimanual examinations. If no abnormal findings are observed, mark the “no abnormal findings” box, leave item 1a blank and go to item 3. If one or more abnormal findings are observed, mark the “abnormal findings” box and continue to item 1a.
- **Item 1a:** Abnormal findings: Mark the box to the left of **each** abnormal finding observed via naked eye, speculum, and/or bimanual examination. If an observed abnormal finding is not listed, mark the “other abnormal findings, specify” box and describe the abnormal finding in the space provided.
- **Item 4:** CVL collection and storage is required at the Enrollment visit.

Screening and Enrollment STI Laboratory Results (SSL-1)

This form is used to document local laboratory results of blood and urine specimens collected at the Screening and Enrollment Visit. Record specimen test results on this form as they become available.

This form is faxed to SCHARP DataFax only if the participant enrolls in the study, and only after completion of her Enrollment Visit.

Note: If a participant screens more than once for the study (i.e., has multiple screening attempts), and eventually enrolls in the study, only the Screening STI Laboratory Results form from the successful screening attempt that led to enrollment should be faxed to SCHARP DataFax.

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. See the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.
- **Initial Specimen Collection Date:** Record the date that the first specimen(s) was *collected* (NOT the date results were reported or recorded on the form) for this visit. A complete date is required.
- **Alternate Collection Date:** This date is to be completed ONLY if the specimen was collected on a different day than the rest of the specimens. A specimen collected for the same visit but on a different day should be recorded on the same form. A complete date is required.
- **Not done/Not collected:** For every test, mark *either* the “Not done/Not collected” box *or* enter a test result.
- **Results Reporting**
 - If a specimen was collected but results are not available because the specimen was lost or damaged, line through the results and write an explanation in the Comments section (page 2).
- **Items 1a and 1b:** Record the assigned two-digit rapid test kit code. As of March, 2008, the rapid test kit codes are as follows. **Note:** More test kit codes may be added to the list below as the study proceeds.

Rapid Test	Kit Code
Abbott Determine	01
OraSure OraQuick	02
Uni-Gold Recombigen	03

- If the two HIV rapid test results are discordant, conduct Western Blot testing and record the associated test result in item 1d.
Note: A participant must be confirmed HIV uninfected in order to be eligible for study participation.
- **Item 2a:** If the syphilis (RPR) screening test is reactive, items 2a1 and 2b must be completed.
- **Item 2a1:** Remember to use leading zeros when recording a syphilis titer level. For example, a titer level of 1:20 would be recorded on the form as “1:0020.”

Screening and Enrollment STI Laboratory Results (SSL-2)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on page 1 of the form for a given participant and visit.
- **Alternate Collection Date:** This date is to be completed **ONLY** if the specimen was collected on a different day than the rest of the specimens. A specimen collected for the same visit but on a different day should be recorded on the same form. A complete date is required.
- **Not done/Not collected:** For every test, mark *either* the “Not done/Not collected” box *or* enter a test result.
- **Results Reporting**
 - If a specimen was collected but results are not available because the specimen was lost or damaged, line through the results and write an explanation on the comments line.

SAMPLE. Do NOT FAX
TO DATAFAX



Visit Code . 0

1

MTN 001 (146)

PKN-1 (061)

Participant ID

- -
Site Number Participant Number Chk

**Pharmacokinetics—
Non-intensive**

Specimen Collection Date

dd MMM yy

1. Participant weight: kg

MID-STUDY PERIOD

Not done/
Not collected

2. PK blood draw: : **Time (24-hr clock)**
hr min **End of form.**

END OF STUDY PERIOD

Not done/
Not collected

- 3. Pre-dose blood draw: : **Time (24-hr clock)**
hr min
- 4. Observed dose of oral tenofovir:..... : **Time (24-hr clock)**
hr min
- 5. Observed dose of vaginal tenofovir gel: : **Time (24-hr clock)**
hr min
- 6. 1–3 hour post-dose blood draw: : **Time (24-hr clock)**
hr min
- 7. 3–5 hour post-dose blood draw: : **Time (24-hr clock)**
hr min
- 8. 5–7 hour post-dose blood draw: : **Time (24-hr clock)**
hr min

GENITAL SPECIMENS FOR STORAGE

Not done/
Not collected

9. Cervicovaginal Lavage (CVL) fluid: : **Time (24-hr clock)**
hr min **End of form.**

10. Was menstrual blood present at the time of genital specimen collection?
yes no

Comments: _____

Pharmacokinetics—Non-intensive (PKN-1)

This form is used to document collection of pharmacokinetic (PK) laboratory specimens for non-intensive PK participants at the Mid-study period and End-of-study period visits. A separate form should be used for the Mid-study period and End-of-study period visits.

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. See the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.
- **Specimen Collection Date:** Record the date that the first specimen(s) was *collected* (NOT the date results were reported or recorded on the form) for this visit. A complete date is required.
- **Not done/Not collected:** For every test, mark *either* the “Not done/Not collected” box *or* enter the time of specimen collection.
- **Item 2:** This item applies to the Mid-study period visits only. For End-of-study period visits, mark the “Not done/Not collected” box and proceed to item 3.
- **Items 3–10:** Complete at End-of-study period visits only. For Mid-study period visits, leave these items blank.
- **Item 3:** Per protocol, the pre-dose blood draw is required for all non-intensive PK participants and should occur 15–30 minutes prior to the observed dose(s) of study product(s).
- **Items 4–5:** Record the time (using a 24-hour clock) that the participant administered the observed dose of study product(s) at the site clinic. If the participant is in the oral period, record the time of the observed oral tenofovir dose in item 4 and mark the “Not done/Not collected” box for item 5. If the participant is in the vaginal use period, record the time of the observed vaginal tenofovir gel dose in item 5 and mark the “Not done/Not collected” box for item 4. If the participant is in the dual use period, record the times of each respective observed dose of study product (oral and vaginal) in items 4 and 5.
- **Items 6–8:** Choose the item that corresponds to the participant’s randomized post-dose sampling time (1–3 hours, 3–5 hours, or 5–7 hours post-dose), and record the time of blood draw (using a 24-hour clock). Mark the “Not done/Not collected” box for the remaining items. If no post-dose blood specimen was collected or stored, mark the “Not done/Not collected” box for each item and record the reason in the Comments section at the bottom of the form.
- **Item 9:** Record the time (using a 24-hour clock) that the CVL specimen was collected. If CVL was not collected or stored, mark the “Not done/Not collected” box and record the reason in the Comments section at the bottom of the form.

***Note:** Per protocol, the post-dose blood and CVL collections should occur with 15–30 minutes of each other (either sample may be collected first). For each of the three study periods, the same sampling time point (within 15 minutes) should be used. For example, if a participant is randomized to specimen collections 1–3 hours post-dose, and the Week 6 Visit post-dose blood and CVL are collected 2 hours post-dose, then the Week 13 and Week 20 post-dose blood and CVL collections should also occur 2 hours post-dose (plus or minus 15 minutes).*

SAMPLE. Do NOT FAX
TO DATAFAX



Visit Code . 0

1

MTN 001 (146)

PKI-1 (062)

Participant ID

- -
Site Number Participant Number Chk

**Pharmacokinetics—
Intensive**

Specimen Collection Date

dd MMM yy

1. Participant weight: kg

MID-STUDY PERIOD

Not done/
Not collected

2. PK blood draw:

Time (24-hr clock)
hr min
 :

End of form.

END OF STUDY PERIOD

Not done/
Not collected

3. Pre-dose blood draw:

Time (24-hr clock)
hr min
 :

4. Observed dose of oral tenofovir:.....

:

5. Observed dose of vaginal tenofovir gel:

:

6. 1-hour post-dose blood draw:

:

7. 2-hour post-dose blood draw:

:

8. 4-hour post-dose blood draw:

:

9. 6-hour post-dose blood draw:

:

10. 8-hour post-dose blood draw:

:

GENITAL SPECIMENS FOR STORAGE

Not done/
Not collected

11. Cervicovaginal Lavage (CVL) fluid:

Time (24-hr clock)
hr min
 :

12. Cervical cytology brush:

:

13. Vaginal tissue biopsy:

:

End of form.

14. Was menstrual blood present at the time of genital specimen collection?

yes no

Comments: _____

Pharmacokinetics—Intensive (PKI-1)

This form is used to document collection of pharmacokinetic (PK) laboratory specimens for intensive PK participants at the Mid-study period and End-of-study period visits. A separate form should be used for the Mid-study period and End-of-study period visits.

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. See the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.
- **Specimen Collection Date:** Record the date that the first specimen(s) was *collected* (NOT the date results were reported or recorded on the form) for this visit. A complete date is required.
- **Not done/Not collected:** For every test, mark *either* the “Not done/Not collected” box *or* enter the time of specimen collection.
- **Item 2:** This item applies to the Mid-study period visits only. For End-of-study period visits, mark the “Not done/Not collected” box and proceed to item 3.
- **Items 3–14:** Complete at End-of-study period visits only. For Mid-study period visits, leave these items blank.
- **Item 3:** Per protocol, the pre-dose blood draw is required for all intensive PK participants and should occur 15–30 minutes prior to the observed dose(s) of study product(s).
- **Items 4–5:** Record the time (using a 24-hour clock) that the participant administered the observed dose of study product(s) at the site clinic. If the participant is in the oral period, record the time of the observed oral tenofovir dose in item 4 and mark the “Not done/Not collected” box for item 5. If the participant is in the vaginal use period, record the time of the observed vaginal tenofovir gel dose in item 5 and mark the “Not done/Not collected” box for item 4. If the participant is in the dual use period, record the times of each respective observed dose of study product (oral and vaginal) in items 4 and 5.
- **Items 6–10:** Record the time of blood draw (using a 24-hour clock) for each of the required post-dose blood sampling times (1, 2, 4, 6, and 8 hours post-dose). If a post-dose blood specimen was not collected or stored, mark the “Not done/Not collected” box and record the reason in the Comments section at the bottom of the form.
- **Items 11–13:** Record the time (using a 24-hour clock) that each of the genital specimens (CVL, cervical cytology brush and vaginal tissue biopsy) was collected. If a genital specimen was not collected or stored, mark the “Not done/Not collected” box and record the reason in the Comments section at the bottom of the form.

***Note:** Per protocol, the blood and genital specimen collections should occur within 15–30 minutes of the assigned sampling time, and within 15–30 minutes of each other (either blood or genital specimens may be collected first.) For each of the 3 study periods, the same sampling time point (within 15 minutes) should be used. For example, if a participant is randomized to the 2-hour post-dose genital specimen collections, the genital specimens should be collected between 1 hour 30 minutes and 2 hours 30 minutes post-dose. If, at the Week 6 Visit, the samples are collected 2 hours 15 minutes post-dose, site staff should attempt to collect the same samples 2 hours 15 minutes post-dose (plus or minus 15 minutes) at the Week 13 and Week 20 Visits.*

SAMPLE *DO NOT FAX*
TO DATAFAX

MTN 001 (146)



FC-1 (064)

Visit Code

1

Participant ID

- -
Site Number Participant Number Chk

Flow Cytometry

Specimen Collection Date

dd MMM yy

Not done/
Not collected

1. FLOW CYTOMETRY

Absolute Count

1a. Lymphocyte *cells/mm³*

% Absolute Count

1b. CD3 (CD3/CD4) AND *cells/mm³*

% Absolute Count

1c. CD4 (CD3/CD4) AND *cells/mm³*

% Absolute Count MFI

1d. CD38 (CD3/CD4/CD38) AND *cells/mm³* AND

% Absolute Count MFI

1e. HLA-DR (CD3/CD4/HLA-DR) AND *cells/mm³* AND

% Absolute Count

1f. Dual Positive AND *cells/mm³*

(CD3/CD4/CD38/HLA-DR).....

MFI: x-axis (HLA-DR) MFI: y-axis (CD38)

AND

Comments: _____

Flow Cytometry (FC-1)

Purpose: To document flow cytometry laboratory results.

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. See the Data Collection section of the Study Specific Procedures (SSP) for more specific information on assigning visit codes.
- **Specimen Collection Date:** Record the date that the first specimen(s) was *collected* (NOT the date results were reported or recorded on the form) for this visit. A complete date is required.
- **Not done/Not collected:** Mark this box in the event that a specimen is collected, but a result is not available due to specimen loss or damage. Explain in the Comments section at the bottom of the form why the result is not available.

SAMPLE. Do NOT FAX
TO DATAFAX



MTN 001 (146)

ENR-1 (070)

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	
Site Number				Participant Number						Chk	

Enrollment

Visit Date

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
dd		MMM			yy		

1. Date the informed consent form for enrollment was marked or signed:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
dd		MMM			yy

2. Was the participant willing and able to provide written informed consent for specimen storage and future research?

yes no

 → **If no, go to item 3.**

2a. Date the informed consent form for specimen storage and future research was marked or signed:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
dd		MMM			yy

3. Randomization envelope number:

OR N/A

4. Date assigned:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
dd		MMM			yy

5. Time assigned:

: 24-hour clock

hr min

6. Study regimen sequence:

→ **If not a US participant, go to item 8.**

7. Intensive PK sampling time point:

pre-dose 2 hours 4 hours 6 hours

8. Was the participant randomized to a Week 21 In-depth interview?

yes no

 → **If not a replacement participant, go to item 10.**

9. Participant ID of participant being replaced:

<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>
----------------------	----------------------	----------------------	---	----------------------	----------------------	----------------------	----------------------	----------------------	---	----------------------

10. Date study product(s) dispensed:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
dd		MMM			yy

11. How many **cartons** of tenofovir gel were dispensed?

of **cartons** dispensed

12. How many **bottles** of oral tenofovir were dispensed?

of **bottles** dispensed

13. Participant height:

cm

Comments: _____

Enrollment (ENR-1)

This form is used to document a participant's study enrollment/randomization. This form is completed at the Enrollment Visit for participants determined to be eligible for the study. This form is faxed to SCHARP DataFax only if the participant is enrolled (that is, she is assigned a randomization envelope or a Replacement Participant Randomization for replacement participants), and only after completion of the Enrollment Visit.

Item-specific Instructions:

- **Item 3:** Consent for specimen storage and future research is optional and does not affect a participant's study eligibility.
- **Item 2a:** If the participant re-screened for the study and signed another enrollment informed consent as part of the re-screening process, record the most recent date she signed the enrollment informed consent prior to study randomization. If a participant reconsents to study participation or specimen storage and future research during her study follow-up (i.e., due to an updated IRB/EC-approved informed consent form) do not update the response to item 2a.
- **Item 3:** Record the three-digit envelope number present on the randomization envelope assigned to this participant. If this is a replacement participant, mark the "N/A" box.
- **Item 4:** Record the date the randomization envelope or Replacement Participant Randomization was assigned to the participant. If the participant was assigned a randomization envelope, this date should match the "date assigned" recorded for this participant on the appropriate Envelope Tracking Record. If the participant is a replacement participant, this date should match the "date assigned" recorded for this participant on the appropriate Replacement Participant Randomization Tracking Record.
- **Item 5:** Record the time (using a 24-hour clock) when the envelope or Replacement Participant Randomization was assigned to the participant. This time should match the "time assigned" recorded on the Envelope Tracking Record or Replacement Participant Randomization Tracking Record for a given participant.
- **Item 6:** Record the study regimen letter code present on the study randomization contained inside the randomization envelope, (or on the Replacement Participant Randomization, if a replacement participant).
- **Item 7:** This item is for participants at US sites only. Mark the box that corresponds to the intensive PK sampling time point (for collection of genital samples) present on the study randomization document (or on the Replacement Participant Randomization, if a replacement participant.)
- **Item 8:** Mark the box that corresponds to the Week 21 in-depth interview randomization on the study randomization document (or on the Replacement Participant Randomization, if a replacement participant.)
- **Item 9:** This item is for replacement participants only. Record the Participant ID (PTID) present on the study randomization of the participant who is being replaced.
- **Item 10:** Record the exact day, month, and year study product(s) (tenofovir gel and/or tenofovir (TDF) tablets) were first dispensed to this participant.
- **Item 11:** Record the number of vaginal tenofovir gel cartons dispensed to the participant. *NOTE: A standard number of two cartons should be dispensed at the Enrollment Visit.*
- **Item 12:** Record the number of oral tenofovir (TDF) bottles dispensed to the participant. *NOTE: A standard number of one bottle should be dispensed at the Enrollment Visit.*

SAMPLE. Do NOT FAX
TO DATAFAX



MTN 001 (146)

EBA-1 (072)

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	
Site Number				Participant Number						Chk	

Enrollment Behavior Assessment

Visit Date

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
dd		MMM		yy	

I am now going to ask you some questions about your sexual behavior. Some of these questions are personal and sensitive, but understanding sexual behavior is important for HIV prevention. Your honest answers will be very helpful to us. There is no right or wrong answer to these questions. Remember, we do not have your name on these papers, and all of your answers will be kept confidential.

There are many different ways people have sex. Some of the questions are about vaginal sex, and some are about anal sex. Vaginal sex means when a man puts his penis inside your vagina. Anal sex means when a man puts his penis inside your anus.

1. In the **past 3 months**, how many sex partners have you had? By sex partner, I mean someone with whom you have had vaginal or anal sex. # of partners
- **If 0, participant is ineligible. Go to statement above item 9 on page 3.**
- 1a. Were any of these sex partners casual partners? By casual partner, I mean someone whom you do not consider to be your main partner.
- | | | |
|--------------------------|--------------------------|---|
| yes | no | |
| <input type="checkbox"/> | <input type="checkbox"/> | |
| yes | no | |
| <input type="checkbox"/> | <input type="checkbox"/> | → If no, go to statement above item 5 on page 2. |
2. In the **past 3 weeks**, did you have vaginal sex?
- 2a. In the **past 3 weeks**, how often did you have vaginal sex?
Showcard #2.
- | | | | | |
|------------------------------|--------------------------|--------------------------|--------------------------|-----------------------------|
| <i>less than once a week</i> | <i>1-3 times a week</i> | <i>4-6 times a week</i> | <i>once a day</i> | <i>more than once a day</i> |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

I know that you have been counseled to use male condoms for each act of vaginal sex, but I also know that it is sometimes difficult to use condoms all the time. We are interested in your actual experiences using male condoms with vaginal sex, so your honest and accurate answers are very important to us.

- 2b. In the **past 3 weeks**, how often did your partner(s) use a male condom during vaginal sex?
Showcard #3.
- | | | | | |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| <i>never</i> | <i>rarely</i> | <i>sometimes</i> | <i>most of the time</i> | <i>always</i> |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Enrollment Behavior Assessment (EBA-1)

This form is used to collect baseline information about the participant's sexual behaviors. This is an interviewer-administered form, and it is administered only once to each enrolled participant as part of her Enrollment visit.

Interview tips:

See Study-Specific Procedures (SSP) Manual for detailed interviewing techniques.

- Help the participant feel comfortable. Develop a rapport or connection with the participant.
- Avoid re-phrasing items, as doing so can change the meaning of the items and make them inconsistent with other interviews.
- Use probes to help the participant remember an answer, clarify a response, or to help report something more accurately.
- It is important for you to review the forms for accuracy and completeness once the interview is complete. By reviewing the form briefly while the participant is still there, you can go back to an item that may have accidentally been skipped.

***Note:** Responses to all of the items on this form are based on participant recall at the time the form is being administered. Any clarifications and/or updates to this form should be made during the Enrollment Visit interview only, unless requested otherwise by SCHARP. Once the participant has completed the Enrollment Visit interview in which this form is administered, do not make any further updates or changes to the responses recorded on this form.*

Item-specific Instructions:

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write "don't know" or "refused," and initial and date the note in the white space next to the item.

SAMPLE. DO NOT FAX TO DATAFAX



MTN 001 (146)

EBA-2 (073)

Participant ID

Participant ID form with boxes for Site Number, Participant Number, and Chk

Enrollment Behavior Assessment

No data recorded on this page checkbox

3. In the past 7 days, how many times did you have vaginal sex? ... # of times [] [] -> If 0, go to item 4.

3a. In the past 7 days, how many times did your partner(s) use a male condom during vaginal sex? ... # of times [] []

4. The last time you had vaginal sex, did your partner use a male condom? ... yes [] no []

I am now going to ask you some questions about a different way that people have sex. This way is anal sex. I am asking you these questions because understanding sexual behavior is important for HIV prevention. Remember, all of your answers will be kept confidential.

5. Have you ever had anal sex? ... yes [] no [] -> If no, go to statement above item 9 on page 3.

6. In the past 3 weeks, did you have anal sex? ... yes [] no [] -> If no, go to statement above item 9 on page 3.

6a. In the past 3 weeks, how often did you have anal sex? Showcard #2

Frequency options for anal sex: less than once a week, 1-3 times a week, 4-6 times a week, once a day, more than once a day

I know that you have been counseled to use male condoms for each act of anal sex, but I also know that it is sometimes difficult to use condoms all the time. We are interested in your actual experiences using male condoms with anal sex, so your honest and accurate answers are very important to us.

6b. In the past 3 weeks, how often did your partner(s) use a male condom during anal sex? Showcard #3

Frequency options for partner condom use: never, rarely, sometimes, most of the time, always

Enrollment Behavior Assessment (EBA-2)

Item-specific Instructions:

- **No data recorded on this page:** Mark this box if no data is recorded on this page other than the Participant ID and the Staff Initials/Date.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don’t know” or “refused,” and initial and date the note in the white space next to the item.

SAMPLE *Do NOT FAX TO DATAFAX*



MTN 001 (146)

EBA-3 (074)

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	
Site Number				Participant Number						Chk	

Enrollment Behavior Assessment

7. In the **past 7 days**, how many times did you have anal sex?.....

of times

→ **If 0, go to item 8.**

7a. In the **past 7 days**, how many times did your partner(s) use a male condom during anal sex?

of times

8. The **last time** you had anal sex, did your partner use a male condom?

yes	no
<input type="checkbox"/>	<input type="checkbox"/>

I am now going to ask you some different types of personal and sensitive questions. Some of the questions may not apply to you, but we ask the same questions of all study participants.

9. For the next question, I am going to ask you about items that women sometimes insert inside their vaginas. For each item, please tell me if you inserted it inside your vagina in the **past month**. It is possible to answer "yes" more than once.

9a. water?

yes	no	# of times in past week
<input type="checkbox"/>	<input type="checkbox"/>	→ <input type="text"/> <input type="text"/>

9b. water with vinegar? **Note for U.S. sites:** This includes all commercial douching products.

<input type="checkbox"/>	<input type="checkbox"/>	→ <input type="text"/> <input type="text"/>
--------------------------	--------------------------	---

9c. water with soap?

<input type="checkbox"/>	<input type="checkbox"/>	→ <input type="text"/> <input type="text"/>
--------------------------	--------------------------	---

9d. paper, cloth, cotton, or cotton wool?

<input type="checkbox"/>	<input type="checkbox"/>	→ <input type="text"/> <input type="text"/>
--------------------------	--------------------------	---

9e. tampons?

<input type="checkbox"/>	<input type="checkbox"/>	→ <input type="text"/> <input type="text"/>
--------------------------	--------------------------	---

9f. fingers without anything else?

<input type="checkbox"/>	<input type="checkbox"/>	→ <input type="text"/> <input type="text"/>
--------------------------	--------------------------	---

9g. anything else? Specify below.

<input type="checkbox"/>	<input type="checkbox"/>	→ <input type="text"/> <input type="text"/>
--------------------------	--------------------------	---

Local Language: _____

English: _____

Enrollment Behavior Assessment (EBA-3)

Item-specific Instructions:

- **Item 9:** Read each item 9a–9g aloud and mark the participant’s response. For each item to which she replies “yes,” ask how many times in the **past week** (the last 7 days) she has used that particular item. Record the response in the “# of times in **past week**” boxes. If “yes” is marked for item 9g, record the participant’s verbatim (word-for-word) response. If the response is given in a language other than English, provide the English translation in the space provided.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don’t know” or “refused,” and initial and date the note in the white space next to the item.

SAMPLE *DO NOT FAX*
TO DATAFAX

MTN 001 (146)

■ ■ ■ ■ ■ ■ ■ ■ ■ ■ Visit Code

FPM-1 (075)

□ □ □

1

Participant ID

□ □ □ - □ □ □ □ □ □ - □
Site Number Participant Number Chk

Family Planning Methods

Visit Date

□ □ □ □ □ □ □ □
dd MMM yy

1. Which family planning method or methods is the participant currently using? Mark "none" or all that apply.

- 1a. none
- 1b. vaginal ring
- 1c. spermicide
- 1d. diaphragm
- 1e. sponge
- 1f. intrauterine contraceptive device (IUCD)
- 1g. natural methods such as the withdrawal or rhythm method
- 1h. male condoms
- 1i. female condoms
- 1j. family planning pills or birth control pills
- 1k. injectable contraceptives (such as Depo-Provera)
- 1l. implantable contraceptives, such as Norplant, Jadelle, or Implanon
- 1m. Ortho Evra/The Patch
- 1n. surgical sterilization of participant (tubal ligation, hysterectomy)
- 1o. surgical sterilization of current sex partner(s)
- 1p. other, specify:

→ **If Enrollment Visit, participant is ineligible.
If follow-up visit, counsel regarding use of allowable methods of contraception, per protocol.**

Comments: _____

Family Planning Methods (FPM-1)

This form is completed by a site staff member to collect information about the family planning methods that the participant is currently using. It is completed at the Enrollment Visit and at each regularly scheduled follow-up visit.

Item-specific Instruction:

- **Item 1:** Transcribe the family planning methods as documented during the baseline or follow-up Medical History Assessments.

SAMPLE. Do NOT FAX TO DATAFAX

MTN 001 (146)



FV-1 (121)

Visit Code . 0

1

Participant ID

- -
Site Number Participant Number Chk

Follow-up Visit

Visit Date

dd MMM yy

1. hCG for pregnancy: *not done* *negative* *positive*
1a. Specify reason(s): ← → **If positive, complete Pregnancy Report and History form and Product Hold/Discontinuation form.**

2. Were any new adverse experiences reported at this visit? *yes* *no* → **If no, go to item 3.**
2a. How many **new** AE Log pages were completed for this visit? # of pages
3. At this visit, how many **unused applicators** of tenofovir gel did the participant return? # of **unused applicators** returned
4. At this visit, how many **unused tablets** of oral tenofovir did the participant return? # of **unused tablets** returned
5. At this visit, how many **applicators** of tenofovir gel were dispensed? # of **applicators** dispensed
6. At this visit, how many **tablets** of oral tenofovir were dispensed? # of **tablets** dispensed

Comments: _____

Follow-up Visit (FV-1)

This form is used to document the required (regularly scheduled) follow-up visits. It is completed at each regularly scheduled follow-up visit, regardless of whether the visit is conducted within the protocol-specified window or made up outside the visit window.

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. Refer to the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.
- **Item 1:** Record the hCG urine pregnancy test result. If a urine pregnancy test result is not available (specimen not collected and/or test not done), mark the “not done” box and complete item 1a. *Note: A Pregnancy Report and History form must be completed for each pregnancy.* Once a participant tests positive for hCG urine pregnancy and a Pregnancy Report and History form (PR-1) has been completed for this pregnancy, subsequent positive pregnancy test results should not be recorded on a new PR-1 unless they represent a new pregnancy.
- **Item 2:** Mark the “yes” box if a new (previously unreported) AE is reported or observed at this visit. If the box is marked “yes,” record in item 2a how many **new** AE Log pages were completed for this visit. For example, if two new AEs were reported, record “02.” Note that the Visit Code recorded in item 10 of these two AE Log pages should be the same as the Visit Code recorded on this form.
- **Item 3:** Record the number of **unused** vaginal tenofovir gel applicators the participant returned at this visit only, as determined by site clinic staff.
- **Item 4:** Record the number of **unused** oral tenofovir tablets the participant returned at this visit only, as determined by site clinic staff.
- **Item 5:** Record the number of **applicators** of vaginal tenofovir gel given to the participant at this visit. This will be the same amount documented on the **Study Product Request Slip**, unless documentation from the pharmacy staff states otherwise. For End-of-study period visits (6-Week, 13-Week, and 20-Week visits), include applicators dispensed for the in-clinic observed doses for PK.
- **Item 6:** Record the number of **tablets** of oral tenofovir given to the participant at this visit. This will be the same amount documented on the **Study Product Request Slip**, unless documentation from the pharmacy staff states otherwise. For End-of-study period visits (the 6-Week, 13-Week, and 20-Week visits), include tablets dispensed for the in-clinic observed doses for PK.

SAMPLE *DO NOT FAX*
TO DATAFAX



Visit Code

1

MTN 001 (146)

FGS-1 (130)

Participant ID

- -
Site Number Participant Number Chk

Follow-up Genital Symptoms

Visit Date

dd MMM yy

1. Since your last study visit, have you experienced any of the following symptoms:

	yes	no	dd	MMM	yy	Continuing from previous visit
1a. genital sores?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	OR <input type="checkbox"/>
1b. genital/vaginal itching?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	OR <input type="checkbox"/>
1c. genital/vaginal burning?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	OR <input type="checkbox"/>
1d. genital/vaginal pain (other than during sex)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	OR <input type="checkbox"/>
1e. pain during sex?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	OR <input type="checkbox"/>
1f. difficulty when urinating?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	OR <input type="checkbox"/>
1g. burning when urinating?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	OR <input type="checkbox"/>
1h. abnormal or unusual genital/vaginal discharge?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	OR <input type="checkbox"/>
1i. unusual genital/vaginal odor?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	OR <input type="checkbox"/>
1j. menstrual symptoms worse than your usual menstrual symptoms?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	OR <input type="checkbox"/>
1k. lower abdominal pain?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	OR <input type="checkbox"/>
1l. other genital symptoms?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	OR <input type="checkbox"/>

111. If yes, specify below.

If no, go to item 1m.

If yes to any, conduct pelvic exam if clinically indicated. Update or complete Adverse Experience Log when applicable.

Local Language: _____

English: _____

	yes	no	dd	MMM	yy	Continuing from previous visit
1m. vaginal bleeding or spotting between your usual menstrual periods?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	OR <input type="checkbox"/>
1n. blood-tinged discharge?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	OR <input type="checkbox"/>

If yes to any, complete Genital Bleeding Assessment form if indicated. Conduct pelvic exam if indicated. Update or complete Adverse Experience Log when applicable.

Comments: _____

21-APR-08

0 1

Follow-up Genital Symptoms (FGS-1)

This form is interviewer-administered, and is used to document genital symptoms reported by the participant during study follow-up. It is completed at each regularly scheduled follow-up visit.

Interview tips:

Refer to the Study-Specific Procedures (SSP) Manual for detailed interviewing techniques.

- It is important for you to review this form for accuracy and completeness once the interview is complete. By reviewing the form briefly while the participant is still there, you can go back to an item that may have accidentally been skipped.

Note: *Responses to all of the items on this form are based on participant recall at the time the form is being administered. When administering this form, **do not** refer back to previously completed Genital Symptoms forms (Baseline and Follow-up). Any clarifications and/or updates to this form should be made only during the visit in which this form is completed, unless requested otherwise by SCHARP. Once the participant has completed the visit, do not make any further updates or changes to the responses recorded on this form. If, at a subsequent study visit, the participant reports additional symptoms she experienced at baseline or at a time point covered by a previous Follow-up Genital Symptoms form, do **not** update any of the previously completed forms. Instead, record the new information on the current Follow-up Genital Symptoms form and explain the discrepancy in both the Comments section and/or in the participant's chart notes. If the participant reports additional symptoms that were ongoing at enrollment, record these on the Pre-existing Conditions form.*

Once the interview is complete, review the completed Genital Symptoms form (Baseline or Follow-up) from the previous visit and identify any symptoms that were a) reported as ongoing, and b) documented on an AE Log. If the same symptoms are reported as not present at the current visit (response on current visit's Follow-up Genital Symptoms form is "no"), query the participant for an outcome date and record this in item 6a of the associated AE Log.

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. Refer to the SSP for more specific information on assigning visit codes.
- **Item 1:** Read each item 1a–1n aloud. For any item marked "yes," conduct a pelvic exam if clinically indicated (and not already required for the visit). For each item marked "yes," complete an Adverse Experience (AE) Log if the symptom is new or has increased in severity. If the symptom was first reported on the participant's Baseline Genital Symptoms and Pre-existing Conditions forms and it has not increased in severity or frequency, **do not** complete an AE Log—do record on this form that the condition has not increased in severity or frequency since enrollment/baseline.
- **Item 1j:** This item is intended to capture dysmenorrhea reported during follow-up visits. If the participant reports dysmenorrhea and/or any other symptom(s) related to menstruation, probe for further information (i.e., type and severity of symptoms), then compare to participant's usual baseline menstrual symptoms (as documented on the Local Baseline Medical History Assessment and the Baseline Genital Symptoms form) to determine whether an AE should be reported.
- **Item 1l:** If "yes" is marked, record the participant's verbatim response on the "Local Language" line. If the response is given in a language other than English, provide the English translation on the "English" line.
- **If yes: When did you first experience this symptom?:** For each item marked "yes," record the day, month, and year the participant first began experiencing symptoms; if necessary, use a calendar to probe. If the participant provides a date that is prior to the date of the previous visit, mark "continuing from previous visit" and leave the day, month, and year boxes blank. If the participant states that a symptom began on the exact date of the previous visit, clarify whether or not the symptom was present at the time the visit occurred. If she states that the symptom was present during the previous visit, mark "Continuing from previous visit" and leave the day, month, and year boxes blank. If the participant states that the symptom occurred on the same day as the previous visit, but after she had completed the visit, record the day, month, and year of the previous visit and leave the "continuing from previous visit" box blank.
- **Continuing from previous visit:** Mark this box for symptoms reported as continuing since the time of the previous visit. If this box is marked, leave the "If yes: When did you first experience symptoms?" boxes blank. If a date is recorded, leave the corresponding "continuing from previous visit" box blank.
- **Items 1m–1n:** If the participant reports vaginal bleeding or spotting between usual menstrual periods, or any blood-tinged genital/vaginal discharge, refer to the SSP.

SAMPLE *DO NOT FAX*
TO DATAFAX



Visit Code

MTN 001 (146)

SLR-1 (131)

Participant ID

- -
Site Number Participant Number Chk

STI Laboratory Results

Initial Specimen Collection Date

dd MMM yy

Alternate Collection Date

Not done/ Not collected dd MMM yy

dd MMM yy

Not done/ Not collected dd MMM yy

1. HIV TEST RESULTS

1a. Rapid test 1
1b. Rapid test 2
1c. HIV ELISA.....

If positive for any, complete HIV Test Results and Product Hold/Discontinuation forms.

2. STI SEROLOGY

2a. Syphilis RPR test
2a1. Syphilis titer..... 1:
2b. Syphilis Treponomal test
If non-reactive, go to item 3.
If negative, go to item 3.
If positive, complete Adverse Experience Log when applicable.

3. OTHER STI TESTS

3a. *N. gonorrhoea*
3b. *C. trachomatis*
3c. Hepatitis B Surface Antigen
If either is positive, complete Adverse Experience Log when applicable.
If reactive, complete Adverse Experience Log when applicable.

Comments: _____

STI Laboratory Results (SLR-1)

This form is used to document local laboratory results of blood and urine specimens collected during study follow-up. Record specimen test results on this form as they become available. Fax this form to SCHARP DataFax once results for all collected specimens are recorded on this form.

If a test result(s) recorded on this form indicates that the participant has a new laboratory-confirmed infection or diagnosis, this infection/diagnosis must be recorded as an adverse experience on the Adverse Experience Log form.

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. See the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.
- **Initial Specimen Collection Date:** Record the date that the first specimen(s) was *collected* (NOT the date results were reported or recorded on the form) for this visit. A complete date is required.
- **Alternate Collection Date:** This date is to be completed ONLY if the specimen was collected on a different day than the rest of the specimens. A specimen collected for the same visit but on a different day should be recorded on the same form. A complete date is required.
- **Not done/Not collected:** For every test, mark *either* the “Not done/Not collected” box *or* enter a test result.
- **Results Reporting**
 - If a specimen was collected but results are not available because the specimen was lost or damaged, line through the results and write an explanation in the Comments section.
- **Item 1:** If items 1a, 1b, or 1c are positive, conduct Western Blot testing and record the associated test results on the HIV Test Results form and hold study product(s) until the participant’s HIV status is confirmed.
- **Items 1a and 1b:** Record the assigned two-digit rapid test kit code. As of March, 2008, the rapid test kit codes are as follows. *Note: More test kit codes may be added to the list below as the study proceeds.*

Rapid Test	Kit Code
Abbott Determine	01
OraSure OraQuick	02
Uni-Gold Recombigen	03

- **Item 2:** If the syphilis screening test is reactive, items 2a1 and 2b must be completed.
- **Item 2a1:** Remember to use leading zeros when recording a syphilis titer level. For example, a titer level of 1:20 would be recorded on the form as “1:0020.”
- **Items 2b–3c:** If a result is positive at any time during the study, provide treatment according to WHO guidelines. If a result is positive during study follow-up, report the relevant infection(s) as adverse experience(s) on the Adverse Experience Log form and hold study product(s). Complete an MTN 001 Study Product Hold/Resume Slip and mark “hold.” Complete items 1–3 of the Product Hold/Discontinuation form and fax it to SCHARP DataFax.

SAMPLE. Do NOT FAX
TO DATAFAX

Visit Code

□□□□.□□

1

MTN 001 (146)

PLR-1 (143)

Page 1 of 1

Participant ID

□□□□-□□□□□□-□
Site Number Participant Number Chk

Initial Specimen Collection Date

□□ □□□□ □□
dd MMM yy

Pelvic Laboratory Results

Alternate Collection Date
Not done/ Not collected dd MMM yy
□ □□□ □□□□ □□□□

1. VAGINAL WET PREP STUDIES

Not done

□

1a. Homogeneous vaginal discharge *negative* *positive*
□ □

□

1b. pH □□ → **If > 4.5 mark as positive.** → □

□

1c. Whiff test □ □

□

1d. Clue cells > 20% □ □

□

1e. *Trichomonas vaginalis* □ □

□

1f. Buds and/or hyphae (yeast) □ □

Wet Prep:

Staff Initials/Date

Not done/ Not collected

□

2. **HSV Culture** *negative* *positive*
□ □

HSV Culture:

Staff Initials/Date

Alternate Collection Date
Not done/ Not collected dd MMM yy
□ □□□ □□□□ □□□□

3. PAP SMEAR

- negative for intraepithelial lesion or cancer (malignancy)
- ASC-US
- ASC-H
- SIL-low grade (LSIL)
- SIL-high grade (HSIL)
- AGC
- AGC-favor neoplastic
- cancer

Pap Smear:

Staff Initials/Date

Comments: _____

□□□□ [x] 21-APR-08

01
Language

Pelvic Laboratory Results (PLR-1)

This form is used to document results of specimens collected during the Screening, Enrollment, and follow-up pelvic exams. Record test results on this form as they become available. Fax this form to SCHARP DataFax once results for all collected specimens are recorded on this form.

If a test result(s) recorded on this form indicates that the participant has a laboratory-confirmed infection or diagnosis, this infection/diagnosis must be recorded as either a pre-existing condition on the Pre-existing Conditions form (for Enrollment test result(s) only), or an adverse experience on the Adverse Experience (AE) Log (for follow-up visit test result(s) only). Per protocol, otherwise eligible participants diagnosed at screening or enrollment with a UTI/STI/RTI requiring treatment (per WHO guidelines) are not eligible to enroll in the study until treatment is complete and symptoms have resolved.

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. Refer to the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.
- **Initial Specimen Collection Date:** Record the date that the first specimen(s) was *collected* (NOT the date results were reported or recorded on the form) for this visit. A complete date is required.
- **Alternate Collection Date:** This date is to be completed ONLY if the specimen was collected on a different day than the rest of the specimens. A specimen collected for the same visit but on a different day should be recorded on the same form. A complete date is required.
- **Results Reporting**
 - If a specimen was collected but results are not available because the specimen was lost or damaged, line through the results and write an explanation on the comments line.
- **Item 1:** A vaginal wet prep is required at the Screening, Enrollment, 6-Week, 13-Week, and 20-Week Visits, and when clinically indicated. If a vaginal wet prep was not performed, mark the “Not done/Not collected” box. If a vaginal wet prep was performed but not all assays were completed, mark the “Not done” box for each uncompleted wet prep assay. If any and/or all assays were required but not completed, record the reason in the Comments section.
- **Item 1a:** Mark the “positive” box if homogeneous vaginal discharge was observed. If homogeneous discharge was observed and is considered to be abnormal, mark “abnormal vaginal discharge” in item 1a of the Screening and Enrollment Pelvic Exam form, or the Follow-up Pelvic Exam form completed for this pelvic exam.
- **Item 3:** If done, record the Pap Smear result. Mark only one box. *Note: A Pap Smear result is required at the Screening Visit only, and only for those participants who do not have documentation of a normal Pap test result in the 12 calendar months prior to Screening. Per protocol, only participants with a negative Pap Smear result will be eligible to enroll in the study. Refer to the SSP Manual for further information.*
 - **negative for intraepithelial lesion or cancer (malignancy):** Includes all normal findings and any findings of infection (trichomonas, candida, etc.), reactive changes/inflammation, glandular changes due to hysterectomy, or atrophic changes.
 - **ASC-US:** Mark this box when abnormal/atypical squamous cells of undetermined significance are reported.
 - **ASC-H:** Mark this box when abnormal/atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion (HSIL) are reported.
 - **SIL-low grade (LSIL):** Mark this box when low-grade squamous interepithelial lesions are reported. This category includes presence of human papillomavirus (HPV) infection, mild dysplasia, and cervical interepithelial neoplasia (CIN 1).
 - **SIL-high grade (HSIL):** Mark this box when high-grade squamous interepithelial lesions are reported. This category includes the presence of moderate to severe dysplasia, carcinoma in situ (CIS), CIN 2, and CIN 3, or changes suspicious for invasive cancer.
 - **AGC:** Mark this box when atypical/abnormal glandular cells are reported. This category includes endocervical (from cervical canal) atypical cells; endometrial atypical cells; glandular atypical cells.
 - **AGC-favor neoplastic:** Mark this box when atypical/abnormal glandular cells that favor cell growth (neoplastic changes) are reported. This category includes endocervical cells and glandular cells.
 - **cancer:** Mark this box when cancer or adenocarcinoma is reported. This includes endocervical, endometrial, extrauterine, and other (not specified) cancers/adenocarcinomas.

SAMPLE. Do NOT FAX
TO DATAFAX

Visit Code

MTN 001 (146)

FPE-1 (145)

Participant ID

- -
Site Number Participant Number Chk

Follow-up Pelvic Exam

Exam Date

dd MMM yy

1. Naked eye, speculum, and bimanual exam assessments: *not done*

If not done, specify reason in Comments. End of form.

no abnormal findings

abnormal findings

If no abnormal findings, go to item 3.

1a. Abnormal findings: *Mark all that apply.*

- enlarged/tender inguinal lymph nodes
- abnormal vaginal discharge
- abnormal cervical discharge
- blood-tinged discharge
- blood in vagina—no identified source
- blood from cervical os
- bleeding from site of epithelial disruption
- erythema

- ulceration
- laceration
- abrasion
- peeling
- petechia
- ecchymosis
- vesicles
- edema
- abnormal cysts

- grossly white finding
- mass
- warts—on and/or interior to labia minora
- warts—exterior to labia minora
- adnexal tenderness
- cervical motion tenderness
- uterine tenderness
- other abnormal findings, specify: _____

Complete or update Adverse Experience Log when applicable.

2. Do any pelvic exam findings from this visit warrant a product hold? *yes* *no*

If yes, complete Product Hold/Discontinuation form.

3. Cervical Ectopy: Percentage of cervical surface area.

0%	1-25%	26-50%	51-75%	> 75%
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Comments: _____

Follow-up Pelvic Exam (FPE-1)

This form, along with the non-DataFax Pelvic Exam Diagrams, is used to document the pelvic exams conducted during study follow-up.

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. See the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.
- **Item 1:** Document those abnormal findings observed during naked eye, speculum, and bimanual examination. If a pelvic exam was required but not done, mark the “not done” box and record the reason the required pelvic exam was not done in the Comments section at the bottom of the page. If no abnormal findings are observed, mark the “no abnormal findings” box, leave item 2 blank and go to item 3. If one or more abnormal findings are observed, mark the “abnormal findings” box and continue to item 1a.
- **Item 1a:** Mark the box to the left of **each** abnormal finding observed via naked eye, speculum, and bimanual examination. If an observed abnormal finding is not listed, mark the “other abnormal findings, specify” box and describe the abnormal finding in the space provided.

SAMPLE *Do NOT FAX*
TO DATAFAX



Visit Code

MTN 001 (146)

SL-1 (151)

Participant ID

- -
Site Number Participant Number Chk

Safety Laboratory Results

Initial Specimen Collection Date

dd MMM yy

Alternate Collection Date
Not done/ Not collected dd MMM yy

1. URINE TESTS

Not done		<i>negative or trace</i>	1+	2+	3+	4+	Severity Grade <i>If applicable</i>	AE Log Page #	Not reportable as an AE
<input type="checkbox"/>	1a. Protein	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/>	OR <input type="checkbox"/>
<input type="checkbox"/>	1b. Leukocyte esterase (LE)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	} If positive for LE or nitrites, perform culture if standard of care. } Complete Adverse Experience Log when applicable.		
<input type="checkbox"/>	1c. Nitrites	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			
<input type="checkbox"/>	1d. Culture.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			

Alternate Collection Date
Not done/ Not collected dd MMM yy

2. HEMOGRAM

Not reported			Severity Grade <i>If applicable</i>	AE Log Page #	Not reportable as an AE
<input type="checkbox"/>	2a. WBC	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> $\times 10^3/mm^3$	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/>	OR <input type="checkbox"/>
<input type="checkbox"/>	2b. Hemoglobin	<input type="text"/> <input type="text"/> <input type="text"/> g/dL	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/>	OR <input type="checkbox"/>
<input type="checkbox"/>	2c. Hematocrit	<input type="text"/> <input type="text"/> <input type="text"/> %			
<input type="checkbox"/>	2d. Platelets	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> $\times 10^3/mm^3$	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/>	OR <input type="checkbox"/>

Safety Laboratory Results (SL-1)

This form is used to document local safety laboratory results of specimens collected during screening, enrollment, and study follow-up. Record specimen test results on this form as they become available from the local lab. Fax this form to SCHARP DataFax once results for **all** collected specimens are recorded on the form.

If a test result(s) recorded on this form indicates that the participant has a laboratory-confirmed infection or diagnosis, this infection/diagnosis must be recorded as either a pre-existing condition on the Pre-existing Conditions form (for Enrollment Visit test result(s) only), or an adverse experience on an Adverse Experience (AE) Log (for follow-up visit test result(s) only).

Item-specific Instructions:

- **Initial Specimen Collection Date:** Record the date that the first specimen(s) was *collected* (NOT the date results were reported or recorded on the form) for this visit. A complete date is required.
- **Alternate Collection Date:** This date is to be completed **ONLY** if the specimen was collected on a different day than the rest of the specimens. A specimen collected for the same visit but on a different day should be recorded on the same form only when obtained within the same visit window. A complete date is required.
- **Not done/Not collected:** For every test, mark *either* the “Not done/Not collected” box *or* enter a test result.
- **Results Reporting**
 - If a specimen was collected but results are not available because the specimen was lost or damaged, line through the results and write an explanation in the Comments section on page 2.
 - If the site lab does not produce test results in the units used on this form, the results must be converted before the laboratory CRF is faxed to SCHARP. Refer to Study-Specific Procedures (SSP) Manual for conversion instructions.
 - It may be necessary to round the result reported by the lab up or down to the level of precision allowed on the CRF. For example, a lab-reported hemoglobin value of 11.06 g/dL would be recorded as 11.1 g/dL.
 - If the site lab does not produce test results in the units used on this form, *first* perform the conversion, *then* round the converted result if necessary.
 - If the result reported by the lab has less digits than on the form, fill in “0” for each missing digit. For example a hematocrit value of “42%” would be recorded as “42.0%.”
- **Severity Grade:**
 - If any abnormal laboratory values meet the criteria for severity grade 1 or greater, record the grade in the appropriate box next to the results. Assign severity grades according to the *Female Genital Grading Table for Use in Microbicide Studies* and the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*.
 - Always compare the severity grade range to the value that was recorded on the CRF (not the lab-reported value).
 - When working with calculated severity grade ranges (e.g., 1.1–1.5 times the site lab upper limit of normal), the calculated range may have more significant digits than the lab result.
 - Treat all missing digits in the lab value as zeros.
 - If the lab value falls between two calculated severity grade ranges, assign it the higher grade.
 - There may be situations in which a lab value falls within a site’s lab normal ranges and also within a gradable range per the *Female Genital Grading Table for Use in Microbicide Studies* or the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*. Per the protocol-specific AE reporting requirements, report this as an AE, as appropriate, and grade it according to the appropriate *DAIDS Table*.
- **AE Log Page #:** If the lab value is reportable as an AE, record the page number of the AE Log which is most closely associated with the abnormal lab value.
- **Not Reportable as an AE:** Mark if the lab value is gradable per the *Female Genital Grading Table for Use in Microbicide Studies* or the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, but is not reportable as an AE. This includes Pre-existing Conditions and abnormal lab values that do not meet protocol-specific AE reporting requirements.

SAMPLE *DO NOT FAX*
TO DATAFAX

MTN 001 (146)



SL-2 (152)

Visit Code

Participant ID

- -
Site Number Participant Number Chk

Safety Laboratory Results

Not done/ Not collected **Alternate Collection Date**
dd MMM yy

3. CHEMISTRIES

3a. AST (SGOT) *U/L* OR

3b. ALT (SGPT) OR

3c. Creatinine *mg/dL* OR

3c1. Calculated creatinine clearance *mL/min*

Not done/ Not collected **Alternate Collection Date**
dd MMM yy

3d. Phosphorus (Phosphate) *mg/dL* OR

Alternate Collection Date
dd MMM yy

4. Plasma *not required* *stored* *not stored* *Reason:* _____

Comments: _____

Safety Laboratory Results (SL-2)

Item-specific Instructions:

- **Alternate Collection Date:** This date is to be completed ONLY if the specimen was collected on a different day than the rest of the specimens. A specimen collected for the same visit but on a different day should be recorded on the same form only when obtained within the same visit window. A complete date is required.
- **Not done/Not collected:** For every test, mark *either* the “Not done/Not collected” box *or* enter a test result.
- **Results Reporting**
 - If a specimen was collected but results are not available because the specimen was lost or damaged, line through the results and write an explanation in the Comments section.
 - If the site lab does not produce test results in the units used on this form, the results must be converted before the laboratory CRF is faxed to SCHARP. Refer to Study-Specific Procedures (SSP) Manual for conversion instructions.
 - It may be necessary to round the result reported by the lab up or down to the level of precision allowed on the CRF. For example, a lab-reported hemoglobin value of 11.06 g/dL would be recorded as 11.1 g/dL.
 - If the site lab does not produce test results in the units used on this form, *first* perform the conversion, *then* round the converted result if necessary.
 - If the result reported by the lab has fewer digits than on the form, fill in “0” for each missing digit. For example a hematocrit value of “42%” would be recorded as “42.0%.”
- **Severity Grade:**
 - If any abnormal laboratory values meet the criteria for severity grade 1 or greater, record the grade in the appropriate box next to the results. Assign severity grades according to the *Female Genital Grading Table for Use in Microbicide Studies* and the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*.
 - Always compare the severity grade range to the value that was recorded on the CRF (not the lab-reported value).
 - When working with calculated severity grade ranges (e.g., 1.1–1.5 times the site lab upper limit of normal), the calculated range may have more significant digits than the lab result.
 - Treat all missing digits in the lab value as zeros.
 - If the lab value falls between two calculated severity grade ranges, assign it the higher grade.
 - There may be situations in which a lab value falls within a site’s lab normal ranges and also within a gradable range per the *Female Genital Grading Table for Use in Microbicide Studies* or the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*. Per the protocol-specific AE reporting requirements, report this as an AE, as appropriate, and grade it according to the appropriate *DAIDS Table*.
- **AE Log Page #:** If the lab value is reportable as an AE, record the page number of the AE Log which is most closely associated with the abnormal lab value.
- **Not Reportable as an AE:** Mark if the lab value is gradable per the *Female Genital Grading Table for Use in Microbicide Studies* or the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, but is not reportable as an AE. This includes Pre-existing Conditions and abnormal lab values that do not meet protocol-specific AE reporting requirements.
- **Item 4:** Plasma archive is required at the Enrollment, 6-Week, 13-Week, 20-Week, and 21-Week Visits. If a plasma specimen was required but not collected, mark the “not stored” box and record the reason.

SAMPLE. Do NOT FAX
TO DATAFAX

MTN 001 (146)

SPA-1 (180)



Visit Code

1

Participant ID

- -
Site Number Participant Number Chk

Study Product Adherence and Behavior Assessment

Visit Date

dd MMM yy

Instructions: Complete items 1–3c before the interview. Also, prior to the interview, circle the correct study product (tenofovir gel, tenofovir tablets, tenofovir gel and tablets together) in the statement above item 4 to read aloud.

1. Participant's current study regimen period: vaginal tenofovir oral tenofovir dual use (vaginal and oral tenofovir)
- If oral tenofovir, go to item 3.**

2. Date and time of last three applications of vaginal tenofovir gel prior to this visit starting with the most recent:

Not done/ Not collected

	dd	MMM	yy	hr	min	
<input type="checkbox"/> 2a.	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	} If participant is in the vaginal study period, go to statement above item 4.
<input type="checkbox"/> 2b.	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	
<input type="checkbox"/> 2c.	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	

3. Date and time of last three doses of oral tenofovir tablets prior to this visit starting with the most recent:

Not done/ Not collected

	dd	MMM	yy	hr	min
<input type="checkbox"/> 3a.	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="checkbox"/> 3b.	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="checkbox"/> 3c.	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

I would like to ask you some questions about the way you have been using the study product during this study period. By study product, I mean [tenofovir gel tenofovir tablets tenofovir gel and tablets together]. We need to understand what people really are doing and why, so please report your experience as it happened. Do not worry if you did not use your study product every day. It is common for people to miss some days, and while some people use their study product every day, others may not be able to do so. We would like to know what is really happening for you.

4. In the **past 3 weeks**, how often did you use the study product?
Showcard #4.

never less than once a week 1–3 times a week 4–6 times a week once a day

Study Product Adherence and Behavior Assessment (SPA-1)

This form is used to collect information about the participant's study product use (both vaginal and oral) and sexual behavior during her study follow-up. This is an interviewer-administered form (with the exception of items 1–3c), and is administered at the Week 3, 6, 10, 13, 17, and 20 Visits.

***Note:** Responses to all of the items on this form are based on participant recall at the time the form is being administered. Any clarifications and/or updates to this form should be made only during the interview in which this form is completed, unless requested otherwise by SCHARP. Once the interview is finished, do not make any further updates or changes to the responses recorded on this form.*

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. See the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.
- **Item 4:** Read each response category aloud, using the appropriate showcard to help the participant respond.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don't know” or “refused,” and initial and date the note in the white space next to the item.

SAMPLE. DO NOT FAX
TO DATAFAX



Visit Code .

1

MTN 001 (146)

SPA-2 (181)

Participant ID

- -
Site Number Participant Number Chk

Study Product Adherence and Behavior Assessment

5. In the **past 3 weeks**, what was the longest number of days in a row that you missed using the study product? This does not include doses that you missed, but were able to make up prior to your next scheduled dose.

of days

→ **If 00, go to item 8 on page 3.**

6. For the days you did not use the study product, what were the reasons?
Mark all that apply.

- 6a. away from home
- 6b. feeling sick because of using study product
- 6c. had other health problems not related to study product
- 6d. instructed by study staff to stop using study product
- 6e. tired of using study product daily
- 6f. busy/interfered with daily activities
- 6g. forgot
- 6h. gave study products(s) away
- 6i. sold study product
- 6j. someone took study product
- 6k. menses
- 6l. lack of privacy
- 6m. participant thought it interfered with sex
- 6n. partner thought it interfered with sex
- 6o. partner did not approve
- 6p. lost study product
- 6q. ran out of study product
- 6r. other, specify:

Local Language: _____

English: _____

Study Product Adherence and Behavior Assessment (SPA-2)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on all other pages of this form for a given participant and visit.
- **Item 6: Do not** read any of the response categories aloud. Instead, read the question and mark the box(es) that correspond to each reason reported by the participant. If the participant reports a reason that is not listed, mark the “other, specify” box and record the participant’s verbatim (word-for-word) response. If the response is given in a language other than English, provide the English translation in the space provided.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don’t know” or “refused,” and initial and date the note in the white space next to the item.

SAMPLE. Do NOT FAX TO DATAFAX

MTN 001 (146)



SPA-3 (182)

Visit Code [][] . []

1

Participant ID

[][][] - [][][][][] - []
Site Number Participant Number Chk

Study Product Adherence and Behavior Assessment

7. In the past 3 weeks, how many days did you not use the study product? This does not include doses that you missed but were able to make up prior to your next scheduled dose.

of days [][] → If 00, go to item 8.

7a. In the past 7 days, how many days did you not use the study product? This does not include doses that you missed but were able to make up prior to your next scheduled dose.

of days []

8. In the past 3 weeks, did you ever insert study gel into your anus?.....

yes [] no [] → If no, go to statement above item 9.

8a. In the past 3 weeks, how many times did you insert study gel into your anus?

of times [][]

I am now going to ask you some questions about your sexual behavior. Some of these questions are personal and sensitive, but understanding sexual behavior is important for HIV prevention. Your honest answers will be very helpful to us. There are no right or wrong answers to these questions. Remember, we do not have your name on these papers, and all of your answers will be kept confidential.

There are many different ways people have sex. Some of the questions are about vaginal sex, and some are about anal sex. Vaginal sex means when a man puts his penis inside your vagina. Anal sex means when a man puts his penis inside your anus.

9. In the past 3 weeks, have you had a new sex partner? By sex partner, I mean someone with whom you have had vaginal or anal sex.

yes [] no []

Now I am going to ask you some questions about vaginal sex only.

10. In the past 3 weeks, did you have vaginal sex?

yes [] no [] → If no, go to statement above item 14 on page 6.

10a. In the past 3 weeks, how often did you have vaginal sex? Showcard #2.

less than once a week [] 1-3 times a week [] 4-6 times a week [] once a day [] more than once a day []

Study Product Adherence and Behavior Assessment (SPA-3)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on all other pages of this form for a given participant and visit.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don’t know” or “refused,” and initial and date the note in the white space next to the item.

SAMPLE. Do NOT FAX TO DATAFAX



Visit Code [][] . []

1

MTN 001 (146)

SPA-4 (183)

Participant ID

[][][] - [][][][][] - []
Site Number Participant Number Chk

Study Product Adherence and Behavior Assessment

No data recorded on this page

I know that you have been counseled to use male condoms for each act of vaginal sex, but I also know that it is sometimes difficult to use condoms all the time. We are interested in your actual experiences using male condoms with vaginal sex, so your honest and accurate answers are very important to us.

10b. In the **past 3 weeks**, how often did your partner(s) use a male condom during vaginal sex?
Showcard #3.

never [] rarely [] sometimes [] most of the time [] always []

11. In the **past 7 days**, how many times did you have vaginal sex? # of times [][] **If 00, go to item 12.**

11a. In the **past 7 days**, how many times did your partner(s) use a male condom during vaginal sex? # of times [][]

12. The **last time** you had vaginal sex:

12a. did your partner use a male condom? yes [] no [] **If participant is in the oral tenofovir period, go to item 12f on page 5.**

12b. did you use the tenofovir gel that same day? yes [] no []

If no, and participant is in the vaginal tenofovir period, go to statement above item 14 on page 6.
If no and participant is in the dual use period, go to item 12f on page 5.

12c. did you use the tenofovir gel **before** sex? yes [] no [] **If no, go to item 12d.**

12c1. How long before? # [][][] minutes [] hours []
Mark only one measurement of time (e.g., minutes or hours).

12d. did you use the tenofovir gel **after** sex? yes [] no [] **If no, go to item 12e on page 5.**

12d1. How long after? # [][][] minutes [] hours []
Mark only one measurement of time (e.g., minutes or hours).

Study Product Adherence and Behavior Assessment (SPA-4)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on all other pages of this form for a given participant and visit.
- **No data recorded on this page:** Mark this box if no data is recorded on this page other than the Participant ID and the Staff Initials/Date.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don’t know” or “refused,” and initial and date the note in the white space next to the item.

SAMPLE. Do NOT FAX
TO DATAFAX

MTN 001 (146)



SPA-5 (184)

Visit Code

Participant ID

- -

Site Number Participant Number Chk

Study Product Adherence and Behavior Assessment

No data recorded on this page

12e. did you use the tenofovir gel at a different time than usual because you had sex?

yes no

If participant is in the vaginal tenofovir period, go to statement above item 14 on page 6.

12f. did you use the tenofovir tablets that same day?

yes no

If no, go to statement above item 14 on page 6.

12g. did you use the tenofovir tablets **before** sex?

yes no

If no, go to item 12h.

12g1. How long before?
Mark only one measurement of time (e.g., minutes or hours).

#

minutes

hours

12h. did you use the tenofovir tablets **after** sex?

yes no

If no, go to item 12i.

12h1. How long after?
Mark only one measurement of time (e.g., minutes or hours).

#

minutes

hours

12i. did you use the tenofovir tablets at a different time than usual because you had sex?

yes no

13. Did you have vaginal sex today or yesterday?

yes no

If no, go to statement above item 14 on page 6.

13a. Thinking about when you had vaginal sex today and yesterday, did you have any vaginal sex **without** using a male condom?

yes no

If yes, go to statement above item 14 on page 6.

Study Product Adherence and Behavior Assessment (SPA-5)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on all other pages of this form for a given participant and visit.
- **No data recorded on this page:** Mark this box if no data is recorded on this page other than the Participant ID and the Staff Initials/Date.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don’t know” or “refused,” and initial and date the note in the white space next to the item.

SAMPLE: DO NOT FAX TO DATAFAX



Visit Code [][] . []

1

MTN 001 (146)

SPA-6 (185)

Participant ID

[][][] - [][][][] - []
Site Number Participant Number Chk

Study Product Adherence and Behavior Assessment

13b. When you had vaginal sex today and yesterday, did you and your partner experience any of the following:

- 13b1. the male condom burst, broke or had a tear during sex or during removal of the penis from your vagina? yes no [] []
13b2. the male condom slipped off completely during sex or during removal of the penis from your vagina? yes no [] []
13b3. semen or fluid spilled from the male condom into your vagina? yes no [] []

13c. When you had vaginal sex today and yesterday, did your partner ever:

- 13c1. insert his penis inside your vagina before putting a male condom on? yes no [] []
13c2. remove the male condom and continue having vaginal sex? yes no [] []

I am now going to ask you some questions about another way that people have sex. This way is anal sex, which is when a man puts his penis inside his partner's anus. I am asking you these questions because understanding sexual behavior is important for HIV prevention. Remember, all of your answers will be kept confidential.

14. In the past 3 weeks, did you have anal sex? yes no [] [] If no, go to instructions above item 18 on page 10.

14a. In the past 3 weeks, how often did you have anal sex? Showcard #2.

less than once a week 1-3 times a week 4-6 times a week once a day more than once a day [] [] [] [] []

Study Product Adherence and Behavior Assessment (SPA-6)

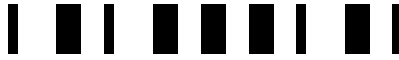
Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on all other pages of this form for a given participant and visit.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don’t know” or “refused,” and initial and date the note in the white space next to the item.

SAMPLE. Do NOT FAX
TO DATAFAX

MTN 001 (146)



SPA-7 (186)

Visit Code

1

Participant ID

- -
Site Number Participant Number Chk

Study Product Adherence and Behavior Assessment

No data recorded on this page

I know that you have been counseled to use male condoms for each act of anal sex, but I also know that it is sometimes difficult to use condoms all the time. We are interested in your actual experiences using male condoms with anal sex, so your honest and accurate answers are very important to us.

14b. In the **past 3 weeks**, how often did your partner(s) use a male condom during anal sex?

Showcard #3.

never rarely sometimes most of the time always

15. In the **past 7 days**, how many times did you have anal sex?.....

of times **→ If 00, go to item 16.**

15a. In the **past 7 days**, how many times did your partner(s) use a male condom during anal sex?

of times

16. The **last time** you had anal sex:

16a. did your partner use a male condom?

yes no **→ If participant is in the oral tenofovir period, go to item 16f on page 8.**

16b. did you insert the tenofovir gel into your vagina that same day?

yes no

If no, and participant is in the vaginal tenofovir period, go to statement above item 18 on page 10.

If no and participant is in the dual use period, go to item 16f on page 8.

16c. did you use the tenofovir gel **before** sex?

yes no **→ If no, go to item 16d.**

16c1. How long before?
Mark only one measurement of time (e.g., minutes or hours).

minutes
 hours

16d. did you use the tenofovir gel **after** sex?

yes no **→ If no, go to item 16e on page 8.**

16d1. How long after?
Mark only one measurement of time (e.g., minutes or hours).

minutes
 hours

Study Product Adherence and Behavior Assessment (SPA-7)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on all other pages of this form for a given participant and visit.
- **No data recorded on this page:** Mark this box if no data is recorded on this page other than the Participant ID and the Staff Initials/Date.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don’t know” or “refused,” and initial and date the note in the white space next to the item.

SAMPLE. Do NOT FAX TO DATAFAX

MTN 001 (146)



SPA-8 (187)

Visit Code [][] . []

1

Participant ID

Site Number [][] - Participant Number [][][][] - Chk []

Study Product Adherence and Behavior Assessment

No data recorded on this page

16e. did you use the tenofovir gel at a different time than usual because you had sex?

yes [] no []

If participant is in the vaginal tenofovir period, go to statement above item 18 on page 10.

16f. did you use the tenofovir tablets that same day?

yes [] no []

If no, go to statement above item 18 on page 10.

16g. did you use the tenofovir tablets before sex?

yes [] no []

If no, go to item 16h.

16g1. How long before? Mark only one measurement of time (e.g., minutes or hours).

[][] minutes [] hours []

16h. did you use the tenofovir tablets after sex?

yes [] no []

If no, go to item 16i.

16h1. How long after? Mark only one measurement of time (e.g., minutes or hours).

[][] minutes [] hours []

16i. did you use the tenofovir tablets at a different time than usual because you had sex?

yes [] no []

17. Did you have anal sex today or yesterday?

yes [] no []

If no, go to statement above item 18 on page 10.

17a. Thinking about when you had anal sex today and yesterday, did you have any anal sex without using a male condom?

yes [] no []

If yes, go to statement above item 18 on page 10.

Study Product Adherence and Behavior Assessment (SPA-8)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on all other pages of this form for a given participant and visit.
- **No data recorded on this page:** Mark this box if no data is recorded on this page other than the Participant ID and the Staff Initials/Date.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don’t know” or “refused,” and initial and date the note in the white space next to the item.

SAMPLE. Do NOT FAX
TO DATAFAX

MTN 001 (146)



SPA-9 (188)

Visit Code .

Participant ID

- -

Site Number Participant Number Chk

Study Product Adherence and Behavior Assessment

No data recorded on this page

17b. When you had anal sex today and yesterday, did you and your partner experience any of the following:

17b1. the male condom burst, broke or had a tear during sex or during removal of the penis from your anus? *yes* *no*

17b2. the male condom slipped off completely during sex or during removal of the penis from your anus? *yes* *no*

17b3. semen or fluid spilled from the male condom into your anus? *yes* *no*

17c. When you had anal sex today and yesterday, did your partner ever:

17c1. insert his penis inside your anus before putting a male condom on? *yes* *no*

17c2. remove the male condom and continue having anal sex? *yes* *no*

Study Product Adherence and Behavior Assessment (SPA-9)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on all other pages of this form for a given participant and visit.
- **No data recorded on this page:** Mark this box if no data is recorded on this page other than the Participant ID and the Staff Initials/Date.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don’t know” or “refused,” and initial and date the note in the white space next to the item.

Study Product Adherence and Behavior Assessment (SPA-10)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on all other pages of this form for a given participant and visit.
- **Item 18:** Read each item 18a–18g aloud and mark the participant’s response. For each item to which she replies “yes,” ask how many times in the **past week** (the last 7 days) she has used that particular item. Record the response in the “# of times in **past week**” boxes. If “yes” is marked for item 18g, be sure to record the participant’s verbatim (word-for-word) response. If the response is given in a language other than English, provide the English translation in the space provided.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don’t know” or “refused,” and initial and date the note in the white space next to the item.

SAMPLE. Do NOT FAX TO DATAFAX



Visit Code

□□□.□□

1

MTN 001 (146)

PSA-1 (201)

Participant ID

□□□-□□□□□□-□
Site Number Participant Number Chk

Product Sharing Assessment

Visit Date

□□ □□□□ □□
dd MMM yy

Instructions: Before the interview, circle the correct study product (tenofovir gel, tenofovir tablets, tenofovir gel and tablets together) in the statement above item 1 to read aloud. Complete items 1-3h at the end-of-study period visits (Weeks 6, 13, and 20) only.

I am now going to ask you some questions about sharing of study product during this study period. By study product, I mean [tenofovir gel tenofovir tablets tenofovir gel and tablets together]. I know that you are counseled to not share your study product with other people, but I also know that this is not always possible.

1. Since you started using the study product, has anyone asked you for your study product?..... yes no
□ □ -> If no, go to item 2 on page 2.

Who asked you for your study product:

Table with 6 columns: Question, yes, no, n/a, # of tablets shared, # of applicators shared. Rows include husband or primary male sex partner, other sex partner(s), children, other relative(s), friend(s) who do not have sex with, neighbor(s), other study participants, and other, specify.

Local Language: _____
English: _____

Product Sharing Assessment (PSA-1)

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. See the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.
- **Items 1a–1h:** Read each item aloud and mark the participant’s response. For each item to which she replies “yes,” ask how many study tablets and applicators were shared. Record the responses in the “#of tablets shared” and “# of applicators shared” boxes. For each “yes,” response, both the “# of tablets shared” and the “# of applicators shared” boxes should be completed. Use leading zeros when needed so that all boxes are filled. If “yes” is marked for “other, specify,” record the participant’s verbatim (word-for-word) response. If the response is given in a language other than English, provide the English translation in the space provided.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don’t know” or “refused,” and initial and date the note in the white space next to the item.

SAMPLE: Do NOT FAX TO DATAFAX



Visit Code

□□□.□□

1

MTN 001 (146)

PSA-2 (202)

Participant ID

□□□-□□□□□□-□
Site Number Participant Number Chk

Product Sharing Assessment

2. Since you started using the study product, have you ever sold, traded, or given away your study product? yes no

If no, go to item 3 on page 3.

Who did you sell, trade, or give your study product to:

	yes	no	n/a	# of tablets sold/traded/given	# of applicators sold/traded/given
2a. husband or primary male sex partner?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	□□	□□
2b. other sex partner(s)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	□□	□□
2c. your children?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	□□	□□
2d. other relative(s)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	□□	□□
2e. friend(s) who you do not have sex with?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	□□	□□
2f. neighbor(s)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	□□	□□
2g. other study participants?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	□□	□□
2h. other, specify:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	□□	□□

Local Language: _____

English: _____

Product Sharing Assessment (PSA-2)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on all other pages of this form for a given participant and visit.
- **Items 2a–2h:** Read each item aloud and mark the participant’s response. For each item to which she replies “yes,” ask how many study tablets and applicators were sold/traded/given. Record the responses in the “#of tablets sold/traded/given” and “# of applicators sold/traded/given” boxes. For each “yes,” response, both the “# of tablets sold/traded/given” and the “# of applicators sold/traded/given” boxes should be completed. Use leading zeros when needed so that all boxes are filled. If “yes” is marked for “other, specify,” record the participant’s verbatim (word-for-word) response. If the response is given in a language other than English, provide the English translation in the space provided.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don’t know” or “refused,” and initial and date the note in the white space next to the item.

SAMPLE. Do NOT FAX
TO DATAFAX



Visit Code

MTN 001 (146)

PSA-3 (203)

Participant ID

- -
Site Number Participant Number Chk

Product Sharing Assessment

3. Since you started using the study product, has anyone taken your study product without your permission? *yes* *no* **→ If no, end of form.**

Who do you think took your study product:

	<i>yes</i>	<i>no</i>	<i>n/a</i>	<i># of tablets taken</i>	<i># of applicators taken</i>
3a. husband or primary male sex partner?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
3b. other sex partner(s)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
3c. your children?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
3d. other relative(s)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
3e. friend(s) who you do not have sex with?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
3f. neighbor(s)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
3g. other study participants?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
3h. other, specify:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>

Local Language: _____

English: _____

Product Sharing Assessment (PSA-3)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on all other pages of this form for a given participant and visit.
- **Items 3a–3h:** Read each item aloud and mark the participant’s response. For each item to which she replies “yes,” ask how many study tablets and applicators were taken. Record the responses in the “#of tablets taken” and “# of applicators taken” boxes. For each “yes,” response, both the “# of tablets taken” and the “# of applicators taken” boxes should be completed. Use leading zeros when needed so that all boxes are filled. If “yes” is marked for “other, specify,” record the participant’s verbatim (word-for-word) response. If the response is given in a language other than English, provide the English translation in the space provided.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don’t know” or “refused,” and initial and date the note in the white space next to the item.

SAMPLE. DO NOT FAX
TO DATAFAX

MTN 001 (146)



AA-1 (272)

Visit Code

1

Participant ID

- -
Site Number Participant Number Chk

Acceptability Assessment

Visit Date

dd MMM yy

Instructions: Complete item 1 before the interview.

1. Which study regimen period is the participant in?

- vaginal tenofovir —————> **If vaginal tenofovir, go to item 2.**
- oral tenofovir —————> **If oral tenofovir, go to item 3.**
- dual use (both vaginal and oral tenofovir) —————> **If dual use, go to item 4.**

2. One goal of this study is to understand how acceptable daily use of the vaginal tenofovir gel is to women and their partners. I would like to ask you about your experience using the tenofovir gel. Your honest answer will be very helpful to us. If daily use of tenofovir gel is found to protect people from HIV, how likely would you be to use it? **Showcard #1**

very likely
 likely
 unlikely
 very unlikely

} —————> **Go to item 5.**

3. One goal of this study is to understand how acceptable daily use of oral tenofovir tablets is to women and their partners. I would like to ask you about your experience using oral tenofovir. Your honest answer will be very helpful to us. If daily use of oral tenofovir is found to protect people from HIV, how likely would you be to use it? **Showcard #1**

very likely
 likely
 unlikely
 very unlikely

} —————> **Go to item 5.**

4. One goal of this study is to understand how acceptable daily use of vaginal tenofovir gel and oral tenofovir tablets is to women and their partners. I would like to ask you about your experience using vaginal and oral tenofovir. Your honest answer will be very helpful to us. If daily use of vaginal tenofovir gel and oral tenofovir is found to protect people from HIV, how likely would you be to use them? **Showcard #1**

very likely
 likely
 unlikely
 very unlikely

5. How worried are you that you will become HIV-positive in the next year? **Showcard #5**

very worried
 somewhat worried
 not very worried
 not at all worried

Acceptability Assessment (AA-1)

This form is used to collect study product acceptability information from study participants. This is an interviewer-administered form except for item 1, which should be completed by study staff before starting the interview. This form is administered at each 6-Week and 13-Week visit.

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. See the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.

SAMPLE. Do NOT FAX
TO DATAFAX

MTN 001 (146)

AA-2 (273) Visit Code

□□□.□□

1

Participant ID

□□□-□□□□□□-□
Site Number Participant Number Chk

Acceptability Assessment

6. Are you currently married?

yes no
□ □

If yes, go to item 8.

7. Do you currently have a primary male sex partner? By primary partner, I mean someone you have sex with on a regular basis, and who you consider to be your main partner.

yes no
□ □

If no, end of form.

8. Is he HIV-positive?

yes no don't know
□ □ □

If yes, go to item 10.

9. How worried are you that he will become HIV-positive in the next year?
Showcard # 5

very worried somewhat worried not very worried not at all worried
□ □ □ □

10. Did he accompany you here to the clinic during this study period?

yes no
□ □

11. Did he know that you were using the study product?

yes no don't know
□ □ □

If no or don't know, end of form.

12. What was his reaction to your use of the study product? *Mark all that apply.*

- 12a. he liked it
- 12b. he did not like it
- 12c. he thought it improved sex
- 12d. he thought it worsened sex
- 12e. he thought it interfered with sex
- 12f. he had no reaction
- 12g. don't know
- 12h. other, specify:

Local Language: _____

English: _____

Acceptability Assessment (AA-2)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on all other pages of this form for a given participant and visit.

SAMPLE. Do NOT FAX
TO DATAFAX



Visit Code

1

MTN 001 (146)

IV-1 (350)

Participant ID

--
Site Number Participant Number Chk

Interim Visit

Visit Date

dd MMM yy

1. What is the reason for this interim visit? *Mark all that apply.*

- 1a. in-person visit to report new symptoms → **Complete Adverse Experience Log.**
- 1b. phone call from participant to report new symptoms → **Complete Adverse Experience Log.**
- 1c. follow-up of an AE → **Update Adverse Experience Log if indicated.**
- 1d. participant needs study product
- 1e. participant is returning unused study product
- 1f. other, specify: _____

2. hCG for pregnancy: *not done* *negative* *positive* → **If positive, complete Pregnancy Report and History form and Product Hold/Discontinuation form.**

2a. Specify reason(s): ← _____

3. Besides this form, what other DataFax forms with the same visit code as this form were completed for this visit? *Mark "none" or all that apply.*

- 3a. none
- 3b. Follow-up Pelvic Exam
- 3c. Pelvic Laboratory Results
- 3d. STI Laboratory Results
- 3e. Adverse Experience Log (new)
- 3f. Product Hold/Discontinuation
- 3g. Safety Laboratory Results
- 3h. Follow-up Genital Symptoms
- 3i. other, specify: _____

→ 3e1. How many **new** AE Log pages were completed for this visit? # of pages

4. At this visit, how many **unused applicators** of tenofovir gel did the participant return? # of **unused applicators** returned

5. At this visit, how many **unused tablets** of oral tenofovir did the participant return? # of **unused tablets** returned

6. At this visit, how many **applicators** of tenofovir gel were dispensed to the participant? # of **applicators** dispensed

7. At this visit, how many **tablets** of oral tenofovir were dispensed to the participant? # of **tablets** dispensed

Comments: _____

Interim Visit (IV-1)

This form is used to document interim visits during follow-up. Refer to the Study-Specific Procedures (SSP) Manual for a definition and examples of interim visits that require an Interim Visit form to be completed. Note that all DataFax forms completed for an Interim Visit must have the same interim Visit Code as the Interim Visit form.

Item-specific Instructions:

- **Visit Code:** The following guidelines should be used for assigning the interim visit code:
 - Record the two-digit whole number visit code for the most recent scheduled regular visit.
 - Record the number that corresponds to the Interim Visit in the third box (the box to the right of the decimal point):
 - XX.1 = First Interim Visit after the most recent scheduled regular visit.
 - XX.2 = Second Interim Visit after the most recent scheduled regular visit.
- **Item 1:** Mark the box to the left of each reason(s) this Interim Visit was conducted. Mark all that apply.
- **Item 2:** A urine pregnancy test is required at each interim visit. Record the hCG urine pregnancy test result. If a required urine pregnancy test result is not available (specimen not collected and/or test not done), mark the “not done” box and complete item 2a.

*Note: A **Pregnancy Report and History** form must be completed for each pregnancy. Once a participant tests positive for hCG urine pregnancy and a **Pregnancy Report and History** form (PR-1) has been completed for this pregnancy, subsequent positive pregnancy test results should not be recorded on a new PR-1 (unless they represent a new pregnancy).*
- **Item 3:** For each DataFax form completed for this visit, mark the box to the left of the form name. Mark all boxes that apply. Note that marking a box indicates that a DataFax form with the same visit code as this form will be faxed to SCHARP DataFax.
 - **none:** Mark this box if the Interim Visit form is the **only** DataFax form completed for this visit.
 - **Adverse Experience Log (new):** Mark this box if a new (previously unreported) AE is reported or observed at this visit. If the box to the left of “Adverse Experience Log (new)” is marked, record in item 3e1 how many **new** AE Log pages were completed for this visit. For example, if two new AEs were reported, record “02.” Note that the Visit Code recorded in item 10 of these two AE Log pages should be the same as the Visit Code recorded on this form.
 - **other, specify:** Mark this box if a DataFax form(s) other than the ones listed was completed for this visit. Specify the form name(s) on the line provided.
- **Item 4:** Record the number of **unused** tenofovir gel applicators the participant returned at this visit only, as determined by site clinic staff.
- **Item 5:** Record the number of **unused** oral tenofovir tablets the participant returned at this visit only, as determined by site clinic staff.
- **Item 6:** Record the number of tenofovir gel applicators given to the participant at this visit.
- **Item 7:** Record the number of oral tenofovir tablets given to the participant at this visit.

SAMPLE. Do NOT FAX
TO DATAFAX



Visit Code

1

MTN 001 (146)

HTR-1 (351)

Participant ID

- -
Site Number Participant Number Chk

HIV Test Results

Sample 1

1. HIV Western Blot
Not done/ Not collected Specimen Collection Date
dd MMM yy
negative positive indeterminate
If negative, go to item 5, and contact MTN Network Lab.

Sample 2

2. HIV Western Blot
Not done/ Not collected Specimen Collection Date
dd MMM yy
negative positive indeterminate
If positive, go to item 5.
If negative or indeterminate, contact MTN Network Lab.

Sample 3

3. HIV Western Blot
Not done/ Not collected Specimen Collection Date
dd MMM yy
negative positive indeterminate

Sample 4

4. HIV Western Blot
Not done/ Not collected Specimen Collection Date
dd MMM yy
negative positive indeterminate

FINAL HIV STATUS

5. Final status: negative positive other, specify: _____
If positive, permanently discontinue all study products.

Comments: _____

HIV Test Results (HTR-1)

This form documents confirmatory HIV test results and final HIV status. This form is completed each time a participant has a positive HIV rapid test or HIV ELISA test result during follow-up.

*Record specimen test results on this form as they become available from the local lab. Fax this form to SCHARP DataFax once results for **all** required specimens are available and recorded and item 5 has been completed.*

Item-specific Instructions:

- **Visit Code:** The visit code recorded on this form should be the same visit code recorded on the STI Laboratory Results form documenting a positive HIV ELISA or rapid test result.
- **Specimen Collection Date:** Record the date the specimen was collected (NOT the date results were reported or recorded on the form). For Sample 1, the Specimen Collection Date should be the same date as the collection date of the positive HIV rapid or ELISA specimen.
- **Not done/Not collected:** Mark this box in the event that a specimen is collected, but a result is not available due to specimen loss or damage. Explain in the Comments section at the bottom of the form why the result is not available.
- **Item 5:** Once a participant's HIV status has been determined, record the final HIV status. If the final HIV status is not clearly negative or clearly positive, mark the "other, specify" box and specify reason(s) on the line provided. If the participant's final HIV status is determined to be positive (according to the protocol testing algorithm), report the HIV infection as an AE on an AE Log form.

SAMPLE. DO NOT FAX
TO DATAFAX



Visit Code

1

MTN 001 (146)

FAA-1 (372)

Participant ID

- -
Site Number Participant Number Chk

Final Acceptability Assessment

Visit Date

dd MMM yy

Instructions: Complete item 1 before the interview.

1. Which study regimen period is the participant in?

- vaginal tenofovir —————> **If vaginal tenofovir, go to item 2.**
- oral tenofovir —————> **If oral tenofovir, go to item 3.**
- dual use (both vaginal and oral tenofovir) —————> **If dual use, go to item 4.**

2. One goal of this study is to understand how acceptable daily use of the vaginal tenofovir gel is to women and their partners. I would like to ask you about your experience using the tenofovir gel. Your honest answer will be very helpful to us. If daily use of tenofovir gel is found to protect people from HIV, how likely would you be to use it? **Showcard #1**

very likely
 likely
 unlikely
 very unlikely

} —————> **Go to item 5.**

3. One goal of this study is to understand how acceptable daily use of oral tenofovir tablets is to women and their partners. I would like to ask you about your experience using oral tenofovir. Your honest answer will be very helpful to us. If daily use of oral tenofovir is found to protect people from HIV, how likely would you be to use it? **Showcard #1**

very likely
 likely
 unlikely
 very unlikely

} —————> **Go to item 5.**

4. One goal of this study is to understand how acceptable daily use of vaginal tenofovir gel and oral tenofovir tablets is to women and their partners. I would like to ask you about your experience using vaginal and oral tenofovir. Your honest answer will be very helpful to us. If daily use of vaginal tenofovir gel and oral tenofovir is found to protect people from HIV, how likely would you be to use them? **Showcard #1**

very likely
 likely
 unlikely
 very unlikely

5. How worried are you that you will become HIV-positive in the next year? **Showcard #5**

very worried
 somewhat worried
 not very worried
 not at all worried

Final Acceptability Assessment (FAA-1)

This form is used to collect study product acceptability information from study participants. This is an interviewer-administered form except for item 1, which should be completed by study staff before starting the interview. This form is administered at the 20-Week visit.

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. See the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.

SAMPLE. Do NOT FAX
TO DATAFAX

MTN 001 (146)



FAA-2 (373)

Visit Code .

Participant ID

- -
Site Number Participant Number Chk

Final Acceptability Assessment

6. Are you currently married?

yes no

➔ If yes, go to item 8.

7. Do you currently have a primary male sex partner? By primary partner, I mean someone you have sex with on a regular basis, and who you consider to be your main partner.

yes no

➔ If no, go to item 16 on page 3.

8. Is he HIV-positive?

yes no don't know

➔ If yes, go to item 10.

9. How worried are you that he will become HIV-positive in the next year? **Showcard #5**

very worried somewhat worried not very worried not at all worried

10. Did he accompany you here to the clinic during this study period?

yes no

11. Did he know that you were using the study product?

yes no don't know

➔ If no or don't know, go to item 16 on page 3.

12. What was his reaction to your use of the study product?
Mark all that apply.

- 12a. he liked it
- 12b. he did not like it
- 12c. he thought it improved sex
- 12d. he thought it worsened sex
- 12e. he thought it interfered with sex
- 12f. he had no reaction
- 12g. don't know
- 12h. other, specify:

Local Language: _____

English: _____

Final Acceptability Assessment (FAA-2)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on all other pages of this form for a given participant and visit.

SAMPLE. Do NOT FAX
TO DATAFAX



Visit Code .

1

MTN 001 (146)

FAA-3 (374)

Participant ID

- -

Site Number

Participant Number

Chk

Final Acceptability Assessment

13. Since you joined the study, how supportive was he about your use of the study gel?

Showcard #6

very supportive

somewhat supportive

not very supportive

not at all supportive

14. Since you joined the study, how supportive was he about your use of the study tablets?

Showcard #6

very supportive

somewhat supportive

not very supportive

not at all supportive

15. What did he prefer that you use—using the study gel or the study tablets?

- study gel
- study tablets
- neither—disliked both study products
- both—liked both study products equally

16. What did you prefer—using the study gel or taking the study tablets?

- study gel
- study tablets
- neither—disliked both study products
- both—liked both study products equally

Comments: _____

Final Acceptability Assessment (FAA-3)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on all other pages of this form for a given participant and visit.

SAMPLE TO DATAFAX



Note: Number pages sequentially (001, 002, 003) for each participant.

Page [][]

MTN 001 (146)

PH-1 (410)

Participant ID

[][][] - [][][][][] - []
Site Number Participant Number Chk

Product Hold/Discontinuation

1. Date product hold was initiated this study period: [][] [][][] [][] Visit Code [][] . []

2. Product being held this study period: [] oral tenofovir [] vaginal tenofovir gel [] oral and vaginal tenofovir

3. Why is product being held? Mark only one.

- 3a. pregnant or breastfeeding
3b. Grade >= 3 hypophosphatemia
3c. Grade >= 2 STI/RTI requiring treatment
3d. HIV infection
3e. Hepatitis B infection
3f. Grade >= 3 nausea and/or vomiting
3g. Grade >= 3 diarrhea
3h. Grade >= 3 AST/ALT elevation
3i. creatinine clearance < 50 mL/min
3j. other adverse experience
3k. use of prohibited medication(s)
3l. participant non-compliant with study product use procedures
3m. other, specify: _____

AE Log page #(s) [][][] [][][] [][][]

4. Date last tablet was taken this study period: [][] [][][] [][] OR []

5. Date last applicator was used this study period: [][] [][][] [][] OR []

6. Was the participant instructed to resume product use this study period? [] yes [] no (discontinued) [] no (hold continuing for another reason)
In item 6a, record the date and visit code on which product would have been resumed if not being held for another reason.

6a. Date participant instructed to resume product use this study period: [][] [][][] [][] Visit Code [][] . []

Comments: _____

Product Hold/Discontinuation (PH-1)

This form is used to document unexpected temporary holds and discontinuations of study product use within a given study period. Do not complete a new Product Hold/Discontinuation (PH-1) form at the End-of-study period visits, as discontinuation of product use for a given study period is expected at these visits.

This form is completed each time a participant is instructed to temporarily stop (hold) or discontinue study product use at an unscheduled timpani within a given study period. Only complete this form if product use in the current study period is held or discontinued. For example, if the participant has an adverse experience that warrants hold of oral study product, only complete the PH-1 form if she is in the oral or dual use period.

If more than one reason contributes to a product hold or discontinuation, complete one Product Hold/Discontinuation form for each reason listed in item 3. For example, if a participant is in the oral tenofovir period and has Grade 3 nausea and diarrhea at the 3-Week Visit, complete one PH-1 form with item 3f marked and one PH-1 form with item 3g marked. Assign page # "001" to one PH-1 form and page # "002" to the other PH-1 form. Record visit code 03.0 in item 1 on each form. If a participant has an ongoing product hold and another reason for a product hold/discontinuation occurs during that time, complete a new PH-1 form for the new reason. For example, a participant has product held at her 3-Week Visit for a Grade 2 STI. The site completes a PH-1 form and records visit code 03.0. The participant returns at 4 weeks for an interim visit and tests positive for pregnancy. Complete a new PH-1 form for the pregnancy, assign the next sequential page number, and record the appropriate interim visit code in item 1 on the form.

In the case of temporary product holds, do not wait for information about product resumption to fax the form—fax this form to SCHARP DataFax as soon as items 1 through 5 have been completed. Refax the form once item 6 has been completed.

Item-specific Instructions:

- **Item 1:** Record the date and visit code at which the participant was instructed by a study staff member to hold or discontinue study product use in the current study period. If study product is being held or discontinued as a result of an adverse experience, the visit code recorded in item 1 on this form should match the visit code recorded in item 10 of the AE Log documenting the product hold/discontinuation.
- **Item 2:** Mark the product that corresponds to the participant's current study period. For example, if the participant is in the oral tenofovir period, mark the 'oral tenofovir' box. If the participant is in the vaginal tenofovir period, mark the 'vaginal tenofovir gel' box. If the participant is in the dual use period, mark the 'oral and vaginal tenofovir' box.
- **Item 3:** Mark the box to the left of the reason why the participant is being instructed to hold or discontinue study product use in the current study period. If study product is being held or discontinued due to an adverse experience, record the page number(s) of the AE Log documenting the study product hold or discontinuation. If the study product hold/discontinuation is due to a reason other than the ones listed, mark "other, specify" and record the reason for the hold/discontinuation on the line provided.
- **Item 4:** Record the date of the participant's last dose of oral tenofovir during the current study period. Use a best estimate if the actual date cannot be determined. Mark "N/A" if the participant is in the vaginal period or if the participant did not use oral tenofovir during the current study period.
- **Item 5:** Record the date of the participant's last dose of vaginal tenofovir gel during the current study period. Use a best estimate if the actual date cannot be determined. Mark "N/A" if the participant is in the oral period, or if the participant did not use vaginal tenofovir gel during the current study period.
- **Item 6:** Complete this item once study staff have determined that the participant can resume study product use during the current study period based on resolution of the reason marked in item 3, or have determined that she is discontinued from study product use for the current study period. Mark this item "yes" if study staff instructed the participant that she can resume use of study product during the current study period. If the participant was discontinued from study product use for the current study period, mark the "no (discontinued)" box and end the form—leave item 6a blank. If the participant is eligible to resume study product use during the current study period based on resolution of the reason marked in item 3, but is continuing on study product hold for a reason recorded on another (separate) Product Hold/Discontinuation form, mark the "no (hold continuing for another reason)" response box. If a reason for product hold remains ongoing from one study period to the next, complete item 6 at the end of the first study period. Complete a new PH-1 form at the start of the next study period if the reason requires a product hold during the next study period. Record on the new form the same reason and AE Log page #, if applicable, that are recorded in item 3 of the original PH-1 form.
- **Item 6a:** Record the date and visit code on which the participant was told by a study staff member that she could resume study product use during the current study period. If "no (hold continuing for another reason)" is marked for item 6, in item 6a record the date the participant would have been instructed to resume study product use based on resolution of the reason marked in item 3 of the form.

SAMPLE. Do NOT FAX TO DATAFAX



Note: Number pages sequentially (001, 002, 003) for each participant.

Page [][][]

MTN 001 (146)

AE-1 (420)

Participant ID

[][][] - [][][][][] - []
Site Number Participant Number Chk

Adverse Experience Log

Date Reported to Site

[][] [][][] [][]
dd MMM yy

1. Adverse Experience (AE)

2. Onset Date

Record diagnosis if available. Include anatomical location, if applicable.

[][] [][][] [][]
dd MMM yy

3. Severity

- Grade 1 - Mild
- Grade 2 - Moderate
- Grade 3 - Severe
- Grade 4 - Life-threatening
- Grade 5 - Death

4. Relationship to Study Product

- Definitely related
- Probably related
- Possibly related
- Probably not related
- Not related

Record reason why AE is "not related" in Comments below.

5. Study Product Administration

- No change
- Held
- Permanently discontinued
- N/A
- Change in administration
Comment below.

6. Status/Outcome

- Continuing
- Resolved
- Death
- Severity/frequency increased
Report as new AE.
- Continuing at end of study participation

6a. Status/Outcome Date

Leave blank if Status/Outcome is "Continuing."

[][] [][][] [][]
dd MMM yy

7. Treatment Mark "None" or all that apply.

- None
- Medication(s)
Report on Concomitant Medications Log.
- New/Prolonged hospitalization
Comment below.
- Procedure/Surgery
Comment below.
- Other
Comment below.

8. Is this an SAE according to ICH guidelines?

yes no

11. Was this AE a worsening of a pre-existing condition?

yes no

9. Has/will this AE be reported as an EAE?

10. This AE was first reported at visit:.....
Visit code required (regular or interim)

[][] [][]

Comments: _____

Adverse Experience Log (AE-1)

Purpose: To document any Adverse Experience (AE) reported by the participant or clinically observed as defined by the protocol.

General Information/Instructions: Do not record a condition as an AE if it existed at enrollment as a pre-existing condition, unless it increases in severity or frequency. If a cluster of symptoms reported on separate AE Log pages is later attributed to a single diagnosis, change the earliest reported symptom to the final diagnosis. In addition, mark the AE Log pages for the other symptoms with the words “Delete due to diagnosis on AE page #” (specify page number of diagnosis AE).

Item-specific instructions:

- **Page:** Number pages sequentially throughout the study, starting with 001. Do not repeat page numbers. Do not renumber any AE Log pages after faxing, unless instructed by SCHARP.
- **Item 1:** Whenever possible, provide a diagnosis instead of listing a cluster of symptoms. If no diagnosis is identified, each symptom must be recorded on a separate page of the AE Log. If an abnormal lab value is reported, record the lab assay with the direction (i.e., increased or decreased) of the abnormality. For example, “decreased hematocrit” or “increased ALT.”
- **Item 2:** At minimum, month and year are required. Record one of the following, as appropriate: the date on which the participant reports first experiencing the AE; if the AE is discovered during the study visit exam, record the date of the study visit exam; if the AE is an abnormal lab result, record the date on which the specimen was collected.
- **Item 3:** To grade the severity of an AE, consult the *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Experiences* and the *Female Genital Grading Table for Use in Microbicide Studies* (as appropriate).
- **Item 4:** When judging causal association (relationship) between an AE and the study agent consult the terms used in DAIDS-sponsored studies as documented in the *Manual for Expedited Reporting of Adverse Events to DAIDS*.
 - **NOTE: IN CASES OF DEATH**, when relationship of study product is under investigation, write “Pending” in the adjacent white space until relationship has been determined. Update accordingly.
- **Item 5:**
 - **No change:** Mark if the AE does NOT result in a study product hold, permanent discontinuation, or change in administration.
 - **Held:** Mark if the AE results in a study product hold. If multiple AEs are reported at the same visit, mark “Held” for the AE(s) that contributed to the product hold.
 - **Permanently discontinued:** Mark if the AE results in permanent discontinuation of study product. If multiple AEs are reported at the same visit, mark “Permanently discontinued” for the AE(s) that contributed to the permanent discontinuation.
 - **N/A (not applicable):** Mark if the AE occurred after the participant had completed all administration of the study product, or the study product is held or permanently discontinued for a different AE or other reason, or the AE is Grade 5-death.
- **Item 6:**
 - **Continuing:** AE is continuing at the time it is reported.
 - **Resolved:** Condition is no longer present, or returned to the pre-enrollment severity/frequency. If a participant is taking a medication to control an AE that arose during study participation, it is not considered resolved.
 - **Death:** Mark only if the severity of this AE is Grade 5. Any other AEs continuing at the time of death should be changed to “continuing at end of study participation.”
 - **Severity/frequency increased:** If an AE increases in severity or frequency after it has been reported on the AE Log, line through the “Continuing” box previously marked and mark “Severity/frequency increased.” Record the date of increase in the “Status/Outcome Date.” Report the increase in severity or frequency as a new AE. For this new AE, the “Onset Date” will be the date that the severity or frequency increased. Note that decreases in severity should not be recorded as new AEs.
 - **Continuing at end of study participation:** Mark this box whenever an AE is continuing at the time of participant study termination.
- **Item 6a:** At minimum, month and year are required. Record one of the following, as appropriate: the date on which the participant no longer experienced the AE; or the date of the study visit or specimen collection at which the change in status/outcome is first noted.
- **Item 7:** Indicate if treatment was clinically indicated for the AE, regardless of whether the treatment was actually used. Also mark this item if the participant self-treated.
- **Items 8 and 9:** For questions about ICH guidelines and EAE reporting, refer to the *Manual for Expedited Reporting of Adverse Events to DAIDS*.

SAMPLE *Do NOT FAX TO DATAFAX*



Note: Number pages sequentially (01, 02, 03) for each participant.

Page

MTN 001 (146)

CM-1 (423)

Participant ID

- -
 Site Number Participant Number Chk

Concomitant Medications Log

No medications taken at Screening/Enrollment. _____
 Staff Initials/Date
 ➔ Fax to SCHARP DataFax.

No medications taken throughout study. _____
 Staff Initials/Date
 ➔ End of form. Fax to SCHARP DataFax.

Medication (generic name)										
Indication								Staff Initials/Log Entry Date		
Date Started			Date Stopped			OR <input type="checkbox"/> Continuing at end of study		Taken for a reported AE?		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>			<input type="checkbox"/> yes	<input type="checkbox"/> no	
Dose/Units		Route	PO	IM	IV	TOP	IHL	VAG	REC	other, specify:
		Mark only one.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Frequency		Mark only one.								
		<input type="checkbox"/> prn	<input type="checkbox"/> qd	<input type="checkbox"/> tid	<input type="checkbox"/> qhs	<input type="checkbox"/> qxh: every <input type="text"/> hrs				
		<input type="checkbox"/> once	<input type="checkbox"/> bid	<input type="checkbox"/> qid	<input type="checkbox"/> other, specify: _____					
								Record AE Log page(s):		
		<input type="text"/>		<input type="text"/>						
		<input type="text"/>		<input type="text"/>						

Medication (generic name)										
Indication								Staff Initials/Log Entry Date		
Date Started			Date Stopped			OR <input type="checkbox"/> Continuing at end of study		Taken for a reported AE?		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>			<input type="checkbox"/> yes	<input type="checkbox"/> no	
Dose/Units		Route	PO	IM	IV	TOP	IHL	VAG	REC	other, specify:
		Mark only one.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Frequency		Mark only one.								
		<input type="checkbox"/> prn	<input type="checkbox"/> qd	<input type="checkbox"/> tid	<input type="checkbox"/> qhs	<input type="checkbox"/> qxh: every <input type="text"/> hrs				
		<input type="checkbox"/> once	<input type="checkbox"/> bid	<input type="checkbox"/> qid	<input type="checkbox"/> other, specify: _____					
								Record AE Log page(s):		
		<input type="text"/>		<input type="text"/>						
		<input type="text"/>		<input type="text"/>						

Medication (generic name)										
Indication								Staff Initials/Log Entry Date		
Date Started			Date Stopped			OR <input type="checkbox"/> Continuing at end of study		Taken for a reported AE?		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>			<input type="checkbox"/> yes	<input type="checkbox"/> no	
Dose/Units		Route	PO	IM	IV	TOP	IHL	VAG	REC	other, specify:
		Mark only one.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Frequency		Mark only one.								
		<input type="checkbox"/> prn	<input type="checkbox"/> qd	<input type="checkbox"/> tid	<input type="checkbox"/> qhs	<input type="checkbox"/> qxh: every <input type="text"/> hrs				
		<input type="checkbox"/> once	<input type="checkbox"/> bid	<input type="checkbox"/> qid	<input type="checkbox"/> other, specify: _____					
								Record AE Log page(s):		
		<input type="text"/>		<input type="text"/>						
		<input type="text"/>		<input type="text"/>						

Concomitant Medications Log (CM-1)

All medication(s) that are used by the participant during the study, other than study product, must be documented on this form. This includes, but is not limited to, prescription medications, non-prescription (i.e., over-the-counter) medications, preventive medications and treatments (e.g., allergy shots, flu shots, and other vaccinations), herbal preparations, vitamin supplements, naturopathic preparations, and recreational drugs.

- When to fax this form:
 - when pages have been updated or additional Log pages have been completed (only fax updated or new pages);
 - when the participant has completed study participation; and/or
 - when instructed by SCHARP.
- **Page:** Number pages sequentially throughout the study, starting with 01. Do not repeat page numbers. Do not renumber any Concomitant Medications Log pages after faxing, unless instructed by SCHARP.
- **No medications taken at Screening/Enrollment:** Mark this box if no medications were taken by the participant at the time of the Screening or Enrollment visit. Record “Staff Initials/Date.”
- **No medications taken throughout study:** Mark this box at the Termination visit if no medications were taken by the participant throughout the entire study. Record “Staff Initials/Date.”
- **Medication:** Record the generic name for all medications. For combination medications, record the generic names of the first three main active ingredients.
- **Indication:** For health supplements, such as multivitamins, record “general health.” For preventive medications, record “prevention of [insert condition]” (e.g., for flu shot, record “prevention of influenza”). For recreational drugs, record “recreation.”
- **Date Started:** If the participant is unable to recall the exact date, obtain participant’s best estimate. At a minimum, the year is required.
- **Date Stopped:** At the participant’s Termination visit, the “Date Stopped” must be recorded for each medication OR the “Continuing at end of study” box must be marked. At a minimum, the month and year is required.
- **Dose/Units:** If the participant does not know the dose or units, draw a single line through the blank response boxes and initial and date. For prescription combination medications, record the dosage of first three main active ingredients. For multivitamin tablets or liquids, record number of tablets or liquid measurement (e.g., one tablespoon).
- **Route and Frequency:** Below is a list of common route and frequency abbreviations.

Route Abbreviations:

PO oral	IM intramuscular	IV intravenous	TOP topical	IHL inhaled	VAG vaginal	REC rectal
----------------	-------------------------	-----------------------	--------------------	--------------------	--------------------	-------------------

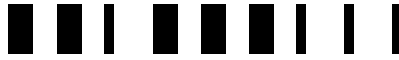
Frequency Abbreviations:

prn as needed	qd every day	tid three times daily	qhs at bedtime
once one time	bid twice daily	qid four times daily	qhx every x hours

- **Taken for a reported AE?:** If the medication was not taken for a reported AE, mark the “no” box and leave the AE Log page boxes blank

SAMPLE *DO NOT FAX*
TO DATAFAX

MTN 001 (146)



PR-1 (440)

Visit Code .

1

Participant ID

- -
Site Number Participant Number Chk

Pregnancy Report and History

PREGNANCY REPORT

1. Date of onset of last menstrual period: ^{dd} ^{MMM} ^{yy}
2. Estimated date of delivery: ^{dd} ^{MMM} ^{yy}

PREGNANCY HISTORY

3. Has the participant ever been pregnant before? ^{yes} ^{no} → **If no, end of form.**

3a. Is this the participant's first pregnancy since enrollment in this study? ^{yes} ^{no} → **If no, end of form.**

3b. Number of full term live births (≥ 37 weeks):

3c. Number of premature live births (< 37 weeks):

3d. Number of spontaneous fetal deaths and/or still births (≥ 20 weeks):

3e. Number of spontaneous abortions (< 20 weeks):

3f. Number of therapeutic/elective abortions:

3g. Number of ectopic pregnancies:

4. Does the participant have a history of pregnancy complications or fetal/infant congenital anomalies before study enrollment? ^{yes} ^{no} → **If yes, document in participant's records.**

Comments: _____

Pregnancy Report and History (PR-1)

Purpose: Complete this form when reporting a pregnancy of a study participant post enrollment through termination.

General Information/Instructions: Record the visit code of the visit at which study staff became aware that the participant is/was pregnant.

Item-specific instructions:

- **Item 1:** Complete date required. Record best estimate if date not known.
- **Item 2:** Complete date required.

SAMPLE. Do NOT FAX
TO DATAFAX



Visit Code

1

MTN 001 (146)

PO-1 (441)

Participant ID

- -
Site Number Participant Number Chk

Pregnancy Outcome

Outcome unknown at end of study. _____
Staff Initials/Date
▶ **End of form. Fax to SCHARP DataFax.**

1. How many pregnancy outcomes resulted from the reported pregnancy?

2. OUTCOME #1

dd MMM yy

2a. Outcome Date

2b. Specify Outcome: Mark only one.

full term live birth (≥ 37 weeks) }
 premature live birth (< 37 weeks) }
 spontaneous fetal death and/or still birth (≥ 20 weeks) }
 spontaneous abortion (< 20 weeks) }
 ectopic pregnancy }
 therapeutic/elective abortion }
2b1. Method: C-section vaginal
Complete AE Log and EAE Reporting form.

2c. Were any fetal/infant congenital anomalies identified? yes no not assessed

If only one outcome, end of form.

3. OUTCOME #2

dd MMM yy

3a. Outcome Date

3b. Specify Outcome: Mark only one.

full term live birth (≥ 37 weeks) }
 premature live birth (< 37 weeks) }
 spontaneous fetal death and/or still birth (≥ 20 weeks) }
 spontaneous abortion (< 20 weeks) }
 ectopic pregnancy }
 therapeutic/elective abortion }
3b1. Method: C-section vaginal
Complete AE Log and EAE Reporting form.

3c. Were any fetal/infant congenital anomalies identified? yes no not assessed

Comments: _____

21-APR-08

0 1
Language

13-115
Staff Initials / Date

Pregnancy Outcome (PO-1)

This form is used to report the pregnancy outcome(s) of a pregnancy reported post enrollment through termination. A **Pregnancy Outcome** form is required for each **Pregnancy Report and History** form completed for a participant. This form is completed when information about a pregnancy outcome becomes available to study staff. If an outcome is unknown at study end, mark the “Outcome unknown at end of study” box at the top of the page and fax to DataFax. When the outcome is known, draw a line through this box, record the outcome, and refax. A pregnancy outcome can be an infant or a fetus. The conception of twins should result in reporting of two outcomes. If a pregnancy results in more than two outcomes, contact SCHARP for guidance on how to complete this form.

- **Visit Code:** Record the visit code of the participant’s corresponding **Pregnancy Report and History** form.
- **Specify Outcome:** If the outcome is therapeutic/elective abortion, note that while the abortion itself is not an Adverse Experience (AE), if the abortion is performed due to a pregnancy complication, the pregnancy complication should be reported on an **Adverse Experience Log**, with “procedure/surgery” marked under “Treatment.”

Congenital anomalies: This item should be updated if information becomes available during the mother’s (the study participant’s) study follow-up period regarding a congenital anomaly. If a woman on study has a baby with a congenital anomaly and the infant does not have his/her own participant ID, report the event as an AE and record in item 1 “Congenital Anomaly in Offspring.” Record the PTID of the woman on study (mother) on the form, just as you would for any other AE reported for the participant.

SAMPLE. Do NOT FAX
TO DATAFAX



Visit Code

0

1

MTN 001 (146)

MV-1 (463)

Page 1 of 1

Participant ID

Site Number - Participant Number - Chk

Missed Visit

Form Completion Date

dd MMM yy

1. Target Visit Date: dd MMM yy

2. Reason visit was missed. *Mark only one.*

- 2a. unable to contact participant
- 2b. unable to schedule appointment(s) within allowable window
- 2c. participant refused visit
- 2d. participant relocated
- 2e. participant incarcerated
- 2f. participant admitted to a health care facility
- 2g. participant withdrew from the study —————> **Complete a Termination form.**
- 2h. participant deceased —————> **Complete a Termination form. Complete an Adverse Experience Log if applicable. Complete EAE Reporting form.**
- 2i. other, specify:

Comments: _____

Missed Visit (MV-1)

Purpose: Complete this form whenever an enrolled participant misses a required visit according to the visit window.

General Information/Instructions: If the QC Report indicates that a visit is overdue, confirm that the visit was missed before completing a Missed Visit form. Fax this form when it is determined that a visit has been missed and cannot be completed within the visit window. Record the Visit Code of the visit that was missed. Record the date that the form was completed. (This will not necessarily be the date of the missed visit).

Item-specific Instructions:

- **Item 1:** Record the target date of the visit. A complete date is required.
- **Item 2:** Record the reason the participant missed the visit.

SAMPLE *DO NOT FAX*
TO DATAFAX



MTN 001 (146)

PT-1 (465)

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	
Site Number				Participant Number						Chk	

Participant Transfer

Form Completion Date

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<i>dd</i>		<i>MMM</i>			<i>yy</i>

1. Name of transferring study site: _____

2. Name of receiving study site: _____

3. Visit Code of last completed contact with participant: .

4. Date participant records were sent to receiving study site:
dd MMM yy

Comments: _____

Participant Transfer (PT-1)

Purpose: Complete this form when a participant is transferring to another study clinic/site.

General Information/Instructions: The Participant Transfer form is completed by the transferring site (the site that the participant is leaving).

For more information on Participant Transfer and Receipt, refer to the protocol, Study Specific Procedures (SSPs), and/or Manual of Operations (MOP).

Item-specific instructions:

- **Item 4:** Complete date required.

SAMPLE. DO NOT FAX
TO DATAFAX



MTN 001 (146)

PRC-1 (466)

Participant ID

- -

Site Number

Participant Number

Chk

Participant Receipt

Form Completion Date

dd

MMM

yy

Note: Do not assign a new Participant ID. Record the Participant ID assigned by the original study site.

1. Name of receiving study site: _____

2. Name of transferring study site: _____

3. Date informed consent signed at receiving study site:
dd MMM yy

yes

no

4. Did participant provide informed consent for specimen storage at receiving study site?

→ If no, end of form.

4a. Date informed consent for specimen storage signed:
dd MMM yy

Comments: _____

Participant Receipt (PRC-1)

Purpose: Complete this form when a transferred participant has provided informed consent at the receiving study clinic/site.

General Information/Instructions: The Participant Receipt form is completed by the receiving site (the site at which the participant will be continuing his or her study visits).

For more information on Participant Transfer and Receipt, refer to the protocol, Study Specific Procedures (SSPs), and/or Manual of Operations (MOP).

Item-specific instructions:

- **Participant ID: Do not** assign a new Participant ID. Record the Participant ID assigned by the original study site.
- **Item 3:** Complete date required.
- **Item 4a:** Complete date required.

SAMPLE *DO NOT FAX*
TO DATAFAX



MTN 001 (146)

ESI-1 (489)

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	
Site Number				Participant Number						Chk	

End of Study Inventory

Form Completion Date

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<i>dd</i>		<i>MMM</i>			<i>yy</i>		

1. What is the **highest** visit code (scheduled or interim) for this participant, recorded on a form submitted via DataFax?.....

visit code

<input type="text"/>	<input type="text"/>	.	<input type="text"/>
----------------------	----------------------	---	----------------------

2. How many interim visits were conducted for this participant during the study and recorded on a form submitted via DataFax?.....

of interim visits

<input type="text"/>	<input type="text"/>	<input type="text"/>
----------------------	----------------------	----------------------

3. Indicate the **highest** page number submitted for this participant for each of the following forms:

3a. Adverse Experience Log (AE-1) *page #* **OR** *no pages submitted*

3b. Concomitant Medications Log (CM-1) *page #*

3c. Pre-existing Conditions (PRE-1) *page #*

3d. Product Hold/Discontinuation (PH-1) *page #* **OR** *no pages submitted*

Comments: _____

End of Study Inventory (ESI-1)

This form is used to confirm that SCHARP has received all study data for a given participant. Complete this form once for each enrolled participant after participant has terminated from the study (as documented by a Termination form).

- **Form Completion Date:** Complete date required.
- **Item 1:** Record the highest visit code (last visit for which DataFax forms were submitted). If the participant's last visit was missed (as documented by a Missed Visit form), record the visit code of the missed visit.
- **Item 2:** Record the total number of Interim Visit DataFax forms submitted for this participant. If no Interim Visit forms were submitted for the participant, record "000" in the boxes.

SAMPLE. Do NOT FAX TO DATAFAX



MTN 001 (146)

TM-1 (490)

Participant ID

Site Number - Participant Number - Chk

Termination

1. Termination Date: dd MMM yy Date the site determined that the participant was no longer in the study.

2. Reason for termination. Mark only one.

2a. scheduled exit visit/end of study -> End of form.

2b. death, indicate date and cause if known

2b1. date of death dd MMM yy OR date unknown
2b2. cause of death OR cause unknown

Complete or update Adverse Experience Log. Complete EAE Reporting form as applicable.

2c. participant refused further participation, specify:

2d. NOT APPLICABLE FOR THIS PROTOCOL.

2e. participant relocated, no follow-up planned

2f. investigator decision, specify:

2g. NOT APPLICABLE FOR THIS PROTOCOL.

2h. NOT APPLICABLE FOR THIS PROTOCOL.

2i. inappropriate enrollment -> End of form.

2j. invalid ID due to duplicate screening/enrollment -> End of form.

2k. other, specify:

2l. early study closure -> End of form.

3. Was termination associated with an adverse experience? yes no don't know If no or don't know, end of form.

3a. Record AE Log page:

Comments:

Termination (TM-1)

Purpose: Complete this form for every enrolled participant at either the scheduled exit/end of study visit or when the participant is no longer participating in the study.

General Information/Instructions: A complete date is required, unless termination is due to death. If a participant is terminated prior to completing all study product administration, complete a Product Hold/Discontinuation form.

Item-specific Instructions:

- **Item 1:** Complete date required.
- **Item 2:** Mark only the primary reason for termination.
 - **Item 2a:** Scheduled exit visit/end of study: (Only mark 2a if the participant completes the protocol-defined final visit).
 - **Item 2b1:** At a minimum, the month and year are required.
 - **Item 2l:** Early study closure: Only mark 2l when instructed by SCHARP.
- **Item 3a:** Record the page number of the Adverse Experience Log on which the AE was recorded. In situations where more than one AE is associated with termination, record the AE that most strongly influenced the decision to terminate.

PTID: _____

Screening Visit Date: _____
dd-MMM-yy

B. Reproductive History

Has the participant ever been pregnant? Yes No **If No, skip to Section C. Family Planning.**

Number of pregnancies: _____

Number of full term live births (greater than or equal to 37 weeks): _____

If number of pregnancies and number of full term live births are the same, skip to section C.

Number of premature live births (less than 37 weeks): _____

Number of spontaneous fetal deaths and/or still births (greater than or equal to 20 weeks): _____

Number of spontaneous abortions (less than 20 weeks): _____

Number of therapeutic/elective abortions: _____

Number of ectopic pregnancies: _____

Record information on any gynecologic and obstetrical procedures or surgeries here:

Record information on any fetal/infant congenital anomalies here:

PTID: _____

Screening Visit Date: _____

dd-MMM-yy

D. Medical History

Since becoming sexually active, have you ever had or do you currently have.....	YES	NO
a)...any problems with your scalp, like infection or hair loss?		
b)...any problems with your eyes, like infection, cataracts, or needing glasses?		
c)...any problems with your ears, like infection, pain, or difficulty hearing?		
d)...any problems with your nose, like chronic congestion or nosebleeds?		
e)...any problems with your teeth, mouth or throat, like an abscess or difficulty swallowing or thrush?		
f)...any problems with swollen glands or swollen feet?		
g)...any problems with your heart or blood vessels, like chest pain, palpitations or high blood pressure?		
h)...any problems with your lungs, like difficulty breathing, cough, TB, pneumonia or asthma?		
i)...any problems with your liver, like jaundice?		
j)...any problems with your kidneys or bladder, like blood in urine or urinary incontinence?		
k)...any problems with your stomach, spleen, pancreas or intestines, like nausea, vomiting, diarrhea, bloody stools or heartburn?		
l)...any problems with your muscles or bones, like chronic pain, swelling, arthritis, numbness, tingling, or broken bones?		
m)...any problems with headaches, fainting spells, muscle weakness, seizures, memory loss, dizziness, or paralysis?		
n)...any problems with your skin, like a rash, dry skin, swelling, shingles or infection?		
o)...any problems with diabetes, thyroid, or goiter?		
p)...any problems with your blood, like anemia, sickle cell, or easy bruising/bleeding?		
q)...any cancer?		
r)...any problems with fatigue, unintentional weight loss, immune deficiency or unexplained fever?		
s)...any problems related to your vaginal area, such as genital sores, vaginal itching, vaginal soreness, burning when urinating, genital bleeding not related to your menses?		
t)...any other obstetric or gynecologic procedures or problems, like hysterectomy, tubes tied, vaginal prolapse, rectal-vaginal fistula, etc?		
u) ...any sexually transmitted infections or diseases (herpes, warts, syphilis, etc)?		
v)...any history of sexual abuse, trauma or rape?		
w)...any problems with alcohol abuse or drug use? (<u>note</u> : record usual alcohol intake on the line below; also record any drug use on Concomitant Meds Log form)		
x)...any allergic or anaphylactic reaction (tightening in your chest, difficulty breathing or hives) to medications, vaccines, latex, or had any other allergies?		
y) ...any mental illness, depression, suicidal ideation/attempt, or psychosis?		
z)...any hospitalizations or emergency medical visits?		
aa)...any other problems or infections that we haven't already discussed?		

PTID: _____

Screening Visit Date: _____
dd-*MMM*-yy

E. Detailed Problem Descriptions of Participant-Reported Medical Conditions/Events

For each item marked "YES" in the table above (Section D), provide a detailed description of the medication condition(s)/event(s) referred to by that item (table row).

At the Enrollment Visit, review each condition/event marked as "ongoing" and confirm whether the condition/event is still ongoing at Enrollment. Update the entry as needed. All conditions/events marked as "ongoing" as of the Enrollment Visit need to be recorded on the Pre-Existing Conditions form.

_____	<input type="text"/> <input type="text"/> <input type="text"/> /	<input type="text"/> <input type="text"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>
organ system	month and year diagnosed		symptom or diagnosis	ongoing problem	resolved problem

If ongoing, determine GRADE: _____
If ongoing, describe frequency and severity: _____

_____	<input type="text"/> <input type="text"/> <input type="text"/> /	<input type="text"/> <input type="text"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>
organ system	month and year diagnosed		symptom or diagnosis	ongoing problem	resolved problem

If ongoing, determine GRADE: _____
If ongoing, describe frequency and severity: _____

_____	<input type="text"/> <input type="text"/> <input type="text"/> /	<input type="text"/> <input type="text"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>
organ system	month and year diagnosed		symptom or diagnosis	ongoing problem	resolved problem

If ongoing, determine GRADE: _____
If ongoing, describe frequency and severity: _____

NOT A DATAFAX FORM. DO NOT FAX TO DATAFAX

PTID: _____

Screening Visit Date: _____
dd-MMM-yy

_____ /
organ system month and year diagnosed

symptom or diagnosis

ongoing resolved
problem problem

If ongoing, determine GRADE: _____

If ongoing, describe frequency and severity: _____

_____ /
organ system month and year diagnosed

symptom or diagnosis

ongoing resolved
problem problem

If ongoing, determine GRADE: _____

If ongoing, describe frequency and severity: _____

_____ /
organ system month and year diagnosed

symptom or diagnosis

ongoing resolved
problem problem

If ongoing, determine GRADE: _____

If ongoing, describe frequency and severity: _____

_____ /
organ system month and year diagnosed

symptom or diagnosis

ongoing resolved
problem problem

If ongoing, determine GRADE: _____

If ongoing, describe frequency and severity: _____

NOT A DATAFAX FORM. DO NOT FAX TO DATAFAX

PTID: _____

Screening Visit Date: _____
dd-MMM-yy

_____	<input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>
organ system	month and year diagnosed	symptom or diagnosis	ongoing problem	resolved problem

If ongoing, determine GRADE: _____
If ongoing, describe frequency and severity: _____

_____	<input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>
organ system	month and year diagnosed	symptom or diagnosis	ongoing problem	resolved problem

If ongoing, determine GRADE: _____
If ongoing, describe frequency and severity: _____

_____	<input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>
organ system	month and year diagnosed	symptom or diagnosis	ongoing problem	resolved problem

If ongoing, determine GRADE: _____
If ongoing, describe frequency and severity: _____

_____	<input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>
organ system	month and year diagnosed	symptom or diagnosis	ongoing problem	resolved problem

If ongoing, determine GRADE: _____
If ongoing, describe frequency and severity: _____

The information in Section E was reviewed and updated at the Enrollment Visit by:

Staff Initials: _____ **Date:** _____

If more pages are needed, add additional pages to the end of the form.

SAMPLE. Do NOT FAX TO DATAFAX

Not a DataFax form. Do not fax to DataFax.

MTN 001 (146)

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>
Site Number				Participant Number					Chk

Screening Eligibility

Form Completion Date

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
dd		MMM		yy	

Complete items 1-4 before the interview.

- | | | | |
|---|--------------------------|--------------------------|---|
| 1. Was the participant willing and able to provide a written informed consent for screening?..... | yes | no | |
| | <input type="checkbox"/> | <input type="checkbox"/> | → If no to either, participant is ineligible. End of form. |
| 2. Was the participant willing and able to provide adequate locator information?..... | yes | no | |
| | <input type="checkbox"/> | <input type="checkbox"/> | |
| 3. Was the participant previously enrolled in this study? | yes | no | |
| | <input type="checkbox"/> | <input type="checkbox"/> | → If yes, participant is ineligible. End of form. |
| 4. Is documentation of a normal Pap test result in the last 12 calendar months available?..... | yes | no | |
| | <input type="checkbox"/> | <input type="checkbox"/> | → If no, perform Pap test as necessary. |

I am now going to ask you some more questions about yourself. Some of these questions are personal and sensitive, but remember that we do not have your name on these papers and all of your answers will be kept confidential.

- | | | | |
|--|--------------------------|--------------------------|--|
| 5. Have you ever had an adverse or bad reaction to latex (such as latex condoms or gloves)? | yes | no | |
| | <input type="checkbox"/> | <input type="checkbox"/> | → If yes to any, participant is ineligible. |
| 6. Do you have any current male sex partner(s) who have had an adverse or bad reaction to latex (such as latex condoms or gloves)? | <input type="checkbox"/> | <input type="checkbox"/> | |
| 7. Have you ever had an adverse or bad reaction to either of the study products (Tenofovir (Viread) oral tablet or Tenofovir 1% vaginal gel and/or applicator)? | <input type="checkbox"/> | <input type="checkbox"/> | |
| 8. Have you ever been diagnosed with a pathologic bone fracture not related to trauma?..... | <input type="checkbox"/> | <input type="checkbox"/> | |
| 9. Are you breastfeeding?..... | <input type="checkbox"/> | <input type="checkbox"/> | |
| 10. Do you plan to become pregnant during the 21 weeks of study participation?..... | <input type="checkbox"/> | <input type="checkbox"/> | |
| 11. Do you plan to use a diaphragm, vaginal ring, and/or spermicide for birth control at any time during your study participation?..... | <input type="checkbox"/> | <input type="checkbox"/> | |
| 12. Do you plan to use acyclovir, valacyclovir, post-exposure prophylaxis for HIV exposure, Truvada, or non-study vaginal products (other than tampons) at any time during your study participation? | <input type="checkbox"/> | <input type="checkbox"/> | |
| 13. Have you had more than three male sex partners in the past month (30 days)? | <input type="checkbox"/> | <input type="checkbox"/> | |

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	21-APR-08
--------------------------	--------------------------	--------------------------	-------------------------------------	-----------

01	13-135
Language	Staff Initials / Date

Screening Eligibility – Page 1 of 4 (nonDF)

This form is used to document the participant's eligibility for the study at screening. This is a mixed form—some of the items are interviewer-administered (items 5–25), while other items are not (items 1–4 and 26–27). Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

***Note:** If the participant provides a response indicating that she is ineligible for the study, continue to administer this form through item 25. Do not inform her that she is ineligible for the study until the form has been administered. Also, avoid letting the participant know the reason why she is ineligible, to prevent socially desirable reporting.*

Item-specific Instructions:

- **Items 1–4:** These items are NOT interviewer-administered and should not be read aloud to the participant.
- **Item 2:** Adequate locator information is defined in site standard operating procedures (SOP).
- **Item 3:** Review the Screening and Enrollment Log to verify that the participant has not previously enrolled in the study.
- **Item 4:** Per protocol, a participant must have either a normal Pap test result at screening or documentation of a normal Pap test result in the 12 calendar months prior to screening in order to be eligible to enroll in the study. If the participant does not provide documentation of a normal Pap test result in the 12 calendar months prior to screening, conduct a Pap Smear test for this participant as part of the Screening Visit pelvic exam.

SAMPLE. Do NOT FAX TO DATAFAX

Not a DataFax form. Do not fax to DataFax.

MTN 001 (146)

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	
Site Number				Participant Number						Chk	

Screening Eligibility

14. In the past 4 weeks, how many times have you had vaginal sex?
By vaginal sex, I mean when a man puts his penis inside your vagina.....

<input type="text"/>	<input type="text"/>	→ If < 4, participant is ineligible. Go to item 16.
----------------------	----------------------	---

15. Do you anticipate having vaginal sex at least once per week during your study participation?

yes	no	
<input type="checkbox"/>	<input type="checkbox"/>	→ If no, participant is ineligible.

16. Do you have a regular menstrual cycle that is 21 days or longer?

yes	no	
<input type="checkbox"/>	<input type="checkbox"/>	
		→ If yes, go to item 17.

16a. Is it because of the birth control you are using, such as Depo-Provera or Norplant?

yes	no	
<input type="checkbox"/>	<input type="checkbox"/>	→ If no, participant is ineligible.

17. In the past 3 months (90 days), have you given birth, or had a miscarriage or abortion?

yes	no	
<input type="checkbox"/>	<input type="checkbox"/>	→ If no, go to item 18.

17a. When did you last give birth, have a miscarriage or abortion?

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
dd		MMM			yy		

If date is within the last 60 days, participant is ineligible. Otherwise, schedule enrollment for when participant is no longer within 90 days of last pregnancy outcome.

18. In the past 3 months (90 days), have you had any gynecological surgery? This would include such procedures as: dilation and curettage (D&C), surgery of the uterus, ovaries, or fallopian tubes (including tubal ligation), biopsy, or cryotherapy (freezing) of the cervix?

yes	no	
<input type="checkbox"/>	<input type="checkbox"/>	→ If no, go to item 19.

18a. When did you last have gynecological surgery?

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
dd		MMM			yy		

If date is within the last 60 days, participant is ineligible. Otherwise, schedule enrollment for when participant is no longer within 90 days of last gynecological surgery.

Screening Eligibility – Page 2 of 4 (nonDF)

No additional instructions needed.

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Not a DataFax form. Do not fax to DataFax.

MTN 001 (146)

Participant ID

Site Number			Participant Number						Chk	

Screening Eligibility

19. In the past year (12 months), have you used a needle to inject drugs that were not prescribed to you by a medical professional?

yes	no
<input type="checkbox"/>	<input type="checkbox"/>

If yes, participant is ineligible.

20. In the past month (30 days), have you participated in any other research study that involves drugs, medical devices, or vaginal products?

yes	no
<input type="checkbox"/>	<input type="checkbox"/>

If no, go to item 21.

20a. When did you last participate in one of these studies?

dd		MMM			yy		

If participant is currently participating in another investigational drug, device, or vaginal product research study, participant is ineligible. Otherwise, schedule enrollment when participant is no longer within 30 days of other study participation.

Screening Eligibility – Page 3 of 4 (nonDF)

No additional instructions needed.

SAMPLE *Do NOT FAX TO DATAFAX*

Not a DataFax form. Do not fax to DataFax.

MTN 001 (146)

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	
Site Number				Participant Number						Chk	

Screening Eligibility

- 21. Do you agree to not participate in any other research study that involves drugs, medical devices, or vaginal products?
- 22. From the day of your study enrollment, through one month after you finish your study participation, do you agree to use one of the following types of birth control: Depo-Provera ("the shot"), hormonal contraceptives ("the pill"), Ortho-Evra ("the patch"), an intrauterine device (IUD - inserted at least 30 days prior to enrollment), female sterilization, or have vaginal sex with a male partner who has had a vasectomy?
- 23. Are you willing to use the study products, which are tenofovir oral tablets and tenofovir 1% vaginal gel, once a day as directed by study staff?
- 24. Are you willing to attend all scheduled study visits?
- 25. Are you willing to undergo all study evaluations, including a pelvic exam, urine testing, and blood draws?

yes	no
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

If no to any, participant is ineligible.

Complete item 26 when Screening urine hCG result is available.

- 26. Is the participant pregnant?
- 27. Does the participant have any other condition that, in the opinion of the site investigator, would preclude provision of informed consent, make participation in the study unsafe, complicate interpretation of study objectives, or otherwise interfere with achieving study objectives?

yes	no
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

If yes, participant is ineligible.

If yes, participant is ineligible.

Screening Eligibility – Page 4 of 4 (nonDF)

Item-specific Instructions:

- **Item 22:** If the participant's chosen effective method of contraception is sterilization (of participant or her sexual partner(s)), participant self-report is acceptable and sufficient documentation in order to enroll the participant.
- **Item 26:** This item is NOT interviewer-administered and should not be read aloud to the participant. Record the Screening Visit urine hCG result here.
- **Item 27:** This item is NOT interviewer-administered and should not be read aloud to the participant. This item should be completed by the site investigator or his/her designee once the Screening Visit has been completed. If, for some reason other than those listed on any of the screening forms, the investigator or designee feels the participant is **not** a good candidate for the study, mark the "yes" box, record the reason in the participant's chart notes, and do not enroll the participant in the study.

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MTN 001 (146)

Page 1 of 2

Participant ID

Site Number			Participant Number						Chk	

Screening Summary

Form Completion Date

dd		MMM			yy		

1. Is the participant eligible based on review of all screening data? ^{yes} ^{no}

→ **If yes, end of form.**

2. The participant is ineligible because she: *Mark all that apply.*
 - 2a. is not between the ages of 18 and 45 at screening
 - 2b. is not able and willing to provide written informed consent to be screened for and/or to take part in the study
 - 2c. is not in general good health, as determined by the site investigator of record or designee
 - 2d. is HIV-infected
 - 2e. has an abnormal Pap test result
 - 2f. is not sexually active (has not had vaginal intercourse at least four times in the four weeks prior to screening)
 - 2g. is unwilling to use an effective method of contraception (as defined in the protocol) from enrollment through one month after study exit
 - 2h. has had an IUD inserted in the 29 days prior to enrollment
 - 2i. is unwilling to undergo all study-related assessments (clinical and laboratory)
 - 2j. is unwilling to adhere to follow-up visit schedule
 - 2k. is unwilling to use tenofovir oral tablets and/or tenofovir 1% vaginal gel as directed by study staff
 - 2l. does not agree to refrain from participation in another study that involves drugs, medical devices, or vaginal products during study participation
 - 2m. has had more than three male sex partners in the month prior to screening
 - 2n. is using or plans to use acyclovir, valacyclovir, post-exposure prophylaxis for HIV exposure, Truvada, or non-study vaginal products (other than tampons) during study participation
 - 2o. does not have a predictable menstrual cycle
 - 2p. is not willing or able to provide adequate locator information
 - 2q. has a history of adverse reaction to latex
 - 2r. has a male sex partner with a history of adverse reaction to latex
 - 2s. is using or plans to use a diaphragm, vaginal ring, and/or spermicide for contraception during study participation

Screening Summary – Page 1 of 2 (nonDF)

This form is used to document the participant's eligibility for the study based on the entire screening process. This form is completed once all Screening Visit evaluations and forms/documentation have been completed and reviewed. If a participant is found to be ineligible at the Screening or Enrollment Visit (prior to randomization), use this form to document the reason(s) the participant was not eligible for study participation. Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

Item-specific Instructions:

- **Item 2:** If the participant is NOT eligible for enrollment in the study, *mark all* of the listed reasons that apply:
 - **Item 2a:** Review **Screening Consent and Demographics** forms.
 - **Item 2b:** Review **Screening Consent and Enrollment** forms.
 - **Item 2c:** Review **Clinical Eligibility** form from the Screening and Enrollment Visits.
 - **Item 2d:** Review **Screening and Enrollment STI Laboratory Results** form from the Screening Visit, OR if an **HIV Test Results** form is completed at the Screening Visit, review the **HIV Test Results** form.
 - **Item 2e:** Review **Pelvic Laboratory Results** form from the Screening Visit.
 - **Item 2f:** Review **Screening Eligibility** form.
 - **Item 2g–2l:** Review **Screening Eligibility, and Enrollment Eligibility** forms.
 - **Item 2m:** Review **Screening Eligibility** form.
 - **Item 2n:** Review **Screening Eligibility, and Enrollment Eligibility** forms.
 - **Item 2o–2r:** Review **Screening Eligibility** form.
 - **Item 2s:** Review **Screening Eligibility, and Enrollment Eligibility** forms.

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Not a DataFax form. Do not fax to DataFax.

MTN 001 (146)

Participant ID

Site Number			Participant Number					Chk		

Screening Summary

- 2t. has a history of pathologic bone fracture, not related to trauma
- 2u. has a history of adverse reaction to either study product (tenofovir oral tablets, tenofovir 1% vaginal gel and/or applicator)
- 2v. has a history of prior participation in the study
- 2w. has a laboratory value or abnormality at screening that is exclusionary per protocol
- 2x. had a gynecological surgical procedure within 90 days of enrollment
- 2y. is pregnant or plans to become pregnant during the study period
- 2z. is within 90 days of last pregnancy outcome at enrollment
- 2aa. has an abnormal physical or pelvic exam finding that is exclusionary, per investigator or designee
- 2ab. is diagnosed with a current UTI, or an STI and/or other RTI requiring treatment according to WHO guidelines
- 2ac. has a significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory immunologic disorder or infectious disease, including active TB, or any other medical condition that is exclusionary, per site investigator
- 2ad. has a history of non-therapeutic injection drug use in the 12 months prior to screening
- 2ae. has participated in another study that involves drugs, medical devices or vaginal products in the 30 days prior to enrollment
- 2af. does not intend to have vaginal intercourse at least once per week during study participation
- 2ag. is breastfeeding
- 2ah. exceeded the 30-day screening window
- 2ai. has any other condition that, in the opinion of the Investigator, would preclude provision of informed consent, make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

Screening Summary – Page 2 of 2 (nonDF)

Item-specific Instructions:

- **Item 2t–2v:** Review **Screening Eligibility** form.
- **Item 2w:** Review **Safety Laboratory Results** form from the Screening Visit.
- **Item 2x–2z:** Review **Screening Eligibility and Enrollment Eligibility** forms.
- **Item 2aa:** Review **Screening and Enrollment Pelvic Exam** forms from both the Screening and Enrollment Visits; **and** the **Physical Exam** form; **and** the **Clinical Eligibility** form from both the Screening and Enrollment Visits.
- **Item 2ab–2ac:** Review **Clinical Eligibility** forms from both the Screening and Enrollment Visits.
- **Item 2ad:** Review **Screening Eligibility** form.
- **Item 2ae–2ag:** Review **Screening Eligibility and Enrollment Eligibility** forms.
- **Item 2ah:** Review **Screening Consent** form *and* date of enrollment as recorded on the **Enrollment** form.
- **Item 2ai:** Review **Screening Eligibility and Enrollment Eligibility** forms.

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MTN 001 (146)

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	
Site Number				Participant Number						Chk	

Enrollment Eligibility

Visit Date

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
dd		MMM		yy	

Complete item 1 before the interview.

1. Was the participant willing and able to provide a written informed consent for enrollment?

yes

no

If no, participant is ineligible. End of form.

To confirm your eligibility for the study, I need to ask you a few more questions.

2. In the past month (30 days), have you participated in any other research study that involves drugs, medical devices, or vaginal products?

yes

no

3. Are you breastfeeding?

4. Do you plan to become pregnant during the 21 weeks of study participation?

5. In the past 3 months (90 days), have you had any gynecological surgery? This would include such procedures as: dilation and curettage (D&C), surgery of the uterus, ovaries, or fallopian tubes (including tubal ligation), biopsy, or cryotherapy (freezing) of the cervix?

6. Are you currently using, or do you plan to use a diaphragm, vaginal ring, and/or spermicide for birth control at any time during your study participation?

7. Are you currently using, or do you plan to use acyclovir, valacyclovir, post-exposure prophylaxis for HIV exposure, Truvada, or non-study vaginal products (other than tampons) at any time during your study participation?

8. In the past 3 months (90 days), have you given birth, or had a miscarriage or abortion?

9. Have you had an intrauterine device (IUD) inserted in the past 29 days?

If yes to any, participant is ineligible.

Enrollment Eligibility – Page 1 of 2 (nonDF)

This form is used to document the participant's eligibility for the study at enrollment. This is a mixed form—some of the items are interviewer-administered (items 2–15), while other items are not (items 1, 16–17). Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

General Interviewer Tips:

Refer to the Study-Specific Procedures (SSP) Manual for detailed interviewing techniques.

- Help the participant feel comfortable. Develop a rapport or connection with the participant.
- Avoid re-phrasing items, as doing so can change the meaning of the items and make them inconsistent with other interviews.
- Use probes to help the participant remember an answer, clarify a response, or to help report something more accurately.

It is important for you to review the forms for accuracy and completeness once the interview is complete. By reviewing the form briefly while the participant is still there, you can go back to an item that may have accidentally been skipped.

Item-specific Instructions:

- **Items 2–15:** These items were also asked during the Screening Visit. They must be asked again in order to confirm the participant's eligibility for the study per the inclusion/exclusion criteria stated in the protocol. If the participant provides a response indicating that she is ineligible for the study, continue to administer this form through item 15. Do not inform her that she is ineligible for the study until the form has been administered. Also, refrain from indicating to the participant the reason why she is ineligible, to prevent socially desirable reporting.

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MTN 001 (146)

Participant ID

Site Number			Participant Number						Chk		

Enrollment Eligibility

Visit Date

dd		MMM			yy		

- 10. Do you agree to not participate in any other research study that involves drugs, medical devices, or vaginal products while participating in this study? yes no
- 11. Do you anticipate having vaginal sex at least once per week during your study participation? yes no
- 12. From today through one month after you finish your study participation, do you agree to use one of the following types of birth control: Depo-Provera ("the shot"), hormonal contraceptives ("the pill"), Ortho-Evra ("the patch"), an intrauterine device (IUD - inserted at least 30 days prior to enrollment), female sterilization, or have vaginal sex with a male partner who has had a vasectomy? yes no
- 13. Are you willing to use the study products, which are tenofovir oral tablets and tenofovir 1% vaginal gel, once a day as directed by study staff? yes no
- 14. Are you willing to attend all scheduled study visits? yes no
- 15. Are you willing to undergo all study evaluations, including a pelvic exam, urine testing, and blood draws? yes no

If no to any, participant is ineligible.

Complete item 16 when Enrollment urine hCG result is available.

- 16. Is the participant pregnant?..... yes no

If yes, participant is ineligible.

Complete item 17 after reviewing all Screening and Enrollment forms.

- 17. Does the participant have any other condition that, in the opinion of the site investigator, would preclude provision of informed consent, make participation in the study unsafe, complicate interpretation of study objectives, or otherwise interfere with achieving study objectives? yes no

If yes, participant is ineligible.

Enrollment Eligibility – Page 2 of 2 (nonDF)

Item-specific Instructions:

- **Item 12:** If the participant's chosen effective method of contraception is female sterilization or sexual activity with a vasectomized partner, participant self-report is sufficient documentation, per protocol, that this eligibility criterion has been met.
- **Item 16:** This item is NOT interviewer-administered and should not be read aloud to the participant. Record the Enrollment Visit urine hCG result here.
- **Item 17:** This item is NOT interviewer-administered and should not be read aloud to the participant. This item should be completed by the site investigator or his/her designee once the Enrollment Visit procedures have been completed, but prior to study randomization. If, for some reason other than those listed on any of the screening forms, the investigator or designee feels the participant is **not** a good candidate for the study, mark the "yes" box, record the reason in the participant's chart notes, and do not enroll the participant in the study.

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MTN 001 (146)

Participant ID

Site Number			Participant Number						Chk	

Clinical Eligibility

Visit Date

<i>dd</i>		<i>MMM</i>		<i>yy</i>	

1. At this visit, was the participant diagnosed by study staff with any of the following sexually transmitted infections (STIs) or reproductive tract infections (RTIs) requiring treatment per WHO guidelines:

- | | <i>yes</i> | <i>no</i> |
|---|--------------------------|--------------------------|
| 1a. chlamydia? | <input type="checkbox"/> | <input type="checkbox"/> |
| 1b. gonorrhea? | <input type="checkbox"/> | <input type="checkbox"/> |
| 1c. syphilis? | <input type="checkbox"/> | <input type="checkbox"/> |
| 1d. symptomatic BV? | <input type="checkbox"/> | <input type="checkbox"/> |
| 1e. symptomatic vaginal candidiasis (yeast)? | <input type="checkbox"/> | <input type="checkbox"/> |
| 1f. trichomoniasis? | <input type="checkbox"/> | <input type="checkbox"/> |
| 1g. chancroid? | <input type="checkbox"/> | <input type="checkbox"/> |
| 1h. genital HSV-1 or HSV-2 (active lesions)? | <input type="checkbox"/> | <input type="checkbox"/> |
| 1i. genital warts of the labia minora, vagina, or cervix, any other symptomatic genital warts, or genital warts exterior to the labia minora requiring treatment? | <input type="checkbox"/> | <input type="checkbox"/> |
| 1j. cervicitis? | <input type="checkbox"/> | <input type="checkbox"/> |
| 1k. other vaginitis? | <input type="checkbox"/> | <input type="checkbox"/> |
| 1l. pelvic inflammatory disease (PID)? | <input type="checkbox"/> | <input type="checkbox"/> |
| 1m. genital sores or ulcers? | <input type="checkbox"/> | <input type="checkbox"/> |
| 1n. any other STI or RTI requiring treatment? Specify:
_____ | <input type="checkbox"/> | <input type="checkbox"/> |

If yes to any, treat per protocol and SSP. Do not enroll participant until treatment is complete and all symptoms have resolved.

Clinical Eligibility – Page 1 of 2 (nonDF)

This form is completed at the Screening and Enrollment Visits only, and is used to document the participant's clinical eligibility for the study. It is completed once at the Screening Visit, and again at the Enrollment Visit. For the Screening Visit, this form is completed once the screening pelvic exam and wet mount have been conducted. For the Enrollment Visit, this form is completed once the enrollment pelvic exam and wet mount have been conducted. Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

Note: *Because a participant is not eligible for enrollment if she is currently diagnosed with any of the UTIs/STIs/RTIs on this form, and because the Pre-existing Conditions form only documents ongoing conditions at the time of enrollment, none of the UTIs/STIs/RTIs recorded on this form should be documented on the Pre-existing Conditions form.*

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Not a DataFax form. Do not fax to DataFax.

MTN 001 (146)

Participant ID

Site Number			Participant Number						Chk	

Clinical Eligibility

2. At this visit, was the participant diagnosed with a urinary tract infection (UTI)?

yes	no
<input type="checkbox"/>	<input type="checkbox"/>

If yes, treat per protocol and SSP. Do not enroll participant until treatment is complete and all symptoms have resolved.

3. At this visit, does the participant have a clinically apparent pelvic exam finding (observed by study staff) involving Grade 2 or higher genital lesions, erythema, and/or edema?

yes	no
<input type="checkbox"/>	<input type="checkbox"/>

4. At this visit, does the participant have any other abnormal physical or pelvic exam finding that, in the opinion of the investigator or designee, would exclude her from the study?

<input type="checkbox"/>	<input type="checkbox"/>
--------------------------	--------------------------

5. At this visit, does the participant have any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease, including active tuberculosis, or any other medical condition that, in the opinion of the site investigator, could make participation unsafe for the participant?

<input type="checkbox"/>	<input type="checkbox"/>
--------------------------	--------------------------

If yes to any, participant is ineligible at this time. End of form.

6. Is the participant in general good health, as determined by the site Investigator of Record or designee?

yes	no
<input type="checkbox"/>	<input type="checkbox"/>

If no, participant is ineligible. End of form.

Comments: _____

Clinical Eligibility – Page 2 of 2 (nonDF)

No additional instructions needed.

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MTN 001 (146)

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Site Number			Participant Number				Chk

Physical Exam

Exam Date

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
dd		MMM		yy	

VITAL SIGNS

1. Were vital signs done?..... *yes* *no* → **If no, specify reason in Comments.**

Weight kg BP / mmHg

Height cm Pulse per minute

Oral Temp . °C Respirations per minute

Vital Signs: _____ Staff Initials / Date

FINDINGS

not evaluated *normal* *abnormal* **Items 2 and 3 are required. If not evaluated or abnormal, please specify.**

 2. General appearance _____

 3. Abdomen _____

Items 4-15 are optional. If abnormal, please specify.

 4. HEENT _____

 5. Neck _____

 6. Lymph Nodes _____

 7. Heart _____

 8. Lungs _____

 9. Extremities _____

 10. Neurological _____

 11. Skin _____

 12. Breast Exam _____

 13. Other, specify: _____

 14. Other, specify: _____

 15. Other, specify: _____

→ **If abnormal and ongoing for any at Enrollment, record on Pre-existing Conditions form. If abnormal during follow-up, update or complete Adverse Experience Log when applicable.**

Findings: _____ Staff Initials / Date

Comments: _____

Physical Exam (nonDF)

This form is used to document the participant's vital signs and physical exam findings. Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

Item-specific Instructions:

- **Vital Signs:** Remember to use leading zeros when needed. The staff member who completes these items should initial and date in the space provided.
- **Findings:** The staff member who completes these items should initial and date in the space provided.
- **Items 2 and 3:** These items are required when a physical exam is performed.
- **Items 4–15:** These items are optional.
- **Items 13–15:** Use these items to list any additional organ systems that were evaluated. If no other organ systems other than the ones listed in items 2-12 were evaluated, mark these items as “not evaluated.”

SAMPLE *Do NOT FAX TO DATAFAX*

Not a DataFax form. Do not fax to DataFax.

MTN 001 (146)

Participant ID

- -

Site Number Participant Number Chk

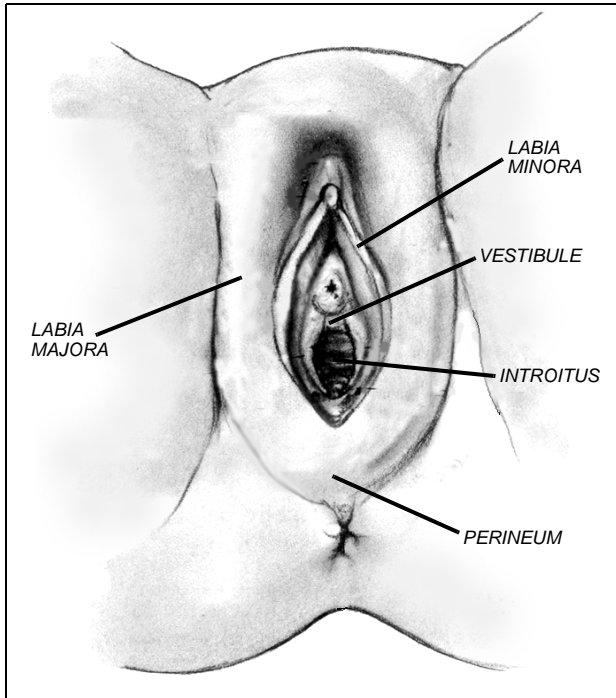
Pelvic Exam Diagrams

no normal variants or abnormal findings observed

Exam Date

dd MMM yy

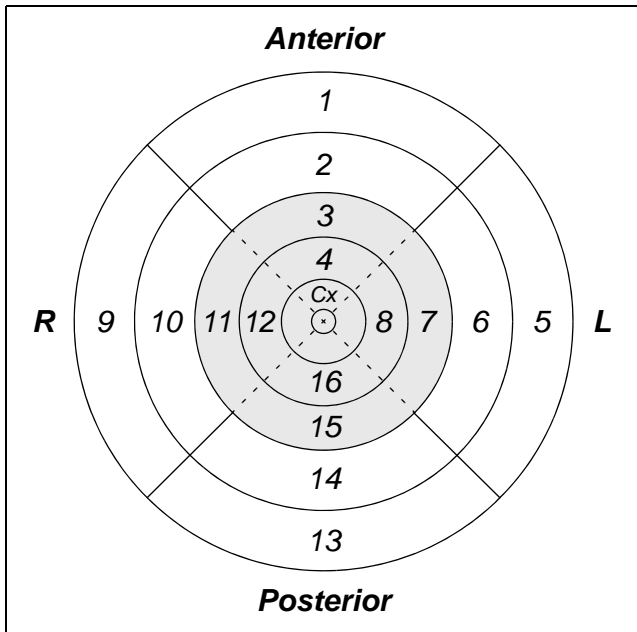
External Genitalia



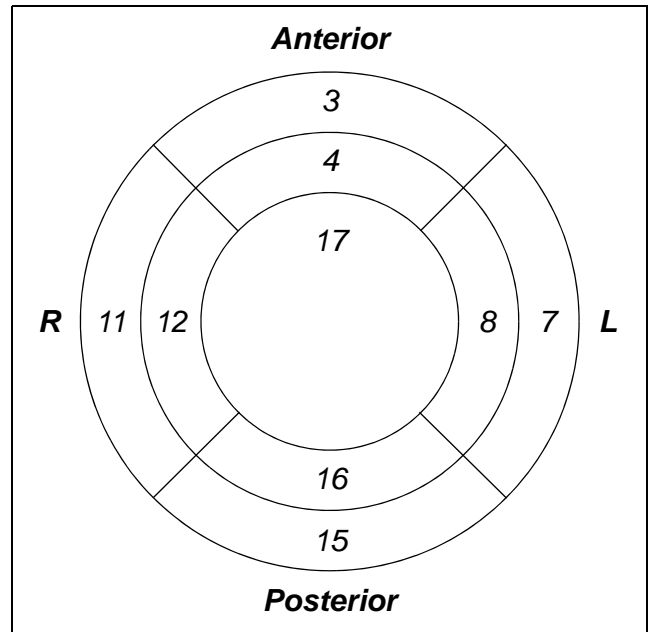
Legend for Vagina/Cervix

1. Anterior vagina, distal half
2. Anterior vagina, proximal half
3. Anterior fornix
4. Cervical trunk, anterior
5. Left lateral vagina, distal half
6. Left lateral vagina, proximal half
7. Left lateral fornix
8. Cervical trunk, left lateral
9. Right lateral vagina, distal half
10. Right lateral vagina, proximal half
11. Right lateral fornix
12. Cervical trunk, right lateral
13. Posterior vagina, distal half
14. Posterior vagina, proximal half
15. Posterior fornix
16. Cervical trunk, post
17. Cervical face

Vagina



Cervix



Pelvic Exam Diagrams – Page 1 of 1 (nonDF)

This form is used to document all variants of normal and all abnormal findings observed during study pelvic exams (screening through study exit). This form is completed each time a pelvic exam is performed unless the site is using another document as source for the pelvic exam. Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

Item-specific Instructions:

- All variants of normal (normal findings) and all abnormal findings must be documented on this form. Variants of normal need only be recorded on this form, and not on any of the DataFax Pelvic Exam forms. The following findings are considered normal variants:
 - anatomic variants
 - mucus retention cysts
 - atrophic changes
 - Nabothian cysts
 - gland openings
 - Gartner’s duct cysts
 - skin tags
 - ectopies
- If there are no variants of normal or abnormal findings observed mark the “no normal variants or abnormal findings observed” box.
- Documenting findings on the cervix: If helpful, draw the os in the center of the diagram labeled “Cervix” (lower right corner).

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Not a DataFax form. Do not fax to DataFax.

Participant ID

Site Number			Participant Number					Chk			

Follow-up Medical History Log

Page

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Medical Condition	Onset Date (dd- MMM -yy)	Staff Initials/Log Entry Date	Is this condition reportable as an AE? yes <input type="checkbox"/> no <input type="checkbox"/> <i>AE Log Page #</i> <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr></table> ←			
Outcome Date (dd- MMM -yy)	Severity Grade					
Comments						

Medical Condition	Onset Date (dd- MMM -yy)	Staff Initials/Log Entry Date	Is this condition reportable as an AE? yes <input type="checkbox"/> no <input type="checkbox"/> <i>AE Log Page #</i> <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr></table> ←			
Outcome Date (dd- MMM -yy)	Severity Grade					
Comments						

Medical Condition	Onset Date (dd- MMM -yy)	Staff Initials/Log Entry Date	Is this condition reportable as an AE? yes <input type="checkbox"/> no <input type="checkbox"/> <i>AE Log Page #</i> <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr></table> ←			
Outcome Date (dd- MMM -yy)	Severity Grade					
Comments						

Medical Condition	Onset Date (dd- MMM -yy)	Staff Initials/Log Entry Date	Is this condition reportable as an AE? yes <input type="checkbox"/> no <input type="checkbox"/> <i>AE Log Page #</i> <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr></table> ←			
Outcome Date (dd- MMM -yy)	Severity Grade					
Comments						

Follow-up Medical History Log (non-DataFax)

This form is used to track symptoms reported by the participant during a study follow-up. This form is also used to track symptoms ongoing at Enrollment.

Review this log at every visit. If a condition has no outcome date listed, assess the status of that condition at the current visit and update the entry as needed.

Once the participant's Enrollment Visit is completed, record any ongoing symptoms (ongoing at the time of Enrollment) onto this form. Review each of these symptoms at the participant's first follow-up visit and update the entries as needed.

Item-specific Instructions:

- **Page:** Number pages sequentially throughout the study, starting with 001. Do not repeat page numbers.
- **Medical Condition:** Whenever possible, provide a diagnosis instead of listing a cluster of symptoms.
- **Onset Date:** At a minimum, month and year are required.
- **Outcome Date:** At a minimum, month and year are required. Record one of the following, as appropriate:
 - the date on which the participant no longer experiences the medical condition,
 - the date of the study visit or specimen collection at which the change in status/outcome is first noted, or
 - if condition is continuing at end of study, record "CES" in the space provided.
- **Severity:** To determine the severity, consult the *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Experiences*. If a symptom increases in severity, record the date the severity increased as the "Outcome date", and record a new entry for the symptom with the increased grade.
- **Is this condition reportable as an AE:**
 - Refer to the protocol for AE reporting criteria.

SAMPLE *Do NOT FAX TO DATAFAX*

Not a DataFax form. Do not fax to DataFax.

MTN 001 (146)

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Site Number			Participant Number				Chk	

Genital Bleeding Assessment

Visit Date

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
dd		MMM		yy	

This form should not be completed for pregnant participants. This form is completed whenever an episode of unexpected genital bleeding is self-reported by the participant and/or clinically observed with no identifiable source. Completion of this form is not required for episodes of expected genital bleeding.

- First day of participant's last menstrual period: **OR** *amenorrheic*
Obtain from Follow-up Medical History form.
 ↓
If amenorrheic, go to item 4.
- Last day of participant's last menstrual period:
- Length in days of participant's last menstrual period (based on dates recorded in items 1 and 2): days
- First day of genital bleeding episode:
- Last day of genital bleeding episode: **OR** *ongoing*
- Total number of days of genital bleeding: days **OR** *ongoing*
- According to the participant, was the amount of genital blood a normal amount, lighter amount, or heavier amount when compared to the heaviest flow day of her regular menses? *normal* *lighter* *heavier* *unknown* *N/A*
- According to the participant or the clinician, what color was the genital blood? Mark "unknown," or all that apply. *bright red* *brown* *unknown*
- According to the participant, did she continue to use study gel during this genital bleeding episode? *yes* *no* *N/A*
 → **If yes or N/A, go to item 11 on page 2.**

Genital Bleeding Assessment – Page 1 of 3 (nonDF)

This form is completed by the study clinician, and used to guide study clinicians' assessment of genital bleeding events that occur during follow-up. This form is completed each time an episode of unexpected genital bleeding is self-reported by a study participant and is either not observed during pelvic examination, or is clinically-observed with no identifiable source. Specifically, this form guides clinicians to collect and consider information on the many factors that may contribute to the unexpected genital bleeding event. Study clinicians should review the Baseline Medical History form and refer to the Study-Specific Procedures (SSP) Manual to determine whether or not an episode of genital bleeding is unexpected.

Item-specific Instructions:

- **Item 1:** Mark “amenorrheic” if the participant has been without menses for at least the past three cycle intervals, or the past 6 months, whichever is shorter.
- **Item 5:** If the participant experienced intermittent bleeding as part of the same episode of genital bleeding, record the last date in which she experienced bleeding for that episode.
- **Item 6:** Record the total number of days in which the participant experienced bleeding during this genital bleeding episode. For example, if the participant experienced bleeding over 7 consecutive days and bled each of the 7 days, record “07.” If the participant experienced genital bleeding over a 6-day period, but only bled on days 1, 2, 4, and 7, record “04.”
- **Item 7:** Mark “unknown” in cases where the information is not known by the participant. Mark “N/A” if the genital bleeding was not reported by the participant, but was observed during the pelvic examination only.
- **Item 8:** Mark “unknown” in cases where the information is not known by the participant or the clinician.
- **Item 9:** Mark “NA” if the genital bleeding episode occurred during the oral study period or during one of the one-week washout periods (between Weeks 6 and 7, Weeks 13 and 14, and Weeks 20–21). Also mark “NA” if the participant is in the vaginal or dual use study periods, but her vaginal tenofovir gel use was already held or discontinued due to another reason.

SAMPLE *Do NOT FAX TO DATAFAX*

Not a DataFax form. Do not fax to DataFax.

MTN 001 (146)

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Site Number			Participant Number				Chk

Genital Bleeding Assessment

10. Number of days between last application of study gel and first day of genital bleeding episode: days

11. According to the participant, did the genital bleeding occur within 2 days after...

	yes	no	
11a. vaginal sex?	<input type="checkbox"/>	<input type="checkbox"/>	
11b. painful vaginal sex?	<input type="checkbox"/>	<input type="checkbox"/>	
11c. application of the study gel?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> N/A
11d. painful or uncomfortable application of the study gel?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11e. painful or uncomfortable insertion or removal of any other vaginal product/preparation?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11f. a pelvic or colpo exam?	<input type="checkbox"/>	<input type="checkbox"/>	

If yes to any, record related details in Comments on page 3.

If yes, record date of last pelvic/colpo exam in Comments on page 3.

11g. condom use? yes no

12. Is the participant currently using injectable contraceptives? *Review Concomitant Medications Log.* yes no **If no, go to item 13.**

12a. When was her last injection? *dd* *MMM* *yy*

12b. When is/was her next injection due? **Go to item 14 on page 2.**

13. Is the participant currently using (non-injectable) hormonal contraceptives? *Review Concomitant Medications Log.* yes no **If no, go to item 14 on page 2.**

13a. Has the participant missed one or more days of contraceptives in the week before the genital bleeding started? yes no **If no, go to item 14 on page 2.**

Genital Bleeding Assessment – Page 2 of 3 (nonDF)

Item-specific Instructions:

- **Item 12:** If the participant reports currently using injectable contraceptives, make sure the injectable contraceptives are listed on the participant's Concomitant Medications Log.
- **Item 13:** Non-injectable hormonal contraceptives include oral contraceptives ("the pill"), Ortho-Evra ("the patch"), and vaginal rings. If the participant reports currently using non-injectable hormonal contraceptives, make sure these are listed on the participant's Concomitant Medications Log.

SAMPLE *DO NOT FAX TO DATAFAX*

Not a DataFax form. Do not fax to DataFax.

MTN 001 (146)

Participant ID

Site Number			Participant Number						Chk	

Genital Bleeding Assessment

13b. Did the participant miss two or more days of contraceptives? yes no

→ **If yes, go to item 14.**

13c. **For participants using oral contraceptives only:** Did the participant make up the missed dose of oral contraceptives? yes no

14. Based on all information available, is this bleeding unexpected? yes no

→ **If no, end of form. DO NOT complete AE Log.**

14a. Is this unexpected bleeding menstrual or non-menstrual?

menstrual

↓

**Complete AE Log.
Report as "menorrhagia" or "menometrorrhagia." Grade per "menorrhagia" row of the Female Genital Toxicity Table.**

non-menstrual

↓

**Complete AE Log.
Report as "metrorrhagia" or "postcoital bleeding." Grade per "metrorrhagia" or "postcoital bleeding" row of the Female Genital Toxicity Table.**

14b. Record Adverse Experience Log page: AE Log Page #

Comments: _____

Genital Bleeding Assessment – Page 3 of 3 (nonDF)

Item-specific Instructions:

- **Item 13c:** This item applies only to those participants using oral contraceptives. For participants who do not use oral contraceptives, leave item 13c blank and go to item 14.
- **Item 14:** Review the Baseline Medical Assessment form and refer to the Study-Specific Procedures (SSP) Manual to determine whether or not the genital bleeding is unexpected.
- **Item 14a:** If the unexpected genital bleeding is:
 - **menstrual** - grade the AE of menorrhagia [defined as prolonged (more than 7 days) or excessive (>80 mL) uterine bleeding] or menometrorrhagia (defined as prolonged uterine bleeding occurring at irregular intervals) using the “menorrhagia” row of the *Female Genital Grading Table for Use in Microbicide Studies* (protocol Appendix IV).
NOTE: unexpected menstrual bleeding is defined as menstrual bleeding that is heavier in volume or longer in duration than the participant’s usual menses (as documented on the Baseline Medical History form). Refer to the SSP for further information.
 - **non-menstrual** - grade an AE of metrorrhagia (intermenstrual bleeding) using the “metrorrhagia” row of the *Female Genital Grading Table for Use in Microbicide Studies* (protocol Appendix IV). Grade an AE of postcoital bleeding using the “postcoital bleeding” row of the *Female Genital Grading Table for Use in Microbicide Studies*.
NOTE: unexpected non-menstrual genital bleeding—regardless of severity—that is associated with an observed pelvic exam finding should be reported as an AE, with the AE description = “bleeding source and location” (e.g., ulceration-vaginal). Unexpected non-menstrual bleeding—regardless of severity—that is associated with an underlying cause (e.g., fibroids, uterine laceration, trauma) should be reported as an AE, with the diagnosis as the AE description. Refer to the SSP for further information.
- **Item 14b:** Record the AE Log page number of the AE reported for this unexpected genital bleeding episode. When determining the relationship to study product, carefully review the information recorded in items 11–13c of this form. Record information relevant to the product relatedness determination in the Comments section of the AE Log.

MTN 001 Africa Sites - LDMS Specimen Tracking Sheet

For login of MTN 001 stored specimens into LDMS

MTN 001 – Africa Sites - LDMS Specimen Tracking Sheet (non-DataFax)

Purpose: This non-DataFax form is used to document collection and entry of MTN 001 specimens into the Laboratory Data Management System (LDMS).

General Information/Instructions: A copy of this form accompanies specimens for storage (in their original specimen collection containers) to the LDMS entry laboratory. Once the specimens have been entered into LDMS, this form is kept on file at the LDMS entry laboratory. If the site chooses, a copy of this completed form may be made once the specimens have been entered into LDMS and the copy kept in the participant's study notebook. This is not required, however. Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

Item-specific Instructions:

- **Visit Code:** Record the visit code of the visit at which the LDMS specimens were collected.
- **Specimen Type:** For the post-dose blood and CVL specimens, circle the collection timepoint used for these specimens.
- **NUMBER OF TUBES or SPECIMENS COLLECTED:** In the box to the left of each primary additive type, record the total number of tubes or specimens collected. If no LDMS specimens of the primary specimen type were collected, record "0".
- **Initials – Sending Staff:** The clinic staff person who completed the form and/or who is sending the LDMS form and specimens to the LDMS entry lab, records his/her initials here.
- **Initials - Receiving Staff:** The laboratory staff person who received this form (and the LDMS specimens accompanying the form), records his/her initials here.
- **LDMS Data Entry Date:** Record the date the LDMS specimens listed on this form were entered into LDMS.
- **LDMS Data Entry Date - LDMS Staff:** The LDMS laboratory staff person who entered the specimens into LDMS, records his/her initials here.

Participant ID			Visit Code	Specimen Collection Date		
[][] - [][][][] - []			[][] . []	[][]	[][][]	[][]
Site Number	Participant Number	Chk		<i>dd</i>	<i>MMM</i>	<i>yy</i>

SPECIMEN TYPE/VISIT	PRIMARY SPECIMEN TYPE	TIME COLLECTED hh:mm 24-hr clock	NUMBER of TUBES or SPECIMENS COLLECTED (Primary additive)	INSTRUCTIONS FOR PROCESSING LAB
Enrollment	Cervicovaginal Lavage (CVL)	<i>Not applicable</i>	<input type="checkbox"/> NSL (saline)	Keep on ice or refrigerate until specimen is frozen long term. Centrifuge and Freeze supernatant within 8 hours of collection. Store with derivative CVL.
Plasma for storage	Blood (BLD)	<i>Not applicable</i>	<input type="checkbox"/> EDT (Purple top)	Store as plasma with derivative PL 1/2.

PK Specimens

Mid-period Visit	Blood (BLD) Tenofovir Level		<input type="checkbox"/> Non (red top)	Transport to lab and process within eight hours. Freeze immediately after centrifugation. Store with derivative SER.
Pre-dose	Blood (BLD) Tenofovir Level		<input type="checkbox"/> Non (red top)	Transport to lab and process within eight hours. Freeze immediately after centrifugation. Store with derivative SER.
	Blood (BLD) PBMC		<input type="checkbox"/> CPS (CPT Tube)	The time from blood draw to centrifugation and lysis should be eight hours or less. Store with derivative CEL.
1 Hour	Blood (BLD) Tenofovir Level		<input type="checkbox"/> Non (red top)	Transport to lab and process within eight hours. Freeze immediately after centrifugation. Store with derivative SER.
	Blood (BLD) PBMC		<input type="checkbox"/> CPS (CPT Tube)	The time from blood draw to centrifugation and lysis should be eight hours or less. Store with derivative CEL.
2 Hour	Blood (BLD) Tenofovir Level		<input type="checkbox"/> Non (red top)	Transport to lab and process within eight hours. Freeze immediately after centrifugation. Store with derivative SER.
	Blood (BLD) PBMC		<input type="checkbox"/> CPS (CPT Tube)	The time from blood draw to centrifugation and lysis should be eight hours or less. Store with derivative CEL.

Initials: _____ LDMS Data Entry Date: [][] / [][][] / [][] _____
 Sending Staff Receiving Staff *dd* *MMM* *yy* LDMS Staff

Purpose: This non-DataFax form is used to document collection and entry of MTN 001 specimens (US sites only) into the Laboratory Data Management System (LDMS).

General Information/Instructions: A copy of this form accompanies specimens for storage (in their original specimen collection containers) to the LDMS entry laboratory. Once the specimens have been entered into LDMS, this form is kept on file at the LDMS entry laboratory. If the site chooses, a copy of this completed form may be made once the specimens have been entered into LDMS and the copy kept in the participant's study notebook. This is not required, however. Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

Item-specific Instructions:

- **Visit Code:** Record the visit code of the visit at which the LDMS specimens were collected.
- **NUMBER OF TUBES or SPECIMENS COLLECTED:** In the box to the left of each primary additive type, record the total number of tubes or specimens collected. If no LDMS specimens of the primary specimen type were collected, record "0."
- **Initials – Sending Staff:** The clinic staff person who completed the form and/or who is sending the LDMS form and specimens to the LDMS entry lab, records his/her initials here.
- **Initials - Receiving Staff:** The laboratory staff person who received this form (and the LDMS specimens accompanying the form), records his/her initials here.
- **LDMS Data Entry Date:** Record the date the LDMS specimens listed on this form were entered into LDMS.
- **LDMS Data Entry Date - LDMS Staff:** The LDMS laboratory staff person who entered the specimens into LDMS, records his/her initials here.

Participant ID		Visit Code		Specimen Collection Date		
[][]-[][][][]-[]	[][][][][]	[][]	[][]	[][]	[][][]	[][]
Site Number	Participant Number	Chk		<i>dd</i>	<i>MMM</i>	<i>yy</i>

SPECIMEN TYPE/VISIT	PRIMARY SPECIMEN TYPE	TIME COLLECTED hh:mm 24-hr clock	NUMBER of TUBES or SPECIMENS COLLECTED (Primary additive)	INSTRUCTIONS FOR PROCESSING LAB
4 Hour	Blood (BLD) Tenofovir Level		<input type="checkbox"/> Non (red top)	Transport to lab and process within eight hours. Freeze immediately after centrifugation. Store with derivative SER.
	Blood (BLD) PBMC		<input type="checkbox"/> CPS (CPT Tube)	The time from blood draw to centrifugation and lysis should be eight hours or less. Store with derivative CEL.
6 Hour	Blood (BLD) Tenofovir Level		<input type="checkbox"/> Non (red top)	Transport to lab and process within eight hours. Freeze immediately after centrifugation. Store with derivative SER.
	Blood (BLD) PBMC		<input type="checkbox"/> CPS (CPT Tube)	The time from blood draw to centrifugation and lysis should be eight hours or less. Store with derivative CEL.
8 Hour	Blood (BLD) Tenofovir Level		<input type="checkbox"/> Non (red top)	Transport to lab and process within eight hours. Freeze immediately after centrifugation. Store with derivative SER.
	Blood (BLD) PBMC		<input type="checkbox"/> CPS (CPT Tube)	The time from blood draw to centrifugation and lysis should be eight hours or less. Store with derivative CEL.
<i>Circle correct time point:</i> Pre-dose ___ Hour	Cervicovaginal Lavage (CVL)		<input type="checkbox"/> NSL (saline)	Keep on ice or refrigerate until specimen is frozen long term. Centrifuge and Freeze supernatant within 8 hours of collection. Store with derivative CVL.
	Cervical cytology brush (CER)		<input type="checkbox"/> PBS	Keep on ice or refrigerate until processing for storage. Freeze within 8 hours of collection. Store with derivative CTB.
	Vaginal tissue (VGL)		<input type="checkbox"/> NON	Keep on ice or refrigerate until specimen is frozen long term. Freeze within 8 hours of collection. Store with derivative TIS. Enter location of biopsies in specimen comments.

Initials: _____ LDMS Data Entry Date: [][] / [][][] / [][]
 Sending Staff Receiving Staff *dd* *MMM* *yy* LDMS Staff

Item-specific Instructions:

- **Visit Code:** Check to make sure the Visit Code recorded on page 1 and page 2 match.
- **Specimen Type:** For the three PK genital specimens listed at the bottom of the table, record the time point of collection of these specimens. For example, 2, 4, or 6-Hour. For genital specimens collected pre-dose, circle “Pre-dose”.
- **NUMBER OF TUBES or SPECIMENS COLLECTED:** In the box to the left of each primary additive type, record the total number of tubes or specimens collected. If no LDMS specimens of the primary specimen type were collected, record “0.”
- **Initials – Sending Staff:** The clinic staff person who completed the form and/or who is sending the LDMS form and specimens to the LDMS entry lab, records his/her initials here.
- **Initials - Receiving Staff:** The laboratory staff person who received this form (and the LDMS specimens accompanying the form), records his/her initials here.
- **LDMS Data Entry Date:** Record the date the LDMS specimens listed on this form were entered into LDMS.
- **LDMS Data Entry Date - LDMS Staff:** The LDMS laboratory staff person who entered the specimens into LDMS, records his/her initials here.

Section 14 – Data Communiqués

For MTN 001, SCHARP will use “Data Communiqués” to document and communicate data decisions and procedures that are made or revised during the study. By using Data Communiqués, SCHARP avoids having to re-distribute a revised version of the Data Collection section of this SSP every time a form completion clarification or revision is made.

Data Communiqués are considered official study documentation. As such, each time a Data Communiqué is sent (via email), please circulate it among relevant staff for their review, print the Data Communiqué, and place it in this section of each MTN 001 SSP binder in your possession. Consider each Data Communiqué an official part of the SSP.

Each Data Communiqué sent will consist of three sections: a Reminders section, used to remind sites of specific data collection or forms completion procedures; a Clarification section, used to clarify data collection or form completion procedures; and an Updates section, used to communicate when an updated version of a form is being issued or to notify the sites that an updated version of the forms instructions is about to be distributed (for example).

Note that a “Data Communiqué” does not request specific actions or corrections to a particular participant’s data - it is just a listing of general items to keep in mind when performing data collection for the study.



MTN 001 Data Communiqué #1

June 18, 2008

This is official study documentation for MTN 001. Please circulate it among relevant staff for their review, print it, and place it in your MTN 001 SSP Manual in the Data Communiqués section. This document is considered part of the MTN 001 SSP manual.

UPDATES

None.

CLARIFICATIONS

1. Safety Laboratory Results form, items 1b and 1c

For urine leukocyte esterase (LE) and nitrites, results 1+ or greater are considered “positive”. Negative or trace results are considered “negative”.

2. Enrollment form, instruction off of item 8

Please note that the “*If not a replacement participant, go to item 10*” skip instruction applies to “yes” and “no” responses (and not just “no” responses for item 8).

3. Enrollment Behavior Assessment form, item 9, and Study Product Adherence and Behavior Assessment form, item 15

This question asks about items that women sometimes insert inside their vaginas. Mark the “yes” box only if the participant reports that she inserted the given item *inside* her vagina. If she used the given item for external genital washing *only* (e.g., “water”, “water with soap”, “fingers without anything else”), mark the “no” box.

REMINDERS

None.



MTN 001 Data Communiqué #2

October 28, 2008

This is official study documentation for MTN 001. Please circulate it among relevant staff for their review, print it, and place it in your MTN 001 SSP Manual in the Data Communiqués section (Section 14). This document is considered part of the MTN 001 SSP manual.

UPDATES

1. SCHARP Staffing Changes

Karen Patterson has taken over as sole SCHARP Project Manager on MTN 001. Please contact Karen (karen@scharp.org or karenp@scharp.org) regarding any questions related to data collection or data management in MTN 001.

Sara Jasinski (Jasinski@scharp.org) has replaced Jennifer Schille as the Data Coordinator for MTN 001. Sara is responsible for creating and sending out the Data Quality Control (QC) reports.

2. New Flow Cytometry Form, Dated 10-SEP-08

On 29-SEP-08, SCHARP issued a new Flow Cytometry (FC) form (dated 10-SEP-08) to capture flow cytometry test results of PK specimens collected at each End-of-study period Visit. Those sites with capacity for flow cytometry testing (all sites except Umkomaas and Botha's Hill) are required to complete this form and fax it to SCHARP DataFax. The Cleveland and Pittsburgh sites were instructed to print the form on-site and complete it retrospectively for the participants enrolled at their sites who already completed End-of-study Period Visits. The UAB, Bronx, and Uganda sites will receive hard copies of this form from SCHARP as part of their initial CRF shipment.

3. Revised Study Product Adherence and Behavior Assessment Form, Dated 24-OCT-08

On 27-OCT-08, SCHARP issued a revised Study Product Adherence and Behavior Assessment, dated 24-OCT-08. The form was revised, per decision on the 07-OCT-08 Investigators' Call, to include additional questions on vaginal sex in the past 24 hours and questions on anal study gel use. The Cleveland and Pittsburgh sites were instructed to print the form on-site and replace all old versions (dated 21-MAR-08) of the forms with this new version. All unused old versions of the form must be destroyed, as DataFax will no longer accept new submissions of the old form version as of 28-OCT-08. The UAB, Bronx, Uganda, and Durban sites (Umkomaas and Botha's Hill) will receive hard copies of the revised form from SCHARP as part of their initial CRF shipment.

4. Revised LDMS Specimen Tracking Sheets

A revised version of the MTN 001 US Sites - LDMS Specimen Tracking Sheet version 2.0, dated 10-OCT-08 was issued. No changes were made to page 1, except for the version number and date in the footer. On page 2, the information in the “Instructions for Processing Lab” column was updated for the cervical cytology brush (CER) and vaginal tissue (VGL) specimens. These changes are simply corrections to reflect appropriate lab processing procedures. They do not represent any updates made in protocol version 2.0. No changes were made to the instructions on the back of page 2, except for the version number and date in the footer. The Cleveland and Pittsburgh sites were instructed to print the new version of the sheet on-site and replace all old versions (dated 15-APR-08) of the sheet with this new version. The UAB and Bronx sites will receive hard copies of the revised sheet from SCHARP as part of their initial CRF shipment.

The MTN 001 Africa – LDMS Specimen Tracking Sheet was revised (new version 1.0, dated 03-SEP-08). No changes were made to the front of the sheet, except for the date in the footer. The only content change was to correct the “Purpose” section in the instructions on the back of the sheet by removing the text “(US sites only)”. The Uganda and Durban sites (Umkomaas and Botha’s Hill) will receive hard copies of the revised sheet from SCHARP as part of their initial CRF shipment.

5. Revised Replacement Randomization Documents

Both the US and African site versions of the MTN 001 Replacement Randomization Document were revised. On both versions, the text “Date Envelope Opened” was replaced with “Date” to clarify that these documents do not come in randomization envelopes. Also, the “clinic” copy of the US site MTN 001 Replacement Randomization Document was corrected to state “Intensive PK” instead of “Non-Intensive PK”. The revised documents will be included in the original shipment of MTN 001 randomization materials that SCHARP will send to the Durban, UAB, and Bronx sites. SCHARP will mail the revised documents to the Cleveland, Pittsburgh, and Uganda sites with instructions to dispose of copies of the old version.

CLARIFICATIONS

1. Pelvic Laboratory Results form, item 3 - Pap Smear

For participants who provide adequate documentation of a normal Pap Smear result in the 12 months prior to screening (and thus do not require a Pap test at screening), do **not** record the result on the Pelvic Lab Results form. Instead, item 3 should be marked “Not done/Not collected”. The documentation should be placed in the participant’s chart, and should be documented in the chart notes only. Record on the Pelvic Laboratory Results form, item 3, only those Pap Smear results of Pap specimens collected as part of the study.

2. Documenting Lab Value AEs on the Adverse Experience Log

For AEs of gradable laboratory results (e.g., “Increased ALT”), the date the laboratory report is received should be recorded as the “Date Reported to Site” on the AE Log. The date of specimen collection should be recorded as the “Onset Date” on the AE Log.

3. Documenting Syphilis Results

Per SSP Manual Section 12, sites may choose to conduct TPHA testing only. For sites that do not conduct RPR and titer testing, complete these form items (items 2a-2a1 on the Screening and Enrollment STI Laboratory Results form, and items 2a-2a1 on the STI Laboratory Results form), by lining through the response boxes, and initialing and dating the items.

4. Documenting Auxiliary Temperature on the non-DataFax Physical Exam Form

If possible, measure the participant's temperature orally and record it on the form. If only the auxiliary temperature can be measured, record it on the form by lining through the word "oral", writing "auxiliary", and initialing and dating the correction.

5. Documenting Labial Stretching as a Vaginal Practice

If a participant reports labial stretching as a vaginal practice during the behavioral interviews, please record this practice in item 9g on the Enrollment Behavior Assessment or in item 18g on the Study Product Adherence and Behavior Assessment, dated 24-OCT-08. If a stretched labia is observed during the pelvic exam, and is known to be due to the practice of labial stretching, please record this condition on the non-DataFax Pelvic Exam Diagrams form. Do not record this condition on the Screening and Enrollment Pelvic Exam form or on the Follow-up Pelvic Exam form, as it is considered a variant of normal.

REMINDERS

1. Updating Source Documentation Standard Operating Procedure (SOP)

Each time a new or revised case report form (CRF) is issued, please review your site's MTN 001 Source Documentation SOP. Revise the SOP as necessary to account for the new or revised CRF and send the revised SOP to SCHARP (karen@scharp.org) and FHI (kgomez@fhi.org, sjohnson@fhi.org) for their study records.

MTN 001 Data Communiqué #3

November 7, 2008

This is official study documentation for MTN 001. Please circulate it among relevant staff for their review, print it, and place it in your MTN 001 SSP Manual in the Data Communiqués section. This document is considered part of the MTN 001 SSP manual.

UPDATES

None

CLARIFICATIONS

1. Documenting Contraceptive/Family Planning Methods During Study Follow-up

Sites should assess any changes in participants' family planning methods at each study follow-up visit, and should document this information in the participant chart notes. The documentation should include start dates for any new family planning method reported, and stop dates for any family planning method reported as discontinued. Documentation should also include any reported non-adherence to a given family planning method. If the participant reports no changes since her last study visit, record this in the participant chart notes to document that family planning methods were assessed at the given visit.

The participant chart notes are considered source for family planning data during study follow-up, and should be used as source to complete the Family Planning Methods case report form.

2. Documenting Menstrual History During Study Follow-up

Sites should assess any changes in participants' menstrual cycles at each study follow-up visit, and should document this information in the participant chart notes. Documentation should include the start and stop dates of the participant's last menstrual period, as well as any changes in flow or number of days between menses. Documentation should also include any changes in type and severity of menstrual symptoms. If applicable, report any adverse events (AEs) on the AE Log case report form and grade according to the DAIDS Female Genital Grading Table for Use in Microbicide Studies. (Refer to SSP Manual Section 10.5 for further information on clinical management and documentation of genital bleeding events). If the participant reports no changes since her last study visit, record this in the participant chart notes to document that menstrual history was assessed at the given visit. If the participant is amenorrheic, document the amenorrhea in the participant chart notes. If the amenorrhea is unexpected, also document the associated severity grade (per the DAIDS Female Genital Grading Table for Use in Microbicide Studies), if applicable.

The participant chart notes are considered source for menstrual history data during study follow-up. The chart notes (and not the non-DataFax Follow-up Medical History Log) should be used as source when completing items 1 and 2 on the non-DataFax Genital Bleeding Assessment case report form.

3. Measuring and Documenting Participant Weight

The determination of creatinine clearance by the Cockcroft-Gault equation is required at each regularly scheduled study visit through Week 21, and at interim visits if clinically indicated. The equation requires participant weight. Thus, sites must weigh study participants at each regularly scheduled study visit in order to calculate creatinine

clearance for that visit. Due to weighing scale variability, it is important that the same scales be used at each visit, and that sites calibrate their scales on a weekly basis. In addition, site staff should make sure that study participants are wearing indoor clothing without shoes or other heavy items of clothing when they are weighed. These measures will help ensure that changes in creatinine clearance over time are not due to variability in weight measurement.

Participant weight should be documented on the non-DataFax Physical Exam form completed for a given visit. It is transcribed onto the Pharmacokinetics-Intensive or Pharmacokinetics-Non-intensive form at each mid- and end-of-study period visit, since participant weight is also required for the pharmacokinetics (PK) analysis.

4. Protocol Requirements for Intensive Pharmacokinetic (PK) Specimen Collection Times

At the end-of-study period visits, collection of blood and genital specimens must occur, per protocol, between 30 minutes before and 30 minutes after the assigned sample time AND within 30 minutes of each other. For example, a participant comes to the clinic for her Week 6 Visit. She was randomized to a sampling time of 2 hours post-dose, and takes her observed dose of study product at 9:30 AM. The site should aim to collect her 2-hour post-dose blood and genital specimens at 11:30 AM. At minimum, these specimens should be collected no earlier than 11:00 AM and no later than 12:00 PM. If the blood is collected at 11:40 AM, the genital specimens must be collected between 11:10 AM and 12:00 PM.

For the Week 13 and Week 20 Visits, these specimens must also be collected within 15 minutes of the same time point in which they were collected at Week 6. In the example above, the participant had her 2-hour post-dose blood specimen collected at 11:40 AM, which was 2 hours and 10 minutes after the dosing time. At her Week 13 and Week 20 Visits, site staff should aim to collect her 2-hour post-dose blood specimens 2 hours and 10 minutes after dosing as well.

The protocol allows for intensive PK specimens to be collected within defined ranges of time, as noted in the above examples. However, for purposes of analysis, it is important that sites make effort to collect PK specimens as close to the assigned sampling time as possible.

5. Documenting Anal Study Gel Insertion for Participants in the Oral Study Period

Item 8 on the Study Product Adherence and Behavior Assessment (version dated 24-OCT-08) asks about anal insertion of study gel, and is asked at all mid- and end-of-study period visits. When this question was developed and added to the form, the consensus of the protocol team was to ask this question of all study participants in all study periods. The rationale is that, while participants in the oral study period are not dispensed study gel, use of study gel (including anal use) is still possible in the oral period. For example, there could be sharing of study gel among participants, and use of study gel dispensed during a previous study period (vaginal and/or dual). Since anal insertion of study gel will affect the PK measures, this question is asked at all study periods to maximize the chances of capturing all reported insertions of study gel anally.

Item 8 may cause more confusion when asked at the Week 3 and Week 6 Visits of participants randomized to the oral period first. (In total 24 of the 144 participants slated to enroll in the study will be randomized to the oral period first). For these participants, it is recommended that site interviewers provide participants with further explanation if a participant is in the oral study period and does not understand the question. For example, as follow-up the interviewer can ask the participant if she had any study gel in her possession during the 3-week period in question. If she responds “no”, then the interviewer can clarify with the participant that she did not in fact insert study gel anally, and mark “no” for item 8.

REMINDERS

None

MTN 001 Data Communiqué #4

March 27, 2009

This is official study documentation for MTN 001. Please circulate it among relevant staff for their review, print it, and place it in your MTN 001 SSP Manual in the Data Communiqués section. This document is considered part of the MTN 001 SSP manual.

UPDATES

1. Completion of Behavioral CRFs During Periods of Temporary Hold and Permanent Discontinuation of Study Product

Per Clarification Memo #01 (dated Feb. 3, 2009) to protocol version 2.0, a change in administration of the behavioral, adherence, and acceptability assessments occurs during periods of temporary hold or permanent discontinuation of study product. Guidance on the administration of each assessment CRF is listed below.

Note: For visits in which completion of an assessment is scheduled per protocol, the assessment form pages must be faxed to SCHARP DataFax. If a given assessment is not administered as scheduled due to a study product hold/discontinuation (per the guidance below), faxing of the assessment form pages to SCHARP DataFax is still required. Complete the header (PTID, Visit Code, Visit Date) at the top of each blank form page. Write a note at the top of the first page that states, "Form not administered due to study product [hold/discontinuation]." Initial and date the note. Mark the "No data recorded on this page" box in the upper-right corner of each form page in which it is present. Fax all form pages to SCHARP; these will serve as placeholders in the SCHARP DataFax database and provide documentation in DataFax as to why the data is missing. For assessments that are not administered, staff initials and date at the bottom right-corner of each page are not required.

a. Study Product Adherence and Behavior Assessment

The Study Product Adherence and Behavior CRF (SPA) should be administered at Mid-Study and End-of-Study Period Visits only if study product was dispensed at or after the previous regularly scheduled visit the participant completed. Then, the SPA should not be administered again until such time as the participant resumes study product use, in which case administration of the CRF should resume as scheduled (at all subsequent Mid-Study and End-of-Study Period Visits). For example, a participant is dispensed study product at the 3-Week Visit. She then develops an AE a week later that warrants a temporary hold of study product. The SPA should be administered, as scheduled, at the 6-Week Visit, since the participant was dispensed study product at her previous regularly scheduled visit (3-Week Visit). If the participant's product hold turns into a permanent discontinuation of one of the study products (oral or vaginal), then the SPA should not be administered during any subsequent study period in which the discontinued product would have been used. In this case, if the participant's study product hold resulted in permanent discontinuation of oral study product, and her second and third study periods are "vaginal" and "dual" respectively, then the SPA is administered during the "vaginal" period (assuming vaginal product use) but not administered during the dual product use period. If the participant's product hold turns into a permanent discontinuation of both study products (oral and vaginal), then the SPA is not administered again for the participant (i.e., it is not completed at her remaining Mid-Study and End-of-Study Period Visits). Conversely, if the participant is cleared to use study product and is dispensed study product at the 7-Week Visit, then the SPA is administered, as scheduled, at each of the remaining Mid-Study and End-of-Study Period Visits (assuming no further study product holds or discontinuations).

During periods of study product hold and discontinuation, documentation of the last three doses of study product (i.e., completion of items 2-3 on the SPA) is not required. Mark the “Not done/Not collected” boxes.

b. Product Sharing Assessment

Administration of the Product Sharing Assessment CRF (PSA) is required at the 6-Week Visit for all participants, regardless of whether or not study product was held or permanently discontinued during the first study period, since study product was dispensed at the Enrollment Visit. Administration of the PSA is required at the 13-Week Visit if the participant was dispensed study product at any time during the second study period (7-Week Visit through the 13-Week Visit). Administration of the PSA is required at the 20-Week Study Visit if the participant was dispensed study product at any time during the third study period (14-Week Visit through the 20-Week Visit). If no study product was dispensed during a given study period, then the PSA should not be administered/completed at the End-of-Study Period Visit (6-Week, 13-Week, or 20-Week Visit) for that study period.

c. Acceptability Assessment & Final Acceptability Assessment

Administration of the Acceptability Assessment CRF (AA) is required at the 6-Week Visit if the participant used at least one dose of study product during the first study period (Enrollment Visit through the 6-Week Visit). Administration of the AA is required at the 13-Week Visit if the participant used at least one dose of study product during the second study period (7-Week Visit through the 13-Week Visit). Administration of the Final Acceptability Assessment CRF (FAA) is required at the 20-Week Study Visit if the participant used at least one dose of study product during the third study period (14-Week Visit through the 20-Week Visit). If no study product was used during a given study period, then the assessment of acceptability for that period (AA or FAA) should not be administered/completed.

CLARIFICATIONS

1. Documenting Genital Adverse Events (AEs)

As a general guideline for all genital AEs, please record in item 1 of the AE log the appropriate term as it is printed in the DAIDS Female Genital Toxicity Table. This ensures consistency in reporting/MedDRA coding across sites.

REMINDERS

1. Documenting AEs Assessed as “Not Related” to Study Product

If the “Not related” box is marked for item 4 on the AE Log, an alternate etiology for the AE must be recorded in the Comments section of the AE Log.

2. Documenting Genital Bleeding Events

To maintain consistency in AE reporting across all MTN trials, the MTN has developed and uses standard terminology for reporting genital bleeding events. Please refer to section 10.5 of the Study-specific Procedures Manual (SSP) for detailed information on assessing genital bleeding, and for specific terms to use when completing the AE Log form (item 1). If the bleeding is a result of a pelvic exam finding, then record the name and location of the finding (e.g., “vaginal laceration”) as the AE (item 1) on the AE Log form.

For genital bleeding events in which the bleeding is not observed on exam (participant-reported only), or the bleeding is observed on exam but the source cannot be identified, please complete the non-DataFax Genital Bleeding Assessment form. This form serves as a tool to help sites determine whether or not an event is expected, and thus should not be reported as an AE, or if an event is *unexpected*, and thus should be reported as an AE on the AE Log form. For unexpected events, the form also lists out the possible AE terms to record in item 1 of the AE Log form.



MTN 001 Data Communiqué #5 - **REVISED**

September 3, 2009

This is official study documentation for MTN 001. Please circulate it among relevant staff for their review, print it, and place it in your MTN 001 SSP Manual in the Data Communiqués section. This document is considered part of the MTN 001 SSP manual.

UPDATES

1. New SCHARP Clinical Affairs Safety Associate

Molly Swenson has replaced Donna Robinett as the MTN-001 SCHARP Clinical Affairs Safety Associate. Molly is responsible for identifying and placing clinical QCs, and works closely with the Protocol Safety Monitoring Team (PSRT) to monitor MTN-001 safety data. Molly can be reached by e-mail (mollys@scharp.org) or by phone (206-667-5410).

2. New Rectal PK form and Updated Page 2 LDMS Specimen Tracking Sheet, Dated 17-AUG-09

On 17-AUG-09, SCHARP issued a new Rectal PK (RPK) form and updated page 2 (version 3.0) of the LDMS Specimen Tracking Sheet (non-DataFax) for use by the Bronx-Lebanon Hospital site only. Both the new form and updated page reflect the addition of optional rectal PK specimen collection at the Bronx site, per Letter of Amendment #1, dated 07-JUL-09. SCHARP will ship hard copies of both the form and the updated LDMS Specimen Tracking Sheet page to the Bronx site.

CLARIFICATIONS

1. Documenting Genital Bleeding

All cases of participant-reported genital bleeding occurring between usual menstrual periods will be documented on the Baseline Genital Symptoms form (at enrollment) or the Follow-up Genital Symptoms form (at follow-up visits). The non-DataFax Pelvic Exam Diagrams form is used to record all pelvic exam findings, both normal and abnormal. This means that all clinically observed genital blood/bleeding, whether expected, unexpected, menstrual, or non-menstrual, should be documented on the non-DataFax Pelvic Exam Diagrams form. In contrast, the Screening and Enrollment Pelvic Exam form and Follow-up Pelvic Exam form are used to record only abnormal pelvic exam findings. This means that only unexpected menstrual bleeding (excluding early menses) and unexpected non-menstrual bleeding should be recorded on these forms.

Expected non-menstrual bleeding should not be reported as an AE. This may include a small amount of cervical bleeding that can occur with speculum insertion or specimen collection, provided the IoR or designee deems the amount of bleeding to be within the range of normal. If the cervical bleeding observed with speculum insertion or specimen collection exceeds that which is expected, in the opinion of the IoR or designee, then the cervical bleeding should be recorded as an AE of “cervical friability”, and graded according to the “Cervical edema and friability” row of the Female Genital Toxicity Table.

If it is unclear whether a genital bleeding event (during follow-up) is expected or unexpected, complete the non-DataFax Genital Bleeding Assessment form.

2. Week 21 In-depth Interviews for Replacement Participants

Participants who are randomized to the Week 21 in-depth interviews should only complete these interviews if they are evaluable participants (i.e., they have been dispensed study product at least once and have returned to report on study product use at least once in *each* of the three study periods). If a participant who is randomized to the Week 21 interview is not evaluable, she will need to be replaced. The replacement participant (who receives the exact same randomization assignments as the woman she is replacing) should complete the Week 21 interview instead, provided that the replacement participant proves to be evaluable.

3. Split Visits

Split visits (i.e., procedures for a given visit that are conducted on more than one date) are allowed for all visits except the Enrollment Visit. All Enrollment Visit procedures must be conducted on the same day, with the exception of informed consent for enrollment and specimen storage, which may take place at a prior date within the 30-day screening window. The Screening Visit may occur on multiple dates within the 30-day screening window, and follow-up visit procedures may be conducted over more than one date, provided that all dates are within the allowable visit window.

Note that end-of-study period PK procedures cannot be split across days; the end-of-study period PK procedures must all be completed on the same day (see SSP Manual Section 6-Participant Follow-up for more information on PK procedures). Also, note that the Study Product Adherence and Behavior Assessment must be completed on the same day as the end-of-study period PK procedures.

See Section 13.3.3 of the SSP Manual for information on assigning visit codes to split visits.

4. Assigning Interim Visit Codes

A clinic visit is considered an Interim Visit when a participant presents at the site for reasons *other* than to complete required study visit procedures. Interim visits may be performed at any time during the study for reasons that may be administrative (a participant has study-related questions for the staff), product-related (a participant needs additional study product), lab-related (a participant needs a safety lab test repeated for confirmation), or clinical in nature (a participant needs management and/or follow-up of an AE), etc.

A phone call is considered an Interim Visit when it results in the reporting of a new AE. A phone call is also considered an Interim Visit if, on the call, site staff instruct the participant to hold study product, permanently discontinue study product, or resume study product use after a previous hold.

NOTE: *not all interim visits are assigned interim visit codes. An interim visit should be assigned an interim visit code only if 1) data collected at the visit warrants completion of a new DataFax form, such as an AE Log or Product Hold/Discontinuation (PH) Log form, or 2) product use was previously held and is now being resumed, resulting in an update to the PH Log form (items 4-4a). An Interim Visit form must be completed for each and every visit that is assigned an interim visit code. See section 13.3.3 of the SSP Manual for instructions on assigning interim visit codes.*

5. Recording Returned and Dispensed Study Product Counts At End-of-study Period Visits

The Follow-up Visit (FV) form captures the number of unused study applicators (item 3) and unused study tablets (item 4) that a participant returns at a given regularly scheduled follow-up visit. At the end-of-study period visits (Weeks 6, 13, and 20), if one returned unused applicator and/or tablet is used for the in-clinic observed PK dose, do not include that used applicator and/or tablet in the responses to items 3 and 4. For example, a participant presents

for her Week 6 Visit (dual use period) and returns 7 unused applicators and 9 unused tablets. The participant uses one of these applicators and takes one of these tablets for the in-clinic observed PK doses. Thus, on the FV form completed for the Week 6 Visit, site staff should record “06” as the response for item 3, and “08” as the response for item 4.

If, at the end-of-study period visits, a participant does not return unused product (or the product returned is deemed unsuitable for use), one additional study applicator and/or study tablet may be dispensed for the in-clinic observed PK dose. Do include this dispensation in the responses to items 5 (number of applicators dispensed) and 6 (number of tablets dispensed) on the FV form.

6. Recording Urine Dipstick Results

When urine dipstick testing is required per protocol, only the following analytes are required for study purposes: protein, leukocyte esterase (LE), nitrites, and culture (if positive for LE or nitrites; may be omitted if culture is not a part of a site’s standard of care for UTI diagnosis). These results must be recorded on the Safety Laboratory Results form. If a site’s urine dipstick testing yields additional results, such as glucose or blood, these additional results must be documented in the participant’s study records in the form of a local lab report, chart note, or other participant-specific document developed by the site.

7. Early Study Terminations

If a participant reports that she wishes to discontinue her participation in the study, ask if she would be willing to complete an early Study Exit Visit, or at least a final blood draw (for safety labs and HIV testing) and urine collection (for pregnancy testing). Please document her response in her chart notes. If the participant is willing to complete an early Study Exit Visit, complete all Week 21 Visit procedures and CRFs (except complete the Interim Visit form instead of the Follow-up Visit form). Assign the appropriate interim visit code to the early Study Exit Visit. If the participant is only willing to give blood and urine (for safety labs, HIV, and pregnancy testing), complete the following CRFs: Interim Visit, Safety Laboratory Results, STI Laboratory Results, Termination, and End of Study Inventory. If the participant is unwilling to complete any additional study procedures, complete a Termination form and End of Study Inventory form, and fax these forms to SCHARP.

REMINDERS

1. Grading Lab Values According to the DAIDS Toxicity Table

Depending on a site’s normal reference ranges, it is possible that a participant can have a value that falls within the site’s normal range, but is still gradable per the DAIDS Toxicity Table. Always refer to the DAIDS Toxicity Table to determine whether or not a lab value is gradable. For gradable lab values that occur during follow-up (and are not otherwise associated with a clinical diagnosis), refer to the participant’s previous value for the given assay to determine whether or not there is an increase in severity that warrants reporting of a new AE.

2. Completing the Safety Laboratory Results (SL) Form for Gradable Lab Values

If a lab value is gradable per the DAIDS Toxicity Table, regardless of whether the specimen was collected at screening, enrollment, or during follow-up, record the severity grade in the “Severity Grade” box. Record the “AE Log Page #” if the gradable lab value is reportable as a stand-alone AE (e.g., “proteinuria”), or is part of a clinical AE (e.g., “urinary tract infection”). If a gradable lab value does not meet the criteria for AE reporting (i.e., the specimen was collected at screening or enrollment, or the severity grade represents an ongoing pre-existing condition), mark the “Not Reportable as an AE” box. If a severity grade is recorded in the “Severity Grade” box, either an “AE Log Page #” must be recorded, or the “Not reportable as an AE” box must be marked. The same “AE Log Page #” may be recorded for the same item on SL forms completed at consecutive visits, for example, if a lab value AE persists at the same or lesser severity across study visits.

3. Reporting AEs of Gradable Lab Values

When reporting gradable lab value AEs, site staff should first consider whether or not the participant received (or was offered) treatment for the condition. This will determine the text that site staff should record for item 1 on the AE Log form. If the participant did receive (or was offered) treatment for the condition, record a diagnosis for item 1. For example, if a participant has a gradable decreased phosphate value and receives treatment for it, then site staff should record the item 1 text as “hypophosphatemia”. (For purposes of AE reporting, treatment is not limited to the prescribing of medications. In this example, treatment may include a site clinician’s recommendation that the participant supplement her diet with phosphate-rich foods). If the participant is asymptomatic or is not prescribed treatment for the gradable lab value, then site staff should record in item 1 the lab value with the direction of abnormality (increased or decreased). In this example, site staff would record “decreased phosphate” as the text for item 1.

The “Date Reported to Site” on the AE Log form should be the date that site clinic staff first become aware of the gradable lab value. For safety labs, this will be the date the lab report is received at the site clinic. The “Onset Date” (item 2) on the AE Log form should be the date of specimen collection. The “Status/Outcome Date” (item 6a) should be the collection date of the follow-up specimen that yields one of the following: 1) a non-gradable result, 2) a return to baseline severity (if the AE represents the worsening of an ongoing baseline condition), or 3) a result of increased severity (thus requiring completion of a new AE Log). For item 10, record the visit code that is assigned to the specimen collection date; this should be the same visit code that is assigned to the AE “Onset Date”.

4. CBC and Differential Testing

Per protocol, CBC testing is required during follow-up for all participants at the Week 7, Week 14, and Week 21 Visits; differential testing is *not* required at these visits. However, for sites conducting flow cytometry, CBC testing with differential is required at each of the end-of-study period visits (Weeks 6, 13, and 20) to obtain the lymphocyte counts needed for flow cytometry calculations and completion of the Flow Cytometry form.

Note: Differential testing may yield results, such as neutrophils or lymphocytes, that are not recorded on the case report forms. However, if the results during follow-up show a new onset or increase in severity of gradable neutrophil or lymphocyte values (per the DAIDS Toxicity Table), the gradable values must be reported as AEs on the AE Log form.

5. Rounding Lab Values

There may be times when a site must round a given lab value in order to record the result on the appropriate case report form. In these instances, sites must consider *only* the digit to the right of the desired place when rounding. For example, item 3c1 on the Safety Laboratory Results form is used to record calculated creatinine clearance as a 3-digit whole number. If the site calculates the creatinine clearance value as 132.4678 mL/min, then only the tenths digit (the “.4”) is considered when rounding, and the result should be recorded on the form as “132”.

6. Calculating Creatinine Clearance

When calculating creatinine clearance, please remember to use the MTN 001 Creatinine Clearance Calculator that is posted on the MTN web site. Remember to enter the participant’s age at the time of specimen collection (for serum creatinine testing), enter the participant’s weight as a whole number in kilograms, and enter the serum creatinine value in mg/dL rounded to the nearest tenths digit (per the above instructions in Reminder #5). The serum creatinine value used in the MTN 001 Creatinine Clearance Calculator should be identical to the serum creatinine value documented on the Safety Laboratory Results form.

Note: SCHARP is unable to check the accuracy of creatinine clearance calculations at the Screening, Enrollment, Week 7, 14, 21 and Interim Visits, as weight data is not captured on the CRFs or entered into the DataFax database for these visits. Therefore, it is especially important that sites follow the above guidance when calculating creatinine clearance at these visits, in order to ensure that the calculations are correct.

7. Completing Behavioral, Adherence, and Acceptability CRFs

The MTN 001 Enrollment Behavior Assessment, Study Product Adherence and Behavior Assessment, Product Sharing Assessment, Acceptability Assessment, and Final Acceptability Assessment are interviewer-administered forms. Participant responses are recorded directly onto the forms so that the forms themselves serve as source documents. No changes or updates to the forms should be made once the forms are administered and the interviews in which they are administered are complete. This is especially important since risk reduction and adherence counseling that occurs after the interviews have the potential to bias participant responses.

These forms capture primary and secondary endpoint data. To ensure that this data is complete and accurate, it is crucial that the interviewer review the completed form at the end of the interview, while the participant is still in front of him or her. This way, any missing data or inconsistencies can be resolved with the participant while she is still present with the interviewer. Specifically, the interviewer should make sure that all skip patterns are followed to ensure that all items requiring a response have a response, and all items that should be skipped are left blank.

With the understanding that this data is source, SCHARP will only QC these forms if: 1) a key field, such as a PTID, visit code, or visit date is missing or has an error, 2) an item should have been left blank per the skip pattern, but has a response (the QC will ask for the response to be deleted by lining through it, initialing and dating), and 3) an item should have a response but was left blank (the QC will ask for the response boxes to be lined through, for “missing” to be written next to the lined through boxes, and for the item to be initialed and dated).



MTN 001 Data Communiqué #6

December 18, 2009

This is official study documentation for MTN 001. Please circulate it among relevant staff for their review, print it, and place it in your MTN 001 SSP Manual in the Data Communiqués section. This document is considered part of the MTN 001 SSP manual.

UPDATES

1. New SCHARP Clinical Affairs Safety Associate

Yevgeny Grigoriev will take over as the MTN-001 SCHARP Clinical Affairs Safety Associate while Molly Swenson is on maternity leave. Yevgeny will be responsible for identifying and placing clinical QCs, and works closely with the Protocol Safety Monitoring Team (PSRT) to monitor MTN-001 safety data. He can be reached by e-mail (ygrigori@scharp.org) or by phone (206-667-3440).

CLARIFICATIONS

1. Missing Page QCs

SCHARP asks each site to fax completed CRFs to SCHARP DataFax ideally within 1-2 days and up to 5 days after a given visit date. This is documented in each site's Data Management Standard Operating Procedures (SOP). (Exceptions are made for laboratory forms, log forms, and screening forms). If no CRFs are faxed to SCHARP DataFax for a given follow-up visit, SCHARP will not QC for missing forms for that visit until the visit window has closed. However, if one or more forms are faxed to SCHARP DataFax for a given visit, then DataFax will immediately QC for any required forms that are still missing for that visit (even if the visit window has not yet closed). For example, if a site laboratory faxes the Flow Cytometry form to SCHARP for the Week 6 Visit, and the site clinic has not yet faxed any Week 6 Visit CRFs for the participant, then DataFax will QC for the missing Week 6 Visit CRFs. The receipt of the Week 6 Flow Cytometry form will immediately trigger DataFax to QC for the rest of the required Week 6 Visit CRFs, even if the participant's Week 6 visit window has not yet closed. This is expected and is simply a function of DataFax technology. While it is important that sites follow up on these missing pages by completing the forms and faxing them to SCHARP, please note that these "missing page" QCs do not count against sites in the Data Management Quality Reports. These QCs will only raise concern and prompt SCHARP to follow-up with sites if they indicate that sites are not faxing CRFs to SCHARP within the specified time frame.

2. Documenting Number of Completed Adverse Event Log Pages on the Follow-up Visit and Interim Visit Forms

Item 2a of the Follow-up Visit (FV) form and item 3e1 of the Interim Visit (IV) form ask how many new Adverse Event (AE) Log pages were completed for a participant at a given visit. This number includes all AE Log forms with the visit code of the given visit recorded in item 10; even AE Log forms that are subsequently marked for deletion. For example, at visit 3.0 two AEs are reported for a given participant.

Each AE is recorded on an AE Log form with visit code "03.0" recorded in item 10. The second AE is later marked for deletion, since it was found to be a pre-existing condition. The response to FV-1 item 2a should remain "02" to indicate that two AE Log pages were completed for visit 3.0.

Deleted AE Log pages are still accounted for on the FV and IV forms since deleted AE Log pages remain in the database for regulatory purposes.

3. Documenting Highest Page Number Submitted for AE Logs and Product Hold/Discontinuation Logs

Item 3a on the End of Study Inventory Form (ESI) asks for the highest AE Log page number submitted to SCHARP, and item 3d asks for the highest Product Hold/Discontinuation (PH) Log page number submitted to SCHARP for a participant during her MTN 001 study participation. Record the highest log page numbers submitted, even if the logs with the highest page number were marked for deletion.

Deleted AE Log pages and deleted PH Log pages are still accounted for on the ESI form, since these deleted pages remain in the database for regulatory purposes.

4. Recording Topical Medication Use on the Concomitant Medications (CM) Log

When recording topical medication use on the CM Log, record the generic name of the medication in the "Medication" field, and include the percentage of active ingredient(s) if known. For example, "miconazole nitrate 2% cream". For "Dose/Units", record the dose in cubic-centimeters (cc) or milligrams (mg), if known. If the exact quantity is unknown, record the number of applications instead, for example, "1 application".

5. Recording Injections on the Concomitant Medications (CM) Log

Record each injection (e.g., Depo-Provera injection) as its own separate entry, so that the "Date Started" and "Date Stopped" are the same date. Mark the "once" box for "Frequency" and the appropriate box for "Route" (e.g., "IM", or "Other" for subcutaneous injections).

6. Recording Specimen Weights on the Rectal PK Form

When recording weights in items 2a-2c, include the weight of the sponge, insertion tube, AND cryovial.

REMINDERS

1. Fax Times for Enrollment and AE Log Forms

To ensure that SCHARP reports reflect accurate and current data, please fax Enrollment forms to SCHARP DataFax within 1-2 working days after the visit date, and fax AE Log forms to SCHARP within 1 working day after the visit date.

2. Assigning Severity Grade to Phosphate Values

All study phosphate values must be graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 1.0, December 2004; Clarification August 2009). Depending on a site's local laboratory reference ranges, it is possible for a participant's phosphate value to fall within a site's normal range, but still be gradable according to the DAIDS Table.

Per the DAIDS Table, the grade 1 range for serum phosphate is 2.50 mg/dL to < LLN. If a site's lower limit of normal (LLN) is less than or equal to 2.50 mg/dL, then the grade 1 range for that site is simply the value 2.50 mg/dL.

3. Using the Creatinine Clearance Calculator Worksheets

When calculating creatinine clearance, please use the version of the MTN 001 Creatinine Clearance Calculator that is appropriate for your site. Specifically, if your site's local lab reports serum creatinine results in units of $\mu\text{mol/L}$, please use the calculator with the link "Calculated Creatinine Clearance Worksheet CONVERT". Enter the serum creatinine result in $\mu\text{mol/L}$ into the worksheet, and the worksheet will automatically convert the serum creatinine result to units of mg/dL (rounded to the nearest tenths digit). This converted value should be transcribed onto the Safety Laboratory Results CRF exactly as it appears in the worksheet

If your site's local lab reports serum creatinine results in units of mg/dL, no conversion is needed. Please use the calculator with the link "Calculated Creatinine Clearance Worksheet NO CONVERT" to calculate creatinine clearance at your site. Enter into the worksheet the serum creatinine result rounded to the nearest tenths digit, exactly as it appears on the Safety Laboratory Results CRF.

The MTN 001 Creatinine Clearance Calculators are posted on the MTN web site on the MTN 001 Study Implementation Materials page, which can be found at: <http://www.mtnstopshiv.org/node/371>.

Section 15 - Study Reporting Plan

MTN 001 Statistical and Data Management Center (SDMC) Staff

Protocol Statistician:	Barbra Richardson
Project Manager:	Karen Patterson
Statistical Research Associates:	Fang Gai, Sharavi Gandham
Protocol Programmer:	Jackie Fitzpatrick
Data Coordinator:	Sara Jasinski
Document Specialist:	Lori Filipcic
Reporting Programmer	Kate Bader
Laboratory Programmer:	Laura Robins-Morris
Clinical Affairs Safety Associate	Donna Robinett

15.1 Purpose of Reporting Plan

The purpose of this reporting plan is to describe the reports that the MTN SDMC (SCHARP) plans to generate for MTN 001.

The specific purposes of this plan are:

- To identify the purpose and content of each report;
- To identify those responsible for the preparation and distribution of each report;
- To identify who should review the reports so that corrective action (if necessary) is taken; and
- To ensure the Protocol Team approves the plan prior to study initiation.

This reporting plan was prepared by the MTN 001 SDMC Project Manager in collaboration with other MTN 001 SDMC staff.

15.2 Study Reports

Table 15-1 lists the reports the SDMC will produce and distribute via email. Table 15-2 lists the reports the SDMC will produce and make available via the Atlas website:

<http://atlas.scharp.org>

Following the tables is a description of each report that includes the purpose of the report, who will prepare the report, and specific components of the report.

Table 15-1: MTN 001 SDMC Reports Distributed via Email

Report Title	Distribution Frequency	Email Distribution List
Data Quality Control (QC)	Every two weeks, or as needed	<ul style="list-style-type: none"> • Site Study Coordinators • Site Data Managers • CORE Clinical Research Managers • SDMC Project Manager
Clinical Data Quality Control (CQC) Queries	As needed	<ul style="list-style-type: none"> • Site Study Coordinators • Site Data Managers • CORE Clinical Research Managers • SDMC Project Manager
Study Monitoring Committee (SMC)	As determined by the SMC	<ul style="list-style-type: none"> • MTN 001 SMC members and observers • MTN 001 Protocol Chair • MTN 001 Site Investigators
Site Specimen Monitoring Report	Monthly	<ul style="list-style-type: none"> • Site Study Coordinators • Network Lab Representative • SDMC Project Manager
Summary Specimen Monitoring Report	Monthly	<ul style="list-style-type: none"> • Network Lab Representative • SDMC Project Manager

Table 15-2: MTN 001 SDMC Reports Posted on Atlas

Report Title	Update Frequency	Atlas Viewing Area
Enrollment and Retention	Daily	Unsecure
Visit Adherence and Procedure Completion	Monthly	Unsecure
Site Data Management Quality	Monthly	Unsecure
Safety Report	One week prior to each scheduled PSRT call	Secure
Network Lab Assay Results Report	Monthly	Unsecure

15.2.1 Data Quality Control (QC) Report

Purpose: To identify and help correct missing and inconsistent data
Prepared and Distributed by: SDMC Data Coordinator
Components: Quality control notes; overdue visit reminders, missing page reminders

15.2.2 Clinical Data Quality Control (CQC) Queries

Purpose: To identify and help correct inconsistencies/questions identified in safety or clinical data
Prepared and Distributed by: SDMC Clinical Affairs Safety Associate
Components: Queries containing clinically-based questions about safety and clinical data.

15.2.3 Study Monitoring Committee Report

Purpose: To monitor study progress at each site
Prepared and Distributed by: Prepared by SDMC MTN 001 staff and distributed by SDMC Project Manager
Components: Summary by site and for the study overall of study design and history, accrual, retention, demographics, visit adherence. Site data management quality, and other components as requested by the SMC.

15.2.4 Site Specimen Monitoring Report

Purpose: To monitor storage in LDMS of those specimens marked as “stored” on study CRFs
Prepared by: SDMC Laboratory Programmer
Components: Site-specific listing of all discrepancies between the CRF stored specimen data and LDMS data.

15.2.5 Summary Specimen Monitoring Report

Purpose: To monitor storage in LDMS of those specimens marked as “stored” on study CRFs across all sites
Prepared by: SDMC Laboratory Programmer
Components: Summary listing for all sites of all discrepancies between the CRF stored specimen data and LDMS data.

15.2.6 Enrollment and Retention Report

Purpose: To monitor participant accrual and retention as reflected by data submitted to the SDMC (via DataFax)
Prepared by: SDMC Protocol Programmer
Components: Enrollment, includes the number of women enrolled each week and cumulatively. Retention, by visit. Includes: total enrolled (broken down by active, inappropriately enrolled, and lost to follow-up); number expected for a given visit; number not expected for a given visit; and total retention by visit calculated as the number of participants who have completed a visit divided by the total number of participants expected for the visit.

15.2.7 Visit Adherence and Procedure Completion Report

Purpose: To summarize site performance regarding study endpoint data collection

Prepared by: SDMC Statistical Research Associate

Components: Distribution of visits, including the number of days between target and actual visit dates, and the number of days between sequential follow-up visits. Listing of number and % of required PK blood specimens collected, genital specimens collected, safety lab tests completed, pelvic exams completed, pregnancy tests completed, and HIV tests completed.

15.2.8 Site Data Management Quality Report

Purpose: To summarize site performance regarding data management and quality.

Prepared by: SDMC Project Manager

Components: Total number of CRF pages faxed to SCHARP, total number of QCs applied, % of QCs resolved, QC rate per 100 CRF pages, and mean days to fax in CRF pages. Reported cumulatively and for the previous month.

15.2.9 Safety Report

Purpose: To help the Protocol Safety Review Team monitor study participant safety as reflected by adverse experiences reported to the SDMC (via DataFax).

Prepared by: SDMC Reporting Programmer and SDMC Clinical Affairs Safety Associate

Components: Cumulative AE data reported to SCHARP via DataFax.

15.2.10 Network Lab Assay Results Report

Purpose: To monitor the receipt of lab assay results from the Network Lab.

Prepared by: SDMC Laboratory Programmer

Components: For each specimen analyzed by a Network Lab, the number of results expected (per CRF data) along with the number and percentage of results received and processed at SCHARP.

Section 16. Week 21 In-Depth Interviews

This section provides information on requirements and procedures for conducting, transcribing, translating, and managing data for week 21 in-depth interviews in MTN 001.

16.1 Introduction

Qualitative data collection (in-depth interviews) will be conducted with a random sample of approximately **forty** randomly selected participants total at five sites participating in this study activity to explore use of study drugs and male condoms during the trial.

Interviews will be conducted by a trained study interviewer using a semi-structured interview guide that has been prepared to collect data on:

- Challenges to use of study products
- Perceived benefits of use
- Preferences between oral and vaginal formulations
- Preferences between a single and dual use regimen
- Partner knowledge of study participation and reaction to product use
- Who knew that they had access to anti-retroviral drugs
- Whether they were ever asked to share (or sell) the product or if someone tried to take it away from them

These in-depth interviews directed by the structured interview guide will provide an opportunity to explore the adherence and acceptability research objectives in greater depth. Interviews will be conducted in a designated private space just before the participants leave the clinic.

16.2 Target number of participants

The Statistical Center for HIV/AIDS Research and Prevention (SCHARP) will generate and maintain the study randomization scheme, randomly selecting a total of about **forty** participants at five participating sites to complete the week 21 in-depth interviews. Site clinic staff will inform participants if they have been randomized to the 21-Week In-Depth Interviews during the randomization process (see Section 4.2.7). The MTN 001 Randomization Envelopes will contain a two-part no carbon required (NCR) Randomization Document that will indicate whether the participant has been randomly assigned to complete the in-depth interview at Week 21. Each site should develop a procedure through which they can easily identify the participants randomized to the Week 21 interviews. For example, a site might choose to place a yellow sticker on the front of each of the study notebooks of participants who have been randomized to complete the week 21 in-depth interview, so that these participants can be identified when they return for their week 21 visit. These participants will be asked, during the informed consent process, to consent to the in-depth interview (SSP section 16.4.2). At the 20-week study visit, site clinic staff should remind participants who consented to the in-depth interview that they will complete this interview at their next study visit.

Participants who are asked, but do not consent to the in-depth interview, will not complete the interview. In addition, participants who meet the criteria for replacement (SSP section 4.2.7.1) will not participate in the in-depth interviews. If a participant is randomized to the in-depth interview at enrollment, but subsequently meets the criteria for replacement, she will not complete the in-depth interview; rather, the participant enrolled to replace her will receive the same randomization assignments and will complete the in-depth interview in lieu of the original participant.

16.3 Differential Adherence

The purpose of the in-depth interviews is to collect qualitative data on participants who represent differing levels of adherence to study product (i.e., participants who report better adherence to study gel than study tablets, or vice-versa, or participants who report low or high adherence to both study gel and study tablets). In the event that the participants who are randomized to and complete the in-depth interviews do not represent differing levels of adherence, site staff, with input from the behavioral researchers, may select up to two additional study participants (who report differential study product adherence or who they believe would be good informants about product adherence) to complete the in-depth interview.

16.3.1 Identification of participants reporting differential adherence and/or participants who may be good informants about product adherence

SCHARP will periodically send the behavioral researchers at RTI a listing of the adherence data reported by the participants randomized to the in-depth interviews (as documented on the Case Report Forms). The behavioral researchers will review this listing and assess whether or not the data represent different levels of adherence to study products. In the event that the randomized participants at each participating site do not represent different levels of adherence to study products, the behavioral research team will work with the site to identify **up to two** additional participants to complete the week 21 in-depth interviews. These additional participants may be chosen based on differential reporting of adherence to study products (as documented on the Case Report Forms). They may also be chosen if they are identified by site staff as excellent informants (based on specific experiences they may have had using study product(s) or other comments they may have shared with site staff during study visits). If additional participants are needed for the in-depth interview, and if a site identifies a participant that may be a good candidate to participate in the interview (i.e., a participant that represents atypical adherence to study product, or a participant likely to be an excellent informant on study product experiences), the rationale will be communicated and discussed with the behavioral researchers. Participants whom study staff and behavioral researchers have identified as eligible and good candidates for the week-21 in-depth interview may be asked by site staff at the 20-week study visit if they would be willing to complete the in-depth interview at their next study visit. Those participants who are asked and who have consented to the in-depth interviews will complete the interviews at their respective 21-Week study visit.

16.4 Data Collection

During the 21-Week in-depth interview process, the conversation will be recorded to ensure that all participant-provided information has been collected appropriately. In addition to recording of the interview, the interviewer will take notes on his/hers observations during the interview. Therefore, the interview data will consist of voice files, text files of the interview transcripts, and interviewer observational notes.

16.4.1 General Preparation Prior to Interview: Checklists

In preparation for the interview, assemble and bring all necessary items to the interview room, including:

- Interview guide
- Digital tape recorder with a 128MB memory stick, a spare 8MB memory stick, and spare batteries
- Notebook, pencils and/or pens
- Clock or watch to time the interview
- Register, re-imburement log and vouchers/cash [site specific]

To ensure the interview is successful, it is important to prepare prior to the study visit by:

- Preparing the private and confidential room where the interview will be conducted, including arranging the furniture, placing a “Do Not Disturb” sign on the door, and ensuring that all materials are available.
- Check the battery life meter on the digital recorder and make sure you have a full dark colored bar. For each interview, use new batteries just to be sure. Old batteries can be used for transcription.
- Make sure that you are familiar with the way your digital recorder works. Test it and practice recording until you are confident about how to use it correctly (see section 16.4.5).
- Be aware of ambient noise, such as fans, street noise, etc. Place the recorder where it can record the participant’s voice clearly, while still being monitored by the facilitating team. You should test the sound quality in advance.
- Be on time for the interview. It is very important to respect participants’ time.

16.4.2 Reiterating Informed Consent

As part of the enrollment informed consent process, participants will provide consent to participate in a recorded in-depth interview. Before the interview, it is important to review with the participant the information regarding the interviews that was provided to her during the enrollment process. Also, it is important to remind participants that every effort will be made to keep confidential all information that she provides in the interview. Please note that all participants assigned to complete the in-depth interview, whether through randomization or site selection, must sign an informed consent form before they participate in the in-depth interview.

16.4.3 Style of Interviewing

Below are some general tips to keep in mind when interviewing:

- Build rapport. Start with an informal chat on a topic that will be of interest to the participant. For example, try to link the MTN-001 trial with issues/events in the community.
- Motivate the participant to tell her story by showing sincere interest in what she is sharing through eye contact and probing. Silence can also be helpful (see section 13.5 for interviewing techniques).

- Remain non-judgmental. Show understanding but do not show approval or disapproval, or share your own personal experiences. Show respect, acceptance and emotional support through empathetic tone of voice, gestures, responsive facial expression, nods, etc. Use expressions such as “I see” and “that’s interesting,” which show that the interviewer is paying attention without suggesting agreement or disagreement.
- Do not interrupt the participant. Sometimes interviewers are so determined to get their point across that they interrupt and speak "over" the respondent. This is not only inappropriate behavior for the interviewer, but when individuals speak simultaneously the voice recording is unclear and valuable information may be lost as a result.
- A good interviewer listens attentively to every word and sentence, observes gestures, symbols, pauses, and emotions. Take record of all these.
- There are no desirable or undesirable answers. Your manner should reflect great interest and compassion and this will encourage participants to share deeply their experiences.
- “Difficult” questions should be asked when you sense that the conversation is relaxed and you have won the trust of the participant. The questions in the guides are arranged in a progressive order, from the general ones to the more specific.
- Be especially sensitive to the effect the conversation may be having on the participant and how comfortable you are yourself in handling these questions, especially when discussing sexual issues.
- “Difficult” questions can be asked repeatedly in different ways at different points during the interview.
- Sometimes qualitative interviews can bring out strong emotions in a participant. The interviewer can change the topic, stop the interview to allow her to vent her emotions and/or shift to a neutral topic.
- Sometimes participants give answers that they think we want to hear or that they think are expected by the trial, e.g. used condoms all the time. The interviewer can ask participants how easy it is to practice some public health messages or can make a note about her observations and why.
- Be flexible yet focused; keep the dialogue focused. The participant may ask the question even before it is time to discuss it on the guide. The interviewer should judge for herself whether to go along and exhaust the question or to follow it up later.
- The participant may also give another meaning to the question. The interviewer should be flexible enough to encourage new perspectives and experiences while at the same time maintaining focus in the discussion.
- If the participant begins discussing something irrelevant, the interviewer should try to redirect the discussion to the appropriate topic.
- Closing the discussion can be difficult once the participant is relaxed and trusting. Be sure to thank the participant for her willingness to share her experiences and once more assure her of confidentiality.
- Sometimes the conversation may continue off record and important information related to the questions may be disclosed. Take note of this information and ask the participants if you may include these in your formal notes.

16.4.4 Digital recording and managing voice files

This sub-section describes how to use the digital recorder and manage the voice files that it creates from the interview recordings. The 2 US sites will use a Sony ICD-SX68 Stick Recorder with transcription capacity (*Note: US sites will receive individualized training to learn how to use the built in transcription software*) and African sites will use a Sony ICD-SX68 without transcription capacity to record the interviews. The recorders come with a 158MB Memory stick which holds about 185 hours of recording time. Please carefully review the ‘Operating Instructions’ manual for the digital recorder to familiarize yourself with it. After review of the manual, site staff should install the IC recorder software CD on the computer where voice files will be transferred.

Figure 16-1: Sony ICD- SX68DR9 Memory Stick Digital Voice Recorder



16.4.5 Recording Preparation Prior to Interview

Site counselors should practice using the recorder with colleagues to familiarize themselves with all aspects of recording, downloading, saving, labeling, transferring, and transcribing digital recordings. We cannot replace an interview that has been successfully carried out but the recording is lost, damaged, or inaudible.

Make sure to set the clock for the recorder to the current date and time (see page 17-18 of Operating Instructions manual). That way, the default label assigned to a voice file will include the actual interview date in “yyyy_mm_dd” format (i.e., 2005_03_26) when downloaded onto a computer after the interview, which will allow for the files to be arranged in chronological order, making it easy to locate files of interest.

Make sure to set the recording level to “MANUAL”. Hold down the menu button and select the REC LEVEL menu option, use the forward and backwards buttons to select “MANUAL” (see pg 25-26 of the Operating Instructions manual).

16.4.6 Recording the interview

To start recording an interview press and hold the “REC/ PAUSE” button, speak into the microphone and adjust the recording volume as needed, press the “REC/PAUSE” button (the operation indicator lights in red and “REC” will be displayed). To pause a recording, press “REC/PAUSE”, to end a recording, press “STOP”. Each time you start to record an interview and then press the stop button, a separate voice file is made. To avoid having several voice files for the one interview, it is recommended that the “REC/PAUSE” button be used to pause and resume the interview, and press the “STOP” button when finishing the interview.

The Sony ICD-SX68 Memory Stick Recorder is organized into five folders (FOLDER01 to FOLDER05). Each file created is assigned to these folders in a chronological order, or the user can specify a folder.

16.4.7 Procedures Following the Interview

As soon as you stop the recording, your digital voice recorder creates a sound file with a unique identity with date and time.

Transfer of interview data from the recorder to a computer should happen immediately after the interview. *Note: specific data transfer training will be provided to all sites*

- Connect the recorder to the computer using the USB connecting cable.
- Start the Digital Voice Editor (which should have been installed in advance from the CD that comes with the recorder package).
- The Voice Editor’s main window will pop up, showing the folders and file names for the Memory Stick recorder and the computer.
- In the PC section (on the right), open the destination folder (“original downloads”), where the files are to be transferred.
- In the Memory Stick section (on the left), open the folder of interest, select the files to be transferred, and drag and drop them into the destination folder on the PC side.
- After the files have been transferred, they should appear in the destination folder.
- Check the downloaded files. To listen to a voice file double-click on the file, and it will start to play. You can move the cursor on the playtime toolbar to listen to particular portions of the interview. You can take note of the time on the counter to listen to an interview section of interest later e.g. 1:20:06 to 1:35:45.
- Create a new folder on your PC called “voice files-transcription.” Copy the files that you have saved successfully in the “original downloads” folder and save them in the “voice files-transcription” folder. This will be the copy of the recording that you will work with. Do not use the master file in “original downloads.”
- All the voice files in the “voice files-transcription” folder should be relabeled from the default format to follow the following format: Study Staff ID, Clinic name, number of voice files per discussion/interview, date of interview (YYYYMMDD) - e.g. SSCase 1of1 20080723. SS is the staff ID of the note-taker. We hope the file naming format will help the site staff and other MTN-001 collaborators easily identify the files. Sites are free to add other pieces of information that maybe useful in the file name e.g. initials of note taker, etc.
- Once the download is verified you can clear the memory stick of old files so that it will not get prematurely filled up during the next interview. Voice files can be selected, copied or deleted on the E: drive (for the voice recorder) using Windows File Manager.

When the voice files are first downloaded onto a computer, they have “*.msv” as the file extension. Create a folder named “original downloads.” This is your ‘Master tape’ of the interview. Do not change these files in any way (e.g., do not re-label). The voice files in this folder will serve as the original source of interview data and as a backup in case any of the data are lost or damaged in the future; for example, while it is being relabeled, transmitted, or analyzed. If the recorder’s date and time have been set correctly, as described above, the files should be automatically organized in chronological order.

16.4.8 Backup, storage and transmission of voice files

After the files have been set up in the computer, make two CDs of the voice-files. The first will be the original copy of the interview data in the “original downloads” folder and in the “voice files-transcription” folder, and stored in a locked file cabinet or drawer until all interviews are completed and all CDs can be securely mailed to the social science coordinator at RTI International. The second copy will serve as a backup of the original downloads, and should be stored in a locked file cabinet or drawer in the “back up voice files-transcription” folder.

16.5 Data Collation and Management

For the In-Depth interviews data collection, data is defined as the electronic (digital recording and computer files) and manual (interviewers note, transcriptions) copies of all information collected during the interview. The final research output of these data will be written text in reports and paper publications.

16.5.1 Transcriptions

A transcript or transcription is a word-for-word written copy of a voice recorded interview. Transcribing a recording of interviews (in the language of the original interview) is necessary in order to consider and compare what participants say in their interviews. In a face-to-face interview the interviewer can observe non-verbal communication such as hand, face and body gestures. The original audio recording is the most accurate reproduction of the interview; however, one can only listen to the tone of speech but not the non-verbal gestures. Transcriptions accompanied by summaries and observational notes from of the interview provide an objective representation of the interview or discussion.

A typed interview transcript serves as a written record of every word spoken by participants and it can be made accessible for analysis. A transcript provides the means to search for specific words and phrases mentioned in the interview using word processing or specialized qualitative data analysis software.

Here are general instructions about transcribing interviews:

- We recommend that you start to transcribe the interview recordings as soon as possible after the interview.
- You may wish to first listen to parts of the recording or in its entirety once before you start transcribing to become familiar with the voices and content.
- Write down unique identification particulars of the transcription at the top of the first page: time started; time finished; venue of interview; transcriber; translator; and date(s) of transcription and translation.

- Listen to the recording carefully, one phrase or portion at a time, and transcribe verbatim, including all words, in the language of interview. Abbreviations should be kept the way they were said, such as “I’d” and “we’ve.” Do not summarize thoughts or ideas. Do not change from the first person to the third person, i.e. if a participant said “I like it because” do not transcribe as “she likes it because...”
- Sounds, crutch words or incomplete words such as Um,” “Er” or “Ahh...” after single words in a row do not need to be transcribed if it makes reading difficult, unless it is an important part of the narrator’s speech pattern.
- Interviewers use feedback words and sounds such as “uh huh,” “yes” and “hmm” to engage with the interviewee, but they can make transcripts difficult to read. Use your judgment when to leave these out.
- Do not revise the speaker’s words to force them into standard written prose. Leave untouched any sentence fragments, run-on sentences, and incorrect grammar. Commas and dashes may be used to reflect pauses in the spoken words.
- Use the jargon, idioms and metaphors that participants used in the interview; this enriches the data.
- Insert observations about non-verbal communication or the tone of voice of the speakers from the notes taken during interview or the transcription using [square brackets] to give it more depth and feeling e.g. [participant A standing and shouting]; [participant laughing]; [I think participant A misunderstood the question].
- Also include in [square brackets] explanations about why the interview was interrupted or why the recorder was turned off e.g., [Interview interrupted by a child crying].
- Identify inaudible portions of the recording. If one word is inaudible, indicate the gap with a “_”. When multiple words are inaudible, insert “_+” or estimate the elapsed time using the indicator “... # seconds”.
- Place two question marks before and after a word or phrase where you are not sure e.g., “??the partner always laughs??” The interviewer needs to pay extra attention that there is minimal interference with the sound quality during the interview.
- Indicate the end or break of a recording in capital letters, e.g., END 1of2; BEGIN 2of2; END OF INTERVIEW.
- The goal is to create a transcript that is both accurate and understandable to the reader. It need not include every utterance or describe every background noise, but it should reproduce as closely as possible the speaker's words. It should also be consistent in style and level of detail throughout.
- After an interview voice recording is transcribed, it is critical that the transcriber and a second person (the interviewer, if different to the subscriber) read through it for accuracy. In particular, the interviewer should check that cultural words or vocabulary of the participants were transcribed properly and try to fill in anything that was found to be unclear during transcribing.

16.5.2 Translations

Interviews will be conducted in the language that participants are comfortable with. Each site is responsible for all translation activities, or for contracting out for translation services.

After a non-English interview has been carried out, we recommend the following:

- Transcribe verbatim the interview in the original language following the transcription guidelines above. Then, translate the transcript into English under the passage for each speaker.

- Where jargon, idioms and metaphors have been used by participants in the interview try to translate these as directly as possible in order to maintain their original meaning. For example, if participants talk about “small houses” translate this as “small houses” not as some other term. Explanations to outside readers can be written in brackets. Cultural terms that do not have easy translations may be written in the local language and explained through notes written in square brackets, i.e. ukusoma [thigh sex]
- Team members can figure out what works best for them, whether the person who did transcription also translates the document or someone else.

The transcriptions should include all observer notes and feedback notes from the participants. Please note that a certified translator must carry out all translations and that written certification of the translation must be obtained. A copy of the transcript, translated copy, and written certification of the translation must be sent to the RTI International office in San Francisco (see Section 16.4.8 for shipping address) no longer than four weeks after the last interview is completed.

16.5.3 Data Management and Storage

Correct handling, filing and storage of all paper and electronic files and CDs containing study data are important for organizational purposes, quality assurance, monitoring, and the protection of participant confidentiality. The interview data will be in the form of:

- Enrollment data (with Participant ID number so that we can match their information with the trial data during the analysis).
- Transcripts and translations accompanied by interview notes, filed by interview type. e.g. PTID_date of interview_name of interviewer

The main components of the data management system are:

- To protect participant’s confidentiality, use PTIDs on interview data (forms, voice files and transcripts) so that the data are not directly linked to the participant’s name or other personal identifiers. Also, store interview materials separate from documents bearing participant’s identifiers such as informed consent form, and locator forms.
- Storage of paper documents (in the participants file) and CD backups in locked file cabinets and electronic documents on password-protected, secure computers at the project offices for the study sites.
- Access to the study data only by designated study staff.
- Routine backup and transfer of data to RTI. Ensure that you backup your work on a daily basis.

16.5.4 Electronic files

All electronic study data, documents and voice recordings should be routinely backed up as follows:

- Electronic study files should be automatically backed up each day on the office server.
- Staff should make CD backups of interview recordings and other study documents at least once a week.

16.5.5 Data storage

All study material will be completed, checked and filed at each research site. All qualitative back-up data will be kept at the sites throughout and after completion of the data collection. Per protocol sites are required to maintain all records for two years after the study. (see section 3 for data storage requirements following completion of the study). Records will be destroyed after the two year period. Records may not be destroyed without written permission from the MTN-001 protocol team chair.

16.6 Data tracking

This qualitative study falls under the administrative structure of the MTN-001 Trial. The sites responsibilities are outlined in the MTN-001 Protocol and MTN 001 SSP Manual.

16.6.1 Site Investigator responsibilities

- Conduct the study in accordance with the relevant current protocol and recommend amendments where necessary.
- Ensure that all study staff follow ethical procedures as approved by the IRB.
- Maintain adequate and accurate records at the study site in accordance with this protocol and make those records available for inspection to study monitors and auditors.0.

16.6.2 Data monitoring

Data monitoring activities include:

- After each interview, site staff will carefully review all interview data and participant files for any anomalies.
- The interviewer will make a written report of any anomalies.
- Transcriptions will be checked by a researcher other than the original transcriber before it is transmitted to the social science coordinator. During the analysis any passage of interest will also have the translation verified against the corresponding excerpt in the transcript of the original language of the interview.

16.6.3 Sending Data

When all materials (voice files, summary notes and transcripts) are completed (and no longer than 4 weeks after the completion of the last in-depth interview), each site should securely mail (with the ability to track progress or delivery confirmation) all materials to the Qualitative Data Coordinator at RTI International:

Alexandra Minnis
Women's Global Health Imperative
RTI International
114 Sansome St, Suite 500
San Francisco, CA, 94104 USA
Phone: 415-848-1323
Email: aminnis@rti.org

Please package all materials carefully (for example, each CD should be protected by a case). **Please also be sure to include a log of the all files/materials included in the package. (See Appendix 16-2 for check-list of materials to include).**

Section Appendix 16-1
In-depth Interview Questionnaire

Hello, my name is [FACILITATOR]. I would like to congratulate you for completing the study, and today I would like to discuss your experiences with being in the Tenofovir study. I would like to hear your views and learn about any problems and difficulties as well the positive experiences you have had with the study products. Everything you say is important to our research and will help us to better understand women's experiences using Tenofovir in the trial. Please feel free to speak openly and use any language or words you are most comfortable using. There are no right or wrong answers. Your name will not be written anywhere, which means that no one will know it was you who said something.

Since this discussion is very important to us, I would like to record it, with your permission just to make sure that I do not miss any important things that we will discuss today, and I will also be taking notes while we talk (*confirm their consent*). The tapes and notes will be kept private and safe, your name will not be used and the documents will be destroyed when the trial is finished. The discussion will take a little over one half-hour. Do you have any questions before we start?

A: Study Experiences (3-5 minutes)

1. What are some of the reasons that you joined the study?
[PROBE: getting tested for HIV; learn more about HIV prevention; compensation of the study; curiosity/experience; free medical exam; etc]
2. What are some of the reasons you stayed until the end?
[PROBE: What did you like about the study?
PROBE: What did you dislike about the study?]

B. Study product experience and use (10 minutes)

3. Please tell me about your experience using the gel and applicator.
[PROBE: What are the things you liked about the gel?
PROBE: What are the things you disliked about the gel?
PROBE: How did you feel about using the applicator?]
4. Please tell me about your experience taking the tablets?
[PROBE: What are the things you liked about the tablets?
PROBE: What are the things you disliked about the tablets?]
5. Please tell me about your experience using the gel together with the tablets.
[PROBE: What are the things you liked about using the gel and tablets together?

PROBE: What are the things you disliked about using the gel and tablets together?]

6. In some instances women prefer using the gel, in other instances women prefer taking the tablets, and in other instances women prefer using the gel and tablets together. Please tell me about instances when you preferred using the gel or preferred taking the tablets?

[**PROBE:** Tell me about the instances when you preferred using only the tablets.

Why did you prefer using only the tablets, and not the gel?

PROBE: Tell me about the instances when you preferred using only the gel. Why did you prefer using only the gel, and not the tablets?

PROBE: Tell me about the instances when you preferred taking the tablets and gel together. Why did you prefer using the gel and tablets together?]

C. Product adherence (7-10 minutes)

7. For some women it is not easy to use gel every day; yet for others it is easy. What was your experience?

[**PROBE:** Some women were not able to apply the gel everyday. What do you think could be some of the reasons that made it difficult for them to use the gel everyday? What made it difficult for you to use the gel every day

PROBE: Some women were able to use the gel everyday. What do you think could be some of the reasons that made it easy for them to use the gel everyday? What made it easy for you to use the gel every day?

PROBE: Can you think of a time where you thought it would be very difficult to use the gel, but you were still able to use it? If yes, can you tell me more about it?

PROBE: What do you think would make it easier for you to use gel every day?

PROBE: What were some of the things that did help you to use the gel?

PROBE: What were some of the things that helped you to remember to use the gel? (Would a timer have helped, a friend, a partner?)]

8. For some women it is not easy to take the tablets every day; yet for others it is easy. What was your experience?

[**PROBE:** Some women were not able to take the tablets everyday. What do you think could be some of the reasons that made it difficult for them to take the tablets everyday? What made it difficult for you to take the tablets every day?

PROBE: Some women were able to take the tablets everyday. What do you think could be some of the reasons that made it easy for them to take the tablets everyday? What made it easy for you to take the tablets every day?

PROBE: Can you think of a time where you thought it would be very difficult to take the tablets, but you were still able to use it? If yes, can you tell me more about it?

PROBE: What do you think would make it easier for you to take the tablets every day?

PROBE: What were some of the things that did help you to take the tablets?

PROBE: What were some of the things that helped you to remember to take the tablets? (Would a timer have helped, a friend, a partner?)]

D. Partners and relationship issues (5-7 minutes)

9. Please describe what information you shared with your partner on your trial participation and gel/tablet use? (*when I say partner I mean your husband, or someone who you consider to be your primary male sexual partner*)

[PROBE: What did you tell your partner about your participation in the trial? How did your partner react?

PROBE: How did your partner learn that you were using the gel the first time? How did he react?

PROBE: How did your partner feel about you using the gel?

PROBE: How did your partner learn that you were taking the tablets? How did he react?]

PROBE: How did your partner feel about you taking the tablets?]

10. Sometimes it is possible to use the gel and/or tablets without your partner noticing. What has been your experience?

[PROBE: Tell me about the times when you told your partner that you were using the gel. What are some of the reasons you told him? How often did you tell him?

PROBE: Tell me about the times when you told your partner that you were taking the tablets. What are some of the reasons you told him? How often did you tell him?

PROBE: Have you ever used the gel without your partner knowing? What were the reasons that you did not tell him?

PROBE: Have you ever taken the tablets without your partner knowing? What were

the reasons that you did not tell him?]

PROBE: What would happen if you tried to use the gel and/or tablets without your partner knowing? How would your partner react if he found out you were taking the tablets and/or gel without him knowing?]

11. Do you think it is important for male partners to be involved in the decision to use the gel and/or tablets?

[**PROBE:** What are some of the reasons? How can male partners be more engaged and empathetic about their partner's use? Do you think your partner could help you with using the product every day?]

E. Product Sharing (5-7 minutes)

12. Who knew that you were taking tablets and gel provided by the study?

[**PROBE:** husband/primary partner, family members, neighbours, clients, community members

PROBE: how did they find out?

PROBE: Did you want people to know or would you prefer that only you (or you and your partner) know?]

13. Sometimes family members or friends ask participants in the study to share some of their gel and/or tablets. Tell me about your experience sharing or someone taking away your study products.

[**PROBE:** Tell me about the times that you shared your gel and/or tablets. What are some of the reasons that you shared your study gel and/or tablets?

PROBE: Tell me about the times that someone took your gel and/or tablets without your permission. How did it happen? What are some of the reasons that the other person took your gel and/or tablets without your permission?]

G. Conclusion

14. We do not yet know if the tablets or gel will prevent HIV infection. But thinking ahead to the future, if they are proven to prevent infection, would you use the gel or tablets?

A.E. reporting script: If the patient has mentioned anything at all that qualifies as an A.E., you are required to ensure that she has reported it, and double check in her file. Here are some guidelines for what you might say

During our interview you mentioned ____ (specify A.E.). At the time did you tell clinic staff about (specify A.E.)?

If she says yes: Before you go, I am just going to double check that (specify A.E.) was recorded in your file.

If she says no: For your health and safety, we need to make sure that this is recorded in your file. Before you go, we need to fill out a form to ensure that it has been recorded. Is that okay?

Ask if there are questions or comments on anything about the study or this discussion. Address any outstanding questions/comments that you may have postponed to the end of the discussion.

Thank you for your time and information.

Section Appendix 16-2
Checklist of Required Materials

- ǒ **Name of Interviewer, Date of Interview, Location of Interview**
- ǒ **CD of electronic voice file (US sites only)**
- ǒ **English translation of interview transcript (international sites only)**
- ǒ **Certification of official translation (international sites only)**
- ǒ **Summary notes from interview (if any)**