

MTN 002 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	1.0	15 April 2008	Baseline
2	Protocol	1.0	15 April 2008	Baseline
3	Documentation Requirements	1.0	15 April 2008	Baseline
4	Participant Accrual	1.0	15 April 2008	Baseline
5	Informed Consent	1.0	15 April 2008	Baseline
6	Participant Follow-Up	1.0	15 April 2008	Baseline
7	Visit Checklists	2.0	1 June 2008	“CPT Tube” collection deleted from Day 0
8	Participant Retention	1.0	15 April 2008	Baseline
9	Study Product Considerations for non-Pharmacy Staff	1.0	15 April 2008	Baseline
10	Clinical Considerations	1.0	15 April 2008	Baseline
11	Safety Monitoring and Adverse Event Reporting	3.0	26 August 2008	Updated to reflect the MTN 002 Safety Physicians: Ross Cranston and Katie Bunge
12	Laboratory Considerations	3.0	24 Nov 2008	Clarification on collection of vaginal fluid
13	Data Collection	1.0	15 April 2008	Baseline
14	Data Communques	1.0	15 April 2008	Baseline
15	Study Reporting Plan	1.0	15 April 2008	Baseline

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Section 1. Introduction

This section specifies the sources of procedural information available to MTN 002 study staff, the responsibilities of MTN 002 Investigator of Record (IoR), and the process by which the study site is approved to begin implementation of MTN 002. 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 002 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:

- Questions related to interpretation and proper implementation of the MTN 002 protocol should be directed to the MTN CORE: Megan Valentine and Sherri Johnson at mvalentine@fhi.org and sjohnson@fhi.org.
- Questions related to data collection and management should be directed to the MTN Statistical and Data Management Center (SDMC): Missy Cianciola at missy@ssharp.org.
- Questions related to the collection, processing, testing, storage, and/or shipment of laboratory specimens should be directed to the MTN Network Laboratory (NL): Pamela Kunjara at rsipk@mwri.magee.edu.
- When in doubt as to whether questions pertain to protocol interpretation, data collection, or laboratory procedures, contact the MTN CORE at mtn002mgmt@mtnstopshiv.org.

Questions related to the investigational study product should be directed by the clinical research site (CRS) Pharmacist of Record to the DAIDS Protocol Pharmacist: Scharla Estep at sr72v@nih.gov. Current contact details for the above-listed contact persons and all MTN 002 colleagues and collaborators can be found in the MTN Directory at:

<http://mtnstopshiv.org>

1.2 Investigator Responsibilities

MTN 002 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).

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. These SOPs are located at: <http://www3.niaid.nih.gov/research/resources/DAIDSCLinRsrch/Regulatory/>.

MTN 002 must also 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. The site must file copies of all such regulations, policies, and guidelines in their MTN 002 essential document files (see also Section 3.1).

The IoR must sign both a protocol signature page and an FDA Form 1572 to formally indicate his/her agreement to conduct MTN 002 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.

Copies of the protocol signature page and 1572 with original signatures must be sent to FHI. The site will keep copies of the protocol signature page and 1572 on site with their essential documents (See SSP Section 3).

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. The IoR may delegate his/her obligations and responsibilities for conducting MTN 002 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, the study site must obtain approval to conduct MTN 002 from all required regulatory authorities and IRBs/ECs. The 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 steps can be found in Section 10 of the MTN MOP. The MTN CORE will issue a Site-Specific Study Activation Notice when all study activation requirements have been met. 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 002. 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.

The study site is encouraged to request their IRB/ECs acknowledge receipt for all documents submitted to them, and to request that the IRBs/ECs note both the effective date and the 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 002**

Document	Written Approval Required*
MTN 002 Protocol, Version 1.0	Yes
MTN 002 Letter of Amendment #01	Yes
Informed consent form (for Screening and Enrollment): <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 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 002**

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 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 002 protocol. At the time of this printing, protocol Version 1.0 (dated 29 August 2007) and Letter of Amendment (dated 13 March 2008) reflect 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.

LETTER OF AMENDMENT #01 TO:

**MTN-002
DAIDS Document ID 10600**

**Phase I Study of the Maternal Single-Dose Pharmacokinetics and Placental
Transfer of Tenofovir 1% Vaginal Gel among Healthy Term Gravidas**

Version 1.0 / 29 August 2007

IND # 55,690

Letter of Amendment Date: 24 March 2008

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the MTN-002 study and must be forwarded to your Institutional Review Board (IRB) and/or Ethics Committee (EC) as soon as possible for their information and review. IRB/EC approval is required before implementation of the revisions contained in this LoA.

The following information will also impact the sample informed consent. Site IRB/EC is responsible for assessing whether and how the changes included in this LoA are to be communicated to study participants. All IRB/EC requirements must be followed.

Please file this LoA and all associated IRB/EC correspondence in your essential documents files for MTN-002. You will be required to submit IRB/EC correspondence and approved informed consent forms to the DAIDS Protocol Registration Office for informational purposes; however, you will not receive an approval notification from the DAIDS Protocol Registration Office for the LoA. Failure to submit IRB/EC correspondence and approved informed consent forms to the DAIDS Protocol Registration Office will result in delays in being able to order study product.

Summary of Revisions and Rationale

This LoA does not impact the overall design and study visit schedule for MTN-002.

This LoA adds an exclusion criterion to the MTN-002 protocol and excludes women with previously demonstrated hypersensitivity to any components of tenofovir 1% gel.

This LoA reflects a change in the product packaging and change in the product manufacturer of tenofovir 1% gel.

This LoA clarifies the nature of the tenofovir levels outlined in the Study Procedures Section. Blood, not plasma, levels of tenofovir will be measured.

This LoA modifies data collection methods for neonatal hospital course and outcomes. Neonatal chart abstraction is now included specifically in the study procedures and sample informed consent form. The MTN-002 Protocol Team planned to collect data on neonatal hospital course and outcomes via maternal reports, verbal reports from neonatal providers, and maternal chart abstraction. The inclusion of neonatal chart abstraction allows for a more complete assessment of neonatal hospital course and outcomes.

Implementation

This LoA is official MTN-002 protocol documentation. Prior to implementing the revisions listed below, the MTN-002 study site will submit this LoA to all relevant regulatory authorities and the IRB/EC. The Division of AIDS Regulatory Affairs Branch will submit this LoA to the United States Food and Drug Administration for inclusion in Investigational New Drug (IND) application # 55,690.

Upon receipt of all required regulatory and IRB/EC approvals, the protocol revisions listed below will be implemented.

Detailed modifications of the protocol text are indicated by ~~strikethrough~~ (for deletions) and **bold** for additions.

Detailed Listing of Revisions

1. In Section 5.3 Exclusion Criterion (added):
 - 12. Previously demonstrated hypersensitivity to any components of tenofovir 1% gel**

2. In Section 6.2 Administration, first sentence (added): Four grams of tenofovir 1% gel will be administered vaginally, using the **pre-filled** vaginal applicator provided, by the authorized clinician, approximately two hours prior to the expected time of cesarean section (optimally at least one hour prior to the collection of cord blood).
3. In Section 6.3 Study Product Formulation and Preparation, first paragraph, first through third sentences (added and deleted): Tenofovir gel is a clear, transparent viscous gel **provided in pre-filled vaginal applicators**. ~~packaged in epoxy inner lined aluminum tubes with white polyethylene screw caps equipped with a puncture tip.~~ Each single-dose **vaginal applicator tube** ~~contains~~ **will deliver 4 grams of** ~~nominally 6 grams of~~ tenofovir gel at a concentration of 1% (weight per weight). **The product is** formulated in purified water with edetate disodium, citric acid, glycerin, methylparaben, propylparaben, and hydroxyethylcellulose, with pH adjusted between 4.0 and 5.0. ~~The study gel is applied with a polyethylene applicator capable of administering a 4 gram dose.~~
4. In Section 6.3 Study Product Formulation and Preparation, second paragraph (deleted): ~~Immediately prior to application, the authorized clinician will fill the vaginal applicator by removing the cap from the tube of study gel, puncturing the metal seal on the tube with the pointed tip of the cap, screwing the end of the applicator onto the tube and slowly squeezing gel out of the tube and into the applicator. The plunger will stop when the applicator is full (contains the 4 grams of study product).~~
5. In Section 6.4.1 Study Product Supply, second sentence (deleted and added): Tenofovir 1% gel is manufactured, packaged, labeled, analyzed and released by ~~Gilead Sciences (Foster City, CA)~~ **DPT Laboratories (San Antonio, TX)** in accordance with current good manufacturing practices (cGMP), 21 Code of Federal Regulations, conditions.
6. In Section 6.4.2 Study Product Acquisition, first sentence (added and deleted): Tenofovir 1% gel **in pre-filled** ~~and~~ vaginal applicators will be available through the DAIDS Clinical Research Products Management Center.
7. In Section 6.4.3 Dispensing, first sentence (added and deleted): The tenofovir 1% gel **in pre-filled** ~~tube for a study participant and a~~ vaginal applicators will be dispensed only upon receipt of a written prescription from an authorized prescriber.
8. In Section 6.4.5 Retrieval of Unused Study Products, first sentence (deleted): Physician investigators and authorized study site staff must return any

unused **applicators containing tenofovir 1% gel** study product tubes and unadministered study product in applicators to the pharmacy.

9. In Section 7.3 Pharmacokinetic Measures, Table 3: Pharmacokinetic Measures: Gel Administration Day (Day 0), Pre-Gel Lab Component, second bullet, first sub-bullet (added and deleted): maternal **blood** ~~plasma~~-tenofovir level.
10. In Section 7.3 Pharmacokinetic Measures, Table 3: Pharmacokinetic Measures: Gel Administration Day (Day 0), Post-Gel Lab Component, second bullet (added and deleted): Draw blood for maternal **blood** ~~plasma~~ tenofovir level.
11. In Section 7.4 24 Hour Evaluation, Table 4: 24 Hour Evaluation, Laboratory Component, first bullet (added and deleted): Draw blood for maternal **blood** ~~plasma~~-tenofovir level.
12. In Section 7.4 24 Hour Evaluation, following Table 4 (added): **Infant chart review and abstraction of any neonatal adverse events noted therein will occur for the period of neonatal inpatient admission.**
13. In Section 7.6 Unscheduled Visit, Table 6: Unscheduled Visits, Laboratory Component, ninth bullet (added and deleted): *Maternal **blood** ~~plasma~~ tenofovir level.
14. In Section 7.9.2 Network Laboratory, fifth paragraph, first sentence and second sentence (added and deleted): As stated above, a validated assay for tenofovir in **blood** ~~plasma~~ is currently available. Validated assays for tenofovir in endometrial tissue, amniotic fluid and placental tissue have not yet been developed, but are expected to be ready in 2008~~7~~.
15. In Section 7.9.2 Network Laboratory, last paragraph, first sentence (added and deleted): **Blood** ~~Plasma~~ will also be analyzed for routine pharmacokinetic parameters (C_{max} , T_{max}).
16. In Section 8.3.1 Adverse Events, third paragraph, first sentence (added): Study site staff will document on study CRFs all AEs reported by or observed in study participants from the time of enrollment until study termination, **as well as AEs identified via infant chart review for the infant's inpatient admission period(s)**, regardless of severity and presumed relationship to study product.
17. In Section 10.3 Study Hypothesis, first bullet (added and deleted): Study hypothesis 1: **Blood** ~~Plasma~~ absorption in participants will be detectable in a percentage of women similar to that seen in HPTN 050 (approximately 33%).

18. In Section 10.4 Sample Size, first paragraph, first sentence (added and deleted): The power of the study can be characterized as follows: if the overall absorption rate (defined as the proportion of women with detectable levels of PMPA in ~~blood-plasma~~, endometrium, cord blood, placental tissue, and/or amniotic fluid) was expected to be 33%, 16 women would provide 72% power to exclude absorption rate > 60%.
19. In Section 10.6.2 Primary Analysis, first paragraph, second sentence (added and deleted): Similarly, descriptive statistics for continuous variables will be used to describe levels of tenofovir in levels in ~~blood-plasma~~, in endometrium, in cord blood, in placental tissue, and in amniotic fluid.
20. In Section 10.6.2 Primary Analysis, second paragraph, first sentence and fifth sentence (deleted): Blood ~~plasma~~-pharmacokinetics of tenofovir will be evaluated after vaginal administration.

The ratio of concentrations of tenofovir in maternal blood relative to temporally matched cord blood, amniotic fluid, and endometrial tissue concentrations, and ratio of maternal blood ~~plasma~~-relative to intracellular peripheral blood mononuclear cell (PBMC) tenofovir and tenofovir diphosphate levels will be calculated and summarized using descriptive statistics.

21. In Section 13.3.1 Risks, seventh paragraph, first sentence (added and deleted): This is a single-dose study and maternal ~~blood plasma~~-levels are expected to be inconsistent and low-level, if detected.
22. In Appendix 1, Laboratory Section, fourteenth item (added and deleted): Maternal ~~Blood Plasma~~-Tenofovir Level.
23. In Appendix VI: Sample Informed Consent Form (Screening and Enrollment), What Do I Have to Do If I Am In This Study Section, ninth sentence (added): We will also ask you to sign permission forms so that we can get copies of any hospital records **for you and your baby** for the time that you are in the study.

The above information will be incorporated into the next version of the protocol at a later time if it is amended.

MTN-002
**Phase I Study of the Maternal Single-Dose Pharmacokinetics and Placental
Transfer of Tenofovir 1% Vaginal Gel among Healthy Term Gravidas**

A Study of the Microbicide Trials Network

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

Grant #:
1-U01-AI068633-0

DAIDS Protocol #10600

Co-Sponsored by:
CONRAD

IND# 55690

Protocol Chair:
Richard H. Beigi, MD, MSc., FACOG

Final Version 1.0
29 August 2007

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from NIAID (or others, as applicable), unless it is necessary to obtain informed consent from potential study participants.

MTN-002
**Phase I Study of the Maternal Single-dose Pharmacokinetics and Placental
Transfer of Tenofovir 1% Vaginal Gel among Healthy Term Gravidas**

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MTN-002

Phase I Study of the Maternal Single-dose Pharmacokinetics and Placental Transfer of Tenofovir 1% Vaginal Gel among Healthy Term Gravidas

LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine transaminase
APR	Antiretroviral Pregnancy Registry
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
BUN	blood urea nitrogen
CDC	Centers for Disease Control
CFR	code of federal regulations
cGMP	current Good Manufacturing Practices
CI	confidence interval
CONRAD	Contraceptive Research and Development Organization
CRF	case report form
C _{max}	maximum concentration
CRS	Clinical Research Site
C/S	cesarean section
CT	Chlamydia trachomatis
CTA	clinical trial agreement
DAIDS	Division of AIDS
DNA	deoxyribonucleic acid
EAE	expedited adverse event
EC ₅₀	50% effective concentration
FDA	(United States) Food and Drug Administration
GC	gonococcus
GCP	Good Clinical Practices
GU	genitourinary
HBsAg	Hepatitis B surface antigen
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trials Network
IATA	International Air Transport Association
IND	investigational new drug
IoR	Investigator of Record
IRB	Institutional Review Board
LCMS	liquid chromatography mass spectrometry
LDMS	Laboratory Data Management System
LLOQ	lower limit of quantitation
MTN	Microbicide Trials Network
NIAID	National Institute of Allergy and Infectious Disease
NICHD	National Institute of Child Health and Development
NIH	(United States) National Institutes of Health
OHRP	Office of Human Research Protection
PACTG	Pediatric AIDS Clinical Trials Group
PAB	(DAIDS) Pharmaceutical Affairs Branch
PI	principal investigator
PK	pharmacokinetic
PPD	Pharmaceutical Product Development, Inc
PMTCT	prevention of mother-to-child transmission
PSRT	Protocol Safety Review Team
RCC	Regulatory Compliance Center

RNA	ribonucleic acid
RPR	Rapid Plasma Reagin
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SDA	strand displacement assay
SDMC	Statistical Data Management Center
SIV	simian immunodeficiency virus
SMC	Study Monitoring Committee
SOP	standard operating procedure(s)
ss	steady state
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate
UNAIDS	Joint United Nations Program on AIDS
UPMC	University of Pittsburgh Medical Center

MTN-002

Phase I Study of the Maternal Single-dose Pharmacokinetics and Placental Transfer of Tenofovir 1% Vaginal Gel among Healthy Term Gravidas

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MTN-002

Phase I Study of the Maternal Single-dose Pharmacokinetics and Placental Transfer of Tenofovir 1% Vaginal Gel among Healthy Term Gravidas

INVESTIGATOR SIGNATURE FORM

Final Version 1.0

29 August 2007

A Study of the Microbicide Trials Network (MTN)

Sponsored by:

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

Co-Sponsored by:

CONRAD

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, unless otherwise specified by the Division of AIDS (DAIDS), CONRAD, or the Microbicide Trials Network (MTN) Coordinating and Operations Center. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the Food and Drug Administration (FDA) is notified that the Investigational New Drug application (IND) is discontinued. 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, NICHD, and CONRAD for review prior to submission.

I have read and understand the information in the Investigator's Brochure(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-002

Phase I Study of the Maternal Single-dose Pharmacokinetics and Placental Transfer of Tenofovir 1% Vaginal Gel among Healthy Term Gravidas

PROTOCOL SUMMARY

Short Title: Maternal Pharmacokinetics and Placental Transfer of Tenofovir 1% Vaginal Gel

Clinical Phase: I

IND Sponsor: Division of AIDS (DAIDS)

Protocol Chair: Richard Beigi, MD, MSc

Sample Size: 16

Study Population: Healthy, HIV-uninfected, term gravidas planning elective cesarean section (C/S) between ≥ 37 and < 42 completed gestational weeks and lacking evidence of placental disease

Participating Site: Magee-Womens Hospital of the University of Pittsburgh Medical Center (UPMC)

Study Design: Phase I, single-site, open label, pharmacokinetic (PK) and placental transfer evaluation

Study Duration: Approximately three to six weeks per participant
Approximately 18 total months for planned accrual and study duration

Study Product Regimen:

N	Regimen	Follow-Up		
16	Tenofovir 1% vaginal gel, 4 grams per vagina once	Pharmacokinetic measures (1-12 hours)	24 Hour Evaluation	Two Week Phone Call

Primary Objective:

1. Assess term pregnancy maternal single-dose pharmacokinetics of tenofovir 1% vaginal gel

Secondary Objectives:

1. Characterize the systemic safety profile of single-dose tenofovir 1% vaginal gel in term gravidas
2. Compare 3rd trimester absorption of tenofovir 1% vaginal gel to absorption in non-pregnant recent historic controls
3. Assess amniotic fluid, cord blood, endometrial tissue and placental tissue levels following single-dose tenofovir 1% vaginal gel

1 KEY ROLES

1.1 Protocol Identification

Protocol Title: Phase I Study of the Maternal Single-dose Pharmacokinetics and Placental Transfer of Tenofovir 1% Vaginal Gel among Healthy Term Gravidas

Protocol Number: MTN-002

Date: 29 August 2007

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Sponsor: NICHD
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1.6 Data Center

Data Center: Statistical Center for HIV/AIDS Research & Prevention
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1.7 Study Operations

Study Operations: Family Health International (FHI)
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2 INTRODUCTION

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

According to UNAIDS, an estimated 38.6 million [33.4 million–46.0 million] people worldwide were living with HIV in 2005. An estimated 4.1 million [3.4 million–6.2 million] became newly infected with HIV and an estimated 2.8 million [2.4 million–3.3 million] lost their lives to AIDS in 2005.¹ Given these statistics, it is clear that available prevention options today have been insufficient to stem the tide of the AIDS epidemic, particularly for women, who continue to comprise a growing proportion of new HIV infections around the world. There is an urgent need for prevention methods that women can initiate and control themselves. Topical microbicides represent one such method, and a growing body of data suggests that a safe and effective topical microbicide will be a real option for women in the future. Many candidate microbicides are currently in various stages of preclinical and clinical investigation; tenofovir 1% vaginal gel is a nucleotide reverse transcriptase inhibitor-based topical microbicide candidate with significant promise as a safe and effective means of prevention of HIV transmission.

2.2 Tenofovir Gel and the MTN Research Agenda

HPTN 050 assessed the safety and acceptability of tenofovir 1% vaginal gel for vaginal use among sexually abstinent and active women. HPTN 050 also evaluated the pharmacokinetic parameters of this candidate microbicide also known as PMPA gel. An ongoing expanded safety study (HPTN 059) is now underway to determine the safety of tenofovir 1% gel as a vaginal microbicide over 24 weeks of use, and to gain additional information about the product's acceptability. Another protocol (MTN-001) is currently in the final planning stages and will be a Phase 2 study comparing the safety and pharmacokinetics of oral versus vaginal tenofovir. Thus far, tenofovir gel has been shown to be safe and well-tolerated among young sexually active women.²

To fulfill an ambitious research agenda that is comprehensive in its approach, the MTN agenda also encompasses proactive investigations of safe candidate microbicides into pregnancy. This protocol will be the first investigation of a candidate microbicide among gravid women.

2.3 Candidate Microbicides and Pregnancy

The study of candidate microbicides in pregnancy is compelling for many practical and scientific reasons:

1. Microbicides are intended to be used among reproductive-age sexually active women to minimize and/or eliminate the risk of transmission of HIV and other STIs. One of the common occurrences in this target population is pregnancy, both intended and unintended.

2. Among pregnant and post-partum women, sexual activity is common, including sexual activity with multiple partners.
3. Recent data suggests that pregnancy represents a time of potential heightened risk for the sexual acquisition of HIV.
4. In practical terms, if microbicides become widely available, pregnant women will likely use them with or without evidence of safety. In the absence of safety data there could be recommendations to perform a pregnancy test prior to each use, which would provide a logistical barrier to widespread use.
5. Anti-HIV microbicides potentially might be used for the prevention of maternal-to-child transmission of HIV; therefore precise pharmacokinetic information and investigation are needed.

Pregnancy is a common occurrence in young sexually active women of childbearing age, yet precise rates are difficult to calculate. Rough estimates indicate that the pregnancy rate among young sexually active women not using contraception in the United States/1,000 women/year is 100, with the peak ages being in the 20-29 age range.³ Pregnancy is estimated to occur in approximately 85% of non-contracepting sexually-active females per year. It is important to remember that this number may be drastically different in other less-developed parts of the world where HIV is common. When studying the same population of women using multiple forms of contraception, including perfect and non-perfect use, the pregnancy rate approximates 0.5-15%/year.^{4,5} The projected use of microbicides among the target population is to be frequent and widespread, and therefore, pregnancy will become a common occurrence for the typical users.

Among pregnant and post-partum women, numerous investigators have demonstrated that sexual activity is common, and sometimes encompasses multiple partners, which increases the risk of HIV and STI transmission. Solberg et al., using puerperal recollection of sexuality during the previous pregnancy, demonstrated that although the majority of women decreased coital frequency as pregnancy progressed, the large majority continued sexual activity, with 90% sexually active in the first trimester and greater than 50% sexually active in the 3rd trimester.⁶ Klebanoff et al. found similar results using the Collaborative Perinatal Project dataset, demonstrating that 90% were sexually active in the first trimester and greater than 25% were still engaging in coitus at 38-39 gestational weeks.⁷

A subsequent publication by Read and Klebanoff using the Vaginal Infections in Prematurity study data demonstrated that greater than 14% of women had more than one sexual partner in the previous year, and 4% stated they had more than one sexual partner during the incident pregnancy.⁸ Lastly, Rowland et al. using post-partum survey data demonstrated that within six weeks postpartum, nearly 50% of women had

resumed sexual activity.⁹ These studies taken together highlight the fact that pregnancy is a time of frequent sexual activity with an ongoing risk for HIV acquisition.

Preliminary studies have suggested an increased risk of HIV seroconversion in pregnancy, yet were not directly set up to assess that specific question.^{10,11} The issue of susceptibility to HIV during pregnancy has recently been more directly addressed by Gray et al.¹² As part of the Rakai Community Cohort Study, HIV acquisition was investigated over a five year period (1994-1999). The study identified 2625 women who began a pregnancy with a negative HIV serology study, reported sexual activity, and had follow-up postpartum serology available. This was compared to 24,258 non-pregnant/non-lactating sexually-active women with complete serology. Using multivariate modeling, the risk ratio for HIV acquisition during pregnancy was 2.15 (95%CI 1.39-3.37) compared to non-pregnant/non-lactating women. This analysis controlled for numerous behavioral characteristics, including sexual activity of the male partners that suggests the pregnancy itself was physiologically responsible for the increased risk of HIV seroconversion. These findings have significant implications in terms of maternal to child transmission of HIV given the high viral loads that accompany new HIV infection and the documented importance of viral load on maternal-child transmission.¹³ These findings compel the medical community to improve HIV prevention strategies in this potentially vulnerable physiologic time period of pregnancy.

A potential role exists for microbicides in decreasing maternal-child intrapartum transmission. If microbicides were demonstrated to effectively decrease lower genital tract viral load late in pregnancy, this method could be used in regions of the world where oral and intravenous medications are logistically difficult to use. In addition, use of microbicides could augment the current armamentarium of drugs used in pregnancy, and may provide a local method to decrease perinatal HIV transmission without exposing fetuses to systemic levels of medications. Investigation in these regards is necessary to realize this full potential.

2.4 Tenofovir Gel

Tenofovir 1% vaginal gel (tenofovir gel) was chosen as a high priority microbicide candidate for a number of reasons, including its activity in target cells for HIV infection (Langerhans dendritic cells; monocyte/macrophages, and T cells) of the vagina and cervix and the low frequency of local and systemic toxicity observed in the HPTN 050 Phase I study of tenofovir 1% gel. In addition, animal studies have demonstrated that tenofovir gel prevents establishment of systemic infection in macaques when administered prior to or following intravaginal challenge with simian immunodeficiency virus (SIV) and that it inhibits vaginal transmission of SIV in macaques.¹⁴

The tenofovir gel formulation is a novel nucleotide analog belonging to the class of acyclic phosphonomethylether nucleotides with potent activity against retroviruses. The most recent clinical data of the tenofovir gel comes from a Phase I safety and tolerability study (HPTN 050), in which 84 low risk (60 HIV-uninfected and 24 HIV-infected) women applied either 0.3% or 1% tenofovir gel once or twice daily. Both formulations were well

tolerated in both HIV-uninfected and HIV-infected women. The adverse event (AE) and safety profile in HPTN 050 was reviewed recently by the FDA which subsequently allowed the initiation of the HPTN-059 extended safety protocol for vaginal tenofovir.

Tenofovir gel has been chosen as the first microbicide to be tested in pregnancy for several reasons. Tenofovir gel is the agent farthest along in clinical testing of the topical antiretroviral agents being developed and evaluated as microbicides. As such, it is expected to enter large scale Phase IIb/III trials within the next one to two years. Parallel evaluations in pregnant women during Phase I testing and demonstrations of safety would potentially allow continuation of use during pregnancy for women enrolled in Phase III trials. Oral tenofovir disoproxil fumarate is classified by the FDA as a pregnancy category B drug.

In addition, oral tenofovir is being studied for use in prevention of peripartum maternal-to-child transmission of HIV-1 in late pregnancy. Data on the first cohort of 15 women enrolled to Pediatric AIDS Clinical Trials Group (PACTG) Protocol 394 have been presented.¹⁵ Women were given an oral dose of 600 mg of tenofovir either at the onset of labor or four hours before scheduled cesarean delivery, and pharmacokinetics and safety in the mother and infant were evaluated. No significant adverse events in the women or infants were attributed to tenofovir. The maternal tenofovir concentrations were similar to those seen after chronic dosing with 300 mg daily in non-pregnant individuals, despite the dose of 600 mg. Median cord blood levels were 76 ng/mL (range 0-309 ng/mL) and the median cord blood/maternal ratio was 0.69. All levels were below the level of quantitation (25 ng/mL) in the infants at 12, 24, and 36 hours of age. The study is continuing with a dose of 900 mg to the mother at onset of labor or before cesarean delivery. Another study, HPTN 057 is also evaluating maternal intrapartum and neonatal pharmacokinetics and safety of tenofovir. Both of these studies are in preparation for a large Phase III trial (expected sample size of approximately 2000 pregnant women) evaluating the use of oral tenofovir with emtricitabine and nevirapine for prevention of perinatal transmission and development of resistance of HIV-1. This selection is based on the expected effectiveness and safety of oral tenofovir in pregnancy. Given the low levels of tenofovir detected in the cord blood after a maternal oral dose of 600 mg, levels after intravaginal exposure to 40 mg would be expected to be lower, but must be evaluated.

Additional safety data regarding the use of tenofovir in pregnancy are available from the Antiretroviral Pregnancy Registry (APR). Through April 1, 2007, 266 cases of first trimester exposure and 208 cases with exposure to tenofovir later in pregnancy have been reported with no increase in birth defects or unusual pattern of defects detected (first trimester: 7 of 266 (2.6%); later in pregnancy: 3 of 208 (1.4%)).¹⁶

2.5 Mechanism of Action

Tenofovir disoproxil fumarate (TDF) is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. TDF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form

tenofovir diphosphate. 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 .¹⁷

2.6 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. The EC₅₀ (50% effective concentration) values for tenofovir were in the range of 0.04 μ M to 8.5 μ M. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), 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 1.6 μ M to 4.9 μ M).

2.7 Animal Studies

Pharmacokinetics

Single-dose pharmacokinetics of vaginal administration in female rabbits has been previously examined (0.5 mL, 1% w/v tenofovir, 5 mg per animal, 50 μ Ci/kg).¹⁴ 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.¹⁴ 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 pharmacokinetics, excretion and tissue distribution of ¹⁴C-PMPA (radiolabeled tenofovir) were evaluated in rats following intravaginal administration of an earlier formulation of tenofovir gel containing propylene glycol.¹⁸ 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 maximum concentration (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 µg 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 ¹⁴C-PMPA (10 mg/kg, 100 µCi/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 pharmacokinetics of radiolabeled tenofovir were evaluated via plasma and vaginal biopsies collected from four rhesus monkeys following single-dose intravaginal administration of tenofovir 1% vaginal gel. Radioactivity was detected starting at 15 minutes post application, with peak concentration of tenofovir in vaginal tissue at 8 hours and remaining high at 12 hours. No significant radioactivity was detected in whole blood or plasma.

Toxicology

The pre-clinical toxicity of tenofovir gel has been evaluated in 14-day rat and 10-day rabbit vaginal irritation and toxicity studies.^{19,20} Daily intravaginal administration of tenofovir gel produced no vaginal irritation in rats (≤ 10% tenofovir) and minimal to mild vaginal irritation in rabbits (3% or 10% tenofovir).

Tenofovir and TDF administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to six fold those observed in humans caused bone toxicity. 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.

Evidence of renal toxicity was noted in four animal species.¹⁷ Increases in serum creatinine, BUN, 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.

Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 16 times (mice) and five times (rats) those observed in humans at the therapeutic dose for HIV infection.¹⁷ 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 five times that observed in humans at the therapeutic dose. TDF was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, TDF was negative when administered to male mice.

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. 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.

2.8 Safety in Pregnancy

Tenofovir gel has not been studied in pregnancy in humans to date. Oral tenofovir, however, has been used in pregnancy and limited data exist. The Antiretroviral Pregnancy Registry has collected data on greater than 5,900 live births that have been exposed to one or more antiretroviral agent. Of that cohort, 474 of the fetuses were exposed to tenofovir. Overall ten birth defects have been recorded. The registry concluded that there was no pattern of defects linked to tenofovir exposure given the overall low rate of 2.1% (within accepted background rate of defects in the population of around 3%).

Tenofovir has been studied in gravid rhesus monkeys and does cross the placenta following subcutaneous administration in this simian model.²¹ Based on the low plasma protein binding in pharmacologic studies, it is expected that tenofovir will cross the human placenta with systemic dosing.

In particular, the preliminary data from PACTG Protocol 394 suggest that the single dose administration of the tenofovir gel formulation would not pose undue risk to participants and their fetuses. As stated previously, no significant adverse events in the women or infants were attributed to tenofovir. The maternal tenofovir concentrations were similar to those seen after chronic dosing with 300 mg daily in non-pregnant individuals, despite the dose of 600 mg. Median cord blood levels were low and all levels were below the level of quantitation in the infants at 12, 24, and 36 hours of age. The study is continuing with a dose of 900 mg to the mother at onset of labor or before cesarean delivery. Given the low neonatal levels detected after oral administration in PACTG 394, we would not expect detectable levels in the neonates born to mothers receiving single-dose vaginal product in MTN-002. Likewise, given the low systemic levels noted with vaginal administration in HPTN 050, we would not expect significant concentration of tenofovir in the breast milk of MTN-002 participants.

The single vaginal dosing in this study in addition to the term status of the fetus makes any significant effect on the fetus highly unlikely, assuming placental transfer does take place. In addition, systemic absorption of tenofovir from the vaginal gel appears to be minimal, (approximately 1% of the therapeutic oral dose) and the perceived risk of an effect on bone mineral density is extremely low from a single-dose vaginal study, if existent at all.

2.9 Clinical Studies

HPTN 050, also known as Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel is the most recently published study of tenofovir vaginal gel. Eighty-four (60 HIV-uninfected and 24 HIV-infected) women applied either 0.3% or 1% tenofovir gel once or twice daily. Both of the tenofovir gel formulations were well tolerated in both HIV-uninfected and HIV-infected women. Although 91% reported at least one AE, the majority (88%) were mild and limited to the GU tract. 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 were detected in plasma or cervicovaginal lavage after 14 days of tenofovir gel use but three women had plasma mutations associated with low level tenofovir resistance at day 0 and 14 (M41L, L210M, \pm T215I/Y). Systemic absorption was limited (maximum serum levels 3.1-25.8 ng/ml). The AE and safety profile in HPTN 050 was reviewed recently by the FDA during their review of the HPTN-059 extended safety protocol for vaginal tenofovir.

A male tolerance study of tenofovir 1% vaginal gel (CONRAD A04-099) was recently completed, and is currently in the analysis stage.

Several other tenofovir 1% vaginal gel studies are ongoing or in development. These include:

- HPTN 059: Phase II Expanded Safety and Acceptability Study of the Vaginal Microbicide 1% Tenofovir Gel
- CONRAD A04-095: Single Dose and 14-Day Once or Twice-daily Pharmacokinetic Study of the Vaginal Microbicide Agent 1% Tenofovir Gel
- CAPRISA 004: Safety and Effectiveness Study of a Candidate Vaginal Microbicide for Prevention of HIV (Phase IIb, two-arm, double-blinded, randomized, placebo controlled trial comparing coitally dependent 1% tenofovir gel with a placebo gel)
- MTN-001: Phase II Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir
- MTN-003: Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate (DF) Tablet and Tenofovir DF-Emtricitabine Tablet for the Prevention of HIV-1 Infection in Women
- MTN-007: Phase I Rectal Safety of Tenofovir Gel

2.10 Vaginal Gel Pharmacokinetics

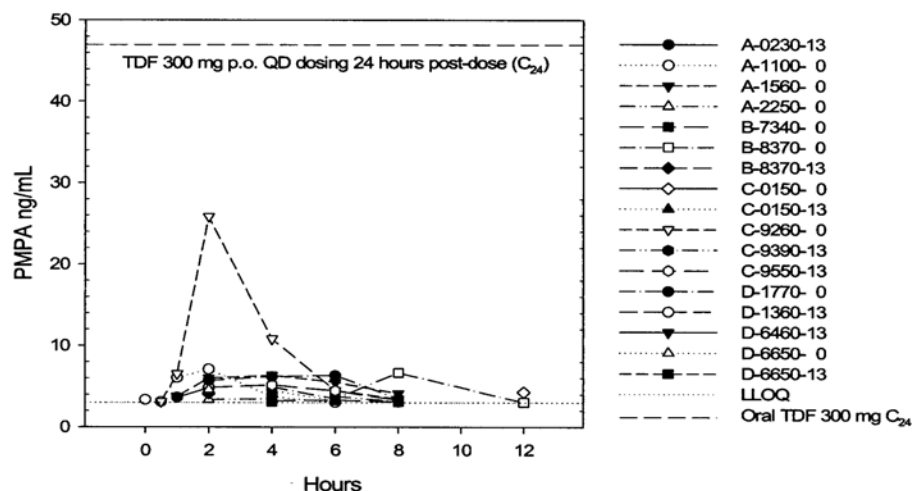
Limited vaginal pharmacokinetic data in primates and humans demonstrate that tenofovir gel is broadly distributed in vaginal tissues following vaginal application and can penetrate to epithelial tissues.²² The amount of tenofovir administered by intravaginal application of 4 grams of a 1% dose is 40 mg. This dose of tenofovir is slightly more than half the amount absorbed following oral ingestion (approximately 25% or 75 mg) of a 300 mg tablet of TDF.

Tenofovir (0.3% and 1%) gel was recently tested in the HPTN 050 Phase I study. In this trial, tenofovir gel was administered intravaginally in four groups of women: sexually abstinent HIV-uninfected and HIV infected women, and sexually active HIV-uninfected and HIV-infected women. The women and their male partners (in the sexually active cohorts) were also asked to assess the acceptability of the product. Results from the HPTN 050 Phase I study have shown tenofovir 1% gel to be safe and acceptable.² In light of the favorable findings, an expanded safety and tolerability study of tenofovir gel is underway (HPTN 059).

HPTN 050 also addressed pharmacokinetics of vaginally administered tenofovir gel. Fourteen of 25 women (56%) with pharmacokinetic results had low, but detectable, serum tenofovir levels (limit of quantitation: 3.0 ng/mL) at some point in the 12 hours after dosing on either Day 0 (following the first dose) or on Day 13 (after daily dosing); three of the 14 had detectable levels on both days. The maximum tenofovir concentrations (C_{max}) ranged from 3.0 - 25.8 ng/mL, with no clear dose-concentration relationship identified. For the woman with the 25.8 ng/mL level, this peak level occurred two hours following the dose; the level rapidly declined to 10.9 ng/mL at four hours and was undetectable at 12 hours following the dose. Besides the outlier with the highest tenofovir level, the next highest C_{max} was 7.1 ng/mL. Considering all women in the PK cohort, the median tenofovir C_{max} was 3.4 ng/mL (interquartile range: below limit of quantitation [3.0 ng/mL] to 4.7 ng/mL). The median C_{max} for all subjects (3.4 ng/mL) corresponds to approximately 1% of the maximum ($C_{max, steady-state (ss)}$) and 7% of the minimum (C24 single dose) blood concentrations at steady-state with 300 mg daily oral tenofovir dosing.²³ Findings from CONRAD A04-095 are expected to further inform the pharmacokinetic data on vaginally administered tenofovir gel.

Figure 1 presented below demonstrates tenofovir blood concentration following vaginal administration of tenofovir 1% gel in HPTN 050. All levels for all women with measurable tenofovir levels in the blood are shown. (14 of 25; lower limit of quantitation (LLOQ) approximately 3.0 ng/mL [dotted line]). Legend indicates “cohort” – “ID” – “study day”. For reference the tenofovir level associated with the median 24 hour post-dose blood concentration following an oral 300 mg tenofovir dose is indicated with dashed line.

Figure 1 - Tenofovir Blood Concentrations vs. Time after Vaginal Administration



First letter = Cohort

Cohort A - HIV -uninfected/sexually abstinent

Cohort B - HIV -uninfected/sexually active

Cohort C - HIV-infected/sexually abstinent

Cohort D - HIV-infected/sexually active

4 digits = last 4 digits of participant identifier

Last digit = day of study

The current study will expand the ongoing evaluation of tenofovir gel into the term pregnant population. It is conceivable that the absorption and pharmacokinetics of tenofovir gel in the 3rd trimester of pregnancy may differ from the non-pregnant data above, given increased blood flow to the pelvic tissues and engorgement of the pelvic vessels. With hypothesized increased absorption from the pelvic tissues, the potential for placental transfer exists. This protocol will also evaluate that endpoint.

The validated LCMS (liquid chromatography mass spectrometry) method planned for MTN-002 has a limit of quantitation (LOQ) of 5 ng/mL, but uses only 50 microliters of fluid. Previous methods have had a LOQ of 3 ng/mL but used 250 microliters. Since assay sensitivity is largely determined by mass in the sample, not concentration, this likely represents a 3 fold improvement in sensitivity if we use a similar volume as in previous studies. To improve even further, we are planning to dedicate 1 mL serum for the blood tenofovir assay to further increase the sensitivity, possibly below 1 ng/mL. This may increase the number of samples quantifiable in the blood assuming similar pharmacokinetics as in HPTN 050.

No PK analysis is planned beyond description of C_{max} and T_{max} . Estimates of vaginal absorption, systemic clearance, volume of distribution, and half-life require accurate assessment of the initial rise in concentration, area under the concentration time curve (AUC), and terminal elimination slope. Since only the concentration at 1 – 3 time points near C_{max} in only some women (based on HPTN 050 experience) may be expected to be measurable, data from this study cannot be used to estimate initial absorption, AUC, or terminal elimination slope.

2.11 Study Hypothesis

We hypothesize that:

- Plasma absorption in participants will be detectable in a percentage of women similar to that seen in HPTN 050 (approximately 33%)
- Of women with detectable levels of tenofovir, a small fraction will have detectable levels in endometrium, cord blood, placental tissue, and amniotic fluid

2.12 Justification of Dosing

Choice of the tenofovir 1% gel concentration for MTN-002 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. The tolerability of the 1% gel was confirmed in the HPTN 050 Phase I study, the Phase I dose ranging study of tenofovir gel (0.3% once daily, then 1% once daily, then 0.3% twice daily followed by 1% twice daily). 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. Six separate studies provided evidence for efficacy of the gel over a range of tenofovir concentrations of 0.3% to 10%. Although the total data are limited and a powered statistical determination as to the efficacy of 1% tenofovir 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, the amount of tenofovir administered by intravaginal application of 4 grams of a 1% dose (40 mg) is similar to the orally absorbed amount that has been shown to be highly active against HIV and results in a reduction of plasma HIV 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 oral 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 durable barrier to HIV transmission may be possible. In terms of weighing potential risks and benefits, the 1% tenofovir gel minimizes the potential risks of vaginal epithelial toxicity while providing the potential benefit of delivering sufficient tenofovir to achieve an initial and possibly durable barrier to infection.

3 OBJECTIVES

3.1 Primary Objectives

- Assess term pregnancy maternal single-dose pharmacokinetics of tenofovir 1% vaginal gel

3.2 Secondary Objectives

- Characterize the systemic safety profile of single-dose tenofovir 1% vaginal gel in term gravidas
- Compare 3rd trimester absorption of tenofovir 1% vaginal gel to absorption in non-pregnant recent historic controls²
- Assess amniotic fluid, cord blood, endometrial tissue and placental tissue levels following single-dose tenofovir 1% vaginal gel

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-002 will be a Phase I, single-site, open label investigation into the single-dose pharmacokinetic parameters and placental transfer of tenofovir gel when administered to term gravidas scheduled for elective cesarean section. We will enroll 16 healthy HIV-uninfected women, obtain baseline blood samples, place the gel in the vagina with a target administration time approximately two hours prior to the expected time of cesarean section (optimally a minimum of one hour prior to the collection of cord blood), and then obtain blood samples at the following times: 1, 2, 4, 6, 8, 12 and 24 hours following gel placement. In addition, amniotic fluid, placenta, and endometrial specimens will be collected.

4.2 Summary of Major Endpoints

- Maternal 3rd trimester pharmacokinetic measures (AUC, C_{max},)
- Endometrial tenofovir levels
- Placental transfer (cord blood tenofovir levels, placental tissue tenofovir levels, amniotic fluid tenofovir levels)

4.3 Description of Study Population

The study population will consist of 16 pregnant women aged 18-45 who are healthy, non-HIV infected and at term. The gravidas will be expected to be scheduled for elective cesarean section (CS) at ≥ 37 and < 42 completed gestational weeks and will lack evidence of placental disease (no hypertension, diabetes mellitus, collagen vascular disease, placental abruption, etc.) as described in Section 5.3.

4.4 Time to Complete Enrollment

Time to complete study enrollment is expected to be approximately eighteen months.

4.5 Study Group

A single study arm is planned. A total of approximately 16 women will be enrolled. Additional participants will be enrolled to ensure that a total of 16 evaluable participants complete the study.

The following types of participants will be replaced:

- Participants who are enrolled but do not receive study gel
- Participants who receive study gel but whose time of cesarean delivery is greater than 8 hours following the time of study gel administration

4.6 Sequence and Duration of Trial Periods

Acknowledging that it is not always possible to complete study evaluations/visits on the targeted dates/times, evaluations/visits may be completed within a specified window around the target date/time.

The time of cesarean section may be changed for clinical, administrative, or other reasons outside the control of the study staff. Gel administration that occurs outside the specified window due to such changes will not be considered a protocol violation.

Table 1: Visit Windows

Visit	Screening and Enrollment	Gel Administration	0-12 hr PK	24 Hour Evaluation	Two Week Phone Call
Window	Up to four weeks prior to expected date of gel administration (Day 0) and with reasonable allowance for turn-around-time of laboratory analyses drawn at Screening and Enrollment	Up to four hours prior to the expected time of cesarean section, with an optimal minimum of one hour prior to the expected time of cord blood collection	15 minutes +/- scheduled blood draw	22 – 26 hours	Day 10 – Day 18
Target	No target	Defined as Day 0, Time 0 2 hours prior to expected time of cesarean delivery	1, 2, 4, 6, 8, 12 hours following gel placement	24 hours following gel placement	Day 14

4.7 Expected Duration of Participation

The expected duration of participation for individual enrolled participants will depend on how long they enroll prior to the date of cesarean section, but may range from approximately three to six weeks. Participants who have Adverse Events (AEs) which are not resolved at the Two Week Phone Call will be followed beyond this point using Unscheduled Visits as necessary until a clinically acceptable resolution of the AE(s) (at the discretion of the Site Principal Investigator (PI) or NIH (Medical Monitors) has been documented, including resolution date, if possible. No further study data (for purposes of data analysis) will be collected for these participants after the Two Week Phone Call.

4.8 Site

A single site is planned for this trial: University of Pittsburgh, Pittsburgh, USA

5 STUDY POPULATION

5.1 Selection of the Study Population

5.1.1 Composition

It is anticipated that the study population will be primarily composed of Caucasian and African-American women consistent with the primary racial and ethnic composition of patients at Magee-Womens Hospital of UPMC. Women of other racial and ethnic backgrounds will not be excluded. As this study will be assessing the pharmacokinetics of a vaginally applied product among pregnant women, only female participants will be enrolled.

5.1.2 Recruitment

Members of the research team including the Site PI will recruit potential participants during the antenatal period using IRB-approved materials.

5.2 Inclusion Criteria

Women must meet all of the following criteria (by self-report, unless otherwise indicated) to be eligible for inclusion in the study:

1. Age 18-45 years at screening and enrollment, inclusive, and verified per site standard operating procedure (SOP).
2. Willing and able to provide written informed consent for screening and enrollment
3. General good health as determined by the site Investigator of Record (IoR) or designee at Screening and Enrollment Visit
4. HIV-uninfected (per HIV Testing Algorithm, Appendix II)
5. HBsAg negative at Screening and Enrollment Visit or documented negative during this pregnancy
6. Pregnancy with the following characteristics:
 - Viable
 - Singleton
 - Without ultrasound evidence of significant fetal congenital anomaly (in the opinion of the IoR or designee)
 - Term (37 0/7 to 41 6/7 weeks, inclusive, with gestational dating criteria per SOP) at the time of planned cesarean section
 - Planned cesarean section
7. Normal Pap (or completed evaluation of abnormal Pap) in the 12 calendar months prior to screening per SOP
8. Willing to:
 - abstain from vaginal sex, anal sex, and receptive oral sex for at least two weeks after gel placement
 - abstain from intravaginal products and practices (including douching) during study participation
 - not participate in other drug or device study during study participation
 - participate as required by protocol, including study product administration, assessments and follow-up schedule

5.3 Exclusion Criteria

Women who meet any of the following criteria (by self-report, unless otherwise indicated) will be excluded from the study:

1. Maternal or fetal condition that necessitates urgent cesarean section (e.g. active labor, non-reassuring fetal heart tracing)
2. Documented rupture of the amniotic membranes, as defined in the SOP
3. Known maternal disease with predictable negative affect on placental function (e.g. hypertension, diabetes mellitus, collagen vascular disease, clinically significant maternal anemia)
4. Known placental/fetal abnormalities that could affect placental transfer (e.g. placental abruption, placenta previa, placenta accreta, intrauterine growth restriction, two vessel cord, etc.)
5. Serum creatinine at Screening and Enrollment Visit greater than 1.0 mg/dL
6. AST and/or ALT at screening greater than 1.5 ULN (upper limit of normal)
7. Current or recent (within 48 hours) use of vaginal medications at the Screening and Enrollment visit (per participant report)
8. Untreated sexually transmitted infection or (as applicable) exposure to partner's infection, including chlamydia, gonorrhea, trichomoniasis, non-gonococcal urethritis
Note: women diagnosed with an STI during screening or in the process of enrollment will be offered or referred for treatment in accordance with CDC guidelines. These participants will be eligible for enrollment once they have completed treatment(s) and are asymptomatic for the STI(s).
9. Symptomatic vaginitis, including bacterial vaginosis and vulvovaginal candidiasis (participants with asymptomatic signs of bacterial vaginosis and/or yeast are still eligible for enrollment)
10. Participation in any other investigational drug or device trial within 30 days prior to enrollment visit
11. At screening or enrollment, 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

6 STUDY PRODUCT

6.1 Regimen

All study participants will receive a single vaginal dose of 4 grams of tenofovir 1% gel followed by 24 hours of intensive PK sampling.

6.2 Administration

Four grams of tenofovir 1% gel will be administered vaginally, using the vaginal applicator provided, by the authorized clinician, approximately two hours prior to the expected time of cesarean section (optimally at least one hour prior to the collection of cord blood).

6.3 Study Product Formulation and Preparation

Tenofovir gel is a clear, transparent viscous gel packaged in epoxy inner-lined aluminum tubes with white polyethylene screw caps equipped with a puncture tip. Each single-dose tube contains nominally 6 grams of tenofovir gel at a concentration of 1% (weight per weight) formulated in purified water with edetate disodium, citric acid, glycerin, methylparaben, propylparaben, and hydroxyethylcellulose, with pH adjusted between 4.0 and 5.0. The study gel is applied with a polyethylene applicator capable of administering a 4 gram dose. The product must be stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F).

Immediately prior to application, the authorized clinician will fill the vaginal applicator by removing the cap from the tube of study gel, puncturing the metal seal on the tube with the pointed tip of the cap, screwing the end of the applicator onto the tube and slowly squeezing gel out of the tube and into the applicator. The plunger will stop when the applicator is full (contains the 4 grams of study product).

6.4 Study Product Supply and Accountability

6.4.1 Study Product Supply

Tenofovir 1% gel and applicators will be provided by CONRAD (Arlington, VA). Tenofovir 1% gel is manufactured, packaged, labeled, analyzed and released by Gilead Sciences (Foster City, CA) under current good manufacturing practices (cGMP), 21 Code of Federal Regulation, conditions.

6.4.2 Study Product Acquisition

Tenofovir 1% gel and vaginal applicators will be available through the DAIDS Clinical Research Products Management Center. The Pharmacist of Record can obtain the

study product for this protocol by following the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

6.4.3 Dispensing

The tenofovir 1% gel tube for a study participant and a vaginal applicator will be dispensed only upon receipt of a written prescription from an authorized prescriber. The study product should be kept in the pharmacy until the day of the planned cesarean section.

6.4.4 Accountability

The Pharmacist of Record is required to maintain complete records of all study products received from the DAIDS Clinical Research Products Management Center and subsequently dispensed. All unused study products must be returned to the DAIDS Clinical Research Products Management Center after the study is completed or terminated. The procedures to be followed are provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

6.4.5 Retrieval of Unused Study Products

Physician investigators and authorized study site staff must return any unused study product tubes and unadministered study product in applicators to the pharmacy.

6.5 Concomitant Medications and Procedures

With the exception of those not permitted under inclusion/exclusion criteria, concomitant medications will be permitted. These include both prescription and non-prescription medications.

All concomitant medications reported throughout the course of the study will be recorded on the participant's chart on forms designated for that purpose. Inpatient medications (including medications for anesthesia, intravenous fluids, and others), prescription medications, over-the-counter preparations, vitamins and nutritional supplements, and herbal preparations will all be recorded as concomitant medications. Forms will include a place to record the time of administration for all medications up until 24 hours following the administration of the study gel.

6.5.1 Prohibited Medications and Practices

Vaginal douching will not be permitted to protect the integrity of the lower genital tract and reduce the possibility of adverse events due to agents other than the study products. However, in the event that prohibited practices are reported following

administration of study gel, the protocol-specified visit schedule will continue for such participants for safety assessment through study exit. All concomitant medications will be recorded on Concomitant Medication Records.

Vaginal, anal, and receptive oral sex will not be permitted for at least two weeks following gel administration. Women will be advised to follow the instructions of their surgeon.

7 STUDY PROCEDURES

The following should take place for study participants:

- Screening and Enrollment Visit
- Pharmacokinetic Measures (includes gel administration)
- 24-hour Evaluation
- Two Week Phone Call

7.1 Screening and Enrollment Visit

The Screening and Enrollment Visit will occur approximately one to four weeks prior to the participant's scheduled C/S, but no more than four weeks before the expected date of cesarean section. This will allow the receipt of results for laboratory measures employed as components of screening.

Screening and Enrollment procedures are outlined below in Table 2: Screening and Enrollment Visit. If necessary, components of the Screening and Enrollment Visit may occur on different days. If necessary, components of the Screening and Enrollment Visit may take place at a location affiliated with the study site (for example, a satellite clinic).

With the permission of the participant, a physician investigator or designee will be available to answer questions of the primary obstetrician or other clinical care staff regarding the requirements of study participation. Appropriate written materials for clinical care staff members describing study procedures and supporting the correct interpretation of the study protocol will be placed in the participant's prenatal chart after written informed consent has been obtained from the participant.

Participants will be contacted with results of laboratory tests done at the Screening and Enrollment Visit once results are available; all results are likely to be available within approximately one week. Results other than HIV testing may be provided by phone.

Table 2: Screening and Enrollment Visit

Screening and Enrollment Visit	
Component	Procedure/Analysis
Administrative	<ul style="list-style-type: none"> • Obtain written informed consent • Collect locator information • Administer eligibility assessment • Assign Participant ID • Obtain signed records release • Record demographics • Plan for Pharmacokinetic Measures Visit (Date of Planned C/S) • Provide reimbursement for study visit
Clinical	<ul style="list-style-type: none"> • Review prenatal record • Review ultrasound report(s) • Record medical history • Record concomitant medications • Perform targeted physical exam • Perform pelvic exam
Laboratory	<ul style="list-style-type: none"> • Collect pelvic specimens <ul style="list-style-type: none"> ○ Trichomonas culture ○ *Wet prep and vaginal pH ○ *Herpes Culture • Collect urine specimen <ul style="list-style-type: none"> ○ Urine SDA for chlamydia and gonorrhea • Collect blood specimen <ul style="list-style-type: none"> ○ Serum creatinine ○ AST and ALT ○ Rapid HIV test with pre- and post-test counseling ○ *Confirmatory Testing for HIV ○ *HBsAg ○ *RPR ○ *Confirmatory Testing for Syphilis

*As clinically appropriate

7.2 HIV Test Results

Participants will receive their HIV test results in person in the context of a post-test counseling session with a trained study staff member. As rapid testing will be used, results are expected to be available during the study visit.

In the unlikely event that an indeterminate or positive HIV test result occurs, participants will be informed of their results in person by a physician investigator able to participate in a thorough discussion of follow-up testing and treatment options, including prevention of mother-to-child transmission (PMTCT), as appropriate. Confirmation of HIV infection will occur according to guidelines presented in Appendix II.

If applicable, study staff members will make every effort to refer the participant to appropriate clinical and social support resources for HIV-infected pregnant women.

7.3 Pharmacokinetic Measures

For the purposes of scheduling subsequent evaluation and follow-up, the date of gel administration will be considered Day 0. The time of gel administration will be considered Time 0. Timed pharmacokinetic measures are timed by hours passed since gel administration, not cesarean section.

A physician investigator will not be the primary or first assistant surgeon for the cesarean section. A physician investigator will be responsible for collection of study-related specimens in the operating room.

Flow cytometry for CD38 and CD95 will be obtained pre-dose on Day 0. This will be required as a surrogate for cell activation and proliferation markers, respectively, to serve as covariates in the intracellular model building.

If not already in place, a saline lock (or similar device) will be inserted to facilitate the collection of multiple blood specimens. This device may be replaced as needed in the event of a non-functioning device. Specimens will not be drawn from the site of an ongoing intravenous infusion.

Surgery and anesthesia may contribute to a temporary increase in intravascular volume, though this is often a function of the duration of surgery. Accordingly, there may be an increase in volume of distribution, especially for water soluble drugs, that would transiently reduce drug concentrations in the blood. Drugs used in anesthesia (including their time of administration) and operative time are routinely recorded and these data will be captured.

As the majority of these evaluations are likely to occur in the pre-operative area, operating room, and post-operative areas of the hospital, participants will not receive reimbursement for this study visit in these settings, which are expected to be relatively short-term. Rather, reimbursement will be provided for all study participation that occurs in the inpatient setting at the 24 Hour Evaluation or other setting as needed.

Table 3: Pharmacokinetic Measures: Gel Administration Day (Day 0)

Pharmacokinetic Measures		
Component	Procedure/Analysis	
Pre-Gel	Admin.	<ul style="list-style-type: none"> • Update locator information • Place copy of consent in inpatient chart • Review inpatient chart • Administer eligibility assessment/Confirm eligibility • Schedule next study evaluation
	Clinical	<ul style="list-style-type: none"> • Update medical history • Update concomitant medications • Update adverse events • Perform targeted physical exam • Perform pelvic exam
	Lab	<ul style="list-style-type: none"> • Insert/Replace saline lock or similar (if not already inserted) • Draw blood for: <ul style="list-style-type: none"> ○ maternal plasma tenofovir level ○ flow cytometry
Gel	<ul style="list-style-type: none"> • Gel administration by study physician 	
Post-Gel	C/S	<ul style="list-style-type: none"> • Amniotic fluid collection • Endometrial tissue collection
	Clinical	<ul style="list-style-type: none"> • Collect adverse events at each PK time point • Review inpatient chart (during 1-12 hours post-gel)
	Lab	<ul style="list-style-type: none"> • Insert/Replace saline lock as needed • Draw blood for maternal plasma tenofovir level <ul style="list-style-type: none"> ○ 1, 2, 4, 6, 8, and 12 hour time points <ul style="list-style-type: none"> ▪ <i>Note: the above time points are after gel administration.</i> ▪ <i>Some time points may occur before cesarean section.</i> ▪ <i>The allowable window for each blood draw is +/-15 minutes.</i> • Cord blood collection <ul style="list-style-type: none"> ○ may also be collected during cesarean section if possible • Placental tissue collection <ul style="list-style-type: none"> ○ may also be collected during cesarean section if possible

7.4 24 Hour Evaluation

The 24 Hour Evaluation will occur between 22 and 26 hours following product administration.

Table 4: 24 Hour Evaluation

24 Hour Evaluation	
Component	Procedure/Analysis
Administrative	<ul style="list-style-type: none"> • Update locator information • Schedule Two Week Phone Call • Provide reimbursement
Clinical	<ul style="list-style-type: none"> • Review inpatient chart • Record/Update concomitant medications • Record/Update adverse events • *Perform targeted physical exam • *Perform pelvic exam
Laboratory	<ul style="list-style-type: none"> • Draw blood for maternal plasma tenofovir level

*only as clinically indicated

7.5 Two Week Phone Call

The Two Week Phone Call will collect data on any new or outstanding adverse events, as well as other procedures as outlined in Table 5. The window for the phone call is Day 10 to Day 18.

Table 5: Two Week Phone Call

Two Week Phone Call	
Component	Procedure/Analysis
Administrative	<ul style="list-style-type: none"> • Update locator information • Update demographics • *Review inpatient chart • *Review outpatient chart • Trigger staff to send reimbursement for phone call • *Schedule next visit
Clinical	<ul style="list-style-type: none"> • Update concomitant medications • Update adverse events

*as clinically indicated

7.6 Unscheduled Visit

An Unscheduled Visit may occur at any time during study participation, and may be triggered by participant report of an adverse event that is unresolved at the 24 Hour Evaluation, or that is reported following the 24 Hour Evaluation.

Table 6: Unscheduled Visit

Safety Visit	
Component	Procedure/Analysis
Administrative	<ul style="list-style-type: none"> • Update locator information • *Sign records release • *Schedule next visit/call
Clinical	<ul style="list-style-type: none"> • Update concomitant medications • Update adverse events • Perform targeted physical exam • *Perform pelvic exam • *Review inpatient chart • *Review outpatient chart
Laboratory	<ul style="list-style-type: none"> • *Serum creatinine • *ALT • *AST • *RPR • *Confirmatory testing for syphilis • *Rapid HIV Test • *Confirmatory testing for HIV with pre-and post-test counseling • *HBsAg • *Maternal plasma tenofovir level • *Urine SDA for CT and GC • *Urinalysis • *Urine culture and sensitivity • *Wet prep and vaginal pH • *Trichomonas culture • *Herpes culture • *Other laboratory tests deemed clinically appropriate, when possible after consultation with the PSRT

*as clinically indicated

7.7 Final Contact

In most cases the final contact will be the Two Week Phone Call. If necessary, the study site may complete the final contact visit(s), including the script for the Two Week Phone Call, 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.

7.8 Clinical Evaluations and Procedures

Clinical evaluation of participants will include a targeted physical exam as described in Appendix III.

7.9 Laboratory Evaluations

7.9.1 Local Laboratory

The local laboratory, site investigator, or designee will run the following, as indicated:

- Serum creatinine
- AST
- ALT
- Rapid HIV test
- Confirmatory testing for HIV
- Hepatitis B surface antigen
- Rapid plasma reagin
- Confirmatory testing for syphilis
- Wet preparation slide
- Vaginal pH
- Herpes culture
- Urinalysis
- Urine culture and sensitivity
- Flow cytometry

7.9.2 Network Laboratory

The Network Laboratory will run the following:

- Urine SDA for chlamydia and gonorrhea
- Trichomonas culture
- Pharmacokinetic analyses (at NL Pharmacology Core)

The following specimens will be collected for pharmacokinetic analyses of tenofovir according to guidelines outlined in the Site SOPs.

- Maternal blood
- Amniotic fluid
- Cord blood
- Placental tissue

- Endometrial tissue

Based on HPTN 050, 64% of measurable samples fell in the 2 to 6 hour sampling window which was the basis for selection of sampling times to maximize capture of peak levels in the blood. Measurable levels were spread almost evenly among the 2, 4, and 6 hour sample times. Subjects' peak tenofovir concentrations occurred throughout this window. In HPTN 050, 38% of measurable levels were after 4 hours so they are somewhat less likely to be measurable, but will be nearly as informative as the 4 hour sample.

MTN-002 will use a more sensitive tenofovir assay than HPTN 050. Our validated liquid chromatography mass spectrometry (LCMS) method has a limit of quantitation (LOQ) of 5 ng/mL, but uses only 50 microliters of fluid. Previous methods have had a LOQ of 3 ng/mL but used 250 microliters. Since assay sensitivity is largely determined by mass in the sample, not concentration, this likely represents a 3 fold improvement in sensitivity if we use a similar volume as in previous studies. To improve even further, we are planning to dedicate 1 mL serum for the blood tenofovir assay to further increase the sensitivity, possibly below 1 ng/mL. This may increase the number of samples quantifiable in the blood assuming similar pharmacokinetics as in HPTN 050.

As stated above, a validated assay for tenofovir in plasma is currently available. Validated assays for tenofovir in endometrial tissue, amniotic fluid and placental tissue have not yet been developed, but are expected to be ready in 2007. Pharmacokinetic samples may be batch shipped from the NL to the NL Pharmacology Core for assay.

The principal parameter of interest after intravaginal dosing will be the AUC. Plasma will also be analyzed for routine pharmacokinetic parameters (C_{max} , T_{max}).

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, DAIDS Laboratory Requirements, and site standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, and storage 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 as outlined in the site SOPs.

7.11 Specimen Handling

Specimens will be handled in accordance with Requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials.

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. 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. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

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 or designee, Medical Officers, SDMC Clinical Affairs Research Nurse, and Protocol Statistician, will serve as the PSRT. The PSRT will be co-chaired by the protocol safety physicians in the MTN CORE. Close cooperation among the PSRT and other study team members will be necessary to monitor participant safety and respond to occurrences of toxicity in a timely manner. The MTN SDMC prepares routine AE and clinical data reports for review by the PSRT, which meets via conference call approximately every month or as needed throughout the period of study implementation to review safety data, discuss product use management and address any potential safety concerns.

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 NICHD and DAIDS Medical Officers and SDMC Clinical Affairs staff for review.

The PSRT will meet approximately every month 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 decision 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.

In the unlikely event that the protocol team has serious safety concerns that lead to a decision to permanently stop accrual into the study, the protocol team will request a review of the data by the Study Monitoring Committee (SMC) before deciding 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 enrollment, DAIDS will notify the US FDA and the site CRS PI will notify the responsible IRB 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 administered an investigational product and which does not necessarily have a causal relationship with the investigational product. 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, whether or not considered related to the product. The term “investigational product” for this study refers to tenofovir gel.

Study participants will be instructed to contact the study site staff to report any AEs they may experience, except for life-threatening events, for which 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, and 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.

Study site staff will document on study CRFs all AEs reported by or observed in enrolled study participants from the time of enrollment until study termination, regardless of severity and presumed relationship to study product. The Protocol Specific Toxicity

Table (Appendix V) 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 Protocol Specific Toxicity Table will be the grading scale utilized.

8.3.2 Serious Adverse Event

Serious adverse events (SAEs) will be defined per 21 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

Relatedness is an assessment made by a study clinician of whether or not the event is related to the study agent. Degrees of relatedness will be categorized as one of the following.

- *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 Intensive 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 the tenofovir 1% vaginal gel and study gel applicator.

Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December, 2004 and the Protocol Specific Toxicity Table must be used. The DAIDS AE Grading Table 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 Intensive Level during the Protocol-defined EAE Reporting Period, which is the entire study duration for an individual subject (from study enrollment until study termination).

After the end of the Protocol-defined EAE Reporting Period stated above, the study site must report serious, unexpected, clinical suspected adverse drug reactions if the study site staff becomes aware of the event on a passive basis, i.e., from publicly available information.

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-mandated reporting of AEs, SAEs, and other relevant safety information.

8.6 Social Harms Reporting

Although social harms are not expected in this study, the study site will 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. Social harms that are judged by the Investigator of Record to be serious or unexpected will be reported to the responsible site IRB 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.

9 CLINICAL MANAGEMENT

9.1 Toxicity Management

Based on results from previous clinical trials, significant toxicity in study participants is not expected in this trial of a single dose administration with minimal expected systemic absorption of this vaginal gel product. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of orally administered nucleoside analogs alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution is advised when administering nucleotide analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors.

In the event of an expedited adverse event that occurs at the study site and that is judged to be definitely, probably, possibly, or probably not related to the study gel or applicator, product exposure will be minimized to the extent possible via cervicovaginal lavage (if clinically appropriate) and suspected toxicity will be managed according to Site SOPs by a physician on the study team at the discretion of the site investigator. Unless the participant withdraws her consent, she will remain in the study to complete all non-product related evaluations unless clinically contraindicated according to Appendix I.

9.2 Criteria for Withholding Study Product

Participants may decline administration of study product. Physician investigators may decide not to administer study product to participants to protect their safety.

The withholding of study product will occur only under certain criteria. The criteria for an individual participant are:

- Request by participant to not receive study product
- Decision by the principal investigator to protect the participant's safety and/or if the participant is unable or unwilling to comply with study procedures

At least one of the above criteria must be met for the participant to not receive study product.

9.3 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The principal investigators may, with the approval of the PSRT, withdraw participants to protect their safety, and/or if participants are unable or unwilling to comply with study procedures.

Early (premature) termination of study participants will occur only under certain criteria. The criteria for early termination from the study for an individual participant are:

- Request by participant to withdraw
- Request by the principal investigator to protect the participant's safety and/or if the participant is unable or unwilling to comply with study procedures

At least one of the above criteria must be met for the participant to be terminated early from the study.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and General Design

This is a single-dose, single-site, open label study. All the enrolled women will be administered tenofovir 1% vaginal gel. The planned total length of follow-up is 2 weeks.

10.2 Study Major Endpoints

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

- Maternal 3rd trimester pharmacokinetic measures: AUC, C_{max}
- Endometrial tenofovir levels
- Placental transfer : cord blood tenofovir levels, placental tissue tenofovir levels, and amniotic fluid tenofovir levels

10.3 Study Hypothesis

We hypothesize:

- Study hypothesis 1: Plasma absorption in participants will be detectable in a percentage of women similar to that seen in HPTN 050 (approximately 33%)
- Study hypothesis 2: Of women with detectable levels of tenofovir, a small fraction will have detectable levels in endometrium, cord blood, placental tissue, and amniotic fluid

10.4 Sample Size

The power of the study can be characterized as follows: if the overall absorption rate (defined as the proportion of women with detectable levels of PMPA in plasma, endometrium, cord blood, placental tissue, and/or amniotic fluid) was expected to be 33%, 16 women would provide 72% power to exclude absorption rate > 60%. In addition, the lower and upper bounds of the exact 95% confidence interval (CI) around the absorption rate are 13% and 57%, respectively, if the observed number of absorption in a cohort of 16 women was 5 (31%: 5 out of 16).

For endpoints where no or very low absorption rates are expected (e.g., endometrium, cord blood, placental tissue, and amniotic fluid), 16 women would provide 80% power to exclude absorption rate > 25% assuming the true rate of absorption is 5%. In addition, the upper bounds of the exact 95% confidence interval (CI) around the absorption rate are 20% and 30% if the observed number of absorption in a cohort of 16 women was 0 or 1, respectively.

Additional participants may enroll in the study, at the discretion of the protocol team, to replace currently enrolled participants who receive study gel but whose time of cesarean delivery is greater than 8 hours following the time of study gel administration. Thus, in the event that participants are replaced for this purpose, the total sample size at the end of the study may slightly exceed 16 participants who received study gel.

A sample size of 16 women is insufficient to provide a formal statistical assessment for the comparison between the plasma absorption level observed in HPTN 050 and the one that will be observed in this study.

10.5 Participant Accrual, Follow-up, and Retention

The accrual period will be 18 months. The study site will recruit and enroll a total of 16 participants. Each participant will be followed for two weeks following gel administration. Once a participant has enrolled in the study, the study site will make every reasonable effort to retain her for the entire study period.

10.6 Data and Safety Monitoring and Analysis

10.6.1 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 four to six 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.

10.6.2 Primary Analysis

Descriptive statistics to assess women characteristics will be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum). Similarly, descriptive statistics for continuous variables will be use to describe levels of tenofovir in levels in plasma, in endometrium, in cord blood, in placental tissue, and in amniotic fluid. If a substantial number of women are below the limit of detection of the assay, descriptive statistics for continuous variables will not be used. Rather, proportion of women with detectable levels will be computed along with an exact 95% confidence interval based on the Clopper-Pearson method.

Blood plasma pharmacokinetics of tenofovir will be evaluated after vaginal administration. Pharmacokinetic parameter estimates will include peak concentration (C_{max}), time to peak concentration (T_{max}), and area under the concentration time curve (AUC) for tenofovir in the blood. Descriptive statistics will be used to summarize these PK parameters in the cohort. Cord blood, amniotic fluid, placental tissue, and endometrial tissue tenofovir levels will also be summarized using descriptive statistics. The ratio of concentrations of tenofovir in maternal blood relative to temporally matched cord blood, amniotic fluid, and endometrial tissue concentrations, and ratio of maternal blood plasma relative to intracellular peripheral blood mononuclear cell (PBMC) tenofovir and tenofovir diphosphate levels will be calculated and summarized using descriptive statistics.

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 site 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 U.S. 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-002 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 application for this study (#55690). Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed by DAIDS and CONRAD. Training and written instructions outlining management and reporting, study gel dispensing, product accountability, and other study operations will be provided by Family Health International, the Statistical Center for HIV/AIDS Research & Prevention (SCHARP), and the MTN Network Laboratory.

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, site SOPs, 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 Network Laboratory, Family Health International, SCHARP, NIAID, 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. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, the investigators will have obtained IRB approval and the protocol will have been reviewed by the FDA. The investigators will permit audits by the NIH, CONRAD, the FDA, or any of their appointed agents.

13.1 Institutional Review Board

The participating institution is responsible for assuring that this protocol and the associated informed consent documents and study-related documents are reviewed and approved by the Institutional Review Board (IRB) prior to implementation of the protocol. Any amendments to the protocol and/or informed consents must be approved by the IRB and DAIDS prior to implementation.

13.2 Protocol Registration

The study site will complete protocol registration with the DAIDS RCC Protocol Registration Office. 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. Protocol registration material can be sent electronically to epr@tech-res.com. For questions regarding protocol registration, please call (301) 897-1707. MTN CORE (FHI) staff will notify the 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 NIAID Medical Officer. All protocol amendments must be submitted to and approved by the IRB 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. Participation in clinical research includes the risks of loss of confidentiality and discomfort with personal nature of questions.

Waiting for test results may lead to anxiety in participants. Disclosure of STI status may cause sadness or depression in participants. Disclosure of HIV-positive status has been associated with depression, suicidal ideation, and denial, as well as social isolation.

Some of the possible side effects of the study gel are dryness, itching, burning, or pain in the genital area. Administration of tenofovir gel intravaginally at 0.3% and 1% concentrations in the HPTN 050 Phase I study resulted in minimal local irritation and little or no systemic adverse effects were identified. Although 92% of participants reported at least one AE, 87% of those reported AEs were mild, and 77% 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 Phase I study of tenofovir gel, 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, tenofovir levels.

The most common AEs in patients receiving TDF with other antiretroviral (ARV) therapy in clinical trials were mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting, and flatulence. Less than 1% of patients discontinued participation in the clinical studies because of gastrointestinal AEs. Laboratory abnormalities observed in studies occurred with similar frequency in the TDF and placebo-treated groups.

In rare cases, hypophosphatemia, proteinuria, glycosuria, and reduced creatinine clearance have been seen, and several cases of renal tubular injury have been reported. In a previous study, discontinuation for renal toxicity was equally infrequent in the TDF and d4T treated patients; all patients had normal baseline renal function. In a retrospective review, the rate of TDF discontinuation due to increased creatinine was evaluated in a review of a clinical database which included drug treatment, demographic, and laboratory data of 563 HIV-1-infected subjects who had been treated with TDF. Of these subjects, 11 (2%) had discontinued TDF due to elevated creatinine after a median of four months (range 2-9); of the nine for whom renal biopsy was available, all showed evidence of acute tubular injury. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of nucleoside analogues alone or in combination, including TDF, and other ARVs.

Given that Phase I 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.

This is a single-dose study and maternal plasma levels are expected to be inconsistent and low-level, if detected. Available data suggest no risk to the fetus after exposure to higher maternal systemic levels associated with oral dosing. In the unlikely event that appreciable neonatal levels occur, potential side effects may include diarrhea, nausea, vomiting, and flatulence.

There are currently no data on the passage of tenofovir into breast milk following administration of the oral or vaginal formulation of tenofovir. The molecular weight and low plasma protein binding suggest that the drug will be excreted into human breast milk, though the expected concentration in this single-dose study of a vaginal product would be negligible. The effects of exposure on a nursing infant are unknown.

No risks are associated with a collection of a small portion of amniotic fluid immediately prior to rupture of the membranes during cesarean section. Minimal extra time (< 30 seconds) will be added to the surgery because of amniotic fluid collection.

No extra risk to either the mother or fetus is associated with the collection of one aliquot of umbilical cord blood after the delivery of the baby. This is often part of the normal process to determine blood incompatibility between mother and neonate, and is commonly done without consequence. Minimal extra time (< 30 seconds) will be added to the surgery because of cord blood collection; this is not expected to pose a clinically significant risk to participants.

Study participants will experience no additional discomfort from the endometrial sampling since they will be adequately anesthetized for the primary surgical procedure. Additional bleeding may be encountered in the removal of the endometrial sample. This is not anticipated to be clinically important as the routine closure of the uterine incision will proceed immediately after the sample is obtained. Because the material will be of

low volume, it should not affect that participant's future ability to have a vaginal birth after cesarean (VBAC). Prolongation of surgical and anesthetic time should also be minimal. No unforeseen complications have arisen to date in numerous studies employing both endometrial and myometrial sampling at the time of cesarean, and less bleeding is expected with endometrial sampling given more superficial sampling.

13.3.2 Benefits

Participation in this study likely will have no direct benefit to participants yet 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 domestic 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. 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 Appendix VI 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.

Prior to the beginning of the trial, site investigators will have the IRB/EC's written approval/favorable opinion of the protocol, informed consent forms, and any other study-related information to be provided to participants. This study does not plan to enroll children under 18.

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.

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 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. The study site will establish a standard operating procedure for confidentiality protection that reflects the local study implementation plan. In addition to local considerations, the protections described below will be implemented at the site.

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 records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. 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 applied for a Certificate of Confidentiality from the U.S. 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 U.S. Federal, State or local civil, criminal, administrative, legislative or other proceedings. It thus serves to protect the identity and privacy of study participants.

The Allegheny County Health Department (Pittsburgh, PA) mandates the reporting of certain sexually transmitted infections, including chlamydia, gonorrhea, syphilis and HIV. Participants will be informed of this when written informed consent is obtained for the Screening and Enrollment Visit.

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

Pregnant women are the target population of this protocol. During the informed consent process, women will be informed that the collected data on oral TDF in pregnancy thus far does not suggest any deleterious effects. Oral tenofovir disoproxil fumarate is classified by the FDA as a pregnancy category B drug. Animal studies have failed to demonstrate a risk to the fetus. Preliminary data from Pediatric AIDS Clinical Trials Group (PACTG) 394, which investigated fourteen mother-infant pairs using a single oral dose of TDF 600 mg, failed to demonstrate any significant neonatal effects. In addition, tenofovir concentrations in infants were all below the detectable levels at twelve hours of age, and were only detectable earlier in less than half of the infants.

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.” This protocol will include children aged 18 to 21 years old.

13.6.3 Prisoners

MTN-002 does not meet the criteria for prisoner participation per US 45 Code of Federal Regulations (CFR) 46.306 (a)(2)(D). MTN-002 is not suitable for further reviews by local IRBs for the inclusion of prisoners.

13.7 Incentives

Pending IRB approval, participants will be compensated for their time and inconvenience.

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; the participant's primary obstetrician will also be notified with the participant's permission. 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. In compliance with local regulations and in accordance with 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.

13.10 Study Discontinuation

This study may be discontinued at any time by NICHD, NIAID, the MTN, CONRAD, the US FDA, the Office of Human Research Protections (OHRP), other government or regulatory authorities, or the site IRB.

14 PUBLICATION POLICY

DAIDS and MTN policies and a Clinical Trial Agreement (CTA) between CONRAD 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, NICHD and CONRAD for review prior to submission.

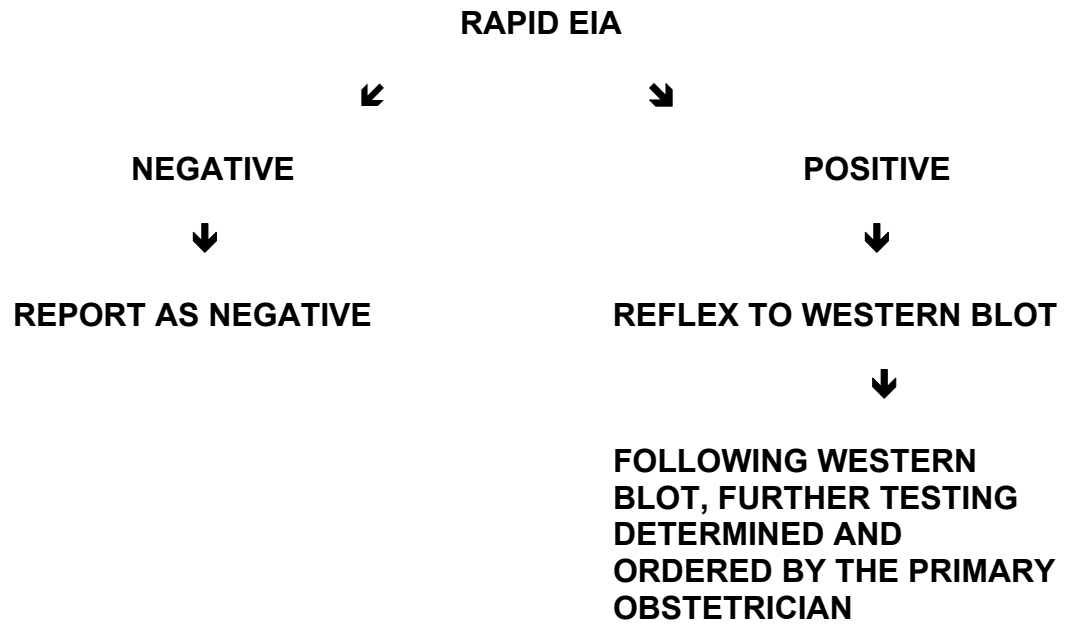
15 APPENDICES

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

	SCREENING AND ENROLLMENT	GEL ADMIN. (DAY OF C/S)	1-12 HOUR PHARMACOKINETIC MEASURES (1, 2, 4, 6, 8, 12 HOURS)	24 HOUR EVALUATION	TWO WEEK PHONE CALL	UNSCHEDULED VISIT
ADMINISTRATIVE						
Informed Consent	x					
Place Copy of Consent in Inpatient Chart		x (pre-gel)				
Administer Elig. Assessment/Confirm Eligibility	x	x (pre-gel)				
Obtain Signed Records Release ♦	x					▲
Assign Participant ID	x					
Record/Update Locator Information	x	x (pre-gel)		x	x	x
Record/Update Demographics	x				x	
Plan/Schedule Next Visit/Call	x	x (pre-gel)		x	▲	▲
Reimbursement	x			x	x	
CLINICAL						
Review Prenatal Record	x					
Review Ultrasound Report(s)	x					
Review Inpatient Chart	▲	x (pre-gel)	▲ (post-gel)	x	▲	▲
Record/Update Medical History	x	x (pre-gel)				
Record/Update Concomitant Medications	x	x (pre-gel)		x	x	x
Pelvic Exam	x	x (pre-gel)		▲		▲
Targeted Physical Exam	x	x (pre-gel)		▲		x
Record/Update Adverse Events		x (pre- and post-gel)	x (post-gel, at each time point)	x	x	x
Insert/Replace Saline Lock or Similar		x (pre-gel)	▲ (post-gel)			
LABORATORY						
Serum Creatinine	x					▲
AST/ALT	x					▲
Rapid HIV Test with Pre- and Post-test Counseling	x					▲
Confirmatory Testing for HIV	▲					▲
HBsAg	▲					▲
Urine SDA for CT and GC	x					▲
Urinalysis						▲
Urine Culture and Sensitivity						▲
Wet Prep and Vaginal pH	▲					▲
Trichomonas Culture	x					▲
Herpes Culture	▲					▲
RPR	▲					▲
Confirmatory Testing for Syphilis	▲					▲
Maternal Plasma Tenofovir Level		x (pre-gel)	x (at each time point)	x		▲
Flow Cytometry		x (pre-gel)				
Collect Amniotic Fluid		x (dur. C/S)				
Collect Endometrial Tissue		x (dur. C/S)				
Collect Cord Blood		x (during or after C/S)				
Collect Placental Tissue		x (during or after C/S)				
GEL ADMINISTRATION						
Gel Administration by Study Physician		x				

X = protocol-defined procedure; ▲ = performed as indicated, ♦ = Obtain again on day of discharge from hospital, if possible
 At Unscheduled Visit, investigator(s) may order other laboratory tests deemed clinically appropriate, when possible after consultation with the PSRT. The target time for gel administration is 2 hours prior to the time of expected C/S. Pelvic exams following the Screening and Enrollment Visit should include components as clinically indicated.

APPENDIX II: HIV TESTING ALGORITHM



APPENDIX III: COMPONENTS OF EXAMINATIONS

Targeted Physical Exam

- Vital signs (may be transcribed from chart if taken in past hour)
 - 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
 - Cervix
 - Uterus
 - Adnexae
- Pelvic exams following the Screening and Enrollment Visit should include components as clinically indicated

APPENDIX IV: DAIDS AE GRADING TABLE

Quick Reference

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (“DAIDS AE grading table”) is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

General Instructions

Estimating Severity Grade

If the need arises to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category “Estimating Severity Grade” located at the top of Page 3. For AEs that are not listed in the table but will be collected systematically for a study/trial, protocol teams are highly encouraged to define study-specific severity scales within the protocol or an appendix to the protocol. (Please see “Template Wording for the Expedited Adverse Event Reporting Section of DAIDS-sponsored Protocols”.) This is particularly important for laboratory values because the “Estimating Severity Grade” category only applies to clinical symptoms.

Grading Adult and Pediatric AEs

The DAIDS AE grading table includes parameters for grading both Adult and Pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both Adult and Pediatric populations, separate sets of parameters for Adult and/or Pediatric populations (with specified respective age ranges) are given in the table. If there is no distinction in the table between Adult and Pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both Adult and Pediatric events of that type.

Determining Severity Grade

If the severity of an AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

Definitions

Basic Self-care Functions	<u>Adult</u> Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. <u>Young Children</u> Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
NA	Not Applicable

Operative Intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual Social & Functional Activities	<u>Adult</u> Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. <u>Young Children</u> Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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CLINICAL				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

CLINICAL				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm ² – 81cm ²)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm ²)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

CLINICAL				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

CLINICAL				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children > 10 cc/kg) indicated
Hypertension				
Adult > 17 years (with repeat testing at same visit)	> 140 – 159 mmHg systolic OR > 90 – 99 mmHg diastolic	> 160 – 179 mmHg systolic OR > 100 – 109 mmHg diastolic	> 180 mmHg systolic OR > 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91 st – 94 th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95 th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval				
Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2 nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 years	1 st degree AV block (PR > normal for age and rate)	Type I 2 nd degree AV block	Type II 2 nd degree AV block	Complete AV block

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

CLINICAL				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Prolonged QTc				
Adult > 16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase in interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

CLINICAL				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea				
Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric < 1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

CLINICAL				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Proctitis (<u>functional-symptomatic</u>) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

CLINICAL				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – Pediatric ≤ 16 years	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

CLINICAL				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (<u>new onset</u>) – Adult ≥ 18 years See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (<u>known pre-existing seizure disorder</u>) – Adult ≥ 18 years For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent breakthrough seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure – Pediatric < 18 years	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

CLINICAL				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

CLINICAL				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (<u>symptoms</u>) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (<u>clinical exam</u>) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

CLINICAL				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Vulvovaginitis (<u>symptoms</u>) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Vulvovaginitis (<u>clinical exam</u>) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non- ketotic coma)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

CLINICAL				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

LABORATORY

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
HEMATOLOGY <i>Standard International Units are listed in italics</i>				
Absolute CD4+ count – Adult and Pediatric > 13 years (HIV <u>NEGATIVE</u> ONLY)	300 – 400/mm ³ <i>300 – 400/μL</i>	200 – 299/mm ³ <i>200 – 299/μL</i>	100 – 199/mm ³ <i>100 – 199/μL</i>	< 100/mm ³ < 100/μL
Absolute lymphocyte count – Adult and Pediatric > 13 years (HIV <u>NEGATIVE</u> ONLY)	600 – 650/mm ³ <i>0.600 x 10⁹ – 0.650 x 10⁹/L</i>	500 – 599/mm ³ <i>0.500 x 10⁹ – 0.599 x 10⁹/L</i>	350 – 499/mm ³ <i>0.350 x 10⁹ – 0.499 x 10⁹/L</i>	< 350/mm ³ < 0.350 x 10 ⁹ /L
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm ³ <i>1.000 x 10⁹ – 1.300 x 10⁹/L</i>	750 – 999/mm ³ <i>0.750 x 10⁹ – 0.999 x 10⁹/L</i>	500 – 749/mm ³ <i>0.500 x 10⁹ – 0.749 x 10⁹/L</i>	< 500/mm ³ < 0.500 x 10 ⁹ /L
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm ³ <i>1.250 x 10⁹ – 1.500 x 10⁹/L</i>	1,000 – 1,249/mm ³ <i>1.000 x 10⁹ – 1.249 x 10⁹/L</i>	750 – 999/mm ³ <i>0.750 x 10⁹ – 0.999 x 10⁹/L</i>	< 750/mm ³ < 0.750 x 10 ⁹ /L
Infant*†, 1 day	4,000 – 5,000/mm ³ <i>4.000 x 10⁹ – 5.000 x 10⁹/L</i>	3,000 – 3,999/mm ³ <i>3.000 x 10⁹ – 3.999 x 10⁹/L</i>	1,500 – 2,999/mm ³ <i>1.500 x 10⁹ – 2.999 x 10⁹/L</i>	< 1,500/mm ³ < 1.500 x 10 ⁹ /L
Fibrinogen, decreased	100 – 200 mg/dL <i>1.00 – 2.00 g/L</i> OR 0.75 – 0.99 x LLN	75 – 99 mg/dL <i>0.75 – 0.99 g/L</i> OR 0.50 – 0.74 x LLN	50 – 74 mg/dL <i>0.50 – 0.74 g/L</i> OR 0.25 – 0.49 x LLN	< 50 mg/dL < 0.50 g/L OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin (Hgb)				
Adult and Pediatric ≥ 57 days (HIV <u>POSITIVE</u> ONLY)	8.5 – 10.0 g/dL <i>1.32 – 1.55 mmol/L</i>	7.5 – 8.4 g/dL <i>1.16 – 1.31 mmol/L</i>	6.50 – 7.4 g/dL <i>1.01 – 1.15 mmol/L</i>	< 6.5 g/dL < 1.01 mmol/L
Adult and Pediatric ≥ 57 days (HIV <u>NEGATIVE</u> ONLY)	10.0 – 10.9 g/dL <i>1.55 – 1.69 mmol/L</i> OR Any decrease 2.5 – 3.4 g/dL <i>0.39 – 0.53 mmol/L</i>	9.0 – 9.9 g/dL <i>1.40 – 1.54 mmol/L</i> OR Any decrease 3.5 – 4.4 g/dL <i>0.54 – 0.68 mmol/L</i>	7.0 – 8.9 g/dL <i>1.09 – 1.39 mmol/L</i> OR Any decrease ≥ 4.5 g/dL <i>≥ 0.69 mmol/L</i>	< 7.0 g/dL < 1.09 mmol/L
Infant*†, 36 – 56 days (HIV <u>POSITIVE</u> OR <u>NEGATIVE</u>)	8.5 – 9.4 g/dL <i>1.32 – 1.46 mmol/L</i>	7.0 – 8.4 g/dL <i>1.09 – 1.31 mmol/L</i>	6.0 – 6.9 g/dL <i>0.93 – 1.08 mmol/L</i>	< 6.00 g/dL < 0.93 mmol/L
Infant*†, 22 – 35 days (HIV <u>POSITIVE</u> OR <u>NEGATIVE</u>)	9.5 – 10.5 g/dL <i>1.47 – 1.63 mmol/L</i>	8.0 – 9.4 g/dL <i>1.24 – 1.46 mmol/L</i>	7.0 – 7.9 g/dL <i>1.09 – 1.23 mmol/L</i>	< 7.00 g/dL < 1.09 mmol/L

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Infant*†, 1 – 21 days (HIV <u>POSITIVE</u> OR <u>NEGATIVE</u>)	12.0 – 13.0 g/dL <i>1.86 – 2.02 mmol/L</i>	10.0 – 11.9 g/dL <i>1.55 – 1.85 mmol/L</i>	9.0 – 9.9 g/dL <i>1.40 – 1.54 mmol/L</i>	< 9.0 g/dL < <i>1.40 mmol/L</i>
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm ³ <i>100.000 x 10⁹ – 124.999 x 10⁹/L</i>	50,000 – 99,999/mm ³ <i>50.000 x 10⁹ – 99.999 x 10⁹/L</i>	25,000 – 49,999/mm ³ <i>25.000 x 10⁹ – 49.999 x 10⁹/L</i>	< 25,000/mm ³ < <i>25.000 x 10⁹/L</i>
WBC, decreased	2,000 – 2,500/mm ³ <i>2.000 x 10⁹ – 2.500 x 10⁹/L</i>	1,500 – 1,999/mm ³ <i>1.500 x 10⁹ – 1.999 x 10⁹/L</i>	1,000 – 1,499/mm ³ <i>1.000 x 10⁹ – 1.499 x 10⁹/L</i>	< 1,000/mm ³ < <i>1.000 x 10⁹/L</i>
CHEMISTRIES <i>Standard International Units are listed in italics</i>				
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN <i>30 g/L – < LLN</i>	2.0 – 2.9 g/dL <i>20 – 29 g/L</i>	< 2.0 g/dL < <i>20 g/L</i>	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN [†]	2.6 – 5.0 x ULN [†]	5.1 – 10.0 x ULN [†]	> 10.0 x ULN [†]
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN <i>16.0 mmol/L – < LLN</i>	11.0 – 15.9 mEq/L <i>11.0 – 15.9 mmol/L</i>	8.0 – 10.9 mEq/L <i>8.0 – 10.9 mmol/L</i>	< 8.0 mEq/L < <i>8.0 mmol/L</i>
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL <i>342 – 428 μmol/L</i>	25.1 – 30.0 mg/dL <i>429 – 513 μmol/L</i>	> 30.0 mg/dL > <i>513.0 μmol/L</i>
Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL <i>342 – 428 μmol/L</i>	> 25.0 mg/dL > <i>428 μmol/L</i>
Calcium, serum, high (corrected for albumin)				

LABORATORY

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL 2.65 – 2.88 mmol/L	11.6 – 12.5 mg/dL 2.89 – 3.13 mmol/L	12.6 – 13.5 mg/dL 3.14 – 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant*†, < 7 days	11.5 – 12.4 mg/dL 2.88 – 3.10 mmol/L	12.5 – 12.9 mg/dL 3.11 – 3.23 mmol/L	13.0 – 13.5 mg/dL 3.245 – 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Calcium, serum, low (corrected for albumin)				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL 1.95 – 2.10 mmol/L	7.0 – 7.7 mg/dL 1.75 – 1.94 mmol/L	6.1 – 6.9 mg/dL 1.53 – 1.74 mmol/L	< 6.1 mg/dL < 1.53 mmol/L
Infant*†, < 7 days	6.5 – 7.5 mg/dL 1.63 – 1.88 mmol/L	6.0 – 6.4 mg/dL 1.50 – 1.62 mmol/L	5.50 – 5.90 mg/dL 1.38 – 1.51 mmol/L	< 5.50 mg/dL < 1.38 mmol/L
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL 5.18 – 6.19 mmol/L	240 – 300 mg/dL 6.20 – 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Pediatric < 18 years	170 – 199 mg/dL 4.40 – 5.15 mmol/L	200 – 300 mg/dL 5.16 – 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 – 5.9 x ULN [†]	6.0 – 9.9 x ULN [†]	10.0 – 19.9 x ULN [†]	≥ 20.0 x ULN [†]
Creatinine	1.1 – 1.3 x ULN [†]	1.4 – 1.8 x ULN [†]	1.9 – 3.4 x ULN [†]	≥ 3.5 x ULN [†]
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL 6.44 – 8.88 mmol/L	161 – 250 mg/dL 8.89 – 13.88 mmol/L	251 – 500 mg/dL 13.89 – 27.75 mmol/L	> 500 mg/dL > 27.75 mmol/L
Fasting	110 – 125 mg/dL 6.11 – 6.94 mmol/L	126 – 250 mg/dL 6.95 – 13.88 mmol/L	251 – 500 mg/dL 13.89 – 27.75 mmol/L	> 500 mg/dL > 27.75 mmol/L
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL 3.05 – 3.55 mmol/L	40 – 54 mg/dL 2.22 – 3.06 mmol/L	30 – 39 mg/dL 1.67 – 2.23 mmol/L	< 30 mg/dL < 1.67 mmol/L
Infant*†, < 1 month	50 – 54 mg/dL 2.78 – 3.00 mmol/L	40 – 49 mg/dL 2.22 – 2.77 mmol/L	30 – 39 mg/dL 1.67 – 2.21 mmol/L	< 30 mg/dL < 1.67 mmol/L

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lactate	< 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
LDL cholesterol (fasting)				
Adult ≥ 18 years	130 – 159 mg/dL <i>3.37 – 4.12 mmol/L</i>	160 – 190 mg/dL <i>4.13 – 4.90 mmol/L</i>	≥ 190 mg/dL <i>≥ 4.91 mmol/L</i>	NA
Pediatric > 2 - < 18 years	110 – 129 mg/dL <i>2.85 – 3.34 mmol/L</i>	130 – 189 mg/dL <i>3.35 – 4.90 mmol/L</i>	≥ 190 mg/dL <i>≥ 4.91 mmol/L</i>	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low	1.2 – 1.4 mEq/L <i>0.60 – 0.70 mmol/L</i>	0.9 – 1.1 mEq/L <i>0.45 – 0.59 mmol/L</i>	0.6 – 0.8 mEq/L <i>0.30 – 0.44 mmol/L</i>	< 0.60 mEq/L <i>< 0.30 mmol/L</i>
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric > 14 years	2.5 mg/dL – < LLN <i>0.81 mmol/L – < LLN</i>	2.0 – 2.4 mg/dL <i>0.65 – 0.80 mmol/L</i>	1.0 – 1.9 mg/dL <i>0.32 – 0.64 mmol/L</i>	< 1.00 mg/dL <i>< 0.32 mmol/L</i>
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL <i>0.97 – 1.13 mmol/L</i>	2.5 – 2.9 mg/dL <i>0.81 – 0.96 mmol/L</i>	1.5 – 2.4 mg/dL <i>0.48 – 0.80 mmol/L</i>	< 1.50 mg/dL <i>< 0.48 mmol/L</i>
Pediatric < 1 year	3.5 – 4.5 mg/dL <i>1.13 – 1.45 mmol/L</i>	2.5 – 3.4 mg/dL <i>0.81 – 1.12 mmol/L</i>	1.5 – 2.4 mg/dL <i>0.48 – 0.80 mmol/L</i>	< 1.50 mg/dL <i>< 0.48 mmol/L</i>
Potassium, serum, high	5.6 – 6.0 mEq/L <i>5.6 – 6.0 mmol/L</i>	6.1 – 6.5 mEq/L <i>6.1 – 6.5 mmol/L</i>	6.6 – 7.0 mEq/L <i>6.6 – 7.0 mmol/L</i>	> 7.0 mEq/L <i>> 7.0 mmol/L</i>
Potassium, serum, low	3.0 – 3.4 mEq/L <i>3.0 – 3.4 mmol/L</i>	2.5 – 2.9 mEq/L <i>2.5 – 2.9 mmol/L</i>	2.0 – 2.4 mEq/L <i>2.0 – 2.4 mmol/L</i>	< 2.0 mEq/L <i>< 2.0 mmol/L</i>
Sodium, serum, high	146 – 150 mEq/L <i>146 – 150 mmol/L</i>	151 – 154 mEq/L <i>151 – 154 mmol/L</i>	155 – 159 mEq/L <i>155 – 159 mmol/L</i>	≥ 160 mEq/L <i>≥ 160 mmol/L</i>
Sodium, serum, low	130 – 135 mEq/L <i>130 – 135 mmol/L</i>	125 – 129 mEq/L <i>125 – 129 mmol/L</i>	121 – 124 mEq/L <i>121 – 124 mmol/L</i>	≤ 120 mEq/L <i>≤ 120 mmol/L</i>
Triglycerides (fasting)	NA	500 – 750 mg/dL <i>5.65 – 8.48 mmol/L</i>	751 – 1,200 mg/dL <i>8.49 – 13.56 mmol/L</i>	> 1,200 mg/dL <i>> 13.56 mmol/L</i>
Uric acid	7.5 – 10.0 mg/dL <i>0.45 – 0.59 mmol/L</i>	10.1 – 12.0 mg/dL <i>0.60 – 0.71 mmol/L</i>	12.1 – 15.0 mg/dL <i>0.72 – 0.89 mmol/L</i>	> 15.0 mg/dL <i>> 0.89 mmol/L</i>
URINALYSIS <i>Standard International Units are listed in italics</i>				
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				

LABORATORY

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h <i>0.200 – 0.999 g/d</i>	1,000 – 1,999 mg/24 h <i>1.000 – 1.999 g/d</i>	2,000 – 3,500 mg/24 h <i>2.000 – 3.500 g/d</i>	> 3,500 mg/24 h > 3.500 g/d
Pediatric > 3 mo - < 10 years	201 – 499 mg/m ² /24 h <i>0.201 – 0.499 g/d</i>	500 – 799 mg/m ² /24 h <i>0.500 – 0.799 g/d</i>	800 – 1,000 mg/m ² /24 h <i>0.800 – 1.000 g/d</i>	> 1,000 mg/ m ² /24 h > 1.000 g/d

APPENDIX V: PROTOCOL SPECIFIC TOXICITY TABLE

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 ruggae 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 ($38^{\circ}\text{C} - 38.4^{\circ}\text{C}$ or $100.4^{\circ}\text{F} - 100.9^{\circ}\text{F}$) 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 $38.5^{\circ}\text{C} - 40^{\circ}\text{C}$ or $101^{\circ}\text{F} - 104^{\circ}\text{F}$	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 VI: SAMPLE INFORMED CONSENT FORM (SCREENING AND ENROLLMENT)

MTN-002

Phase I Study of the Maternal Single-dose Pharmacokinetics and Placental Transfer of Tenofovir 1% Vaginal Gel among Healthy Term Gravidas

Final Version 1.0

August 29, 2007

PRINCIPAL INVESTIGATOR: Richard H. Beigi MD, MSc
PHONE: 412-641-5403
Short Title for the Study: Maternal Tenofovir Gel PK Study

Introduction

This is a study of pregnant women who have normal healthy pregnancies. We are testing a drug called tenofovir gel that in the future may be used to prevent the spread of human immunodeficiency virus (HIV), but this is not yet proven. HIV is the virus that causes AIDS. We are studying this gel in pregnant women to see if it is safe and to see where the drug that is in the gel goes (is found) in the body. You are being asked to be in this study because you have a healthy pregnancy and are planning to have cesarean delivery. This study is being paid for by the United States National Institutes of Health. The person in charge of this study is Richard H. Beigi, MD, MSc.

Before you decide whether to be in this study, we want to explain the purpose of the study, the risks and benefits, and what is expected of you. This consent form gives information that the study staff will discuss with you. You are free to ask questions at any time. If you agree to be in this study, you will be asked to sign this form. You will be offered a copy to keep.

Why Is This Study Being Done?

The main purpose of this study is to see if one dose (about one teaspoon) of study gel placed in the vagina gets absorbed into a pregnant woman's blood, placenta, uterus, baby's umbilical cord blood, and the amniotic fluid around the baby. This is important information to know because pregnant women may be at higher risk to get HIV if they are exposed to it and pregnant women may also want to use tenofovir gel if it is approved for use.

What Do I Have To Do If I Am In This Study?

The visits you will have in this study are described in more detail in other sections below. If you decide to be in this study, you will be asked to participate today and then at the time of your scheduled cesarean (no more than four weeks from now) and for 14 days after. On the day of your cesarean right before the surgery, you will have a single dose of the study gel placed in your vagina and will have your blood drawn. Then you will have seven more blood samples taken over the next 24 hours. During your

cesarean, you will also have a small sample of the amniotic fluid taken and a small sample of the lining of your womb taken to test to see if tenofovir is there. Blood from the umbilical cord and a piece of the placenta will be collected after the cord has been clamped and the placenta delivered. A study physician will examine you about 24 hours after you receive the study gel. You will then be called two weeks after your delivery to see how you are doing. We will also ask you to sign permission forms so that we can get copies of any hospital records for the time that you are in the study. We will also ask that you do not have any vaginal, anal or receptive oral sex for 2 weeks after the gel placement on the day of your cesarean. We also will ask that you do not place anything into your vagina during the study and that you do not take part in any other drug or device study during your participation in this study

Screening and Enrollment Visit:

This visit will continue today after you read, discuss and sign this form. It will take about 90 minutes. The study clinician will review your medical history, including your prenatal chart and ultrasound report or reports, to make sure you meet the requirements for this study. Then you will be asked a few more questions. The questions will be about you, where you live, your health, and the medicines you take. You also will:

- Give urine to test for gonorrhea, and chlamydia. Gonorrhea and chlamydia are infections passed during sex.
- Have a brief physical exam, including an exam of your genital area and inside your vagina using a speculum (like for a Pap smear—a Pap smear is a test for cervical cancer). During the exam a test for Trichomonas (another infection passed during sex) will be done. If you have symptoms of a vaginal infection, like itching or odor, you will get a test for vaginal infections using a swab that will collect a few drops of vaginal discharge. If you have signs of herpes infection, a herpes culture test would be done.
- Give about 6 tablespoons of blood. This blood will be used for:
 - Tests to check on the overall health of your liver and kidneys
 - Tests for HIV in your blood
 - Test for Hepatitis B if you did not have one during this pregnancy
 - Test or tests for syphilis if you have signs of syphilis today

The HIV test results will take about one hour and we will give you your results today. We will give you your other results when they are available (usually less than a week).

Study staff will explain all exam and test results to you. If the tests show that you have any infections passed during sex, study staff will give you treatment for these infections, free of charge. You can also bring your partner here for testing and treatment for these infections, free of charge.

This study does not provide treatment for HIV, but study staff will refer you to available sources of medical care, counseling, and other services you may need if your test is positive. Study staff also will be available to talk with other doctors that you see for your medical care and share your test results (with your permission).

Main Study Visit [The Day of Your Cesarean and for 24 Hours After Gel]:

This visit will take place on the day of your cesarean from the time right before the cesarean until about 24 hours after you receive the study gel. During this time we will:

- Talk to you about any new medical problems since we saw you last
- Ask you about any medications you are taking or have taken since the last time we saw you
- Review your medical chart
- Talk to other medical and nursing staff members who are taking care of you
- Put a copy of this consent form in your medical chart
- Ask if there are any changes in the ways that we can get in contact with you (such as new phone numbers or addresses) and make notes on these
- Do a brief physical exam and pelvic exam (including a check of your cervix)
- Insert a saline lock in your hand or arm (a saline lock is a device that will allow us to draw blood samples without inserting a needle through your skin every time).
- Place 4 grams of study gel into your vagina using a special applicator similar to a tampon.
- Draw 1 teaspoon of blood (before inserting the study gel), and then over the next 24 hours we will draw 7 more teaspoons of blood from you at separate times, through the saline lock. These teaspoons of blood will tell us whether or not the drug has gotten into your blood. The first sample of blood will also be checked with a test called flow cytometry. This test helps scientists understand why medicines do or don't get absorbed into the bloodstream.

During your cesarean, we will also collect about 1 tablespoon of amniotic fluid and a small amount (about half an inch in diameter) of tissue from your womb (the same tissue that comes out with your monthly period) to look for the drug. Amniotic fluid is the liquid inside the water bag in the womb. During or after your cesarean, we will collect 1 teaspoon of the blood from the baby's umbilical cord after it has been separated from the baby and a piece of the placenta after it has been delivered (about half an inch in diameter).

Twenty-four hours after you receive the study gel, you will:

- Have your blood drawn to check for tenofovir in the blood
- Tell the study staff about any problems that you may have
- Tell the study staff about any medications that you may have taken
- Have a brief physical exam by a doctor
- Have your medical chart reviewed by study staff

Final Contact:

We will contact you by phone two weeks after your cesarean to ask how you are doing. If you have a problem that may be related to being in the study we might ask you to come in for a visit or visits. Otherwise, you are done with the study at this point.

Any Time During The Study:

Please tell the study staff about any medical problems you have during the study. You can contact the study staff between regular visits to report these problems. The study staff will check you as needed and either give or refer you for medical care. At each study visit, the study staff will update information on where you live and how to keep in touch with you.

If your participation in the study ended early, we would still ask you to come in for study visits and have the safety check-ups that are talked about in this form. If you start the study but do not get the study gel for some reason, we would not do the tests on your blood that are regularly scheduled for after the study gel.

How Many Women Will Be In this Study?

About sixteen women will be in this study.

How Long Will I be In This Study?

We expect that you will be in this study for six weeks at the most.

Can the Doctor Take Me Off This Study Early?

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

- The study is stopped or canceled.
- Staying in the study would be harmful to you.
- Other reasons that may prevent you from completing the study successfully.

What are the risks of this study?

Risks of Blood Draws:

When your blood is taken, and when you have a saline lock inserted, you may feel discomfort or pain. You may feel dizzy 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 exams of your genital area and inside your vagina. You may have mild vaginal bleeding (spotting) after the exam. If this happens, it will usually stop quickly after the exam.

Risks Related to the Study Drug:

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 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 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 the 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 gel is absorbed into the blood, it is not known whether this will cause any bad effects.

There are other side effects in patients taking the oral form (a pill) of tenofovir which is absorbed into the blood. However, these side effects may have been because of other medicines that patients were taking or because of the HIV itself.

The following side effects have been associated with the use of oral (by mouth) tenofovir pills:

- 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.
- Increased liver function 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. It is unknown if long term use of topical tenofovir will cause bone abnormalities in adults. Bone thinning has been seen in adults and children taking oral tenofovir.

Laboratory tests have shown changes in the bones of patients treated with the pill form of tenofovir. An earlier study has shown that only a small amount of tenofovir gets into the blood with gel use. For that reason and because there will be only one dose of the study gel, the risk of changes to the bones when using the gel is very low.

If you are HIV-infected 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.

Risks Related To Pregnancy

We believe that there is little risk to your pregnancy from this study because you are only getting one dose of the study gel right before you deliver, and we expect only very small amounts of tenofovir to get into your blood, if any. We are not sure if the drug goes into the placenta, the fluid around your baby or your baby's blood and those are some of the reasons we are doing the study. Nearly 500 women have been exposed to multiple doses of the oral form of this drug in pregnancy and there have not been more birth defects in their babies compared to other babies whose mothers never took tenofovir. A recent study found very low amounts of tenofovir in the babies of mothers who took oral tenofovir during pregnancy.

We do not expect any significant risk to your baby in this study. This is because you will only get one dose of the study gel, and we do not expect that much if any of the gel will pass into the baby's blood. Another study found that babies whose mothers took the oral form of tenofovir did not have problems. If your baby's blood did absorb some tenofovir, possible side effects could include increased liver function tests, diarrhea, nausea, vomiting, and flatulence (gas), but we would expect those side effects to be brief and resolve quickly if they occurred. You should let your baby's pediatrician and the study staff know if you believe your baby is experiencing any problems.

Risks to Breastfeeding

We do not know if tenofovir passes into breast milk after women receive the oral or vaginal form of tenofovir. If tenofovir passed into your breast milk, it is not expected that the amount from one dose of the study gel would be high enough to affect the baby. The effects of exposure on a nursing baby are unknown. If your breast milk did absorb some tenofovir, possible side effects in the baby could include increased liver function tests, diarrhea, nausea, vomiting, and flatulence (gas), but we would expect those side effects to be brief and resolve quickly if they occurred. You should let your baby's pediatrician and the study staff know if you believe your baby is experiencing any problems.

Risks from Procedures During your Surgery:

No risks are associated with a collection of a small portion of amniotic fluid (about one tablespoon) immediately before delivery of the baby during cesarean section. Minimal extra time (approximately less than 30 seconds) is expected to be added to the surgery because of amniotic fluid collection.

There is no extra risk to either you or your baby from collecting the umbilical cord blood after the delivery of the baby. Any other samples of cord blood that may be drawn as part of your baby's medical care will be drawn first. Collection of cord blood is often done after delivery as part of the normal care. Minimal extra time (approximately less than 30 seconds) is expected to be added to the surgery because of cord blood collection.

You will not have any additional discomfort from the sampling of tissue from your womb because you should already be numb for the surgery. When we take a piece of tissue from your womb you may have a small amount of extra bleeding, but we would expect this bleeding to stop quickly on its own or to be easy to stop. This specimen collection is not expected to affect your ability to try to have a vaginal birth after cesarean (VBAC) in your next pregnancy. This also is not expected to add much additional time to the surgery (approximately less than 30 seconds).

Other Possible Risks:

You may become embarrassed, worried, or nervous when discussing sexual behaviors, HIV, and other infections passed during sex. You may feel worried or anxious while waiting for your test results. Trained staff members are available to help you deal with any feelings or questions you have.

Possible Risks to Your Privacy

We will make every effort to protect your privacy while you are in this study. Your visits here will take place in private. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly. For example, you could have problems getting or keeping a job or 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.

What are the Benefits of This Study?

You and your baby will get no direct benefit from being in this study. However, you will receive a number of services while taking part in this study, including:

- Information, counseling and testing related to HIV and other infections passed during sex.
- Treatment for infections passed during sex if you have any (including treatment for your partners).
- Referrals to medical care and other services you may need.

Your or others may benefit in the future from information learned in this study. Knowledge gained from this study may help in the development of microbicides for the prevention of HIV infection. You may also get some personal satisfaction from being part of research on preventing HIV.

What Other Choices Do I Have Besides This Study?

You do not have to participate in this study. The decision to not be in this study will not affect your care in any way.

What About Confidentiality?

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 U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study,

such as the court system, about your participation. Also, any scientific publication about this study will not use your name or identify you personally.

People who may review your records include: the U.S. Food and Drug Administration (FDA), (insert Name of Site) IRB, National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study to anyone you choose.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

If you test positive for gonorrhea, chlamydia, syphilis, or HIV, the Commonwealth of Pennsylvania requires that your name be given to the Allegheny County Health Department. You may be contacted and asked questions about your sexual partners.

What Are The Costs To Me?

There is no cost to you for study visits, exams, laboratory tests, or other procedures. This study will not provide prenatal care, delivery, postpartum, or routine newborn care.

Will I Receive Any Payment?

You will receive payment for your time and effort in this study. You will also receive payment for activities affected by your participation in this study.

What Happens If I Am Injured?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. If your infant is injured as a result of being in this study, he or she will be given immediate treatment for injuries as well. However, you or your insurance company (or the infant's insurance company) may have to pay for this care. This institution or the United States National Institutes of Health does not have a program to provide money for your or your infant's injuries. You will not be giving up any of your legal rights by signing this consent form.

What Are My Rights?

Being in this study is completely voluntary. You may choose not to be in or to leave the study at any time. You will be treated the same no matter what you decide. If you choose not to be in or to leave the study, you will not lose the benefit of services to which you would otherwise be entitled at this clinic. Study staff will tell you about any new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. At the end of the study, you will be told when study results may be available and how to learn about them.

What Do I Do If I Have Problems or Questions?

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

Richard H. Beigi, MD, MSc
Magee-Womens Hospital of UPMC
300 Halket Street
Pittsburgh, PA 15213
(412) 641-5403

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

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable.

SIGNATURES

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator

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 be in this study, please sign your name or make your mark below.

Participant's Name (print)

Participant's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness's Signature and Date

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Section 3. Documentation Requirements

Study staff is 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 the 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 002.

3.1 Essential Documents

The Division of AIDS (DAIDS) Standard Operating Procedure (SOP) for Essential Documents specifies the essential documents that study site must maintain for DAIDS-sponsored studies, including MTN 002. 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 002. The suggested structure incorporates guidance received from the DAIDS Clinical Site Monitoring Group (PPD). The study site is not required to adopt the suggested structure, but is encouraged to consider it when developing their filing approach for MTN 002. The study site also is 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 table of contents be developed and maintained in the front page(s) of each file/binder. Within each section of the file/binder, it is recommended that documents be filed in ascending date order (most recent documents in front).
- Certain documents related to the investigational study products will be stored in the site pharmacy. A listing of essential documents to be maintained in the pharmacy is provided in Section 3.3. The list of documents to be kept in the pharmacy should be included in the master table of contents.
- 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 list of documents to be kept in the lab should be included in the master table of contents.

- The suggested filing structure assumes that MTN 002 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 002 Screening and Enrollment Log and Participant Name-ID Number Link Log (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

The study site must maintain adequate and accurate case history records for each study participant.

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 exposure to the investigational product (as directed in the protocol).
- 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 departures/deviations/violations be documented in participant records, along with reasons for the departures/deviations/violations and/or attempts to prevent or correct the departures/deviations/violations, if applicable. The study site also must report protocol deviations to DAIDS and others per guidelines provided in the MTN Manual of Operating Procedures Section 15.4 available at <http://mtnstopshiv.org/downloads/core/manuals/MTN%20MOP%20Final%20All%20Section%20s.pdf>.

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. The study site must adhere to the standards of source documentation specified in the DAIDS SOP for Source Documentation. The DAIDS SOP specifies both requirements and recommendations. The study site must comply with all requirements and is encouraged, but not required, to comply with all recommendations.

It is expected that participant case history records will consist of the following source documents:

- Narrative chart notes
- Clinic prescriptions (“original” kept in the pharmacy)
- Pharmacy records for investigational product dispensing
- 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, the 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 the site to determine the most appropriate source document for each required case history element, Appendix 3-2 provides a guide that the site 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 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 the contact takes place, any specific procedures conducted and, when necessary, adherence to protocol requirements should also be documented. Chart notes also must be used to document the following:

- The study informed consent process (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/deviations/violations that are not otherwise captured on other source documents

The study site is 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 are not sufficient for documenting all procedures. For example, chart notes are 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 the site. The SDMC also will provide several study-specific non-DataFax forms to the 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 participant notebooks, with each notebook containing tabbed sections with case report forms required for each study visit; i.e., Screening and Enrollment Visit, Gel Administration Day, 24 Hour Evaluation, and Two Week Phone Call. A small supply of other “as needed” forms also will be provided. The notebooks will be produced by SCHARP and shipped to the study site. Forms will be printed on letter size paper and three-hole punched.

As shown in 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. The study site must document the forms that it will routinely use as source documents for this study in its Source Documentation SOP, and they 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 onto 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. For participants who enroll in the study, their 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. To maximize participant confidentiality, the PTID should be used whenever possible, and records that bear names or other personal identifiers, such as locator forms and informed consent forms, should be stored separately from records identified by PTID. 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 PITD. 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, the 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. (if applicable)
- 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)
- Handling of participant study records for off-site contacts and visits (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 documents should be maintained in study site pharmacy:

- Current MTN 002 protocol and associated Letters of Amendment and/or Clarification Memos (if applicable)
- Current Investigator's Brochures for Tenofovir 1% Vaginal Gel.
- Copy of the current MTN 002 FDA Form 1572
- Most current Authorized prescribers' signature list
- PAB approved Pharmacy Establishment Plan
- MTN 002 PTID list (provided by the MTN SDMC, in the form of the MTN 002 PTID-Name Link Log)
- MTN 002 product receipt and return documentation
- MTN 002 product storage temperature logs
- MTN 002 investigational agent accountability records
- MTN 002 participant-specific records (including prescriptions)
- MTN 002 communications with site clinic staff
- MTN 002 communications with the DAIDS Pharmaceutical Affairs Branch (PAB) and the NIAID Clinical Research Product Management Center
- MTN 002 communications with the MTN Coordinating and Operations Center (CORE)
- MTN 002 communications with the MTN SDMC
- Other MTN 002 communications
- Other locally-required administrative, operational, and/or regulatory documentation

Pharmacy staff will document the receipt, dispensing, and return of the Tenofovir 1% Gel.

The specifications related to document security and participant confidentiality described in Section 3.2 also apply to records maintained in the study pharmacy. All records must be stored securely in the pharmacy with access limited to authorized 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 pharmacy. Pharmacy staff may provide copies of some participant-specific documentation maintained in the study pharmacy (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.

3.4 Record Retention Requirements

All study records must be maintained for at least two years following the date of marketing approval for the study product for the indication in which they were studied. If no marketing application is to be filed, or if the application is not approved, the records must be retained until two years after the investigation is discontinued and the US Food and Drug Administration (FDA) is notified. All records must be retained on-site throughout the study's period of performance, and for at least three years after completion or termination of the study. Study product records must be stored in the study pharmacy, 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 002 Essential Documents

<p>File/Binder #1: MTN 002 Protocol and Current Informed Consent Form</p> <ol style="list-style-type: none"> 1. MTN 002 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 002 informed consent form
<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 Tenofovir 1% Gel: current version and any subsequent updates 13. 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 002 Study-Specific Procedures (SSP) Manual</p> <ol style="list-style-type: none"> 14. Final version 1.0 (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 002 Study-Specific Standard Operating Procedures</p> <ol style="list-style-type: none"> 15. Final approved version of each SOP, and any subsequent updates to each

Section Appendix 3-1
Suggested Filing Structure for MTN 002 Essential Documents

<p>File/Binder #7: MTN 002 Staffing Documentation</p> <p>16. FDA Form 1572 (copy of original and dated form submitted to the RCC for Protocol Registration, and any subsequent updates)</p> <p>17. MTN 002 Investigator of Record CV (copy of CV submitted to the RCC for Protocol Registration; ensure that the CV is current prior to initiating MTN 002; it is recommended that CVs be signed and dated to document at least annual updating)</p> <p>18. Financial Disclosure Forms (original signed and dated forms, and any subsequent updates)</p> <p>19. Study Staff Roster (original submitted to MTN CORE for study activation, and any subsequent updates)</p> <p>20. Study Staff Identification and Signature Sheet (if not combined with staff roster; original and any subsequent updates)</p> <p>21. Study Staff Delegation of Duties (if not combined with staff roster; original and all updates)</p> <p>22. CVs for Study Staff other than the IoR (ensure that all CVs are current prior to initiating MTN 002; it is recommended that CVs be signed and dated to document at least annual updating)</p> <p>23. Study Staff Job Descriptions</p> <p>24. Documentation of Study Staff Training</p>
<p>File/Binder #8: Local Laboratory Documentation</p> <p>25. Local Laboratory Certification(s), Accreditation(s) and/or Validation(s): file documentation current at time of study activation and all subsequent updates</p> <p>26. 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</p> <p>27. Laboratory Manager CV (or cross-reference to CV contained in File/Binder #7)</p> <p>Note:</p> <ul style="list-style-type: none"> • 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).
<p>File/Binder #9: Monitoring Visit Documentation</p> <p>28. Monitoring Visit Log</p> <p>29. Initiation and Monitoring Visit Reports and Documentation of Response to Visit Findings</p>
<p>File/Binder #10: Documentation of Other MTN Site Visits</p> <p>30. (Non-Monitoring) Site Visit Log</p> <p>31. MTN CORE Site Visit Reports and Documentation of Response to Visit Findings</p> <p>32. MTN SDMC Site Visit Reports and Documentation of Response to Visit Findings</p> <p>33. MTN Network Lab Site Visit Reports and Documentation of Response to Visit Findings</p> <p>34. Other Site Visit Reports and Documentation of Response to Visit Findings</p>
<p>File/Binder #11: Study-Related Sponsor Communications</p> <p>35. Study-Related Communications to and from DAIDS</p> <p>36. Communications to and from DAIDS RCC (includes copies of all submissions to the DAIDS Protocol Registration Office, which will be prepared by the site 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)</p> <p>Notes:</p> <ul style="list-style-type: none"> • Communications related to individual MTN 002 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.
<p>File/Binder #12: Other Study-Related Communications</p> <p>37. Study-Related Communications to and from MTN CORE</p> <p>38. Study-Related Communications to and from MTN SDMC</p> <p>39. Study-Related Communications to and from MTN Network Lab</p> <p>40. Other Study-Related Communications</p> <p>Notes:</p> <ul style="list-style-type: none"> • Communications related to individual MTN 002 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 002 Essential Documents

File/Binder #13: Study Site Staff Meeting Documentation 41. MTN 002 Staff Meeting Agendas, Participant Lists/Sign-In Sheets, and Summaries
File/Binder #14: Conference Call Documentation 42. MTN 002 Protocol Team and Protocol Co-Chairs Conference Call Summaries if applicable 43. MTN 002 Study Coordinators Group Conference Call Summaries if applicable 44. MTN 002 Laboratory Group Conference Call Summaries if applicable 45. MTN 002 Community Educators Group Conference Call Summaries if applicable 46. Summaries of Other MTN 002 Conference Calls
File/Binder #15: DAIDS and Other Reference Documentation 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 002 (45 CFR 46; 21 CFR 50, 54, 56, and 312) 52. Any other relevant manuals or reference documents
File/Binder #16: Site-Specific Study Activation Documentation 53. Site-Specific Study Activation Documents

Section Appendix 3-2
Guide to Required Case History Elements and Source Documents for MTN 002

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.	Demographics form, locator form; Study Eligibility form. Concomitant Medications Log form, Targeted Physical Exam form, Pelvic Exam Diagrams; Pre-existing Conditions form, local lab logs and result reports [§] ; baseline medical history, signed and dated chart notes.
A record of the participant's drug assignment.	MTN 002 participant-specific pharmacy dispensing record.
A record of the participant's exposure to the investigational study products.	MTN 002 Study Product Request Slip, MTN 002 participant-specific pharmacy dispensing record; 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; MTN 002 Study Visit form, C-section Delivery Information form, Flow Cytometry form, Pelvic Exam form; Pelvic Exam Diagrams form, Pre-existing Conditions form, Concomitant Medications Log form, Targeted Physical Exam form, Adverse Experience Log form; Missed Visit form;; End of Study Inventory 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 002 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" or "This is a 44-year old HIV-infected woman here for routine study visit with increased fatigue and pallor; blood smear is positive for malaria."

• **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 002 in Subjective-Objective-Assessment-Plan (SOAP) Format

Sample Chart Note for Screening and Enrollment Visit:

16 JUN 2008: Participant presented for MTN 002 screening and enrollment visit. 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:** Participant eligible per the protocol eligibility criteria, tested HIV negative.
- A:** Participant is eligible for the study thus far.
- P:** Plan for PK measures visit, confirm the day planned for the C/S procedure.
 {staff signature}

Sample Chart Note for PK Measures Visit/Gel Administration Day:

3 SEP 2008: Participant presents for her scheduled C/S procedure. Procedures completed per protocol, visit checklist and SOPs.

- S:** No issues/problems reported during gel administration.
- O:** PK Procedures performed according to protocol with no problems.
- A:** No issues of concern.
- P:** Twenty-Four Hour Evaluation scheduled for 4 SEP 2008.
 {staff signature}

Section Appendix 3-4
MTN 002 DataFax and Non-DataFax Forms

MTN 002 DataFax Forms
Demographics
Enrollment
Pelvic Exam
Pharmacokinetics
Participant Evaluability and Replacement
Adverse Experience Log
Missed Visit
Interim Visit
Termination
End of Study Inventory

MTN 002 Non-DataFax Forms
Targeted Physical Exam
Pelvic Exam Diagrams
MTN 002 LDMS Specimen Tracking Sheet

**Section Appendix 3-5
Use of MTN 002 DataFax Forms as Source Documents**

MTN 002 DataFax Forms	Source?	Comments
Demographics	Yes	.
Concomitant Medications Log	Yes	Form may be source for all items.
Enrollment	Mixed	Item 1 is based on source data recorded on participant informed consent form. May be source for items 2 and 2a.
Pre-Existing Conditions	No	All items are based on data recorded on other source documents.
Interim Visit	Yes	. Form may be used as source for all items
Flow Cytometry	No	Lab report will be source.
C-section Delivery Information	No	Hospital chart will be source.
MTN 002 Study Visit	Yes	Form may be used as source for all items.
Pharmacokinetics	Yes	Form may be used as source for all items.
Participant Evaluability and Replacement	Yes	Form may be used as source for all items.
Missed Visit	Yes	Form may be source for the fact that the visit was missed; source data on the reason why the visit was missed also may be recorded on this form.
Pelvic Exam	No	Visit checklist is source for item 1, Pelvic Exam Diagrams may be source for item 1a.
Adverse Experience Log	Yes	Form may be source for all items.
Termination	No	All items are based on data recorded on other documents as source.
End of Study Inventory	No	

**Section Appendix 3-6
Use of MTN 002 Non-DataFax Forms as Source Documents**

MTN 002 DataFax Forms	Source?	Comments
Study Eligibility	Yes	Form may be source for all items.
Targeted Physical Exam	Yes	Form may be source for all items.
Pelvic Exam Diagrams	Yes	Form may be source for all items.
Maternal PK LDMS Specimen Tracking Sheet	No	All items are based on data recorded on other documents as source.
C-section LDMS Specimen Tracking Sheet	No	All items are based on data recorded on other documents as source.

Section 4. Participant Accrual

This section covers general guidelines for accrual and recruitment methods at the site. Additional information regarding participant accrual can be found in the MTN 002 Protocol Section 10.5.

4.1 Study Accrual Plan and Site-Specific Accrual Targets

The accrual period will be eighteen months. The site will recruit and enroll a total of 16 participants.

The site will report the number of participants screened for and enrolled in the study to the MTN CORE on a weekly basis throughout the accrual period. Based on this information, the CORE will distribute a weekly accrual report to the Protocol Team. In addition, on a monthly basis, the SDMC will report to the Protocol Team the number of participants enrolled based on data received and entered into the study database.

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

- Site-specific accrual goals
- Methods for tracking accrual goals versus actual accrual
- 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

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. The 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 002 Protocol Safety Review Team (PSRT) for guidance on the specific action to be taken. PSRT contact details are provided in Section 11 of this manual.

4.2.1 Screening and Enrollment Visit

The term “screening” refers to all procedures undertaken to determine whether a potential participant is eligible to take part in MTN 002. For this study, both screening and enrollment procedures can occur at the same study visit. However, in some cases the screening date will be different from the enrollment date (See Section 5 on informed consent procedures for more details).

The study eligibility criteria are listed in protocol Sections 5.2 and 5.3. The Study Eligibility non-DataFax case report form also lists all of the study eligibility criteria, and can be used to document the eligibility criteria assessment for each participant. The screening and enrollment procedures are described in protocol Section 7.1, and Figure 4-2 lists the eligibility criteria to be assessed at the screening and enrollment visit.

In the case where an eligibility laboratory result is not available on the day of the screening and enrollment visit, and once the result is available it indicates the participant is not eligible, the site will notify the PSRT to request immediate termination of the participant. Once approval to terminate has been received from the PSRT, the site will contact the SDMC for instructions on how to complete the case report forms.

4.2.2 Scheduled Cesarean Section (Gel Administration Visit)

Once all lab results are received, site staff will confirm that the participant can move forward with study procedures and be scheduled for the next visit. If not confirmed at the screening and enrollment visit, study staff must confirm the date of the scheduled Cesarean section (Gel Administration Visit) within one week of its scheduled date and time of the procedure.

If the participant does not meet all eligibility criteria, she will be discontinued from the study. Study staff will not have to confirm date and time of scheduled Cesarean section for participants who are discontinued from the study.

**Figure 4-2
Eligibility Assessments for MTN 002**

Inclusion and Exclusion Criteria Assessed at Screening and Enrollment Visit
Between the ages of 18 and 45, inclusive, at the time of screening and enrollment as verified by site SOP.
Be willing and able to provide written informed consent
Be in general good health
Be HIV uninfected
Be pregnant with the following characteristics – Viable, singleton, without ultrasound of significant fetal congenital anomaly, term, planned C/S
Have a normal Pap
Agrees to not participate in other investigational drug or device research studies for the duration of study participation
Be willing to undergo all study related assessments (clinical and laboratory), adhere to follow up schedule as required by the protocol
Willing to comply with study gel administration as required per protocol
Has not participated in any other device or drug study in the 30 days prior to enrollment
Be willing to abstain from vaginal sex, anal sex, or oral receptive sex two weeks after gel placement
Be willing to abstain from intravaginal practices and products
No abnormal finding on physical or pelvic examination which precludes participation in the trial
Any liver function test result greater than 1.5 X the site laboratory ULN*
Serum creatinine greater than 1.0 mg/dL*
Negative for Hepatitis B surface antigen (HBsAg)*
Current or recent use of vaginal medications
No UTI/RTI or partner exposure to UTI/RTI at screening or enrollment requiring treatment. (See protocol Section 5.3 for details)*
Have maternal or fetal condition that necessitates urgent cesarean section
Have documented rupture of the amniotic membranes, as defined in the SOP
Have known maternal disease with predictable negative affect on placental function
Have known placental/fetal abnormalities that could affect placental transfer
Have previously demonstrated hypersensitivity to any components of tenofovir 1% gel

*Lab results may be received after the screening and enrollment visit (after enrollment into the study).

4.2.3 Screening/Enrollment HIV Testing

HIV infection status at screening will be assessed using a rapid HIV test. Any test that has been validated at the study site may be selected from among the following three tests:

- Abbott Determine
- OraSure OraQuick
- Uni-Gold Recombigen

If the site chooses to use the OraSure OraQuick and Uni-Gold Recombigen tests, FDA-approved test kits must be used.

Further instructions for performing HIV tests are provided in Section 12. All tests must be documented on local laboratory log sheets or other laboratory source documents. 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

4.2.4 Screening and Enrollment Timeframe

The planned cesarean section or Gel Administration day must occur no more than four weeks (28 days) after screening and enrollment procedures.

4.2.5 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 002. The study site is 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 002**

Sample MTN 002 Screening and Enrollment Log							
Site Name, Clinic Name, and Location:							
	Participant ID	Participant Initials	Date Study Informed Consent Signed*	Eligible?	Enrollment Date	If not enrolled, specify reason	Staff Initials
1				Y N			
2				Y N			

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

4.2.6 Assignment of Participant ID Numbers

SCHARP will provide the study site with a listing of Participant ID (PTID) numbers for use in MTN 002. 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 002 can be found in Section 13. PTIDs will be assigned to all potential participants who provide written informed consent for the study, regardless of whether they enroll in the study. Only one PTID will be assigned to each potential participant. Site staff is responsible for establishing SOPs and staff responsibilities for proper storage, handling, and maintenance of the PTID list such that participant confidentiality is 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 002**

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

Section 5. Informed Consent

This section provides information on informed consent procedures for MTN 002. MTN 002 involves one informed consent for screening and enrollment.

All potential study participants must provide written informed consent before protocol-specified procedures for determining eligibility for study participation are completed. Participants who are found to be eligible for the study will undergo protocol-specified “on study” procedures as outlined in the protocol.

For MTN 002, there is one study informed consent form entitled "Phase I Study of the Maternal Single-Dose Pharmacokinetics and Placental Transfer of Tenofovir 1% Vaginal Gel among Healthy Term Gravidas." This consent form will be administered before any study procedures are performed.

In most cases, enrollment into MTN 002 will not occur the same day that the study informed consent is signed due to the need to wait for screening lab results that are required to confirm study eligibility. Once all pending screening lab results are received, and the study participant is confirmed to be eligible, she can then be enrolled.

This section contains general information and instructions applicable to required informed consent procedures for MTN 002.

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 is 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.

US regulations (45 CFR 46) specify the elements of informed consent must be conveyed to research participants through the informed consent process. It is the responsibility of the Investigator of Record (IoR) to ensure that all potential study participants receive the required information during the informed consent process before any study procedures are completed; The IoR may delegate this responsibility to other study staff.

Because of the 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 the site ...” Please refer to Section Appendix 5-1 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, the 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 the 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 for implementing a change in the version of the informed consent form used
- 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 and Enrollment

The informed consent process for screening and enrollment will be conducted according to site SOPs. Informed consent must be obtained prior to performing any study procedures. For participants who do not provide consent, no procedures (screening or enrollment, or follow up procedures) should be performed and no data that can be linked to the participant's name or other personal identifier(s) should be recorded.

5.2.1 Informed Consent Support Materials

Site-specific informed consent forms: The informed consent forms used at the site must be reviewed and approved by the site's IRBs/EC and DAIDS prior to their use. After the forms are approved, the site is responsible for preparing supplies of their approved forms and for only using the currently approved versions of the forms at all times during the study.

5.2.2 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.

Study staff may want to ask some questions that indicate if the participant understands salient points of the protocol. If the participant does not mention one or more of the salient points, study staff should follow-up with another open-ended question to elicit a response about that point.


When responding to the various questions, potential participants may report back more information than is necessary. This is acceptable, as long as the required information is reported back. If any misinformation is reported back, study staff may explain the correct information.

It is expected that study staff assessing informed consent comprehension will be sufficiently knowledgeable about MTN 002 to make good judgments about potential participants' understanding of the study and help participants grasp protocol 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.

Figure 5-1
Overview of MTN 002 Enrollment Informed Consent Process

Briefly **describe the steps** in the consent process and tell the woman the how long it takes to complete.


 Does she has time to complete this today?

- If yes, proceed.
- If no, schedule return appointment.

 Is she ready to have the **informed consent form** read to her or read it herself?

- If yes, proceed.
- If not, determine what she needs and provide information or schedule return appointment.

Read consent form, section by section, asking if she has questions and discussing as you go along.

 Does she feel comfortable that she understands all aspects of the study?

- If yes, proceed.
- If not, determine what she needs and provide more information at that time or schedule return appointment.
- If participant demonstrates comprehension of all required topics, proceed
- If not discuss misunderstandings and probe problem areas with open-ended questions.
- If participant is fatigued or requests more time, or if study staff judge that participant needs more time, schedule return apt and repeat steps in the process as needed.

Complete all name, signature, and date blocks on the enrollment informed consent form. Offer participant a copy of the form. Document the process per site and DAIDS SOPs.

- Proceed with screening and enrollment procedures (per protocol and this manual).

5.3 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's 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 Appendix 5-2. If the site chooses to use a coversheet, the coversheet should be listed as a source document in their SOPs for Source Documentation for MTN 002 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) documents 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.

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

- The 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 the 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 002

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 002.
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 002?	<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.
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 6. Participant Follow-up

Please refer to the MTN 002 Protocol and SSP sections 4 and 7 for information regarding follow up visits and procedures.

Section 7. Visit Checklists

This section contains examples of checklists detailing the protocol-specified procedures that must be completed at MTN 002 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

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.
- Enter your initials beside only 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 CORE, site staff may modify the checklists included in this section to maximize the efficiency of site-specific study operations. Site staff may alter the sequence of procedures to suit local staffing and logistical requirements, with the following exceptions:

- Informed consent for screening and enrollment must be obtained before any study procedures are performed.
- Amniotic fluid and endometrial tissue must be collected during cesarean section and cord blood and placental tissue must be collected during or after the cesarean section.

NOTE: Checklists in this section are provided as guidelines for the sites. The site can choose to modify these checklists or create their own checklist. Modified checklists should be reviewed by FHI prior to implementation.

Screening and Enrollment Visit: Page 1 of 3

PTID:	Visit Date:
Visit Code: 01.0	Visit Window : Up to 4 weeks prior to C/S

1. _____ Confirm participant identity. Cross-check with the MTN 002 Participant Name-PTID Link Log to determine whether a MTN 002 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. _____ Confirm the date and time when the participant's C/S is scheduled.
 - *If the participant's C/S is scheduled more than 4 weeks from this date, STOP. Reschedule the screening to occur approximately 1-4 weeks prior to C/S.*

4. _____ Confirm that the pregnancy term, at the time of the planned C/S, is 37 0/7 to 41 6/7 weeks (inclusive), using gestational dating criteria per site SOP.

5. _____ Explain the informed consent process.

6. _____ Explain the content and sequence of procedures for the remainder of the visit.

7. _____ Administer and obtain screening and enrollment informed consent with participant according to site SOPs. Complete Consent Process Worksheet.
 - *If the participant does not consent to screening and enrollment, STOP. Do not fax any forms to SCHARP.*

8. _____ Administer and obtain signed records release.

9. _____ Complete **Enrollment** form, item 1.

10. _____ Assign an MTN 002 PTID by completing a new row in the MTN 002 Name-PTID Link Log.

11. _____ Obtain contact information and record on site specific form.

12. _____ Review participant's prenatal record and ultrasound reports
 - *If any placental/fetal abnormalities that could affect the placental transfer, the participant is ineligible for enrollment. STOP. Do not fax any forms to SCHARP.*

 - *If participant has any known maternal disease with a predictable negative affect on placental function, participant is ineligible for enrollment. STOP. Do not fax any forms to SCHARP.*

Screening and Enrollment Visit: Page 2 of 3

PTID:	Visit Date:
Visit Code: 01.0	Visit Window : Up to 4 weeks prior to C/S

➤ *If any maternal or fetal condition that necessitates urgent C/S, participant is ineligible for enrollment. STOP. Do not fax any forms to SCHARP.*

13. _____ Obtain medical history. Document all ongoing medical conditions on **Pre-existing Conditions Form**.

14. _____ Assess concomitant medications. Document all ongoing medications on **Concomitant Medications Log** form.

15. _____ Collect approximately 15-60 mL urine and:
 15a. _____ Prepare urine for SDA for Gonorrhea and Chlamydia.

16. _____ Provide HIV pre-test counseling

17. _____ Collect blood:
 - Red Top
 - Purple Top

18. _____ Explain to study participant that eligibility is based on results as determined by the study HIV algorithm (Protocol Appendix II).

19. _____ Prepare blood for testing at the local lab:
 - Serum Creatinine
 - AST, ALT
 - Rapid HIV test
 - If required, Hepatitis B Antigen testing
 - If indicated, Syphilis serology

20. _____ Complete HIV testing log(s). Before disclosing results to participant, obtain independent review, verification, and sign-off of both results.

21. _____ Provide HIV test result and post-test counseling. Provide referrals if needed/requested. Explain the participant's current study eligibility status.
 - *If rapid test is negative, the participant is considered HIV-uninfected. Continue with remainder of this checklist.*

 - *If rapid test is positive, 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.*

22. _____ Complete **Demographics** form.

Screening and Enrollment Visit: Page 3 of 3

PTID:	Visit Date:
Visit Code: 01.0	Visit Window : Up to 4 weeks prior to C/S

23. _____ Conduct targeted physical exam and record results on the **Targeted Physical Exam** non-Data Fax form.
24. _____ Perform and document pelvic exam per pelvic exam checklist. Complete the Pelvic Exam Diagrams non-DataFax and **Pelvic Exam** forms. Update **Pre-existing Conditions** form with any ongoing pelvic abnormalities.
25. _____ Complete the MTN 002 Eligibility Determination Checklist. If participant is determined to be eligible based on information available continue with the checklist. If participant is determined to be ineligible, STOP. Complete item 2 of the **Enrollment form**. Do not fax any forms to SCHARP.
26. _____ Provide study informational material. Provide site contact information and instructions to contact the site for additional information if needed, prior to the next visit.
27. _____ Provide reimbursement
28. _____ Document the visit in a signed and dated chart note. Complete and review all other participant chart contents for the visit.
29. _____ Once all test results are available, update **Pre-existing Conditions form** with any laboratory-based ongoing conditions. Notify participant of test results and to confirm her C/S date.
30. _____ Review and fax all required DataFax forms to SCHARP DataFax:
 - Demographics
 - Enrollment
 - Pre-existing Conditions
 - Concomitant Medications Log
 - Pelvic Exam
31. _____ Place all study visit checklists, chart notes, case report forms, and other study documents identified with a PTID only in an MTN 002 participant notebook assigned to the participant.

Gel Administration Visit (Day 0): Page 1 of 2

PTID:	Visit Date:
Visit Code: 02.0	Visit Window : Within 4 weeks of Screening and Enrollment Visit

1. _____ Complete participant registration, confirm the participant's identity, and verify her PTID.

2. _____ Review lab results from previous visit. If results preclude participant from continuing in study, inform participant and complete the **Participant Evaluability and Replacement** form and **Termination** form.

3. _____ Confirm this visit is no more than 28 days after the participant's Screening and Enrollment Visit.

4. _____ Review/update locator information

5. _____ Place copy of participant's informed consent form in the inpatient chart

6. _____ Review the inpatient chart, chart notes and other relevant documentation from previous visit(s).

7. _____ Update medical history. Record any new adverse events as well as any pre-existing conditions that have increased in severity or frequency on an **Adverse Experience Log** form.

8. _____ Assess concomitant medications. Review/update **Concomitant Medications Log** form(s). Document review with a signed and dated note on each document reviewed. Initial and date updated entries.

9. _____ Conduct targeted physical exam as per Protocol Appendix III. Complete the **Physical Exam** (non-DataFax) form.

10. _____ Perform and document pelvic exam per pelvic exam checklist. Complete the Pelvic Exam Diagrams non-DataFax and **Pelvic Exam** form.

11. _____ Insert saline lock, if not already in place, and collect blood:
 - Purple Top

11. _____ Prepare blood for testing at the local lab:
 - Maternal plasma tenofovir level
 - Flow cytometry

12. _____ Complete an **LDMS Specimen Tracking Sheet** for samples tested at the MTN Network Lab.

13. _____ Insert Tenofovir 1% gel (conducted by study physician) approximately 2 hours prior to C/S

Gel Administration Visit (Day 0): Page 2 of 2

PTID:	Visit Date:
Visit Code: 02.0	Visit Window : Within 4 weeks of Screening and Enrollment Visit

14. _____ Schedule next study evaluation between 22-26 hours following product administration
15. _____ Collect blood for maternal plasma tenofovir level at the following time points: 1, 2, 4, 6, 8 and 12 hours. Complete **Pharmacokinetics** form at each time point as specimens are collected.
- *Note: the time points are relative to gel administration*
 - *Some time points may occur before C/S*
 - *The allowable window for each blood draw is +/- 15 minutes*
16. _____ Record Adverse Events at each PK time point listed above
17. _____ Review inpatient chart (during 1-12 hours post-gel)
18. _____ Scheduled C/S performed
19. _____ During C/S, collect:
- Amniotic fluid
 - Endometrial tissue
 - If possible, cord blood
 - If possible, placental tissue
20. _____ Following the C/S collect:
- Cord blood (if not collected during C/S)
 - Placental tissue (if not collected during C/S)
21. _____ Complete **MTN 002 Study Visit** form
22. _____ Document the visit in a signed and dated chart note. Complete and review all participant chart contents.
23. _____ Fax all required DataFax forms to SCHARP DataFax:
- MTN 002 Study Visit
 - Pharmacokinetics
 - Pelvic Exam
 - Concomitant Medications Log (any pages that have been updated)
 - Adverse Experience Log (if applicable)
 - Participant Evaluability and Replacement (if applicable)
 - Termination (if applicable)

24-Hour Evaluation: Page 1 of 2

PTID:	Visit Date:
Visit Code: 03.0	Visit Window : Hour 22-26

1. _____ Complete participant registration, confirm the participant's identity, and verify her PTID.
2. _____ Review/update locator information.
3. _____ Review inpatient chart of participant
4. _____ Review inpatient chart of infant
5. _____ Explain the content and sequence of procedures for this visit.
6. _____ Review elements of informed consent as needed.
7. _____ Record and update the **Concomitant Medications Log**.
8. _____ Record and update adverse events on the **Adverse Experience Log** form.
9. _____ If indicated, perform targeted physical exam and complete **Targeted Physical Exam** form.
10. _____ If indicated, perform pelvic exam and complete Pelvic Exam Diagrams non-DataFax and **Pelvic Exam** forms.
11. _____ Collect and prepare blood for maternal plasma tenofovir level. Complete item 11 of **Pharmacokinetics** form. Complete LDMS Specimen Tracking Sheet.
12. _____ Complete an **LDMS Specimen Tracking Sheet** for samples tested at the MTN Network Lab.
13. _____ Schedule the Two Week phone call
14. _____ Reinforce instructions to contact the site if the participant has any questions or concerns prior to the Two-Week phone call.
15. _____ Provide study reimbursement
16. _____ Complete the **MTN 002 Study Visit** form.
17. _____ Complete **C-section/Delivery Information** form.
18. _____ Complete and review all participant chart contents for the visit

24-Hour Evaluation: Page 2 of 2

PTID:	Visit Date:
Visit Code: 03.0	Visit Window : Hour 22-26

19. _____ Fax all required DataFax forms to SCHARP DataFax:

- MTN 002 Study Visit
- Pharmacokinetics
- C-section/Delivery Information

As Needed:

- Concomitant Medications Log (required for updated or new pages)
- Adverse Experience Log (required if any AEs identified or updated)

Two-Week Phone Call: Page 1 of 1

PTID:	Visit Date:
Visit Code: 04.0	Visit Window : Day 10-18

1. _____ Complete participant registration, confirm the participant’s identity, and verify her PTID.
2. _____ Review chart notes and other relevant documentation from previous visit(s).
3. _____ If indicated, review inpatient and outpatient charts.
4. _____ Review/update locator information.
5. _____ Review elements of informed consent as needed.
6. _____ Update demographics form as needed.
7. _____ Complete/update **Adverse Experience Log** form(s) if required.
8. _____ Review/update concomitant medications and update **Concomitant Medications Log** form(s) if required.
9. _____ If indicated, schedule the next visit.
10. _____ Reinforce site contact information and instructions to contact the site with any questions.
11. _____ Send study reimbursement for phone call.
12. _____ Document the phone call in a signed and dated chart note. Complete and review all participant chart contents for the visit.
13. _____ Complete **MTN 002 Study Visit** form
14. _____ Fax the required DataFax form to SCHARP DataFax:
 - MTN 002 Study Visit
 - As Needed:
 - Concomitant Medications Log (required for updated or new pages)
Note: All medications must have a date stopped or be marked as “continuing at end of study” at time of study termination.
 - Adverse Experience Log (required if any AEs identified or updated)
 - Scheduled or Early Termination:
 - Termination
 - End of Study Inventory
 - Participant Evaluability and Replacement

Pelvic Exam: Page 1 of 1

PTID:	Visit Date:
Please indicate to which visit this checklist applies:	
Screening and Enrollment : ____ Gel Administration Day: ____ Interim: ____	

1. ____ Explain the exam procedures to the participant and answer any participant questions.
2. ____ At the screening and enrollment visit only: Affix a SCHARP-provided PTID label to a culture container for Trichomonas evaluation. Write the specimen collection date in ink on the label.
3. ____ Position and drape the participant comfortably.
4. ____ Palpate inguinal lymph nodes. Document abnormal findings on the **Pelvic Exam** form
5. ____ Inspect external genitalia: Note all findings on the Pelvic Exam Diagrams non-DataFax form. Document abnormal findings **Pelvic Exam** form.
6. ____ Insert speculum, using warm water as lubricant if needed. Observe general state and note the position of the cervix.
7. ____ Assess for homogenous discharge. Record observation in chart note.
8. ____ Inspect cervix and vagina: Note all findings on the Pelvic Exam Diagrams non-DataFax form. Document abnormal findings **Pelvic Exam** form.
9. ____ At the screening and enrollment visit only: Swab vaginal fluids from the lateral vaginal wall; place the swab in the Trichomonas culture container (see also SSP Section 12).
10. ____ If indicated, perform Wet Prep and Vaginal pH. Record observation in chart note.
11. ____ If indicated, perform Herpes Culture (at sites where standard of care for diagnosis)
12. ____ Perform bimanual exam. Note all findings on the Pelvic Exam Diagrams non-DataFax form. Document abnormal findings **Pelvic Exam** form.
13. ____ Record the size of speculum used and position of the participant's cervix on the Pelvic Exam Diagrams form.

Section 8. Participant Retention

This section presents information related to definitions, requirements, and procedures for participant retention in MTN 002.

8.1 Retention Definition

The term “retention” generally refers to completion of the subsequent evaluation visit and follow up 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.

During the study, retention will be defined based on whether participants complete required visits and follow-up procedures within the allowable visit windows. Participants who complete their scheduled gel administration, 24 hour evaluation visit and two week follow up phone call within the allowable visit windows will be considered “retained” for those visits.

As indicated above, participants who do not complete the gel administration, 24 hour evaluation visit and two week follow up phone call within the allowable windows, 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 evaluation visit and follow up. Thus retention rates can fluctuate over time and across visits. Importantly, retention shortfalls can be made up by ensuring that participants return for their subsequent evaluation visit and follow up.

The MTN Statistical and Data Management Center (SDMC) will generate reports during the study presenting retention rates for study visits. The SDMC also will generate a final end-of-study retention rate after the study is completed.

8.2 Retention Requirements

The study site will target retention of 100 percent of enrolled study participants at each required follow-up visit.

The purpose of the 100 percent retention target is to ensure the accuracy of study results. The pharmacokinetics measures tested in MTN 002 will be estimated by comparing these measures observed in each participant at seven time points following gel administration and compared to baseline measures.

8.3 Retention SOPs

Site staff is responsible for establishing a standard operating procedure (SOP) for participant retention, and for updating the SOP and retention efforts undertaken to meet the study retention goal of 100 percent at the scheduled gel administration, 24 hour evaluation visit and two week follow up phone call. 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 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 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 and enrollment process, and to continually review/update this information during the subsequent 24 hour evaluation period and two week phone call. 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. 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 likely will be useful, contact information for other contacts should also 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?"). Also probe for additional information that the participant was not able or willing to provide at previous visits.

8.5 Retention Tips

With the consent of the participant, study staff will obtain contact information from people who would be expected to know the whereabouts of the participant enrolled in this study. The need to attend the subsequent evaluation visit and follow up must be emphasized to each study participant. If a participant misses a scheduled study visit, the study site staff will try to establish communication with the participant through all possible means (e.g., telephone, field contact, and writing), without breaching the participant's confidentiality. Study site staff is responsible for developing and implementing site-specific SOPs to achieve complete follow up.

Once participants are enrolled in this study, the study site staff will make every effort to ensure the participation of participants for the evaluation visits and follow up, in order to minimize possible bias associated with loss-to-follow-up. Each site will establish participant retention procedures to target an average retention rate of 100%. Study site staff is responsible for developing and implementing site-specific SOPs to target this goal.

Suggestions for such procedures include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at follow up.
- Collection of detailed locator information at the study Screening and Enrollment Visit, and active review and update of this information at follow up.
- Use of mapping techniques to establish the location of participant residences and other locator venues.
- Regular communication with the study community at large to increase awareness about HIV/ Acquired Immunodeficiency Syndrome (AIDS) and explain the purpose of HIV prevention research and the importance of completing research study visits.
- 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.

- Emphasize the value of the participant's involvement in the study during the study informed consent process and subsequently at follow-up visits. When participants complete scheduled visits, acknowledge and commend their commitment, time, and effort devoted to the study.
- Schedule all follow-up visits at the participant's Screening and 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 time noted.
- Prepare a calendar of scheduled visits for each enrolled participant, based on her enrollment date and gel administration time, Note the times of all scheduled visits in the participant's file for easy reference.
- 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.
- 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 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.
- 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, ask if she would be willing to complete a final test at the end of the study. If the participant refuses this level of involvement, explain that she is always welcome to come back if she wishes.

Section 9. Study Product Considerations for Non-Pharmacy Staff

This section provides information and instructions for non-pharmacy staff related to the ordering, transport, and administration of MTN-002 study product. Please also refer to related information in Sections 4 of this manual.

9.1 Gel Use Instructions

Four grams of tenofovir 1% gel will be administered vaginally, by the authorized clinician, approximately two hours prior to the expected time of cesarean section (optimally at least one hour prior to the collection of cord blood). Detailed instructions for insertion of study gel are listed in Figure 9-1 below.

Figure 9-1

Gel Administration Instructions for MTN 002

<p>Removing the Applicator:</p> <ul style="list-style-type: none">• Tear open the wrapper• Remove the applicator
<p>Inserting the Applicator:</p> <ul style="list-style-type: none">• Hold the applicator containing MTN 002 study gel about half-way along the barrel• Gently inserted the 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>Disposing the Applicator</p> <ul style="list-style-type: none">• Discard the used applicator, plastic wrapper, and cap in accordance with applicable hospital policies• Do NOT return used applicators to the pharmacy

9.2 Ordering of MTN 002 Study Product from the Pharmacy

The Pharmacist of Record will provide the Investigational Drug Study Research Order Form to be used for MTN 002. This Investigational Drug Study Research Order Form will serve as the prescription for MTN 002. Because this is an inpatient study, the site's hospital procedures of keeping the original Investigational Drug Study Research Order Form in the participant's hospital chart with a copy going to the pharmacy will be permitted. All further references to prescription below refer to this copy that will be maintained in the Pharmacy.

In the event that it becomes necessary to view the actual original source document, the site will need to request the participant's hospital records.

9.3 Dispensing from the Pharmacy to Research Staff

Upon receipt of a completed and signed prescription, pharmacy staff will dispense one applicator containing Tenofovir 1% vaginal gel (MTN 002 study product) as close to the time of administration as possible. Study product may be prepared for dispensing based on receipt of the prescription or a faxed/scanned copy, but study product will not be released to clinic staff until the (hard-copy) prescription with original signature is received. The Research Staff must bring the Research Order Form for review by the pharmacist and to verify the Participant ID number. The study product for MTN-002 will be dispensed directly to research study staff.

The research study staff, upon receipt of the MTN 002 study product, will be asked to initial the bottom of the pharmacy copy of the participant's prescription at the time they receive the study product for a participant from the pharmacy.

9.4 Return of Unused Study Gel Supplies

If the study gel is not administered to the participant it must be returned to the pharmacy as soon as possible after it has been determined that it will not be administered to that participant that day. The Pharmacist should indicate in the comments section of the DAIDS Study Product Accountability Record that the MTN 002 study product for that participant was returned to the pharmacy. The returned product should then be placed in quarantine by the Pharmacist.

9.5 Product-Related Scenarios

9.5.1: What if the research study staff and/or authorized clinician think there is something wrong with the applicator?

If there seems to be something wrong with an applicator (for example, it is difficult to push the study gel out of the applicator, if study gel has leaked out, if the applicator appears to be empty or there is some other problem), do not use the applicator and notify the pharmacy. The unused applicator should be returned to the pharmacy when and if a new applicator is dispensed. The DAIDS Protocol Pharmacist should be notified as soon as possible by the Pharmacist of Record.

Section 10. Clinical Considerations

This section presents information on the clinical procedures performed in MTN 002. 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 History and Ascertainment of Concomitant Medications

A focused baseline medical history is obtained from potential study participants at the Screening and Enrollment Visit. Medications used by the participant also are 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 History

The site is encouraged to collect pertinent baseline medical history data (including history of genital symptoms) in their source documentation. 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. Recurring and/or chronic conditions are considered ongoing whether or not they are present/active at baseline.

When obtaining a focused baseline medical history for MTN 002, it is not necessary to document the participant's lifetime medical history and/or history of genitourinary symptoms. Rather, focus on conditions that have occurred and symptoms that were experienced since the participant became pregnant and probe for the most accurate information available on the participant's current health and pregnancy vis-à-vis the reported history. Several additional guidelines are presented below:

- Review the participant's prenatal record, ultrasound reports and, if indicated, her inpatient chart.
- Record symptoms, illnesses, allergies, and surgeries.
- Record both chronic and acute conditions, as well as both ongoing and resolved conditions.
- Record the number, date, and outcome of each of the participant's prior pregnancies, as well as any gynecologic and obstetrical procedures/surgeries.

- Document medications currently taken for all ongoing conditions on the Concomitant Medications Log form, as described in Section 10.1.2.

Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing to elicit complete and accurate history information from study participants.

10.1.2 Initial Ascertainment of Concomitant Medications

The MTN 002 protocol requires documentation of all medications taken by study participants beginning at the Screening and Enrollment Visit and continuing throughout follow-up. Note that for all medications taken up until 24 hours following the administration of study product, the protocol requires that the time of administration be recorded for each medication.

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

Other routes of administration, including intravenous, intravaginal and rectal medications/preparations and topical medications/preparations applied to the external genitalia are of particular interest for this study, as are douches and vaginal cleansers. Be sure to record all such medications/preparations.

The Concomitant Medications Log form is the recommended source document for collecting information on participants’ use of medications.

It is recommended that study clinicians ascertain participants’ baseline medication information in the context of conducting the baseline medical history. In addition to asking open-ended questions to elicit participant report of current medications, use the information obtained in the medical 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 participant’s baseline medical history information and the Pre-existing Conditions form as appropriate.

Pre-existing Conditions

As noted above, a key purpose of conducting the baseline medical history — as well as the targeted physical and pelvic exam at the Screening and Enrollment visit — is to document participants' baseline medical conditions for comparison with signs, symptoms, and conditions that may be identified or reported at subsequent scheduled or interim study visits. For MTN 002, 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 conditions observed and/or reported at the Screening and Enrollment Visit should be reported on the Pre-existing Conditions form. This case report form is completed, based on all other screening and enrollment source documents, including the baseline medical history (present in source documents/chart notes), Targeted Physical Exam form, Pelvic Exam form, all screening laboratory results, chart notes, and any other site-specific source documents.

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 enrollment in the study and are therefore not considered AEs. However, new conditions identified during follow-up that were not present at the time of enrollment, and any pre-existing conditions that increase in severity or frequency during follow-up, are 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 History and Updating of Concomitant Medications

For enrolled participants, an interval medical history and update of concomitant medications are obtained at the Gel Administration Visit. Updates on concomitant medications are also obtained at the 24 Hour Evaluation Visit and the Two Week Phone Call. These procedures are performed at interim visits when clinically indicated. The purpose of these procedures is to determine whether participants have experienced any new illnesses, unexpected symptoms, etc., since the last study visit.

10.2.1 Interval Medical History

At the Gel Administration Visit, retrieve the participant's source documentation with medical history and Pre-existing Conditions forms for reference. When completing the interval history, it is not necessary to actively review/inquire about every body system; it is acceptable to actively inquire about the current status of conditions recorded as ongoing at the time of the prior visit, and then to ask the participant an open-ended question such as “Have you had any other symptoms or health problems since your last visit?” to complete the 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 to determine the best phrasing to elicit complete and accurate follow-up information from study participants.

10.2.2 Updating of Concomitant Medications Information

At each visit in which concomitant medications information is obtained, 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 history information, add the condition to her source documentation and Pre-existing Conditions form (if present at enrollment).

Note that for this protocol, the Concomitant Medications Log form includes a place to record the time of administration, which is required for all medications taken up until 24 hours following administration of study gel.

10.3 Targeted Physical Exams

An assessment of vital signs and an abdominal exam are required at the Screening and Enrollment visit, Gel Administration visit, any unscheduled visit and at the 24 hour evaluation visit if indicated. The site clinician 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 targeted physical exam components. Vital signs may be transcribed from the participant's chart if they were taken in the past hour.

Vital signs:

- Oral temperature
- Blood pressure
- Pulse

Clinical assessments of:

- General appearance
- Abdomen
- Other components as indicated by participant symptoms

The Targeted 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 Screening and 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 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 participant's source documentation, 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 002 for purposes of determining eligibility and identifying safety outcomes. As such, they are critical to meeting the study objectives and ensuring the ongoing safety of study participants. Pelvic exams are performed at the Screening and Enrollment Visit, Gel Administration Visit, and if indicated at the 24-Hour Evaluation Visit and unscheduled visits, per protocol Section 7.

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. Pelvic exam procedures must be performed in the order shown on the exam checklist in Section 7 of this manual. When additional exams are performed to assess genital symptoms, only clinically indicated procedures should be performed. As indicated in greater detail below, all exam findings are reported on the Pelvic Exam Diagrams form. Additionally, any abnormal findings are transcribed on to the Pelvic Exam (DataFax) form.

For participants who enroll in the study, abnormal exam findings identified at the Screening and 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.

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 type and size of speculum and the direction of speculum insertion after each participant's first 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.

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. Transcribe abnormal findings only on the appropriate Pelvic Exam form case report form. Supplemental information may be recorded on the Pelvic Exam Diagrams form, in chart notes, and/or on other source documents.

10.4.2 Detailed Procedural Instructions

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 for abnormal cervical discharge. Record outcome on the Pelvic Exam Diagrams and on the appropriate pelvic exam form.

- Note all findings (variants of normal and abnormal) on the Pelvic Exam Diagrams form. See the variants of normal in section 10.5.3 below. Further document abnormal findings on the appropriate Pelvic Exam case report form.

Collect Vaginal Sample:

- Collect vaginal fluids via (dry) swab for Trichomonas culture, as required by the visit. Collect fluids from the lateral vaginal wall, away from any apparent abnormalities. Document specimen collection for Trichomonas culture on the appropriate pelvic exam checklist. See Section 12 of this manual for detailed culture preparation and assessment procedures.

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 any genital ulcers are observed during follow-up, swab the base of the ulcer using a dry plastic shaft Dacron swab. Use a different swab for each ulcer. If a cluster of ulcers is observed, sample each ulcer in the cluster with the same swab. Otherwise use a different swab for each ulcer. Document specimen collection on the appropriate pelvic exam checklist. See Section 12 of this manual for further instructions for proper swab handling and storage prior to testing at the MTN Network Laboratory.

Perform Bimanual Exam: After completing all tissue examinations and specimen collection, close the speculum blades, gently remove the speculum, and perform bimanual exam for pelvic masses and/or pelvic or uterine tenderness.

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, 2002) for further examples of terminology applied to pelvic exam findings in microbicide studies.

The Pelvic Exam Diagrams form is the recommended source documents for recording relevant descriptors and details of abnormal findings; however supplemental information may be recorded on the Pelvic Exam 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

If a 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 unexpected genital bleeding as an AE, clinically appropriate terminology should be used to reflect the cause or source of the bleeding (e.g., "threatened abortion"), and the bleeding itself should be graded according to the "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 participants should be submitted to the MTN 002 PSRT as described in Section 11.

10.5.1 Participant Reports of Genital Bleeding

As described in Section 10.2, at the Gel Administration Visit, clinicians will obtain interval medical history information from participants. Any reports by participants of genital bleeding will be recorded on baseline and/or interval medical history documents.

10.5.2 Clinician Assessment of Genital Bleeding

Study participants will undergo pelvic exams at the Screening and Enrollment Visit, Gel Administration Visit and if indicated at the 24-Hour Evaluation Visit. Pelvic examinations will be performed and documented as described in Section 10.4.

Reports of genital bleeding should be assessed for whether the bleeding may be related to product use, or whether it may be more likely attributable to another cause. These factors include:

- Complications related to pregnancy
- 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*. Expectedness will be determined based on the participant's baseline medical history (e.g., whether she reports genital bleeding as a pre-existing condition). Lochia 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.

10.5.3 Documentation of Genital Bleeding

Any reports by participants of genital bleeding will be recorded on baseline and/or interval medical history documents. All clinically observed genital blood/bleeding will be documented on the Pelvic Exam Diagrams form and the Pelvic Exam form.

All episodes of unexpected 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 points below.

- Expected genital bleeding should not be reported as an AE.
- Unexpected complications of pregnancy should be reported as an AE according to the Complications of Pregnancy section in the Female Genital Toxicity Table.
- Unexpected genital 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.
- 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 hemorrhage row in the 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 cause 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 at the Screening and Enrollment visit for MTN 002 to diagnose the following sexually transmitted infections and other reproductive tract infections (STIs/RTIs):

- Chlamydia infection
- Gonorrhea infection
- Trichomoniasis

If indicated, the following STIs/RTIs also will be evaluated:

- Bacterial vaginosis (BV)
- Candidiasis (any species)
- Genital ulcer disease

- Syphilis infection

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, condylomata lata (fleshy, moist tissue growths), lymphadenopathy, alopecia, or other signs.
Syphilis infection — latent	Patients are without clinical signs of infection.
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.

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 CDC Sexually Transmitted Diseases Treatment Guidelines.

Should updated guidelines be issued by the CDC during the study, the updated guidelines will then be followed.

Note: Neither asymptomatic bacterial vaginosis nor asymptomatic vaginal candidiasis require treatment per CDC guidelines.

In day-to-day practice, the CDC guidelines — or local site treatment guidelines based on the CDC 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.

CDC Guidelines (2006) can be found at www.cdc.gov/STD/treatment/.

STI/RTI tests of cure are not required in MTN 002; 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 is not eligible for inclusion but should be followed as clinically indicated. If the participant is otherwise eligible, she may be enrolled after completing treatment and all symptoms have resolved. Please contact the MTN NL with any questions related to 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 CDC guidelines via laboratory tests will be excluded from enrollment. The only exception to this is 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.

10.6.3 Adverse Event Reporting Considerations

Per the MTN 002 eligibility criteria, no participant may enter the study with an active STI/RTI diagnosed per CDC 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 002 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).

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 enrollment, the infection is considered a pre-existing condition: report on the Pre-existing Conditions form.
- For HPV, genital warts present before enrollment are considered a pre-existing condition: report on the Pre-existing Conditions form.
- Any outbreaks that occur after enrollment are considered AEs, regardless of whether the viral infection was pre-existing before enrollment: report on an Adverse Experience Log form.

10.7 Urinary Tract Infections

Dipstick urinalyses will be performed at unscheduled visits when clinically indicated, to diagnose urinary tract infections (UTI). See Section 12 for details on the required laboratory procedures.

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. The sensitivity test results should be documented in the participant's chart notes. Once a diagnosis has been made, treatment will be provided per site standards of care and applicable site standard operating procedures (SOPs).

10.8 Product Use Management

For this study, in the event that a participant experiences an expedited adverse event that is judged to be definitely, probably, possibly, or probably not related to the study gel, product exposure will be minimized to the extent possible. If clinically appropriate, a physician may conduct a cervicovaginal lavage to minimize exposure. The suspected toxicity will be clinically managed according to the site SOPs. Product use management decisions and actions are undertaken, under the direction of the IoR/PI, as described in Section 11.

10.8.1 Circumstances In Which Study Product May Be Withheld:

- Request by participant to not receive study product
- Decision by the IoR/PI to protect the participant's safety and/or if the participant is unable or unwilling to comply with study procedures

10.8.2 Documentation of Product Use Management

All product use management decisions must be thoroughly documented in participant's 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.

Section 11. Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN 002. Please also refer to Section 8 of the MTN 002 protocol and the Manual for Expedited Reporting of Adverse Events to DAIDS, which can be found at <http://rcc.tech-res-intl.com>.

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 002 protocol specifies that any untoward medical occurrence experienced by a study participant after enrollment is considered an AE.

The Adverse Experience Log case report form (see Section 13) is used to report all AEs that occur among MTN 002 study participants to the MTN Statistical and Data Management Center (SDMC) via DataFax. The site 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 enrollment 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. If a pre-existing condition worsens (increases in severity or frequency) after enrollment, the worsened condition is considered an AE.

Study staff will also document on study CRFs all AEs identified via infant chart review for the infant's inpatient admission period(s), regardless of severity and presumed relationship to study product.

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 002, including infant AEs, an authorized study clinician must determine whether the AE meets the definition of SAE. The Adverse Experience Log case report form includes an item 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 002, 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 defines levels of EAE reporting that may be used in DAIDS-sponsored studies. For MTN 002 the “intensive” reporting level will be followed.

For each participant, EAE reporting is undertaken for the duration of the participant’s study participation, from enrollment up through study exit. For infants, EAE reporting is completed as applicable for any AEs identified via infant chart review for the infant’s inpatient admission period(s). Note that, just as with infant AEs, infant EAEs are to be reported using the mother’s PTID.

Study site staff must also report 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 if the study site staff become aware of the event on a passive basis (for example, through publicly-available information).

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 as AEs on Adverse Experience Log case report forms. Note that congenital anomalies/birth defects identified in infant offspring are required to be reported as EAEs. When reporting these events as AEs, make sure to include the word "infant" in the AE text (ex. infant congenital anomaly)

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

Table 11-1
Expedited Adverse Event Reporting Requirements for MTN 002

Type of Adverse Event	Intensive 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
Grade 3 suspected adverse drug reactions	Report as EAE if relationship to study product is: <ul style="list-style-type: none"> • Definitely related • Probably related • Possibly related • Probably not related

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.

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, a precise anatomical location should be included in the term or description. This is especially important in MTN 002 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 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 002 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 1.0, dated 29 August 2007, specifies that the Female Genital Grading Table for Use in Microbicide Studies (included in Protocol Appendix V) 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 002, 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 gel are related in time, and a direct association can be demonstrated.
- **Probably Related:** The AE and administration of study gel are reasonably related in time, and the AE is more likely explained by study gel than other causes.
- **Possibly Related:** The AE and administration of study gel are reasonably related in time, and the AE can be explained equally well by causes other than study gel.
- **Probably Not Related:** A potential relationship between the AE and study gel could exist (i.e., the possibility cannot be excluded), but the AE is most likely explained by causes other than study gel.
- **Not Related.** The AE is clearly explained by another cause not related to study gel.

Note: The MTN 002 study product is tenofovir gel. The applicator is not considered part of the study product.

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 002 must be followed clinically until the AE resolves (returns to baseline) or stabilizes. For data collection purposes, information recorded on AE Log case report forms is updated up through the participant's study exit visit (and not after the participant has terminated from the study – see Section 13). 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.

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”)

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 002 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 enrollment, the infection is considered a pre-existing condition: report on the Pre-Existing Conditions form.
- For HPV, genital warts present before enrollment 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 enrollment, 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 enrollment, 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 002 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 should discuss as a group what issues and problems are most likely to be encountered by participants at the 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 002 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 002 PSRT.

11.8 MTN 002 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN 002 protocol and Section 14 of the MTN Manual of Operations for a complete description of the participant safety monitoring procedures in place for MTN 002. Also refer to Section 15 of this manual for a description of the reports prepared by the MTN SDMC in support of MTN 002 safety monitoring procedures.

Participant safety is of paramount importance in MTN 002. 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 clinical 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 002 and follow up on these reports with site staff, the MTN 002 Protocol Team, and drug regulatory authorities when indicated.
- The MTN 002 Protocol Safety Review Team (PSRT) will routinely review safety data reports prepared for MTN 002 by the MTN SDMC. As described further in Section Appendix 11-2, the PSRT will meet via conference call to discuss the accumulating study safety data and any potential safety concerns.
- The MTN Study Monitoring Committee (SMC) also will periodically review MTN 002 study data with a focus on performance indicators such as participant accrual and retention, safety data, protocol adherence, intervention adherence, and data quality. 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
- SMC review summaries
- 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 002. 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 the study site IRB/EC. 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
Female Genital Grading Table for Use in Microbicide Studies

Please refer to the protocol, Appendix V, pages 83 to 83, for the "Female Genital Grading Table for Use in Microbicide Studies.

Section Appendix 11-2 MTN 002 Protocol Safety Review Team Plan

Roles and Responsibilities of the PSRT

Per the MTN 002 protocol, the roles and responsibilities of the MTN 002 Protocol Safety Review Team (PSRT) are to:

1. Conduct regular reviews of standardized study safety data reports (protocol Section 8.1). Once the SDMC begins receiving study follow-up safety data, the PSRT will convene via regularly scheduled monthly conference calls. 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. The protocol specifies a limited number of situations in which study participants must discontinue participation; Investigators will implement these discontinuations in the absence of consultation with the PSRT. In other situations, however, discontinuation or withholding of product must be undertaken in consultation with the PSRT.
3. Respond to Investigator queries regarding study eligibility and general AE management and reporting (not necessarily related to product use; protocol Section 10).
4. Respond to Investigator requests for participant withdrawal from the study (protocol Section 10).

PSRT Composition

The following comprise the MTN 002 PSRT:

- Protocol Chair, Site PI (PSRT Chair)
- MTN Safety Physician(s)
- DAIDS Medical Officer
- NICHD Medical Officer
- Protocol Statistician
- SCHARP Clinical Affairs Safety Associate

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:

- PSRT Chair
- The DAIDS Medical Officer (or designee) and
- One of the MTN 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 and SDMC (SCHARP) Project Manager also will participate in and facilitate PSRT calls and reviews. The DAIDS Program Officer(s), DAIDS PAB Protocol Pharmacist, and Pharmaceutical Co-Sponsors also may attend calls as observers.

Routine Safety Data Summary Reports: Content, Format and Frequency

The SDMC will generate and post on a designated website standard safety data reports for the PSRT 4-5 days prior to each PSRT conference call. 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 (cumulative) adverse events reported
- Listing of AEs marked as “serious” and those AEs that have been reported as EAEs

Reports will include summary information regarding the number and frequency events that meet the criteria above organized by body system (using MedDRA terms) and severity and will include information on relatedness. Each report set will consist of one set of reports listing cumulative data and with new events reported since the last distribution highlighted.

During PSRT conference calls, the DAIDS Medical Officer will summarize any additional EAE Forms received at the DAIDS Safety Office after the cut-off date for the SDMC data summary.

PSRT Communications

Initial PSRT queries from the sites will be sent directly via email to Ross Cranston, Katie Bunge and Nancy Connolly at cranstonr@dom.pitt.edu, kbunge@mail.magee.edu and nancycsc@gmail.com, respectively. All safety data summary reports from the SDMC, all query responses from the PSRT will be distributed via the MTN 002 PSRT alias list. 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 PSRT Chair or Alternate Chair has 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 PSRT Chair or Alternate Chair.

MTN 002 Protocol Safety Review Team Query Form

Page 1 of 2

Instructions: Email completed form to cranstonr@dom.pitt.edu, kbunge@mail.magee.edu and nancycsc@gmail.com.

IMPORTANT: Complete all required fields (grey boxes) 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):

Enrollment Date (dd-MMM-yy):

- Reason for query:**
- Product use consultation:
 - Should use of study gel be temporarily discontinued (held)?
 - Should use of study gel be permanently discontinued?
 - 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 gel:

- Definitely related
- Probably related
- Possibly related
- Probably not related
- Not related

Current study gel 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

MTN 002 Protocol Safety Review Team Query Form, page 2 of 2

Comments: Provide additional details relevant to this query.

End of Form for Site Staff. Email completed form to the MTN 002 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 (mvalentine@fhi.org, sjohnson@fhi.org) for assistance.

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 002.

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 and Prevention can be found at the following website:

- http://www.cdc.gov/ncidod/dhqp/bp_universal_precautions.html

Some laboratory procedures will be performed in the study site clinic or laboratory and others in the MTN Network Laboratory (NL). For samples going to any MTN NL (Pittsburgh or Johns Hopkins), please contact Pam Kunjara prior to the scheduled c-section for LDMS aliquot labels and after all samples are collected for final pick-up.

Pam Kunjara
Magee-Womens Research Institute
204 Craft Ave, Room A540
Pittsburgh, PA 15213
rsipk@mwri.magee.edu
Phone # 412-641-6393
Pager # 412-917-9343

Table 12-1 lists for each test the testing location, specimen type, specimen container and kit/method (if specified). Table 12-2 specifies blood collection by visit type and suggested volumes.

Regardless of whether tests are performed in clinic or laboratory settings, study staff that performs the tests must be trained in proper QC procedures prior to performing the tests for study purposes; training documentation should be available for inspection at any time.

Table 12-1
Overview of Laboratory Testing Locations, Specimens,
And Methods for MTN 002

Test	Testing Location	Specimen Type	Tube/Container	Kit/Method
Trichomonas Test	MTN Network Lab	Vaginal swab	InPouch TV	Network Lab Procedure
*Vaginal wet preparation	In Clinic	Vaginal fluid Swab	N/A	N/A
*Vaginal pH	In Clinic	Vaginal fluid Swab	N/A	Machary Nagel pH Strips
*Herpes culture	Local Lab	Ulcer Swab	Viral Transport Media (Must be appropriate for HSV-2)	Not specified
Urine SDA for Gonorrhea and Chlamydia	MTN Network Lab	Urine	Urine Preservation Tube (UPT)	BD Probetec/ GenProbe Aptima
Creatinine	Local Lab	Serum	Red or marble (serum separator) top tube	Not specified
AST and ALT	Local Lab	Serum	Red or marble top	Not specified
HIV antibody screen	Local Lab	Plasma	Purple (EDTA)	FDA approved rapid test
*Confirmatory Testing for HIV	Local Lab	Plasma or whole blood (<i>serum acceptable</i>)	Purple or red top tube	FDA approved Western blot test
*HBsAg	Local Lab	Serum or Plasma	Red or Purple top tube	Not specified
*RPR	Local Lab	Serum or Plasma	Red or Purple top tube	Not specified
*Confirmatory Test for Syphilis	Local Lab	Serum or Plasma	Red or Purple top tube	Not specified
Tenofovir Levels	MTN Network Lab	Serum	Red top tube	Network Lab Procedure
		Cord Blood	Red top tube	
		Amniotic Fluid	Cryovial	
		Placental Tissue	Cryovial	
		Endometrial Tissue	Cryovial	
Flow Cytometry	MTN Network Lab	Plasma	Purple top tube (EDTA)	Network Lab Procedure

*As clinically appropriate

Sites are responsible to ensure that specimen volumes 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.

Table 12-2
Scheduled Blood Collection by Visit Type and Suggested Volumes

Visit Type	Total Blood Volume (ml)	Volume By Tube Type (ml)	Purpose
Screening and Enrollment Visit	13	Red Top:10	Creatinine, ALT, AST RPR, HBsAg
		Purple Top:3	HIV-1 Antibody Test,
Gel Administration Day	34	Red Top: 4 for each time point	Tenofovir blood levels (pre-gel, 1, 2, 4, 6, 8, 12 hour time points)
		Purple Top: 3 (x2)	Flow cytometry
24 Hour Evaluation	4	Red Top: 4	Tenofovir blood Level
Unscheduled Visit	17	Red Top: 10, 4	Creatinine, ALT, AST RPR, HBsAg, Tenofovir blood Level
		Purple Top: 3	HIV-1 Antibody Test,

Notes: Additional blood may be collected for any clinically indicated testing. Red top tubes contain no additive. Lavender top tubes contain EDTA.

Ideally, one method, one type of test kit, and/or a 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 test kit must be used after study initiation, site laboratory staff must perform a validation study of the new method or test prior to implementing a change in methods. The MTN NL must be notified before implementing the change and the MTN NL can provide further guidance on validation requirements. Similarly, the MTN NL must be notified of changes to normal lab ranges.

Adherence to the specifications of this section is essential to ensure that primary and secondary endpoint data derived from laboratory testing will be considered acceptable to all regulatory authorities.

This section of the MTN 002 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. The MTN NL is available to assist in the creation of any SOPs upon request. Essential SOPs include but are not limited to:

- SOPs created by the site
 - Specimen Collection and transport
 - Chain of Custody *
 - Hematology procedures
 - Chemistry (AST, ALT, Creatinine)
 - Syphilis Serology
 - Urine
 - SDA for GC/CT
 - Dipstick
 - HIV testing
 - HBsAG
 - Herpes Culture (for sites where standard of care)

*Must be approved by the MTN NL for study activation

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. The date of specimen collection 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 provided 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: Tenofovir blood specimens, amniotic fluid, cord blood, placental tissue, and endometrial tissue.

12.3 Procedures for Specimens that can not be evaluated

When possible, specimens will be redrawn or recollected if it is found that they cannot be evaluated per site SOP's. The site will monitor specimen management problems as part of ongoing Quality Assurance. In cases where additional specimens need to be recollected due to a laboratory error (lost or broken specimen or clerical error) or a clinic error (clerical error), a protocol event form provided by the NL 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 to track the collection, storage, and shipment of five types of specimens in MTN 002: Tenofovir blood specimens, amniotic fluid, cord blood, placental tissue, and endometrial tissue.

Detailed instructions for use of LDMS are provided at: <https://www.fstrf.org/ldms> (may require a password).

The site 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. The site 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 002 may be directed to Pam Kunjara 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 area code. 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

The 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 the 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., blood 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 002 Specimens

The table below should be used as a guide when logging in 002 specimens. Please use the LDMS codes listed below 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.

Test	Primary	Additive	Derivative	Sub Add/Derv	Primary Volume	Aliquot Volume	Units
*Blood for Tenofovir levels	BLD	NON	SER	N/A	4.0	1.5	ml
Amniotic Fluid	AMN	NON	AMN	N/A	2.0-4.0	1.0-2.0	ml
Cord Blood	CRD	NON	SER	N/A	4.0	1.5	ml
Placental tissue	PLC	NON	PLC	N/A	1-2	1-2	cm
Endometrial tissue	END	NON	END	N/A	1-2	1-2	cm

**For blood Tenofovir levels, please enter time point of pre-dose using 0.00 pre-dose. All other time points use 1, 2, 4, 6, 8, or 12 hour*

**Table 12-5
Specimen Shipping Summary**

Specimen	Use LDMS?	Ship to:	Shipping schedule
Vaginal Swab for Trichomonas Culture	No	MTN Network Lab - Pittsburgh	Within 48 hours of collection
Blood for PK	Yes	MTN Network Lab – Johns Hopkins	If already processed, may be batched
Amniotic Fluid	Yes	MTN Network Lab – Johns Hopkins	If already processed, may be batch
Cord Blood	Yes	MTN Network Lab – Johns Hopkins	If already processed, may be batched
Placental tissue	Yes	MTN Network Lab – Johns Hopkins	If already processed, may be batched
Endometrial tissue	Yes	MTN Network Lab – Johns Hopkins	If already processed, may be batched
Urine for GC/CT testing	No	MTN Network Lab - Pittsburgh	Batched with Trich pouch

Note: All samples going to the MTN Network Lab – Johns Hopkins should first be sent to the MTN NL – Pittsburgh for LDMS entry and shipping. Please contact the MTN NL for specimen pick-up.

Pam Kunjara
 Magee-Womens Research Institute
 204 Craft Ave, Room A540
 Pittsburgh, PA 15213
 Phone # 412-641-6393
 Pager # 412-917-9343

12.5 Urine Testing for Urinalysis, Chlamydia and Gonorrhea

The urine tests performed at the 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 aliquotted 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, then the urine dipstick last.

Note: Testing for Chlamydia and Gonorrhea is done at screening and when clinically indicated only.

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 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 UPT for subsequent Chlamydia and Gonorrhea testing.

12.5.2 Dipstick Urinalysis

Dip the urinalysis test strip into an aliquot of urine. Perform this test according to site SOPs and the package insert. Assess and record results for blood, glucose, protein, leukocytes and nitrites. If leukocytes or nitrites are positive, perform a urine microscopy and a urine culture according to local SOP. To avoid overgrowth of bacteria, refrigerate specimen before and during transport to laboratory.

Notify the NL immediately if any kit inventory or quality control problems are identified, so that appropriate action can be taken.

12.5.3 Chlamydia and Gonorrhea Testing

Note: Testing for Chlamydia and Gonorrhea is done at screening and when clinically indicated only.

This testing will be done at the MTN NL using the BD Probe Tec Method. Sites will be required to send samples in the BD Urine Preservation Tubes (UPT). Following are collection and transport 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.

Transport instructions for urine samples to Magee-Women's Research Institute

- Fill out a shipping/tracking manifest with the information listed in the example located in appendix 12-2 (Do not use LDMS for urine specimens).
- Place the tubes in a biohazard zip-lock bag. Include manifest.
- Contact MTN NL by phone or pager for pick-up.

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Magee-Womens Research Institute
204 Craft Ave, Room A540
Pittsburgh, PA 15213
Phone # 412-641-6393
Pager # 412-917-9343

12.6 Blood Testing for HIV, Syphilis, Liver and Renal Function, Blood Tenofovir Levels, and Flow Cytometry

The blood tests performed depends 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 primary tubes with a SCHARP-provided PTID label at the time of collection. If samples are to be processed and frozen, label aliquots with LDMS aliquot labels provided by the MTN Network Lab. Contact Pam Kunjara on the day of scheduled c-section in order to have LDMS labels ready.

Pam Kunjara
Magee-Womens Research Institute
204 Craft Ave, Room A540
Pittsburgh, PA 15213
rsipk@mwri.magee.edu
Phone # 412-641-6393
Pager # 412-917-9343

After collection:

- Allow red top tubes (no additive) or marble top (serum separator tubes) to clot, then centrifuge per site SOPs to yield serum for PK levels, syphilis, liver function, and renal function testing. For blood PK levels, the sample must be processed within eight hours from collection. Please contact MTN NL for pick-up and processing. If the lab is unavailable processing may be performed on site.
- Lavender top tubes (additive = EDTA) should be gently inverted at least eight times after specimen collection to prevent clotting. EDTA tubes are used for HIV testing, and flow cytometry.

Note: If locally available tube top colors do not correspond with the tube additives specified above, use appropriate tubes based on the additives, not the listed tube top colors.

12.6.2 HIV Testing

Plasma will be tested for HIV using tests that have been validated at the study site per the Clinical Laboratory Improvement Amendment (CLIA) standards. All tests, and associated QC procedures, must be documented on local laboratory log sheets or other laboratory source documents.

HIV infection status at screening will be assessed using an FDA-approved rapid HIV test per the MTN 002 HIV testing algorithm (see appendix II in the current version of the MTN 002 protocol). If the rapid test is non-reactive, the participant will be considered HIV-uninfected. If the rapid test is reactive, 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. If the WB is positive, the participant will be considered HIV-infected. A second specimen will be drawn for confirmatory testing. If the WB is indeterminate, the site should contact the NL for further instructions.

Notify the NL immediately if any kit inventory or quality control problems are identified, so that appropriate action can be taken.

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, the second lab 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). Any RPR, MHA-TP, and/TPHA test may be used; 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 fourfold 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 002 Protocol Safety Review Team.

12.6.4 Liver and Renal Function Testing

The following tests will be performed to evaluate liver and renal function:

Liver Function

- Aspartate aminotransferase (AST)
- Alanine transaminase (ALT)

Renal Function

- Creatinine

These chemistry tests will be performed on serum.

12.6.5 Blood Tenofovir Levels

The specimens should be kept at room temperature and centrifuged as soon as possible after collection (\leq 8 hours). Contact NL for processing. If the lab is unavailable (i.e. late collection), processing can be done on site.

The whole blood will be centrifuged at 800 RCF (Relative Centrifugal Force) for 10 minutes. If red blood cells are not sufficiently separated from serum, centrifugation for an additional 5 minutes may be required. The serum will be transferred into two approximately equal portions (approximately 1.5ml each) and placed in LDMS labeled cryovials and frozen at approximately -20°C or colder.

Please contact the MTN NL for pick-up and shipping.

Pam Kunjara
Magee-Womens Research Institute
204 Craft Ave, Room A540
Pittsburgh, PA 15213
rsipk@mwri.magee.edu
Phone # 412-641-6393
Pager # 412-917-9343

One set of samples will be shipped to the MTN Network Lab in Baltimore, MD and assayed for PK levels. The other set will be retained at the MTN NL - Pittsburgh until advised by the MTN leadership group.

The shipping address is:

MTN Network Lab Pharmacology Core
Johns Hopkins University
527 Osler
600 N. Wolfe Street
Baltimore, MD 21237

12.6.6 Flow Cytometry for CD38 and HLA-DR

Two (2) EDTA purple top tubes will be collected. One will be sent along with a requisition (Appendix 12-3) via courier to the Flow Cytometry lab U Pitt, Parran Hall, Room 523 and the other will be sent to the Magee clinical lab. The Magee clinical lab will perform a CBC/Diff/platelet in order to obtain WBC and % lymphocyte values needed to calculate final CD38 and HLA-DR. EDTA whole blood is analyzed for CD38 and HLA-DR by methods defined in local SOP's.

To contact the courier for specimens going to the Flow Cytometry Lab at U Pitt, page 412-765-5075. If there is no response to the page within 10 minutes, call 412-647-8125 for further assistance.

Flow Cytometry results will be reported directly to the NL. The NL will obtain the CBC results needed to complete the calculations for Flow Cytometry and submit final results to the clinic on CRF. It is the clinic's responsibility to datafax the results to SCHARP once they have been completed and received.

12.7 Testing of Vaginal 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.

12.7.1 Vaginal pH

When clinically indicated vaginal pH will be assessed as part of on-site evaluations for bacterial vaginosis. Indicator Strips (pH range 3.6 to 6.1) must be used as follows:

- During pelvic examination, collect vaginal fluids using a swab. Dab the vaginal fluids from the swab onto the pH strip.
- 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

When clinically indicated wet mount will be performed. 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 12-6.

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: rsilkr@mwri.magee.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 applicable clinical or laboratory staff is hired, so that appropriate training can take place prior to such staff performing wet mounts for study purposes.

Table 12-6
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 cover slip. 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 percent of the observed epithelial cells in order 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 *Trichomonas* Testing

The InPouch TV is a self-contained system for the detection of *Trichomonas vaginalis*. Prepare vaginal swab as follows:

- To avoid fluid leakage, squeeze the fluid from the top of the InPouch downward toward the bottom of the chamber.
- Tear off the plastic above the white closure.
- To admit the cotton swab, open the InPouch by pulling the closure tape's middle tabs apart.
- Milk the swab between the InPouch walls. Remove the swab and discard.
- Squeeze the top closed, roll top of upper chamber down one complete roll, pushing the medium into the bottom chamber, and fold the tabs over to prevent the InPouch from reopening.
- Fill in patient information and place patient label over the blue BioMed label – not on the viewing chamber.
- Store inoculated pouch upright for up to 48 hours at room temperature. **DO NOT REFRIGERATE!** If held longer than 48 hours, incubation at 37°C is required.
- Contact MTN NL by phone 412-641-6393 or pager 412-917-9343 for pick-up. MTN NL will process the inoculated pouches according to laboratory protocol.

Transport instructions for InPouch TV samples to Magee-Women's Research Institute

- Fill out a shipping/tracking manifest with the information listed in the example located in appendix 12-2 (Do not use LDMS for InPouch TV samples).
- Place the pouch in a biohazard zip-lock bag. Include manifest.
- Contact MTN NL by phone or pager for pick-up.

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204 Craft Ave, Room A540
Pittsburgh, PA 15213
Phone # 412-641-6393
Pager # 412-917-9343

12.7.4 *HSV-2 Culture*

When clinically indicated, HSV-2 culture will be performed. This testing should be done per local site standards. The specimens may be batched and tested at the end of the study unless results are needed for clinical management.

12.8 Testing of Specimens Collected during or after Cesarean Section (Cord Blood, Amniotic Fluid, Placental Tissue, and Endometrial Tissue)

Each of the following specimens will be tested for Tenofovir levels and should be collected, processed, and stored accordingly. Once processed, contact the MTN Network Lab for pick-up and shipment to the MTN Pharmacology Core.

12.8.1 *PK levels in Cord Blood*

Cord blood should be drawn in red top (no preservative) tubes and processed within one hour of collection. Processing can be performed on site if the lab is unavailable within one hour of collection.

The cord blood will be centrifuged at 800 RCF (Relative Centrifugal Force) for 10 minutes. If red blood cells are not sufficiently separated from serum, centrifugation for a further 5 minutes may be required. The serum will be transferred into two approximately equal portions (approximately 1.5ml each) and placed in LDMS labeled cryovials and frozen at approximately -20°C or colder.

12.8.2 PK Levels in Amniotic Fluid

Amniotic fluid will be collected according to surgical procedures and standards. Collect 2-4mls of amniotic fluid and dispense into two (2) cryovials at approximately 1-2mls each. Label each cryovial with the appropriate LDMS aliquot label and freeze at -20°C or lower.

12.8.3 Endometrial and Placental Tissue Biopsy for PK levels

Endometrial and placental tissue biopsies will be collected according to surgical procedures and standards. Two (2) biopsies measuring at least 1cm from each tissue must be collected. Place each 1cm biopsy specimen into a cryovial with no additive and label using the appropriate LDMS aliquot label. Place the cryovials on ice and freeze at -70°C.

12.8.4 Shipping of Specimens for Tenofovir Levels

Contact the MTN Network lab for pick-up and shipment to the MTN Pharmacology Core. Track the specimen in LDMS.

Pam Kunjara
Magee-Womens Research Institute
204 Craft Ave, Room A540
Pittsburgh, PA 15213
rsipk@mwri.magee.edu
Phone # 412-641-6393
Pager # 412-917-9343

One set of samples will be shipped to the MTN Network Lab in Baltimore, MD and assayed for Tenofovir levels. The other set will be retained at the MTN NL - Pittsburgh until advised by the MTN leadership group.

The shipping address is:

MTN Network Lab Pharmacology Core
Johns Hopkins University
527 Osler
600 N. Wolfe Street
Baltimore, MD 21237

Appendix 12-1
Maternal PK- LDMS Specimen Tracking Sheet

Participant ID			Visit Code		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Site Number	Participant Number	Chk			
PK SPECIMEN TIME POINT	PRIMARY SPECIMEN TYPE	DATE COLLECTED dd- MMM -yy	TIME COLLECTED hh:mm <i>24-hr clock</i>	NUMBER OF TUBES COLLECTED	INSTRUCTIONS FOR PROCESSING LAB
Pre-Gel	Maternal Blood (BLD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER
1 Hour	Maternal Blood (BLD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER.
2 Hour	Maternal Blood (BLD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER
4 Hour	Maternal Blood (BLD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER
6 Hour	Maternal Blood (BLD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER
8 Hour	Maternal Blood (BLD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER
12 Hour	Maternal Blood (BLD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER
24 Hour	Maternal Blood (BLD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER Enter into LDMS with Visit Code 03.0

C-section- LDMS Specimen Tracking Sheet

Participant ID			Visit Code	
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Site Number	Participant Number	Chk		

PRIMARY SPECIMEN TYPE	DATE COLLECTED dd-MMM-yy	TIME COLLECTED hh:mm <i>24-hr clock</i>	NUMBER OF TUBES/VIALS COLLECTED	INSTRUCTIONS FOR PROCESSING LAB
Amniotic Fluid (AMN)			<input type="checkbox"/> NON (no additive)	Freeze immediately after collection. Store with derivative AMN
Cord Blood (CRD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER
Placental Tissue (PLC)			<input type="checkbox"/> NON (no additive)	Freeze immediately after collection.
Endometrial Tissue (END)			<input type="checkbox"/> NON (no additive)	Freeze immediately after collection.

Appendix 12-2: Sample Shipping/Tracking Manifest for GC/CT and Trich Pouch

MTN 002

Site:

**Contact person: (fill in)
(Fill in address)**

Phone number:

Fax number:

E-mail address:

Shipment/Transport Date _____

Specimen type: check appropriate column

PTID	Collection Date	Visit Code	Specimen Type	
			Urine (UPT) for GC/CT testing	Vaginal swab (InPouch) for Trich Test

Comments _____

<p>Contact for pick-up Pam Kunjara Magee-Womens Research Institute 204 Craft Ave. Room A540 Pittsburgh, Pa. 15213 Office 412-641-6393 Pager 412-917-9343 rsipk@mwri.magee.edu</p>

Appendix 12-3: Sample Shipping/Tracking Manifest for Flow Cytometry

<p><i>GSPH Specimen Routing Record</i> TEST: _____ #TUBES/TYPE: _____</p> <p><input type="checkbox"/> Flow cytometry _____</p> <p><input type="checkbox"/> Other _____</p> <p>Special Handling : _____</p>	<p>MTN Studies</p> <p>Date: _____ Time: _____ <small>24 hour clock</small></p> <p>PTID: _____</p> <p>Study : _____ Week/Day: _____ _____ _____</p> <p>Study ID: _____ Step: _____ _____ _____</p>
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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 002 case report forms. For questions about this section or about general data collection policies, procedures, or materials, please contact Missy Cianciola <missy@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, USA, and is in the US Pacific Coast time zone. The SCHARP MTN 002 team members, along with their job role and email address, are listed below.

<u>Role on MTN 002</u>	<u>Name</u>	<u>E-mail address</u>
Protocol Statistician	Ben Masse	ben@scharp.org
Project Manager:	Missy Cianciola	missy@scharp.org
Statistical Research Associate:	Karisse Roman	karisse@scharp.org
Protocol Programmer:	Julie Zhou	yzhuo@scharp.org
Data Coordinator:	Suzanne Cullers	scullers@scharp.org
Document Specialist:	Stacie Kentop	stacie@scharp.org
Reporting Programmer	Kate Bader	kate@scharp.org
Laboratory Programmer:	Laura Robins-Morris	lrobins@scharp.org
Clinical Affairs Safety Associate	Molly Swenson	mollys@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 email <datafax@scharp.org>).

SCHARP's Information Technology (IT) group is available to consult with the site to determine the best method for data transmission. The SCHARP IT group can be contacted via e-mail <support@scharp.org>. The SCHARP IT 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 re-fax 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

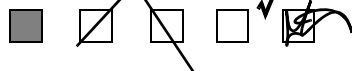
Based on the use of fax technology and Good Clinical Practices (GCPs), the following guidelines should be used for completing DataFax CRFs:

- 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.

Mark only one response box for each item unless the “Mark all that apply” instruction is present.

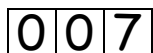
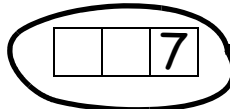
Correct:**Incorrect:**

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:

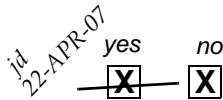
- draw a single horizontal line through the incorrect entry (do not obscure the entry or make it unreadable with multiple cross-outs),
- place the correct or clarified answer near the box, and

- initial and date the correction as shown below:



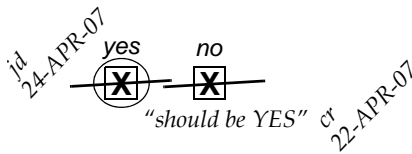
If an **X** is marked in the wrong response box, correct it by doing the following:

- 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:

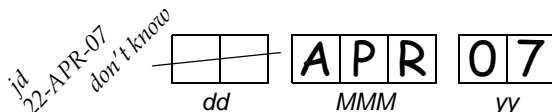


The standards above must **always** be followed whenever a CRF is changed, clarified, or amended, even if the change is made **before** the CRF is faxed to SCHARP for the first time.

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 002 Study-Specific Data Collection Information

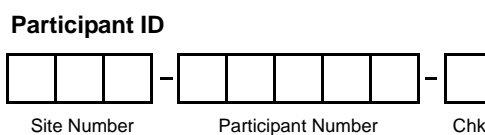
13.3.1 Participant ID numbers (PTIDs)

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 enroll. 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 002.



13.3.2 Study Visit Timing

Screening and Enrollment

The screening and enrollment visit will occur approximately one to four weeks prior to the participant’s scheduled cesarean section (C/S), but no more than four weeks before the expected date of cesarean section.

For MTN 002, a participant is considered enrolled once it has been determined that she is eligible for the study as based on all available screening data. Participants will be considered enrollment into MTN 002 on the same day as the screening and enrollment visit.

If screening laboratory data is received after the screening and enrollment visit, and the laboratory data indicate the participant is not eligible, the site will contact the PSRT to request termination of the participant. If the termination is approved, the site will contact SCHARP for instructions on how to complete case report forms for the termination.

Follow-Up Visits

There are 3 required follow-up visits for this study: the Pharmacokinetic Measures/Gel Administration Day (Day 0) visit, the 24 Hour Evaluation, and the Two Week Phone Call. Per protocol, the 24 Hour Evaluating visit should be completed within between 22 and 26 hours following product administration, and the Two Week Phone Call visit should be completed within Day 10 and 18 following product administration. If these visits are not completed within these allowable time frames (visit windows), the visit is considered “missed.” A Missed Visit case report form is completed and faxed to SCHARP to document that the visit was missed.

Unscheduled (“Interim”) Visits

For this study, an unscheduled clinic visit is considered an “interim visit” when a participant presents at the site for additional clinical/laboratory assessments and/or procedures. An unscheduled/interim visit may occur at any time during study participation, and may be triggered by participant report of a new adverse event occurring between required study visits (i.e., onset of a new adverse experience (AE) between the 24 Hour Evaluation and Two Week Phone Call required visits).

Phone contact with a participant is also considered an unscheduled/interim visit if the phone contact results in reporting of a new AE.

Unscheduled/interim visits where DataFax CRF data are collected are assigned an interim visit code as described in section 13.3.3. The interim visit is documented using the Interim Visit case report form.

It is anticipated that there will be very few interim visits for this study. As such, detailed instructions for CRF completion for interim visits is not provided. For questions about assignment of visit codes and completion of case report forms for interim visits, please contact the SCHARP MTN 002 Project Manager.

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 002 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 visit type, timing, and DataFax visit codes for each visit.

Table 13-1: Visit Timing and Visit Codes

Visit Type	Visit Timing	Visit Code
Screening and Enrollment	Up to Day -28	01.0
Pharmacokinetic Measures/Gel Administration Day	Day 0	02.0
24 Hour Evaluation	Hour 22-26	03.0
Two-Week Phone Call	Day 10 to 18	04.0

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 she has completed her 24 Hour Evaluation visit (Visit Code = 03.0). The visit window of her Two Week Phone Call visit has not yet opened. For this interim visit, record the following 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 Form Completion Schedule

The SCHARP-provided 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 13-2) lists the DataFax and non-DataFax forms that are required to be completed at each study visit.

Table 13-2: MTN 002 Form Completion Schedule

SCREENING AND ENROLLMENT (Up to Day -28)		VISIT CODE: 01.0
Acronym	Form Name	
ENR-1	Enrollment	
DEM-1	Demographics	
PE-1	Pelvic Exam	
Non-DataFax	Pelvic Exam Diagrams	
PRE-1	Pre-existing Conditions	
CM-1	Concomitant Medications Log	
Non-DataFax	Study Eligibility	
Non-DataFax	Targeted Physical Exam	
PHARMACOKINETIC MEASURES: GEL ADMINISTRATION DAY (Day 0)		VISIT CODE: 02.0
Acronym	Form Name	
SV-1	MTN 002 Study Visit	
PK-1	Pharmacokinetics	
PE-1	Pelvic Exam	
Non-DataFax	Pelvic Exam Diagrams	
Non-DataFax	Targeted Physical Exam	
CDI-1	C-section Delivery Information	
FC-1	Flow Cytometry	
Non-DataFax	MTN 002 Maternal PK LDMS Specimen Tracking Sheet	
Non-DataFax	MTN 002 C-section LDMS Specimen Tracking Sheet	
24 HOUR EVALUATION (Hour 22 – 26)		VISIT CODE: 03.0
Acronym	Form Name	
SV-1	MTN 002 Study Visit	
TWO WEEK PHONE CALL (Day 10 to 18)		VISIT CODE: 04.0
Acronym	Form Name	
SV-1	MTN 002 Study Visit	
PER-1	Participant Evaluability and Replacement	
ESI-1	End of Study Inventory	
TM-1	Termination	
IF NEEDED		WILL VARY
Acronym	Form Name	
AE-1	Adverse Experience Log	
MV-1	Missed Visit	
IV-1	Interim Visit	

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 002 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 002 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 002 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

Prior to site activation, SCHARP will provide the site with 18 MTN 002 study participant notebooks. Each notebook contains a tabbed section for each of the 4 study visits. Each section contains all required CRFs for that visit. In addition, a tab for Adverse Experience Log forms is provided a, along with a tab for Concomitant Medication Log forms. SCHARP will also provide the site with bulk supplies of “if needed” CRFs, such as Interim Visit and Missed Visit CRFs.

In the case where a study notebook is assigned to a participant who does not enroll in the study (for example, the Screening and Enrollment visit is started, but the participant is found to be ineligible for the study), please contact the SCHARP MTN 002 Project Manager so that SCHARP can provide you with additional Screening and Enrollment Visit CRFs. Also, please contact the SCHARP MTN 002 Project Manager if any additional CRF supplies are needed for the study.

SCHARP is supplying the site with pre-printed specimen labels to be used on all primary specimen collection containers. One sheet for each PTID is provided, the sheet containing all of the labels needed for the duration of the participant’s study participation (including PK specimens). Please refer to the Laboratory section of the manual for more information on laboratory specimen collection and labeling.

13.5 Case Report Forms and Form-specific Completion Instructions

This section contains each MTN 002 case report forms developed for the study. On the back of each case report form are form-specific completion instructions. 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 the items listed in the form-specific completion instructions, but rather, only those items needing detailed explanation.

Use the Visit Checklist developed for the visit for a suggested order in which the forms should be completed at each visit.

Below are some additional instructions for the **Pre-existing Conditions, Concomitant Medications Log, and Adverse Experience Log** case report forms.

- 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.
- 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 resolves (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 refax the form 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).
- Note that for item 3 of the **Adverse Experience Log** form, the Female Genital Grading Table for Use in Microbicide Studies (Female Genital Tox Table) will be used to assign severity grades to AEs (in addition to the DAIDS Tox Table referred to in the form completion instructions. The Female Genital Tox Table is Appendix V of the protocol (the “protocol Specific Toxicity Table).
- There may be a situation where an AE reported on an **Adverse Experience Log** form needs to be deleted (in the case where the AE is later found to actually be a pre-existing condition, for example). If you have a situation where you need to mark for delete an AE Log form, please contact the MTN 002 Project Manager for instructions.
- On the **Adverse Experience Log** form, 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.

SAMPLE *Do NOT FAX*
TO DATAFAX



MTN 002 (147)

DEM-1 (001)

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	

Demographics

Visit Date

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
dd		MMM		yy	

1. What is the participant's date of birth?..... → If unknown, record age:
dd MMM yy years

male female

2. What is the participant's gender?

3. Does the participant consider herself to be Latina or of Hispanic origin?
yes no

4. What does the participant report as her race? *Mark all that apply.*

- 4a. American Indian or Alaskan Native
- 4b. Asian
- 4c. Black or African American
- 4d. Native Hawaiian or other Pacific Islander
- 4e. White
- 4f. other, specify: _____
(Note: Latina is not a race.)

Demographics (DEM-1)

Purpose: To document participant demographic information.

General Information/Instructions: This form is completed only once for each study participant, at the Screening/Enrollment visit.

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 participant's estimate of their age. Do not complete both answers.
- **Item 2:** This item does not require a response. This item (gender) has been hard-coded as "female" for all study participants.
- **Item 4:** Record the participant's race based on self-definition. In the case of mixed race, mark all that apply and/or "other" and indicate the mixed race background.

SAMPLE *Do NOT FAX*
TO DATAFAX



MTN 002 (147)

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 study informed consent signed or marked:

<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		

2. Is the participant eligible, based on assessment of all study inclusion and exclusion criteria?

yes

no

→ **If no, participant is not eligible.
End of form. Do not fax to
SCHARP DataFax.**

2a. Date of enrollment:

<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		

Comments: _____

Enrollment (ENR-1)

Purpose: This form is used to document participant enrollment into the study.

General Information/Instructions: This form is completed only once for each participant, at the Screening/Enrollment visit.

Item-specific Instructions:

- **Item 2a:** The date the participant was determined to be eligible for the study.

SAMPLE. Do NOT FAX
TO DATAFAX



Visit Code .

1

MTN 002 (147)

PE-1 (141)

Page 1 of 1

Participant ID

- -
Site Number Participant Number Chk

Pelvic Exam

Exam Date

/ /
dd MMM yy

1. Pelvic exam assessment: *not done* *abnormal findings* *no abnormal findings* → **If no abnormal findings, end of form.**
→ **If not done, comment below. End of form.**

1a. Abnormal findings: *Mark all that apply.*

<input type="checkbox"/> enlarged/tender inguinal lymph nodes	<input type="checkbox"/> erythema	<input type="checkbox"/> abnormal cysts
<input type="checkbox"/> abnormal vaginal discharge	<input type="checkbox"/> ulceration	<input type="checkbox"/> grossly white finding
<input type="checkbox"/> abnormal cervical discharge	<input type="checkbox"/> laceration	<input type="checkbox"/> mass
<input type="checkbox"/> blood-tinged discharge	<input type="checkbox"/> abrasion	<input type="checkbox"/> warts
<input type="checkbox"/> blood in vagina—no identified source	<input type="checkbox"/> peeling	<input type="checkbox"/> adnexal tenderness
<input type="checkbox"/> blood from cervical os	<input type="checkbox"/> petechia	<input type="checkbox"/> cervical motion tenderness
<input type="checkbox"/> bleeding from site of epithelial disruption	<input type="checkbox"/> ecchymosis	<input type="checkbox"/> uterine tenderness
	<input type="checkbox"/> vesicles	<input type="checkbox"/> other abnormal findings, specify: _____
	<input type="checkbox"/> edema	

If any are abnormal and ongoing at Enrollment, record findings on Pre-existing Conditions form. If abnormal during follow-up, update or complete Adverse Experience Log when applicable.

Comments: _____

Pelvic Exam (PE-1)

Purpose: To document pelvic exams conducted during the study.

General Information/Instructions: This form is completed each time a pelvic exam is performed.

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.

SAMPLE. DO NOT FAX
TO DATAFAX

MTN 002 (147)



CDI-1 (080)

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	

C-section/Delivery Information

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. Infant gestational age: *weeks*
dd *MMM* *yy* *hr* *min*
2. Skin incision: :
3. Infant delivery: :
4. Infant birth weight: *grams*
5. APGAR score at 1 minute:
6. APGAR score at 5 minutes:
7. APGAR score at 10 minutes: *not done*
8. Infant gender: *male* *female*

Comments: _____

C-section/Delivery Information (CDI-1)

Purpose: To document C-section/delivery details and information on infant status.

General Information/Instructions: This form is completed once for each study participant, when the delivery and infant information is available.

Item-specific Instructions:

- **Item 1:** Record infant gestational age in completed weeks.
- **Items 2 and 3:** When recording time, use a 24-hour clock (e.g., 8:12 p.m. is recorded as 20:12).

SAMPLE *Do NOT FAX*
TO DATAFAX

MTN 002 (147)



SV-1 (075)

Visit Code

.

Participant ID

- -
Site Number Participant Number Chk

MTN 002 Study Visit

Visit Date

dd MMM yy

1. Were any **new** adverse experiences reported at this visit? *yes* *no* → **If no, end of form.**

1a. How many **new** AE Log pages were completed for this visit? # of pages

Comments: _____

MTN 002 Study Visit (SV-1)

Purpose: To document the completion of the required Pharmacokinetic Measures/Gel Administration Day, 24-hour, and Two-week Phone Call visits and whether any new adverse experiences were reported.

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.
- **Item 1:** 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 **1a** 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 11 of these two AE Log pages should be the same as the Visit Code recorded on this form.

SAMPLE: Do NOT FAX TO DATAFAX



Visit Code

0

1

MTN 002 (147)

PK-1 (061)

Participant ID

Site Number - Participant Number - Chk

Pharmacokinetics

Visit Date

dd MMM yy

- 1. Participant height: ... cm
2. Participant weight: ... kg

MATERNAL BLOOD COLLECTION AND GEL ADMINISTRATION

Table with columns for Not done/Not collected, time (dd, MMM, yy, hr, min) and rows for blood draws at 3, 4, 5, 6, 7, 8, 9, 10, 11 hours.

STORED SPECIMEN COLLECTION

Table with columns for Not done/Not collected, time (dd, MMM, yy, hr, min) and rows for Amniotic fluid, Cord blood, Placental tissue, Endometrial tissue.

Comments:

10-DEC-07

01

Language

Staff Initials / Date

Pharmacokinetics (PK-1)

Purpose: To document pharmacokinetics and stored specimen collection as well as study gel administration information.

General Information/Instructions: This form is completed once for each study participant, at the Pharmacokinetic Measures/Gel Administration visit (Day 0).

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.
- **Items 1 and 2:** Use leading zeros when needed.
- **Items 3–15:** When recording time, use a 24-hour clock (e.g., 8:12 p.m. is recorded as 20:12). If any of the specimens/procedures listed in items 3–15 were not collected or performed (or collected and not stored for items 12–15), mark the “Not done/Not collected” box and record the reason in the comments section at the bottom of the form.
- **Item 11:** Note that the 24-hour post-gel blood draw, which is technically part of the 24-hour Evaluation visit, appears on this form, which is completed at the Pharmacokinetic Measures/Gel Administration visit (Day 0). The 24-hour post-gel blood draw has been included here in order to have complete PK data on one form.

SAMPLE *DO NOT FAX*
TO DATAFAX

MTN 002 (147)



FC-1 (064)

Visit Code .

Participant ID

- -
Site Number Participant Number Chk

Flow Cytometry

Initial Specimen Collection Date

dd MMM yy

Alternate Collection Date
dd MMM yy

1. FLOW CYTOMETRY

Not done/ Not collected
1a. Lymphocytes %
%

Absolute Count
cells/mm³

Not done/ Not collected
1b. CD4 (CD3/CD4) AND *MFI*
 1c. CD38 (CD3/CD4/CD38) . AND AND
 1d. CD95 (CD3/CD4/CD95) . AND AND

Comments: _____

Flow Cytometry (FC-1)

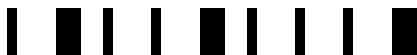
Purpose: To document flow cytometry laboratory results.

General Information/Instructions: This form is completed once for each study participant, at the Pharmacokinetic Measures/Gel Administration Visit (Day 0).

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.

SAMPLE *DO NOT FAX*
TO DATAFAX



MTN 002 (147)

PER-1 (145)

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 Evaluability and Replacement

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"/>
dd		MMM			yy		

1. Is this participant evaluable? That is, did she receive study gel and have a Cesarean delivery within 8 hours of gel administration? yes no

└─▶ **If yes, end of form.**

2. Why is this participant not evaluable?

- she did not receive study gel
- she received study gel but her time of Cesarean delivery was greater than 8 hours following the time of gel administration
- other, specify: _____

3. Will this participant be replaced? yes no

Comments: _____

Participant Evaluability and Replacement (PER-1)

Purpose: To document whether the participant was evaluable based on study criteria and, if not, whether she was replaced.

General Information/Instructions: This form is completed once for each enrolled study participant, and is completed once it is determined if the participant is evaluable.

Item-specific Instructions:

- **Item 1:** Mark “yes” if the participant met both criteria listed in item 1. If the participant met only one or neither of the criteria in item 1, mark the “no” box.
- **Item 2:** Mark the reason the participant is not evaluable. If the “other, specify” box is marked, specify the reason the participant is not evaluable in the space provided.
- **Item 3:** If item 3 is “no,” record the reason the non-evaluable participant will not be replaced in the comments field at the bottom of the form.

SAMPLE *Do NOT FAX TO DATAFAX*

Not a DataFax form. Do not fax to DataFax.

MTN 002 (147)

Participant ID

Site Number			Participant Number						Chk	

Study Eligibility

Form Completion Date

<i>dd</i>		<i>MMM</i>		<i>yy</i>	

- | | | |
|--|--------------------------|--------------------------|
| | <i>yes</i> | <i>no</i> |
| 1. Is the participant age 18–45 years at screening and enrollment, inclusive, and verified per site standard operating procedure (SOP)? | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Is the participant willing and able to provide written informed consent for screening and enrollment? | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Is the participant in general good health as determined by the site Investigator of Record (IoR) or designee at the Screening and Enrollment Visit? | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Is the participant HIV-uninfected (per HIV Testing Algorithm, Appendix II)? | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. Is the participant HBsAg negative at the Screening and Enrollment Visit, or documented negative during this pregnancy? | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Is the participant pregnant with the following characteristics: | <i>yes</i> | <i>no</i> |
| 6a. viable? | <input type="checkbox"/> | <input type="checkbox"/> |
| 6b. singleton? | <input type="checkbox"/> | <input type="checkbox"/> |
| 6c. without ultrasound evidence of significant fetal congenital anomaly (in the opinion of the IoR or designee)? | <input type="checkbox"/> | <input type="checkbox"/> |
| 6d. term (37 0/7 to 41 6/7 weeks, inclusive, with gestational dating criteria per SOP) at the time of planned cesarean section? | <input type="checkbox"/> | <input type="checkbox"/> |
| 6e. planned cesarean section? | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. Does the participant have a normal pap (or completed evaluation of abnormal Pap) in the 12 calendar months prior to screening per SOP? | <i>yes</i> | <i>no</i> |
| | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. Is the participant willing to: | <i>yes</i> | <i>no</i> |
| 8a. abstain from vaginal sex, anal sex, and receptive oral sex for at least 2 weeks after gel placement? | <input type="checkbox"/> | <input type="checkbox"/> |
| 8b. abstain from intravaginal practices (including douching) during study participation? | <input type="checkbox"/> | <input type="checkbox"/> |
| 8c. not participate in other drug or device study during study participation? | <input type="checkbox"/> | <input type="checkbox"/> |
| 8d. participate as required by protocol, including study product administration, assessments and follow-up schedule? | <input type="checkbox"/> | <input type="checkbox"/> |

If no to any, participant is ineligible.

Study Eligibility – Page 1 of 2 (nonDF)

Purpose: This form is used to document participant eligibility for the MTN 002 study.

General Information/Instructions: This form is completed only once for each participant, at the Screening/ Enrollment visit. Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

SAMPLE *DO NOT FAX TO DATAFAX*

Not a DataFax form. Do not fax to DataFax.

MTN 002 (147)

Participant ID

Site Number			Participant Number						Chk	

Study Eligibility

- | | yes | no |
|---|--------------------------|--------------------------|
| 9. Does the participant have a maternal or fetal condition that necessitates urgent cesarean section (e.g., active labor, non-reassuring fetal heart tracing)? | <input type="checkbox"/> | <input type="checkbox"/> |
| 10. Does the participant have documented rupture of the amniotic membranes, as defined in the SOP? | <input type="checkbox"/> | <input type="checkbox"/> |
| 11. Does the participant have known maternal disease with predictable negative affect on placental function (e.g., hypertension, diabetes mellitus, collagen vascular disease, clinically significant maternal anemia)? | <input type="checkbox"/> | <input type="checkbox"/> |
| 12. Does the participant have known placental/fetal abnormalities that could affect placental transfer (e.g., placental abruption, placenta previa, placenta accreta, intrauterine growth restriction, two vessel cord, etc.)? | <input type="checkbox"/> | <input type="checkbox"/> |
| 13. Is the participant's serum creatinine at Screening and Enrollment Visit greater than 1.0 mg/dL? | <input type="checkbox"/> | <input type="checkbox"/> |
| 14. Is the participant's AST and/or ALT at screening greater than 1.5 ULN (upper limit of normal)? | <input type="checkbox"/> | <input type="checkbox"/> |
| 15. Does the participant have current or recent (within 48 hours) use of vaginal medications at the Screening and Enrollment visit (per participant report)? | <input type="checkbox"/> | <input type="checkbox"/> |
| 16. Does the participant currently have an untreated sexually transmitted infection or (as applicable) exposure to partner's infection, including chlamydia, gonorrhea, trichomoniasis, non-gonococcal urethritis? | <input type="checkbox"/> | <input type="checkbox"/> |
| 17. Does the participant have symptomatic vaginitis, including bacterial vaginosis and vulvovaginal candidiasis? | <input type="checkbox"/> | <input type="checkbox"/> |
| 18. Is the participant known to have participated in any other investigational drug or device trial within 30 days prior to enrollment visit? | <input type="checkbox"/> | <input type="checkbox"/> |
| 19. At screening or enrollment, does the participant have 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? | <input type="checkbox"/> | <input type="checkbox"/> |
| 20. Does the participant have previously demonstrated hypersensitivity to any components of tenofovir 1% gel? | <input type="checkbox"/> | <input type="checkbox"/> |

If yes to any, participant is ineligible. ←

Study Eligibility – Page 2 of 2 (nonDF)

Item-specific Instructions:

- **Items 13 and 14:** Complete these items once the laboratory results are available. If these items are completed after the “Form Completion Date” recorded on page 1, be sure to initial and date these entries.
- **Item 16:** Per protocol, women diagnosed with an STI during screening or in the process of enrollment are eligible for enrollment once they have completed treatment(s) and are asymptomatic for the STI(s). If the participant is diagnosed with an STI during screening or enrollment, this item should originally be marked “yes.” Once treatment is completed and the participant is asymptomatic, this item should be updated to “no.”

SAMPLE *Do NOT FAX TO DATAFAX*

Not a DataFax form. Do not fax to DataFax.

MTN 002 (147)

Participant ID

Site Number			Participant Number						Chk	

Targeted Physical Exam

Exam Date

dd		MMM		yy	

VITAL SIGNS

1. Were vital signs done? *yes* *no*
 → **If no, specify:** _____

Oral Temp . °C

BP / mmHg

Pulse 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 any are abnormal and ongoing at Enrollment, record findings on Pre-existing Conditions form. If abnormal during follow-up, update or complete Adverse Experience Log when applicable.**

Findings: Staff Initials / Date

10-DEC-07

Language

Targeted Physical Exam (non-DataFax)

Purpose: To document the participant's vital signs and targeted physical exam findings.

General Information/Instructions: This form is completed each time a targeted physical exam is performed. Because this is a non-DataFax form, do NOT fax to SCHARP DataFax.

Item-specific Instructions:

- **Vital Signs:** 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 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 items 13–15 as “not evaluated.”

SAMPLE *Do NOT FAX TO DATAFAX*

Not a DataFax form. Do not fax to DataFax.

MTN 002 (147)

Participant ID

- -

Site Number Participant Number Chk

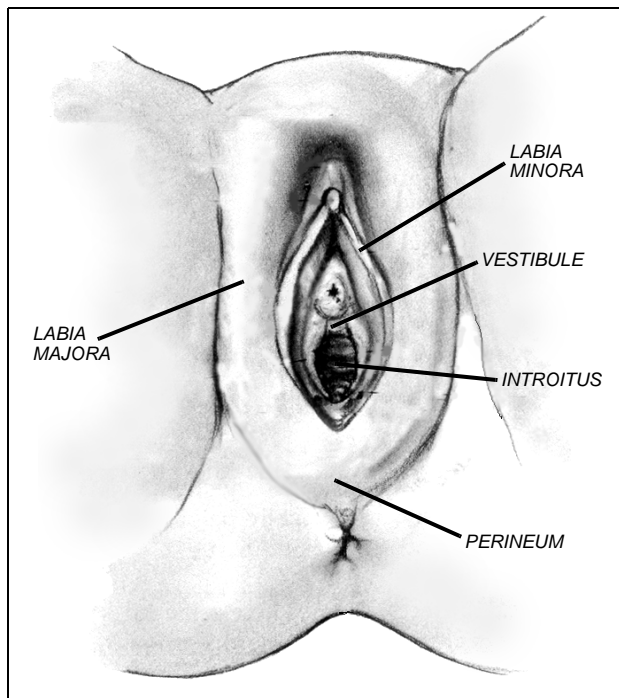
Pelvic Exam Diagrams

no normal variants or abnormal findings observed

Exam Date

dd MMM yy

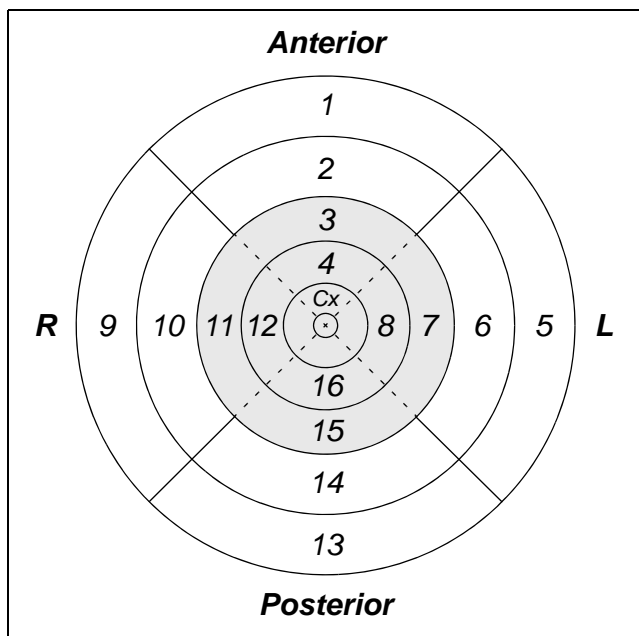
External Genitalia



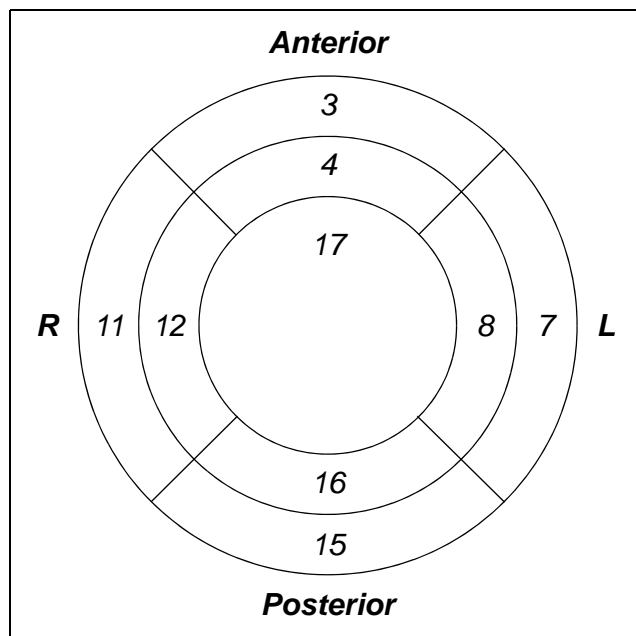
Legend for Vagina/Cervix

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



10-DEC-07

01

Language

Staff Initials / Date

Pelvic Exam Diagrams (non-DataFax)

Purpose: To document all variants of normal and all abnormal findings observed during study pelvic exams.

General Information/Instructions: This form is completed each time a pelvic exam is performed. Because this is a non-DataFax form, do NOT fax to SCHARP DataFax.

Item-specific Instructions:

- All variants of normal (normal findings) and all abnormal findings must be documented on this form. 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).

SAMPLE. Do NOT FAX
TO DATAFAX



Note: Number pages sequentially (01, 02, 03) for each participant.

MTN 002 (147)

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"/> |
| Comments | Is condition ongoing? <i>yes</i> <i>no</i>
<input type="checkbox"/> <input type="checkbox"/> | _____
<small>Staff Initials / Date</small> |
- | | | |
|-----------------------|--|---|
| 2. Description | <i>MMM</i> <i>yy</i> | Date of Diagnosis/ Surgery <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> |
| Comments | Is condition ongoing? <i>yes</i> <i>no</i>
<input type="checkbox"/> <input type="checkbox"/> | _____
<small>Staff Initials / Date</small> |
- | | | |
|-----------------------|--|---|
| 3. Description | <i>MMM</i> <i>yy</i> | Date of Diagnosis/ Surgery <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> |
| Comments | Is condition ongoing? <i>yes</i> <i>no</i>
<input type="checkbox"/> <input type="checkbox"/> | _____
<small>Staff Initials / Date</small> |
- | | | |
|-----------------------|--|---|
| 4. Description | <i>MMM</i> <i>yy</i> | Date of Diagnosis/ Surgery <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> |
| Comments | Is condition ongoing? <i>yes</i> <i>no</i>
<input type="checkbox"/> <input type="checkbox"/> | _____
<small>Staff Initials / Date</small> |
- | | | |
|-----------------------|--|---|
| 5. Description | <i>MMM</i> <i>yy</i> | Date of Diagnosis/ Surgery <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> |
| Comments | Is condition ongoing? <i>yes</i> <i>no</i>
<input type="checkbox"/> <input type="checkbox"/> | _____
<small>Staff Initials / Date</small> |
- | | | |
|-----------------------|--|---|
| 6. Description | <i>MMM</i> <i>yy</i> | Date of Diagnosis/ Surgery <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> |
| Comments | Is condition ongoing? <i>yes</i> <i>no</i>
<input type="checkbox"/> <input type="checkbox"/> | _____
<small>Staff Initials / Date</small> |

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



Note: Number pages sequentially (001, 002, 003) for each participant.

Page [][] [][] [][]

MTN 002 (147)

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

4. Relationship to Study Product

5. Study Product Administration

- Grade 1 - Mild
- Grade 2 - Moderate
- Grade 3 - Severe
- Grade 4 - Life-threatening
- Grade 5 - Death

- Definitely related
- Probably related
- Possibly related
- Probably not related
- Not related

- No change
- Held
- Permanently discontinued
- N/A

Record reason why AE is "not related" in Comments below.

6. Status/Outcome

7. Treatment Mark "None" or all that apply.

- 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

- None
- Medication(s) Report on Concomitant Medications Log.
- New/Prolonged hospitalization Comment below.
- Procedure/Surgery Comment below.
- Other Comment below.

- 8. Is this AE serious according to ICH guidelines? yes no
- 9. Has/will this AE be reported as an EAE? yes no
- 10. Was this AE a worsening of a pre-existing condition? yes no

- 11. This AE was first reported at visit: [][] [][] . [] Visit code required (regular or interim).
- 12. Is this AE reported for the mother or the infant? mother infant

Comments: _____

Adverse Experience Log (AE-1)

Any Adverse Experience (AE) reported by the participant or clinically observed after initiation of study product, regardless of whether or not it is related to study product, must be documented any time during study participation.

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.

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.

Adverse Experience (AE): 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.”

Onset Date: 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.

Severity: To grade the severity of an AE, consult the *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Experiences*.

Relationship to Study Product:

- **Definitely related:** The adverse event and administration of study agent are related in time, and a direct association can be demonstrated.
- **Probably related:** The adverse event and administration of study agent are reasonably related in time, and the adverse event is more likely explained by study agent than other causes.
- **Possibly related:** The 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 study agent.
- **Probably not related:** A potential relationship between study agent and the adverse event could exist (i.e., the possibility cannot be excluded), but 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 not related to the study agent.
- **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.

Study Product Administration: N/A (not applicable) should be marked if the AE occurred after the participant had completed all administration of the study agent, or the study product is held or discontinued for a different AE or other reason, or the AE is Grade 5 - death.

Status/Outcome:

- **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 this box 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.

Status/Outcome Date: 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.

AE Revisions and Updates:

- 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).

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 002 (147)

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)		Time Administered <input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>		24-hr clock hour:minutes OR <input type="checkbox"/> N/A	
Indication				Staff Initials/Log Entry Date	
Date Started <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		Date Stopped <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		Continuing at end of study <input type="checkbox"/> OR <input type="checkbox"/>	
Dose/Units		Route <i>Mark only one.</i> <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"/>		PO IM IV TOP IHL VAG REC other, specify: _____	
Frequency <i>Mark only one.</i> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		prn qd tid qhs qxh: every <input type="text"/> hrs		once bid qid other, specify: _____	
Taken for a reported AE? <input type="checkbox"/> yes <input type="checkbox"/> no				Record AE Log page(s): <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	

Medication (generic name)		Time Administered <input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>		24-hr clock hour:minutes OR <input type="checkbox"/> N/A	
Indication				Staff Initials/Log Entry Date	
Date Started <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		Date Stopped <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		Continuing at end of study <input type="checkbox"/> OR <input type="checkbox"/>	
Dose/Units		Route <i>Mark only one.</i> <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"/>		PO IM IV TOP IHL VAG REC other, specify: _____	
Frequency <i>Mark only one.</i> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		prn qd tid qhs qxh: every <input type="text"/> hrs		once bid qid other, specify: _____	
Taken for a reported AE? <input type="checkbox"/> yes <input type="checkbox"/> no				Record AE Log page(s): <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	

Medication (generic name)		Time Administered <input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>		24-hr clock hour:minutes OR <input type="checkbox"/> N/A	
Indication				Staff Initials/Log Entry Date	
Date Started <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		Date Stopped <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		Continuing at end of study <input type="checkbox"/> OR <input type="checkbox"/>	
Dose/Units		Route <i>Mark only one.</i> <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"/>		PO IM IV TOP IHL VAG REC other, specify: _____	
Frequency <i>Mark only one.</i> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		prn qd tid qhs qxh: every <input type="text"/> hrs		once bid qid other, specify: _____	
Taken for a reported AE? <input type="checkbox"/> yes <input type="checkbox"/> no				Record AE Log page(s): <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	

10-DEC-07

Language

Concomitant Medications Log (CM-1)

Purpose: To document all medication(s) that are used by the participant during the study other than study product. 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. For MTN 002, this form also captures blood products/transfusions.

General Information/Instructions: This form is faxed: 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.

Item-specific Instructions:

- **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.
- **Time Administered:** Time administered is required for all medications taken/administered up until 24 hours following the administration of the study gel. Record time administered using a 24-hour clock (e.g., 8:12 p.m. is recorded as 20:12). Midnight is recorded as 00:00. For medications taken/administered more than 24 hours following administration of the study gel, mark the “N/A” box.
- **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 Abbreviations:

PO oral	IM intramuscular	IV intravenous	TOP topical	IHL inhaled	VAG vaginal	REC rectal
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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	qxh 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 002 (147)



IV-1 (350)

Visit Code .

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
- 1b. phone call from participant to report new symptoms
- 1c. other, specify: _____

2. Besides this Interim Visit form, what other DataFax study forms were completed at this visit?
Mark "none" or all that apply.

- 2a. none —▶ ***If none, end of form.***
- 2b. Adverse Experience Log (AE-1)
 - 2b1. How many new AE Log pages were completed for this visit? # of pages
- 2c. other, specify: _____

Comments: _____

Interim Visit (IV-1)

Purpose: Complete this form when an interim visit occurs during study follow-up.

General Information/Instructions: Any other forms completed for this visit must have the same Visit Code as this Interim Visit form.

Item-specific instructions:

- **Item 2b1:** If any new AE Log pages were completed for AEs newly reported/diagnosed at this visit, record the number of AE Log pages completed at this visit. That is, record the number of AE Log pages with an interim visit code in item 11 that matches the Interim Visit code assigned to this interim visit.

SAMPLE *DO NOT FAX*
TO DATAFAX



Visit Code [][] . [0]

[1]

MTN 002 (147)

MV-1 (463)

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.*

- unable to contact participant
- unable to schedule appointment(s) within window
- participant refused visit
- participant incarcerated
- participant admitted to a health care facility
- participant withdrew from the study → **Complete a Termination form.**
- participant deceased → **Complete a Termination form. Complete an Adverse Experience Log if applicable.**
- other, specify:

Comments: _____

Missed Visit (MV-1)

Purpose: Complete this form whenever an enrolled participant misses a required visit according to the visit window outlined in the protocol or Study Specific Procedures (SSP).

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. A complete date is required.

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 002 (147)

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 #*

<input type="text"/>	<input type="text"/>	<input type="text"/>
----------------------	----------------------	----------------------

OR *no pages submitted*

3b. Concomitant Medications Log (CM-1) *page #*

<input type="text"/>	<input type="text"/>
----------------------	----------------------

3c. Pre-existing Conditions (PRE-1) *page #*

<input type="text"/>	<input type="text"/>
----------------------	----------------------

Comments: _____

End of Study Inventory (ESI-1)

Purpose: To confirm that SCHARP has received all study data for a given participant

General Information/Instructions: Complete this form once for each enrolled participant after participant has terminated from the study (as documented by a Termination form).

Item-specific Instructions:

- **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.
- **Item 3a:** Record the highest page number of the Adverse Experience Log submitted for this participant, even if that page was marked for deletion.
- **Item 3b:** Record the highest page number of the Concomitant Medications Log submitted for this participant.
- **Item 3c:** Record the highest page number of the Pre-existing Conditions form submitted for this participant.

SAMPLE: Do NOT FAX TO DATAFAX



MTN 002 (147)

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.

2c. participant refused further participation, specify:

2d. NOT APPLICABLE FOR THIS PROTOCOL. participant unable to adhere to visit schedule

2e. participant relocated, no follow-up planned

2f. investigator decision, specify:

2g. unable to contact participant

2h. NOT APPLICABLE FOR THIS PROTOCOL. HIV interview

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: OR Specify:

Comments:

Termination (TM-1)

Purpose: This form should be completed for every enrolled participant at either the scheduled exit/end of study visit or when the participant is no longer participating in the study.

Item-specific Instructions:

- **Item 1:** A complete date is 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. If termination is associated with a non-reportable AE, record the event on the “Specify” line.

MTN 002 Maternal PK- LDMS Specimen Tracking Sheet

For login of MTN 002 stored specimens into LDMS

Participant ID

--	--	--	--	--	--	--	--	--	--	--

Site Number

Participant Number

Chk

Visit Code

--	--	--

PK SPECIMEN TIME POINT	PRIMARY SPECIMEN TYPE	DATE COLLECTED dd-MMM-yy	TIME COLLECTED hh:mm 24-hr clock	NUMBER OF TUBES COLLECTED	INSTRUCTIONS FOR PROCESSING LAB
Pre-Gel	Maternal Blood (BLD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER
1 Hour	Maternal Blood (BLD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER.
2 Hour	Maternal Blood (BLD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER
4 Hour	Maternal Blood (BLD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER
6 Hour	Maternal Blood (BLD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER
8 Hour	Maternal Blood (BLD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER
12 Hour	Maternal Blood (BLD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER
24 Hour	Maternal Blood (BLD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER Enter into LDMS with Visit Code 03.0

Comments: _____

Initials: _____

Sending Staff

Receiving Staff

LDMS Data Entry Date: _____

--	--

dd

--	--	--	--

MMM

--	--

yy

/

LDMS Staff

MTN 002 Maternal PK- LDMS Specimen Tracking Sheet

For login of MTN 002 stored specimens into LDMS

Maternal PK - LDMS Specimen Tracking Sheet (nonDataFax)

Purpose: This non-DataFax form is used to document collection and entry of MTN 002 maternal PK blood specimens into the Laboratory Data Management System (LDMS).

General Information/Instructions: A copy of this form accompanies maternal PK blood specimens (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. Use a Visit Code of 02.0 for all specimens except the 24 Hour specimen. The 24 Hour specimen is collected at Visit Code 03.0.
- **NUMBER OF TUBES COLLECTED:** In the box to the left of each additive type, record the total number of tubes 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.

MTN 002 C-section- LDMS Specimen Tracking Sheet

For login of MTN 002 stored specimens into LDMS

Participant ID			Visit Code	
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Site Number	Participant Number	Chk		

PRIMARY SPECIMEN TYPE	DATE COLLECTED dd-MMM-yy	TIME COLLECTED hh:mm 24-hr clock	NUMBER OF TUBES/VIALS COLLECTED	INSTRUCTIONS FOR PROCESSING LAB
Amniotic Fluid (AMN)			<input type="checkbox"/> NON (no additive)	Freeze immediately after collection. Store with derivative AMN
Cord Blood (CRD)			<input type="checkbox"/> Non (red top)	Process within eight hours of collection. Freeze immediately after centrifugation. Store with derivative SER
Placental Tissue (PLC)			<input type="checkbox"/> NON (no additive)	Freeze immediately after collection.
Endometrial Tissue (END)			<input type="checkbox"/> NON (no additive)	Freeze immediately after collection.

Comments: _____

Initials: _____
Sending Staff Receiving Staff

LDMS Data Entry Date: / / _____
dd MMM yy LDMS Staff

MTN 002 C-section- LDMS Specimen Tracking Sheet

For login of MTN 002 stored specimens into LDMS

C-section - LDMS Specimen Tracking Sheet (nonDataFax)

Purpose: This non-DataFax form is used to document collection and entry of MTN 002 c-section stored specimens into the Laboratory Data Management System (LDMS).

General Information/Instructions: A copy of this form accompanies the c-section specimens (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. Use a Visit Code of 02.0 for all specimens.
- **NUMBER OF TUBES/VIALS COLLECTED:** In the box to the left of each additive type, record the total number of tubes or vials 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 002, 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 002 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 002 Data Communiqué #1

May 9, 2008

This is official study documentation for MTN 002. Please circulate it among relevant staff for their review, print it, and place it in your MTN 002 SSP Manual in the Data Communiqués section. This document is considered part of the MTN 002 SSP manual.

UPDATES

1. Flow Cytometry case report form (FC-1)

A Flow Cytometry (FC-1) case report form is included in each MTN 002 Study Participant Notebook, in the “Pharmacokinetic Measures: Gel Administration (Visit 2.0)” tab. Since this form was created, the flow data required for MTN 002 has changed. As such, this case report form is no longer relevant for the study and will not be used. Please remove all copies of the FC-1 form from each of the 002 notebooks, and destroy these forms so that they are not completed. SCHARP will be in contact with the site at a later date with instructions on how to report the 002 flow cytometry data.

CLARIFICATIONS

1. Adverse Experience (AE) Log form, item 3 – severity

Please note that per protocol, the *Female Genital Grading Table for Use in Microbicide Studies* is the primary tool used for grading adverse events for this protocol. This table is Appendix V of the protocol. See Section 11.3 of the Study Specific Procedures (SSP) manual for more information on assigned severity grades to adverse events.

2. Completion of Adverse Experience (AE) Log case report for infant AEs

Note that when completing an AE Log case report form for infant AEs:

- **item 5** (Study Product Administration) will always be “N/A” since the infant is not receiving study product
- **item 7 (Treatment)** – Mark “Medication(s)” if the infant was given medication for the AE. **Do not** record the infant’s medications on the Concomitant Medications Log, but do record the medications given to the infant in the “Comments” field of the AE Log form. Only the mother’s medications are recorded on the Concomitant Medications Log form.
- **Item 10 (Was this AE a worsening of a pre-existing condition?)** will always be “no”
- **Item 12** will always be “infant”

All other items on the AE Log form are completed according to the instructions on the back of the form page.

REMINDERS

None



MTN 002 Data Communiqué #2

October 9, 2008

This is official study documentation for MTN 002. Please circulate it among relevant staff for their review, print it, and place it in your MTN 002 SSP Manual in the Data Communiqués section. This document is considered part of the MTN 002 SSP manual.

UPDATES

1. Revised Flow Cytometry case report form (FC-1)

A revised Flow Cytometry (FC-1) case report form has been issued. The date of this form (lower left-hand corner of the form) is 07-OCT-08. This revised one-page CRF should be printed and added to each MTN 002 Study Participant Notebook in the “Pharmacokinetic Measures: Gel Administration (Visit 2.0)” tab. Any previous versions of this CRF present in the notebooks should be removed and destroyed.

Note that for the first participant enrolled into MTN 002 (who did not complete the Gel Administration visit, Visit 2.0), the revised Flow Cytometry CRF does not need to be completed or faxed to SCHARP. For all other study participants, this CRF is completed as part of the Visit 2.0 evaluations.

CLARIFICATIONS

None.

REMINDERS

None

Section 15 - Study Reporting Plan

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, USA, and is in the US Pacific time zone. The SCHARP MTN 002 team members, along with their job role and email information, are listed below.

<u>Role on MTN 002</u>	<u>Name</u>	<u>E-mail address</u>
Protocol Statistician	Ben Masse	ben@scharp.org
Project Manager:	Missy Cianciola	missy@scharp.org
Statistical Research Associate:	Karisse Roman	karisse@scharp.org
Protocol Programmer:	Julie Zhou	yzhuo@scharp.org
Data Coordinator:	Suzanne Cullers	scullers@scharp.org
Document Specialist:	Stacie Kentop	stacie@scharp.org
Reporting Programmer	Kate Bader	kate@scharp.org
Laboratory Programmer:	Laura Robins-Morris	lrobins@scharp.org
Clinical Affairs Safety Associate	Molly Swenson	mollys@scharp.org

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 002.

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 002 SDMC Project Manager in collaboration with other MTN 002 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:

<https://atlas.scharp.org/cpas/Project/MTN/begin.view?>.

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 002 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 Coordinator • Site Data Manager • CORE Clinical Research Manager • SDMC Project Manager
Clinical Data Quality Control (CQC) Queries	Weekly, or as needed	<ul style="list-style-type: none"> • Site Study Coordinator • Site Data Manager • CORE Clinical Research Manager • SDMC Project Manager
Study Monitoring Committee (SMC)	As determined by the SMC	<ul style="list-style-type: none"> • MTN 002 SMC members and observers • MTN 002 Protocol Chair • MTN 002 Site Investigator
Site Specimen Repository Report	Monthly, the 10th of each month	<ul style="list-style-type: none"> • Site Study Coordinator • Network Lab Representative • SDMC Project Manager

Table 15-2: MTN 002 SDMC Reports Posted on Atlas

Report Title	Update Frequency	Atlas Viewing Area
Enrollment and Retention	Daily	Unsecure
Visit Adherence	Monthly, the 1 st of each month	Unsecure
Site Data Management Quality	Monthly, the 5 th of each month	Unsecure
Safety Report	One week prior to each scheduled PSRT call	Secure
Network Lab Assay Results Report	Monthly, the 5 th of each month	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 002 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 Repository 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 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.

15.2.6 Visit Adherence Report

Purpose: To monitor adherence to the protocol

Prepared by: SDMC Statistical Research Associate

Components: Listing of number and % of required PK blood specimens collected, cervical specimens collected, and administrations of gel use.

15.2.7 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.

15.2.8 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.

15.2.9 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 at SCHARP.