MTN-015
An Observational Cohort Study of Women following HIV-1 Seroconversion in Microbicide Trials

A Study of the Microbicide Trials Network

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

Grant #:
1-U01-AI068633-01

DAIDS Protocol #: 10529

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Final (RAB) Version
Version 1.0
19 June 2007

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LIST OF ABBREVIATIONS AND ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
ART	antiretroviral therapy
BV	bacterial vaginosis
CBC	complete blood count
CD4+	cluster of differentiation 4 (referring to measure of T lymphocytes)
CFR	code of federal regulations
DAIDS	Division of AIDS
DHHS	U.S. Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
EAE	Expedited Adverse Event
EC	ethics committee
GC	Neisseria gonorrhea
GCP	Good Clinical Practices
GEE	Generalized Estimating Equations
hCG	human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus—Type 1
HPTN	HIV Prevention Trials Network
HSV-2	Herpes Simplex Virus—Type II
IATA	International Air Transport Association
ICH	International Conference on Harmonization
IRB	institutional review board
LDMS	Laboratory Data Management System
MTN	Microbicide Trials Network
MTN EC	Microbicide Trials Network Executive Committee
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
NL	Network Laboratory
OHRP	Office of Human Research Protection
PBMC	peripheral blood mononuclear cell
PCP	primary care provider
PCR	polymerase chain reaction
PI	Principal Investigator
PMTCT	Prevention of mother-to-child transmission
PPD	Pharmaceutical Product Development, Inc.
RCC	Regulatory Compliance Center
RNA	ribonucleic acid
RTI	reproductive tract infection
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SDA	strand displacement assay
SDMC	Statistical Data Management Center
SMC	Study Monitoring Committee
SOP	standard operating procedure(s)
STI	sexually transmitted infection
UNAIDS	Joint United Nations Program on AIDS
UW/FHCRC	University of Washington/Fred Hutchinson Cancer Research Center
WHO	World Health Organization

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MTN-015
An Observational Cohort Study of Women following HIV-1 Seroconversion in Microbicide Trials

PROTOCOL SUMMARY

Short Title:	MTN HIV-1 Seroconverter Study
Protocol Chair:	Sharon A. Riddler, MD, MPH
Sample Size:	Approximately 500 women (estimated minimum 165, with 138 available for the evaluation of the primary objective)
Study Population:	Women who have HIV-1 seroconversion during participation in microbicide trials
Participating Sites:	Sites designated by the MTN Executive Committee
Study Design:	Multi-site prospective observational cohort study
Study Duration:	Until May 31st, 2013, with possibility of extension

Primary Objective:

- To compare the plasma HIV-1 RNA level twelve months after HIV-1 seroconversion among antiretroviral treatment (ART) naïve participants assigned to an active microbicidal or chemoprophylactic agent compared to control participants.

Secondary Objectives:

- To characterize the trajectory of CD4+ T-cell counts after HIV-1 seroconversion among antiretroviral treatment naïve participants assigned to an active microbicidal or chemoprophylactic agent compared to control participants.

- To compare the plasma HIV-1 RNA level six months after HIV-1 seroconversion among antiretroviral treatment naïve participants assigned to an active microbicidal or chemoprophylactic agent compared to control participants.

- To evaluate the prevalence of HIV-1 drug resistance mutations in plasma and genital tract specimens after HIV-1 seroconversion among participants assigned to an active microbicidal or chemoprophylactic agent compared to control participants.

- To evaluate the virologic response to initiation of antiretroviral therapy among participants assigned to an active microbicidal or chemoprophylactic agent compared to control participants in microbicide trials and by study specific analysis (for larger trials including current and future trials).

    - The proportion with HIV-1 RNA less than 50 copies/mL six months, twelve months, and twenty-four months following initiation of antiretroviral therapy

- To describe the CD4+ T-cell response to initiation of antiretroviral therapy in participants after seroconversion in microbicide trials.

    - The CD4+ T-cell increase six months, twelve months, and twenty-four months following initiation of antiretroviral therapy

- To compare the HIV-1 drug resistance profile, among antiretroviral therapy recipients, at the time of virologic failure (HIV-1 RNA >200 copies/mL at or after six months of antiretroviral therapy) in participants assigned to an active microbicidal or chemoprophylactic agent compared to control in microbicide trials and by study specific analysis (for larger trials including current and future trials).

- To evaluate the prevalence and persistence of HIV drug resistance mutations in plasma and cervical lavage fluid using more sensitive methods (which may include modified ultrasensitive assays of plasma HIV RNA) in study specific subgroups of seroconverters.

- To describe HIV-1 related (WHO Stage II) and AIDS-defining (WHO Stage III and IV) clinical events and deaths (from any cause) occurring among seroconverters with and without antiretroviral therapy.

- To compare the rate of HIV-1 disease progression among participants assigned to an active microbicidal or chemoprophylactic agent compared to control.

- To describe post-seroconversion changes in sexual behaviors and partnership status of women who seroconvert during participation in microbicide trials.

- To provide a repository of specimens from women who have HIV-1 seroconversion during participation in microbicide trials that can be used for future analyses.

1 KEY ROLES

1.1. Protocol Identification

Protocol Title: An Observational Cohort Study of Women following HIV-1 Seroconversion in Microbicide Trials

Protocol Number: MTN-015

Date: June 19, 2007

1.2. Sponsor and Monitor Identification

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2. INTRODUCTION

2.1. HIV/AIDS Prevention and Microbicides

According to UNAIDS, approximately 40 million people worldwide were living with HIV in 2006.[i] Widespread implementation of HIV-1 prevention services, including behavioral strategies, has had only modest impact on the rate of new HIV-1 infections in most populations[ii], thus continued efforts to identify effective preventative modalities are needed. Many different approaches are being evaluated in clinical trials including behavioral interventions, vaccines, chemoprophylaxis and topical microbicides.[iii] Microbicide clinical trials in HIV-negative participants conducted by the NIH-funded Microbicide Trials Network (MTN) will include Phase I and II safety trials of new compounds as well as larger, Phase IIb and III randomized trials. The variety of potential compounds is broad and includes agents with and without specific HIV-1 inhibitory activity. Trials conducted by the MTN will include both topical microbicides and orally administered antiretroviral agents (also referred to as chemoprophylaxis).

The primary goal of a microbicide is to prevent acquisition of HIV-1 infection. There will, however, be new HIV-1 infections among study participants and ultimately users of microbicides and chemoprophylaxis. It is essential to monitor

these HIV-1 seroconverters in order to better understand the impact of microbicides or chemoprophylaxis on the natural history of HIV-1 infection in those who become infected or are unknowingly already infected while receiving a product. The potential alteration of the clinical course of HIV-1 infection among users of microbicides or chemoprophylaxis may be beneficial or harmful for the exposed individuals. For example, it is possible that the use of a topical microbicide or chemoprophylactic agent will result in a lower inoculum of infecting viral strain. By this mechanism or others not yet understood, it is possible that women who are infected despite the use of topical microbicides or oral chemoprophylaxis will have a lower viral set-point and subsequent slower progression of HIV disease.

A major concern is the possibility that topical microbicides or oral chemoprophylaxis could facilitate infections with or select for drug resistant HIV-1 in those who become infected, or are unknowingly already infected. The primary concern is that women who become infected while using topical or oral antiretroviral agents will undergo seroconversion with concomitant high levels of HIV-1 viral replication in the presence of antiretroviral monotherapy facilitating the emergence of resistance to the antiretroviral agent contained in the product. This is a particular concern with microbicides based on the use of a single antiviral drug such as tenofovir. Currently in North America and Western Europe, approximately 10% of all new infections are attributed to viruses that contain at least one drug resistance mutation but there are no data yet regarding the incidence of resistance among recipients of single or dual drug chemoprophylaxis or microbicides.[iv] There is also the potential for selection of drug resistance in women who unknowingly are already HIV-infected. This may be less of a concern with respect to topically applied products with little or no systemic absorption, as the concentrations absorbed may be too low to select for resistance in systemically circulating virus. However, there may be an impact on the local genital tract viral population, which may be distinct from the systemic circulating virus.

Individuals with recent HIV infection often have high viral loads and may be highly infectious.[v, vi, vii] Risky sexual behavior soon after infection therefore carries high potential for HIV transmission to others. Based on mathematical models of male-to-male sexual transmission of HIV, between 25 and 47% of new infections may be transmitted during the primary infection phase.[viii, ix] Studies using HIV polymerase gene sequencing and phylogenetic analyses suggest that up to one half of new infections might be attributed to persons with early HIV infection.[x, xi, xii] Among serodiscordant couples the risk of HIV transmission was found to be seven times higher during the first five months after seroconversion as compared to later stages of infection when measured prospectively.[v] Clearly, accumulating biological and modeling data suggest that transmission from individuals in the acute and early stages of HIV disease represent a major contribution to continuing the HIV epidemics. What is not known is how effective early detection of new infection and counseling may be to reducing such

transmission. Women who acquire HIV-1 in microbicide trials may be in a unique position to modify their behavior if the conditions that exposed them to HIV-1 are within their control to change.

2.2. Study Hypothesis and Rationale

2.2.1. Study Hypothesis

Exposure to study agents in MTN clinical trials will not impact the natural history of HIV-1 infection as measured by the virologic, immunologic and clinical outcomes of participants with HIV-1 seroconversion during microbicide trials.

2.2.2. Rationale

Evaluation of the effect of topical microbicides or oral chemoprophylaxis use on the natural history of HIV-1 infection is essential for the development of guidance for the use of such products in populations at risk of HIV-1 infection. At this time, no data are available to predict the likelihood of either risk or benefit among microbicide study participants who become HIV-infected during product use. Careful monitoring of topical microbicide and oral chemoprophylaxis study participants who acquire HIV-1 infection during product usage will provide critical knowledge to inform the field.

In MTN Phase II, IIB, and III trials, participants are monitored routinely for HIV-1 seroconversion (typically every 3 months). For the purposes of MTN-015, HIV Prevention Trials Network (HPTN) 035 and HPTN 059 are considered MTN studies from which participants in MTN-015 will be drawn. In addition, studies investigating both topical microbicides and oral chemoprophylaxis will be considered studies from which participants in MTN-015 may be drawn. MTN-015 will routinely collect and monitor laboratory and clinical data from women who become HIV-1 infected during microbicide trials to characterize the natural history of infection and eventually the response to antiretroviral therapy in this population. To provide adequate comparison group(s) for specific analyses of interest, all participants with seroconversion during study participation will be eligible for enrollment into this protocol regardless of the specific product or placebo or the route of administration. This protocol will also include storage of biologic samples to allow further characterization of virologic and immune parameters among subsets of participants using a nested case control approach.

Individuals recently HIV infected often have high viral loads and may be highly infectious.[v,vi,vii] Risky sexual behavior soon after infection therefore carries high potential for HIV transmission to others. Upon becoming aware of recent HIV infection, some but not all individuals change behaviors to reduce their risks of

transmitting HIV.[xiii] Possible mediators of such behavior change include dynamics of partnerships and disclosure. Observation of individuals with recent HIV-1 infection over time can provide information critical to secondary prevention. Many HIV positive individuals in Africa do disclose their status, with rates as high as 92% reported in one South African study. [xiii] However, there is also evidence that disclosure is less common; for example in another South African study 42% of HIV-positive people reported not disclosing their status to a partner with whom they have had recent sexual intercourse, with a high percent of these acts unprotected.[xiv] Moreover, even among the individuals in whom high disclosure was observed there was also considerable delayed disclosure (15% greater than a year) or non-disclosure (21%) to partners. Women who have participated in microbicides trials may have different responses to disclosure as their trial participation may have been known by a partner. The pattern of behavior change among women in this unique situation to reduce transmission is important to describe and may help future counseling programs for HIV positive women in developing countries. Describing the pattern of behavior change among newly HIV infected women in comparison to women who are negative or chronically infected (from HPTN 035 and other datasets), will inform counseling strategies to reduce further HIV infection.

3. OBJECTIVES

For purposes of these analyses, antiretroviral agents employed as study products in a parent MTN trial will not be considered ART.

3.1. Primary Objective

- To compare the plasma HIV-1 RNA level twelve months after HIV-1 seroconversion among antiretroviral treatment (ART) naïve participants assigned to an active microbicidal or chemoprophylactic agent compared to control participants.

3.2. Secondary Objectives

- To characterize the trajectory of CD4+ T-cell counts after HIV-1 seroconversion among antiretroviral treatment naïve participants assigned to an active microbicidal or chemoprophylactic agent compared to control participants.

- To compare the plasma HIV-1 RNA level six months after HIV-1 seroconversion among antiretroviral treatment naïve participants assigned to an active microbicidal or chemoprophylactic agent compared to control participants.

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- To provide a repository of specimens from women who have HIV-1 seroconversion during participation in microbicide trials that can be used for future analyses.

4. STUDY DESIGN

4.1. Identification of Study Design

MTN-015 is a multi-site, prospective observational cohort study. Potential participants will be offered enrollment in MTN-015 following identification of HIV-1 seroconversion in the parent trial (the trial from which they were identified). For the purposes of this protocol, date of seroconversion is defined as the date of HIV-1 seroconversion used in the parent trial. The participant's HIV-1 seroconversion should be confirmed according to the HIV-1 testing algorithm of the parent trial. Study participants may be followed concurrently in the MTN parent trial and MTN-015 for the duration of the parent trial and subsequently continue in MTN-015 for the duration of MTN funding. Participants in MTN-015 may participate in other clinical trials including HIV-1 treatment trials.

This study will utilize two follow-up visit schedules: one based on the date of identification of seroconversion in the parent study and one based on initiation of ART use; see Section 7 for details on each schedule. Participants who have not initiated use of ART at the time of enrollment in MTN-015 will follow the schedule based on the date of identification of seroconversion. Participants who have initiated use of ART at the time of enrollment in MTN-015 will follow the schedule based on the date of ART initiation. Participants who initiate use of ART during follow-up in MTN-015 will have their follow-up schedule adjusted to the schedule based on initiation of ART use. Study sites will be provided with computerized tools (either spreadsheet or web-based) to assist them in determining the appropriate visit schedule to follow for each participant. Past or current use of most ART regimens will constitute initiation of ART for purposes of this study; however, use of single dose nevirapine for PMTCT will not constitute initiation of ART for purposes of this study.

Microbicide study participants are typically screened for HIV-1 infection at the time of study screening; however, not all studies repeat HIV-1 testing at enrollment (e.g. HPTN 035). Instead, specimens are saved for later HIV-1 testing in the event of seroconversion at the first follow-up visit when testing occurs according to the schedule of study procedures. Microbicide study participants who were enrolled in a parent trial but then later determined to have been HIV-1-infected at the time of the enrollment visit will be eligible for MTN-015 (however, these subjects may be excluded from some analyses).

Participants will receive their initial referral to HIV-1 primary care and psychosocial support when their infection is diagnosed in the parent trial; thereafter referrals will continue during MTN-015 as needed for ongoing support and HIV-1 management (See Section 9.1). Study participants will be referred to their primary care provider (PCP) or local health care providers for management of HIV-1 infection, including antiretroviral medications (as indicated), social services and other routine medical care. Antiretroviral medications will not be provided by this protocol. Participants may be referred to HIV-1 treatment trials if applicable. Study participants will receive STI risk reduction counseling, HIV-1 secondary prevention counseling, condoms, STI testing, physical exams, and pelvic exams. They will be provided STI treatment in accordance with WHO guidelines free-of-charge, and will be offered STI testing and treatment for their partners.

4.2. Description of Study Population

The study population will consist of female participants who are identified as infected with HIV-1 during participation in MTN clinical trials who meet the MTN-015 eligibility criteria in Section 5.

4.3. Time to Complete Enrollment

There is no specified time to complete enrollment for MTN-015. Accrual will remain open for the duration of MTN funding.

4.4. Study Groups

There are no assigned study groups for MTN-015.

4.5. Expected Duration of Participation

The expected duration of participation for an individual participant is until May 31st, 2013.

4.6. Sites

This study is open to sites as determined by the MTN Executive Committee. Study sites are listed in Appendix II.

5. STUDY POPULATION

The study population will consist of female participants who are identified as infected with HIV-1 during participation in microbicide clinical trials who meet the eligibility criteria listed below. Potential participants will be recruited for MTN-015

as soon as possible after identification of HIV-1 seroconversion; however, there is no time limit for MTN-015 enrollment after identification of seroconversion. With assistance from the SDMC, the Site PI or designee will identify participants who seroconvert during participation in parent microbicide trials.

5.1. Selection of the Study Population

Composition

Female microbicide clinical trial participants who meet MTN-015 eligibility criteria will be offered enrollment in MTN-015.

Recruitment

Study site staff will recruit potentially eligible study participants. For microbicide trial participants who seroconvert prior to activation of MTN-015, study staff will retrospectively contact the participants for possible enrollment in MTN-015, unless the participants have refused further contact with study staff. For microbicide trial participants who seroconvert after activation of MTN-015, study staff will prospectively contact the participants for possible enrollment in MTN-015 at the time of identified seroconversion. All recruitment materials will be Institutional Review Board/Ethics Committee (IRB/EC)-approved prior to use.

Retention

Each site will establish participant retention procedures to target an average retention rate of 95% per year.

Site staff members may contact participants between scheduled visits in order to facilitate high levels of retention. Each site's approach to this will be specified in its retention SOP. Sites may optionally do this through various methods (e.g., home visit, phone, letter, etc).

Co-Enrollment Guidelines

Co-enrollment in other trials is permitted by this protocol. Participants will be encouraged to report to MTN-015 staff any co-enrollment in other research trials.

5.2. Inclusion Criteria

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

1. HIV-1 seroconversion during participation in any MTN clinical trial (including HPTN 035 and HPTN 059), according to the HIV testing algorithm of the parent MTN trial.

2. Able and willing to provide independent written informed consent to participate in the study.

5.3. Exclusion Criterion

Women who meet the following criterion will be excluded from the study:

1. Has any condition that in the opinion of the investigator or designee, would preclude provision of informed consent, make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

6. STUDY PRODUCT

MTN-015 will not involve the administration of any study product.

7. STUDY PROCEDURES

Information is provided below and in Appendix 1 on when each study procedure is to be performed. Screening and Enrollment evaluations should be completed as soon as possible following the identification of HIV-1 seroconversion. Missed visits will not be considered protocol violations. Written informed consent will be obtained before performing any study procedures.

It is expected that, in most cases, all required visit procedures will be completed at one visit; however, more than one visit may be completed if needed to complete all required procedures. If a participant is being followed in her parent trial, site staff will make every effort to schedule and complete MTN-015 visits on the same day as parent protocol visits. Completion of the parent MTN protocol visit should take priority if time or other factors do not allow for both study visits to be completed on the same day.

Because laboratory testing will be performed at all scheduled study visits, a post-visit contact is required after each visit to provide participants with their test results, clinically relevant post-test counseling, and/or clinically indicated treatment. Study staff may complete these contacts at the study site or at community-based locations, depending on site capacities and site and participant preferences. All contacts will be documented in participant study records and written documentation of test results will be provided upon request to participants and/or their primary HIV-1 care providers.

7.1. Screening and Enrollment Visit

Table 1: Screening and Enrollment Visit

Screening and Enrollment Visit	
Component	**Procedure/Analysis**
Administrative: Screening	Informed Consent Review Parent Study Records to Confirm HIV-1 Seroconversion Eligibility Determination
Administrative: Enrollment	Assign Participant ID Update Locator Information Update Demographics Schedule Next Visit Reimbursement
Clinical	Update Medical History Record Clinical Events Acute Seroconversion Assessment Concomitant Medications Assessment *Antiretroviral Treatment Record Complete Physical Exam (See Appendix IV) Gynecologic Exam (See Appendix IV) *Provide Test Results *Treatment or Referral
Behavioral	Baseline Behavioral Questionnaire *Adherence Questionnaire STI Risk Reduction and Contraception Counseling HIV Secondary Prevention Counseling Provision of Condoms
Urine	Qualitative hCG SDA for Chlamydia and Gonorrhea
Blood	Complete Blood Count Liver and Renal Function Tests Syphilis Serology CD4+ T-Cell Count Plasma HIV-1 RNA HIV-1 Genotypic Resistance Test (MTN NL, archived plasma) HSV-2 Antibody (site lab, regional lab, or MTN NL, archived plasma) HIV ELISA and Western Blot (MTN NL, archived serum)**
Pelvic Samples	Vaginal pH Wet Mount for bacterial vaginosis (BV), Candida, and Trichomonas †Pap Smear at Selected Sites
Specimens for Storage	Vaginal Swabs Cervicovaginal Lavage Plasma Serum Peripheral Blood Mononuclear Cells (PBMC)

*If indicated, **If not previously confirmed in a Network Laboratory, † PAP smears should be done at 6 month intervals in the first year after seroconversion, and then annually if the initial tests are negative.

7.2. Follow-up Visits

This study utilizes two follow-up visit schedules, one based on the date of identification of seroconversion in the parent study and one based on initiation of ART use.

- Participants who have not initiated use of ART at the time of enrollment in MTN-015 will follow the schedule based on the date of identification of seroconversion, which is described in Section 7.2.1. On this schedule, follow-up visits occur at Months 1, 3, and 6 after the date of identification of seroconversion, and every 6 months thereafter. Participants may enroll anytime after seroconversion. Following the enrollment visit, the subsequent visits will be scheduled according to the seroconversion date (for example, a participant who enrolls 4 months after seroconversion would have a second visit at 6 months after seroconversion (2 months after enrollment) and then every 6 months).

- Participants who have initiated use of ART at the time of enrollment in MTN-015 will follow the schedule based on the date of ART initiation, which is described in Section 7.2.2. On this schedule, follow-up visits occur at Week 2 and Months 1, 3, and 6 after the date of ART initiation, and every 6 months thereafter.

- Participants who initiate use of ART during follow-up in MTN-015 will follow the schedule in section 7.2.1, and then switch to the schedule in Section 7.2.2 after initiation of ART use.

As it will not always be possible to conduct follow-up visits on the target dates specified above, visits may be completed at any time during allowable visit windows. For both the non-ART and ART visit schedules, the allowable visit windows are contiguous and extend from the midpoint of one visit interval to the midpoint of the next visit interval. For example, the Month 24 visit window extends from Month 21 through Month 27. For participants who do not complete scheduled visits within the allowable window, the visit will be considered missed and relevant case report forms will be completed to document the missed visit. Missed visits will not be considered protocol violations.

7.2.1. Visits for non-ART Participants

Tables 2 and 3 list procedures that will be conducted for participants who have not initiated use of ART prior to these visits. For participants who have initiated ART prior to these visits, procedures specified in Tables 4 and 5 will be followed.

Table 2: Month 1 and Month 3 Post-Seroconversion Visits

Month 1 and Month 3 Post-Seroconversion Visits	
Component	**Procedure/Analysis**
Administrative	Update Locator Information Schedule Next Visit Reimbursement
Clinical	Update Medical History Update Clinical Events Concomitant Medications Assessment Targeted Physical Exam Gynecologic Exam *Provide Test Results *Treatment or Referral
Behavioral	Follow-up Behavioral Questionnaire (at Month 3 Post-Seroconversion Only) Social Harms Assessment (at Month 3 Post-Seroconversion Only) Provision of Condoms
Urine	*Qualitative hCG *SDA for Chlamydia and Gonorrhea
Blood	Plasma HIV-1 RNA CD4+ T-Cell Count *Syphilis Serology Complete Blood Count (at Month 3 Post-Seroconversion Only) Liver and Renal Function (at Month 3 Post-Seroconversion Only)
Pelvic Samples	*Vaginal pH *Wet Mount for BV, Candida, and Trichomonas */† Pap Smear at Selected Sites
Specimens for Storage	Vaginal Swabs Cervicovaginal Lavage Plasma PBMC

*If indicated; †PAP smears should be done at 6 month intervals in the first year after seroconversion, and then annually if the initial tests are negative.

Table 3: Month 6 and Q6 Months Post-Seroconversion Visits

Month 6 and Q6 Months Post-Seroconversion Visits	
Component	**Procedure/Analysis**
Administrative	Update Locator Information Schedule Next Visit Reimbursement
Clinical	Update Medical History Update Clinical Events Concomitant Medications Assessment Targeted Physical Exam Gynecologic Exam *Provide Test Results *Treatment or Referral
Behavioral	Follow-up Behavioral Questionnaire (Month 12 and Month 24 only) Social Harms Assessment STI Risk Reduction and Contraception Counseling HIV-1 Secondary Prevention Counseling Provision of Condoms
Urine	*Qualitative hCG */**SDA for Chlamydia and Gonorrhea (annually)
Blood	Plasma HIV-1 RNA CD4+ T-Cell Count Complete Blood Count Liver and Renal Function */**Syphilis Serology (annually)
Pelvic Samples	*/**Vaginal pH */**Wet Mount for BV, Candida and Trichomonas */† Pap Smear at Selected Sites (annually)
Specimens for Storage	Vaginal Swabs Cervicovaginal Lavage Plasma PBMC

*If indicated; */**Urine SDA for Chlamydia and Gonorrhea, Syphilis Serology, Vaginal pH, and Wet Mount should be performed at visits annually, with performance of these measures at additional scheduled visits as clinically indicated; †PAP smears should be done at 6 month intervals in the first year after seroconversion, and then annually if the initial tests are negative.

7.2.2. Follow-Up Visits for Participants after ART Initiation

Tables 4 and 5 below list procedures that will be conducted for participants who enroll after initiation of ART or who initiate ART during follow-up in MTN-015.

Table 4: Week 2, Month 1, and Month 3 After Initiation of ART

Week 2, Month 1, and Month 3 After Initiation of ART	
Component	**Procedure/Analysis**
Administrative	Update Locator Information Schedule Next Visit Reimbursement
Clinical	Update Medical History Update Clinical Events Concomitant Medications Assessment Antiretroviral Treatment Record Targeted Physical Exam Gynecologic Exam *Provide Test Results *Treatment or Referral
Behavioral	Follow-up Behavioral Questionnaire (Month 3 only) *If ART is begun more than 24 months after identification of seroconversion, then the Follow-up Behavioral Questionnaire is omitted at post-ART visits.* Adherence Questionnaire (Month 3 only) Social Harms Assessment Provision of Condoms
Urine	*Qualitative hCG *SDA for Chlamydia and Gonorrhea
Blood	Plasma HIV-1 RNA CD4+ T-Cell Count *Syphilis Serology *Complete Blood Count *Liver and Renal Function Tests *HIV-1 Genotypic Resistance Test (at NL)
Pelvic Samples	*Vaginal pH *Wet Mount for BV, Candida, and Trichomonas */† Pap Smear at Selected Sites
Specimens for Storage	Vaginal Swabs Cervicovaginal Lavage (Month 3 only) Plasma PBMC (Week 2 and Month 3 only)

*If indicated; †PAP smears should be done at 6 month intervals in the first year after seroconversion, and then annually if the initial tests are negative.

Table 5: Month 6 and Q6 Months Visits After Initiation of ART

Month 6 and Q6 Months Visits After Initiation of ART	
Component	**Procedure/Analysis**
Administrative Procedures	Update Locator Information Schedule Next Visit Reimbursement
Clinical Assessments	Update Medical History Update Clinical Events Concomitant Medications Assessment Antiretroviral Treatment Record Targeted Physical Exam Gynecologic Exam *Provide Test Results *Treatment or Referral
Behavioral Assessments	Follow-up Behavioral Questionnaire (Month 12 and Month 24 only) *If ART is begun more than 24 months after identification of seroconversion, then the Follow-up Behavioral Questionnaire is omitted at post-ART visits.* Adherence Questionnaire Social Harms Assessment STI Risk Reduction and Contraception Counseling HIV-1 Secondary Prevention Counseling Provision of Condoms
Urine	*Qualitative hCG */**SDA for Chlamydia and Gonorrhea (annually)
Blood	Plasma HIV-1 RNA CD4+ T-Cell Count Complete Blood Count Liver and Renal Function Tests */**Syphilis Serology (annually) *HIV-1 Genotypic Resistance Test (at NL)
Pelvic Samples	*/**Vaginal pH */**Wet Mount for BV, Candida and Trichomonas */† Pap Smear at Selected Sites
Specimens for Storage	Vaginal Swabs Cervicovaginal Lavage Plasma PBMC

*If indicated; */**Urine SDA for Chlamydia and Gonorrhea, Syphilis Serology, Vaginal pH, and Wet Mount should be performed at visits annually, with performance of these measures at other scheduled visits as clinically indicated; †PAP smears should be done at 6 month intervals in the first year after seroconversion, and then annually if the initial tests are negative.

7.2.3. Final Visit – All Participants

The table below lists procedures that will be conducted at the final study visit for all participants.

Table 6: Final Visit

Final Visit	
Component	**Procedure/Analysis**
Administrative	Update Locator Information Reimbursement
Clinical	Update Medical History Update Clinical Events Concomitant Medications Assessment *Antiretroviral Treatment Record Targeted Physical Exam Gynecologic Exam *Provide Test Results *Treatment or Referral
Behavioral	*Adherence Questionnaire Social Harms Assessment HIV-1 Secondary Prevention Counseling STI Risk Reduction and Contraception Counseling Provision of Condoms
Urine	Qualitative hCG SDA for Chlamydia and Gonorrhea
Blood	Plasma HIV-1 RNA CD4+ T-Cell Count Complete Blood Count Liver and Renal Function Tests Syphilis Serology
Pelvic Samples	Vaginal pH Wet Mount for BV, Candida and Trichomonas */† Pap Smear at Selected Sites
Specimens for Storage	Vaginal Swabs Cervicovaginal Lavage Plasma PBMC

*If indicated; †PAP smears should be done at 6 month intervals in the first year after seroconversion, and then annually if the initial tests are negative.

MTN-015 participants will be asked to attend a final study visit prior to their termination of participation in the study. This visit will be similar to other follow-up visits.

7.3. Interim Visits

Interim visits may be performed at any time during follow-up. Possible reasons for interim visits include:

- Administrative reasons, e.g., a participant may have questions for study staff or need to re-schedule a follow-up visit
- Clinical reasons, e.g., to report new symptoms or clinical events, or to report initiation of ART
- Psychosocial reasons, e.g., to request HIV-1-related or other counseling or referrals

All interim visits will be documented in participants' study records and when needed, on applicable case report forms.

7.4. Behavioral Evaluations

Behavioral evaluations will include the Baseline Behavioral Questionnaire and a Follow-up Behavioral Questionnaire. These questionnaires will capture participant responses related to sexual behaviors and partnership status. For participants who do not report past or current use of ART at enrollment, behavioral questionnaires will not include questions on ART adherence, and will be performed at 3, 12, and 24 months post-seroconversion. For participants on ART, behavioral questionnaires will be performed at 3, 12, and 24 months post-initiation of ART and an adherence questionnaire will be completed at Month 3, Month 6, and every 6 months thereafter. All behavioral evaluations, as well as the Social Harms Assessment, will be available in the MTN-015 Study-Specific Procedures Manual at www.mtnstopshiv.org.

7.5. Specimen Collection

Each study site will adhere to the standards of good clinical laboratory practice, the HPTN-MTN Network Laboratory Manual (available at www.mtnstopshiv.org), DAIDS Laboratory Requirements (available at http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Labs/), the MTN-015 Study-Specific Procedures Manual (available at www.mtnstopshiv.org), and site standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, and storage at the site laboratories will be documented when applicable using the Laboratory Data Management System (LDMS).

7.5.1. Local Laboratory Specimens

The specimens listed below will be collected for testing at the local laboratory. Duplicate local laboratory testing for co-enrolled protocols is not required. The results of local laboratory tests that are required for another MTN trial, and that are performed within the allowable visit window for such measures according to this protocol, may be used for MTN-015.

Urine Samples
The Local Laboratory or site research staff will test urine for pregnancy. Sites that have a validated SDA method will test urine for Chlamydia and gonorrhea.

Blood Samples
Study site staff will collect blood samples for the following testing at the local laboratory: CD4+ T-cell counts, plasma HIV-1 RNA, complete blood count, liver and renal function tests, and syphilis serology.

Pelvic Samples
Vaginal pH testing and wet mount testing for bacterial vaginosis, candidiasis and trichomoniasis will be conducted at the sites by clinical and/or laboratory staff who have established proficiency in these procedures per MTN policies and procedures.

Pap smears will be performed at sites with the capacity and expertise to prepare and interpret the smears and provide referrals to appropriate follow-up care to participants with abnormal results.

7.5.2. Regional Laboratory Specimens

Serum or plasma will be stored locally at the site labs for HSV-2 testing. These specimens will be shipped in batches to MTN certified regional labs with the appropriate capacity or the MTN Network Laboratory (NL). Sites that are not certified to perform plasma HIV-1 RNA levels may batch and ship these samples to a certified regional lab or the MTN NL.

7.5.3. Network Laboratory Specimens

Study sites will collect, process, and store the following specimens for later shipment to the MTN Network Laboratory: vaginal swabs, cervicovaginal lavage fluid, serum, plasma, urine and PBMC.

Network laboratory (storage) specimens must be collected for MTN-015 as required. Except for HIV-1 seroconversion plasma from the parent trial, sites

may not use specimens collected or stored for another trial as stored specimens for MTN-015.

Vaginal Swabs
Testing on vaginal swabs will include vaginal flora proteomics and markers of inflammation.

Cervicovaginal Lavage
Testing on cervicovaginal lavage samples will include HIV-1 viral load, determining infectious HIV-1 shedding, standard HIV-1 genotypic resistance testing, and molecular analysis of vaginal flora.

Serum
Testing on serum samples will include HIV-1 ELISA and Western blot (if not previously confirmed in a Network Laboratory).

Plasma
Testing on plasma will include standard genotypic resistance testing, allele-specific polymerase chain reaction (PCR) for relevant drug resistance codons, single genome sequencing, and Herpes Simplex Virus – Type II (HSV-2) type-specific antibody.

Urine
Domestic sites that do not have a validated SDA test will ship urine to the MTN NL for Chlamydia and gonorrhea testing

PBMC
Testing on PBMC will include markers of cell-mediated immunity.

7.6. Specimen Handling

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

7.7. Biohazard Containment

As the transmission of HIV-1 and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the CDC and NIH. All biological specimens will be transported using packaging mandated by CFR 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. This applies to both U.S. and

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

8. ASSESSMENT OF SAFETY

MTN-015 is an observational study involving no investigational products or procedures associated with significant risk to participants. Therefore, few safety concerns are expected as a result of study participation. The study site Investigator of Record is responsible for continuous close safety monitoring of all study participants and for alerting the protocol team if unexpected concerns arise. Study sites will have written procedures for ensuring prompt reporting to the IRB/EC(s), of any unanticipated problem involving risks to subjects or others. No safety events will be captured in the study database.

The Manual for Expedited Reporting of Adverse Events to DAIDS will not be used for this study for the following reasons: 1) this study is observational in nature; 2) this study does not involve a study drug or intervention; and 3) adverse events are not primary or secondary objectives of the study.

The study team will monitor for and track unanticipated problems definitely, probably, or possibly related to study procedures and/or to participation in the study, until participants' time of termination from the study. Study staff will provide clinically appropriate treatment and/or referrals should any such problems occur.

For MTN-015 participants both enrolled and not enrolled in a parent study, any unanticipated problems will be reported to the DAIDS Medical Officer at the same time as the problems are reported to the responsible site IRB/Ethics Committees (ECs) overseeing the research according to pre-established procedures as required by 45 CFR 46. Participants co-enrolled in MTN-015 and a parent study will have serious adverse events (SAEs) and Expedited Adverse Events (EAEs) considered reportable in the parent study reported via the safety reporting system utilized by the parent study. Once a participant is no longer enrolled in the parent study, any unanticipated study-related injury will be reported to the site IRB/EC and DAIDS Medical Officer.

As this study will enroll only HIV-infected participants, participants may experience social harms — non-medical adverse consequences — as a result of their participation in the study. Information on social harms will be collected and captured in the study database. Social harms that are judged by the Investigator of Record to be serious or unexpected will be reported to responsible site IRB/ECs at least annually, or according to their individual requirements. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral

to appropriate resources for the safety of the participant as needed. The SDMC (SCHARP) will provide listings of social harms reported by study participants to the protocol team at a minimum of every 6 months per any applicable DAIDS requirements.

Relationship to study participation or procedures will be assessed based on the following definitions:

- **Possibly related:** unanticipated problem and study participation/procedures are reasonably related in time, and the unanticipated problem could be explained equally well by causes other than study participation/procedures.

- **Probably related:** unanticipated problem and study participation/procedures are reasonably related in time, and the unanticipated problem is more likely explained by study participation/procedures than by other causes.

- **Definitely related:** unanticipated problem and study participation/procedures are related in time, and a direct association can be demonstrated with study participation/procedures.

9. CLINICAL MANAGEMENT

9.1. HIV-1 Infection

Study participants will be referred for HIV-1 care and treatment according to local guidelines at the time of HIV-1 diagnosis in the parent microbicide trial. Written site-specific operating procedures for referral for HIV-1 care and treatment are in place at each study site. Study site investigators have identified facilities offering psychological and social services and medical care, including antiretroviral therapy, to people infected with HIV-1 in the study countries. Some of the research sites are part of health care institutions that provide HIV-1 care and support, and can refer women to those services. Other sites have established referral agreements with programs to expand access to antiretroviral therapy, such as those funded by the US President's Emergency Plan for AIDS Relief (PEPFAR). The level of care provided at the referral sites will be at a level that meets or exceeds the community standard for HIV-1 care. At every study visit, study staff will actively follow-up on prior referrals to HIV-1 care and support services, to determine whether the participant sought the care to which she was referred, determine the outcome of the referral, and determine whether additional referrals are needed. Additional counseling also may be needed to help ensure the participant receives appropriate care. All follow-up actions, outcomes, counseling, and plans for next steps should be documented in detailed chart

notes. Results of laboratory testing in MTN-015 may be helpful in clinical management; these results will be provided to the participant and her medical provider in real-time.

9.2. Reproductive Tract Infection

Participants who are diagnosed with a sexually transmitted infection (STI) or other reproductive tract infection (RTI) will be provided treatment in accordance with current World Health Organization (WHO) guidelines, free of charge. Observed single-dose treatment will be provided whenever possible. Participants with STIs will be encouraged to refer their partners for testing and treatment if applicable. Sites will not be required to offer or provide treatment for asymptomatic bacterial vaginosis or candida noted at study visits.

9.3. Pregnancy

Participants who are found to be pregnant during the study period will continue to be followed. Study sites will refer pregnant participants to providers of obstetric and gynecologic care for counseling and further related care. Every effort will be made to facilitate access to PMTCT. Any PMTCT medication received by the participant will be documented as a concomitant medication. Protocol-defined gynecologic exams and pelvic specimen collection will not be performed on pregnant participants if the following symptoms are reported: vaginal bleeding or spotting, suspected or documented rupture of membranes, or active labor; these participants will be referred to an obstetric/gynecologic care provider.

9.4. Provision of Test Results

Because laboratory testing will be performed at all scheduled study visits, a post-visit contact is required after each visit to provide participants with their test results, clinically relevant post-test counseling, and/or clinically indicated treatment. Study staff may complete these contacts at the study site or at community-based locations, depending on site capacities and site and participant preferences. All contacts will be documented in participant study records and written documentation of test results will be provided upon request to participants and/or their primary HIV-1 care providers.

9.5. Criteria for Discontinuation of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The site investigators may withdraw participants from the study to protect their safety, and/or if participants are unable or unwilling to comply with required study procedures. The investigators may withdraw a participant from the study if any condition in the opinion of the investigator would impose a health risk to the participant. Participants also may be withdrawn if the study sponsors, government or regulatory authorities (including the Office of Human Research

Protection (OHRP)), or site IRBs/ECs terminate the study prior to its planned end date. Site investigators are required to consult the Protocol Chair and Protocol Biostatistician prior to the termination of any study participant. Study staff will record the reason(s) for all withdrawals in participants' study records. In the event that participants who voluntarily withdraw from the study wish to re-join the study, they may resume study procedures and follow-up.

The criteria for discontinuation of further study procedures for an individual participant are:

- Request by participant to withdraw
- Clinical reasons determined by the physician
- Lost to follow-up
- Participant repeatedly non-compliant with study procedures as prescribed

Participants will be asked to complete a final study visit.

10. STATISTICAL CONSIDERATIONS

10.1. Overview and General Design

This is a prospective cohort study of seroconverters identified in microbicide trials. Currently, participants will come from two trials: HPTN 035 and HPTN 059.

The targeted number of seroconverters (i.e. HIV endpoints) in HPTN 035 is 192 while the expected number of HIV endpoints in HPTN 059 is much smaller (0 to 2 seroconverters only). Given that it is difficult to anticipate the number of seroconverters generated by future MTN trials, we will conservatively estimate the available sample size at 192.

10.2. Study Endpoints

10.2.1. Primary Endpoint

Virologic Response
Consistent with the primary study objective, plasma HIV-1 RNA 12 months after identification of HIV-1 seroconversion will be the primary endpoint. Comparison of the plasma HIV-1 RNA level 12 months after HIV-1 seroconversion between active microbicide and placebo/control groups is the primary objective of this study.

10.2.2. Secondary Endpoints

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

- **Immunologic response**. (**CD4+ T cell count)**. $CD4^+$ T cell counts at Weeks 0 and 2, Months 1, 3, 6 and every 6 months thereafter. Time from seroconversion to immunologic failure will be compared between active microbicide and placebo/control groups. Immunologic failure is defined as two consecutive measurements of CD4+ T-cell count within or below the range of 200-250 cells/mm^3, or the development of an AIDS defining illness.

- **Virologic and immunologic responses (CD4+ T-cell count**) **after initiation of ART.** CD4+ T-cell count and blood plasma HIV-1 RNA levels over time after initiation of ART. Time from initiation of ART to immunologic and virologic failure.

- **HIV-1 related and AIDS-defining events**. Occurrence and frequency of HIV-1 related and AIDS-defining events. Time from enrollment to time of first AIDS-defining event or death.

- **Sexual behavior, partnership status, and occurrence of social harms**. Sexual behavior over time following seroconversion at Months 0, 3, 12, and 24 months. Participants who enroll ≥3 months after seroconversion will be followed at 12 months and 24 months only.

- **HIV-1 genotypic mutations and drug resistant virus**. Prevalence of HIV-1 genotypic mutations over time and drug resistant HIV-1 virus in plasma and genital tract. Proportions of infected participants acquiring a drug resistant HIV-1 virus.

10.3. Sample Size

Preliminary data from the University of Washington/Fred Hutchinson Cancer Research Center (UW/FHCRC) Primary Infection Clinic was used to estimate within and between person components of variance in individuals with early HIV-1 infection. These data are taken from 150 days to 2 years post infection and, therefore, should give reasonable estimates of the variability in viral load around the viral set point. The between person variance component is 0.52 (log_{10} $copies^2/ml^2$) and the within person variance component is 0.096 (log_{10} $copies^2/ml^2$).[xv]

In the HPTN 035 trial we expect 192 seroconverters: 128 in the placebo gel and control groups and 64 in the PRO2000 and BufferGel groups assuming an effectiveness of 50% for both active microbicides. This breakdown between groups is conservative since the true effectiveness will most likely be lower. Effectiveness that is lower than 50% will slightly improve the power of this study since the numbers between the active microbicide and placebo/control groups would be more balanced.

However not all of these 192 will be available for the evaluation of the primary endpoint at one year after seroconversion since:

By the time this study is in the field, several participants will have seroconverted more than one year ago. We estimate this number to be around 20 such that we will have 172 eligible seroconverters for the evaluation of the primary objective.

Newly-infected women may have elected to terminate from the parent study and/or do not wish to enroll in this study and/or have been lost to follow-up in the parent study. Of the 172 eligible women, we estimate that 15% of the women eligible for this study will not enroll due to one of the above reasons.

We will target no more than 5% lost to follow-up per year.

Therefore we anticipate that 138 seroconverters (92 from the placebo and control groups and 46 from the active microbicide groups, assuming that the active microbicides reduce HIV acquisition by 50%) will be available for the evaluation of the primary objective one year after seroconversion. The following table gives the power to detect various differences in the viral set point between the active microbicide and placebo/control groups.

Table 7: Power Calculation for Primary Endpoint

Power to detect the indicated difference in $\log_{10}$ HIV RNA (viral set point) between active microbicide and placebo/control groups assuming 46 and 92 individuals in those groups, respectively. The two-sided α level is 0.05.			
	Difference in $\log_{10}$ plasma HIV RNA (viral set point) at 12 months between active microbicide and placebo/control groups		
No. obs/person	0.3	0.4	0.5
1	56%	80%	94%
2	59%	83%	96%
3	61%	84%	96%
4	61%	85%	96%

Thus, we have 80% power to detect a difference of 0.4 $\log_{10}$ copies/ml in viral set point at one year. This difference is comparable to what might be expected with nucleoside monotherapy and the minimum change in viral load that could have a measurable effect on HIV-1 disease progression. Due to the relatively low within-person variation in viral load, multiple measurements on an individual do not produce a significant increase in power. As mentioned above, if the effectiveness of the active microbicides is smaller than 50% then the power in this study would slightly increase since the numbers between the comparison groups would be more balanced.

From the available data and a poll of the site investigators currently conducting HPTN 035, we believe the number of women initiating ART in the first 6-12 months after seroconversion will be very low, less than 10%. Given that the primary analysis will be restricted to seroconverters that have not initiated ART in the first 12 months of seroconversion, the power of the study will decrease slightly. Assuming that 10% of seroconverters will initiate ART within the first 12 months, the study will have at least 76% power to detect a difference of 0.4 $\log_{10}$ copies/ml in viral set point at one year.

10.4. Blinding

Blinding/unblinding processes will be dictated by the parent study from which the participants are coming. Both study staff and participants will be blinded to the random assignments of participants assigned to study treatment groups that include a study product. However, the assignment of participants to the no treatment group (e.g. condom only arm in HPTN 035) cannot be blinded. Randomization documentation and other pharmacy records must not be accessible to study staff members who complete other study procedures with participants.

Blinding will be maintained until all data are entered into the parent study database, all study endpoint data and other data included in the final analysis have been cleaned and verified, and the data are ready for final analysis in the parent study. Unblinding of data will only occur after the unblinding of the data in the parent study. This will be explained to participants as part of the study informed consent process.

There are no circumstances under which it is expected that unblinding will be necessary for the provision of medical treatment or to otherwise protect the safety of study participants. If an Investigator feels that specific product knowledge is necessary to protect participant safety, the Investigator will notify the Protocol Chair, Protocol Biostatistician, and DAIDS Medical Officer (or designees) to consider and jointly rule upon the request.

10.5. Participant Accrual and Retention

All seroconverters, regardless of their seroconversion date, from the ongoing HPTN 035 and 059 trials will be recruited into this study. Although some of these participants would have seroconverted more than a year ago, which would make them ineligible for the primary objective of this study, those participants could be used in the assessment of some of the secondary objectives. All newly identified seroconverters during follow-up in HPTN 035 and 059 will be recruited for this study.

Once a participant has enrolled in the study, the study site will make every reasonable effort to retain her for the entire study period. A maximum of 5% annual loss-to-follow-up of enrolled participants is targeted.

10.6. Data and Safety Monitoring and Analysis

10.6.1. Study Monitoring Committee (SMC)

No Data and Safety Monitoring Board (DSMB) oversight is planned for this observational study. The MTN SMC will conduct interim reviews of study progress (blinded to treatment assignment), including rates of participant accrual, retention, completion of primary and main secondary endpoint assessments, and study or lab issues. These reviews will take place approximately every 4-6 months, or as needed. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. The SMC may consider recommending termination of this study if recruitment and retention are lower than targeted, or if study data quality is poor.

10.6.2. Data Analysis

Primary Analyses

Descriptive analyses of the seroconverters will include calculation of the mean and median viral load by active microbicide and placebo/control groups. A simple t-test can be used to compare log-transformed viral load levels between these two groups. However, caution must be exercised in the interpretation of any difference (or lack of difference) found. Although the overall active microbicide and placebo/control groups should be comparable at baseline (in the parent study) due to randomization, individuals who seroconvert in the active microbicide group may not be comparable to individuals who seroconvert in the placebo/control group. Approaches described by Gilbert et al, Biometrics, 2003 will be used for isolating the effect of an intervention on post-seroconversion outcomes.[xvi] Furthermore, the primary analysis will be restricted to

seroconverters that have not initiated ART in the first 12 months after seroconversion.

Linear regression using the log-transformed viral load levels as the outcome and baseline or other covariates (e.g. CD4+ T-cell) will be used to compute adjusted differences between the active microbicide and placebo/control groups. The interpretation of these adjusted differences is subject to the same cautions noted above.

Sub-group exploratory analyses will be performed to explore difference between type of products and type of controls. Mainly, seroconverters will be grouped by the type of intervention received: (1) PRO2000, (2) BufferGel, (3) Placebo gel, and (4) Condom only.

Secondary Analyses

Secondary analyses of CD4+ T-cell counts will be virtually identical to those described for viral load levels above, although it is typically not necessary to log-transform CD4+ T-cell levels to obtain valid inferences. Descriptive statistics will be used to characterize overall CD4+ T-cell levels and levels within subgroups. T-tests and linear regression will be used to obtain unadjusted and adjusted estimates of the treatment effect. Again, the interpretation of these differences is subject to the same cautions noted above for the primary analyses.

Many other secondary analyses will be performed using the secondary endpoints described in Section 10.2.2. Time-to-event secondary endpoints will be analyzed according to the Kaplan-Meier method where differences between groups will be tested using the stratified log-rank test while secondary endpoints involving repeated assessment over time (e.g. sexual behavior) will be compared at selected time points. At each of the selected time points, comparison of the two groups will be made using Fisher exact test or Wilcoxon rank-sum test as appropriate. More generally, GEE (Generalized Estimating Equation) methods and robust variance estimates will be used to evaluate group.

Data on behaviors that are associated with HIV-1 transmission such as sexual intercourse without a condom, the frequency of sexual intercourse, and the numbers of sexual partners will be measured over time among women in this study and compared to the same behaviors reported by women in ongoing microbicide trials (including parent trials) who are HIV-1 negative and to large household surveys of women (Demographic Health Surveys) in the same countries as the women in this study are located.

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 will be generated and distributed to the study sites for verification and resolution.

11.2. Source Documents and Access to Source Data/Documents

Source documents and access to source data/documents will be maintained in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. The investigator will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with 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-015 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

Study implementation will be directed by this protocol and further guided by the Study-Specific Procedures Manual 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, study-specific procedures manual, and local counseling practices

- Confirm the quality and accuracy of information collected at the study site and entered into the study database, including the validation of data reported on case report and DataFax forms

- Assess the resolution of any past or ongoing issues identified at previous monitoring visits

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

13. HUMAN SUBJECTS PROTECTIONS

The investigators will make efforts to minimize risks of study procedures to human participants. Volunteers will take part in a thorough informed consent process throughout their participation in the study. Before beginning the study, the investigators will have obtained IRB/EC approval. The investigators will permit audits by the NIH or any of their appointed agents.

13.1. Institutional Review Boards

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

13.2. Protocol Registration and Study Activation

Each study site will complete protocol registration with the DAIDS Regulatory Compliance Center (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. MTN CORE staff will notify each study site when all activation requirements have been met by issuing a site-specific study activation notice. Study implementation may not be initiated until the activation notice is issued.

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and NIAID Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRBs/ECs and the RCC prior to implementing the amendment.

13.3. Risk/Benefit Statement

Risks

Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection. Pelvic examination may cause mild discomfort and/or vaginal bleeding or spotting. Disclosure of STI status may cause sadness or depression in volunteers. Participation in clinical research includes the risks of loss of confidentiality and discomfort with personal nature of questions. Participation in any study that only enrolls HIV-infected participants may be associated with the risk of social harms, including negative effects experienced in the context of intimate or other social relationships.

Benefits

Participation in this study may provide no direct benefit to volunteers. Some volunteers may have the opportunity to access earlier treatment for HIV-1 infection due to monitoring of CD4+ T cell counts and plasma HIV-1 RNA. Study participants will receive STI risk reduction counseling, HIV-1 secondary prevention counseling, condoms, STI testing, physical exams, and pelvic exams. They will be provided STI treatment in accordance with current WHO guidelines free-of-charge, and will be offered STI testing and treatment for their partners. Additionally laboratory abnormalities in hematology or liver or kidney function tests will be provided to the participant and her primary care provider (with her permission). Lastly, the participant may appreciate the opportunity to contribute to the body of knowledge in the field of microbicide research.

13.4. Informed Consent Process

Written informed consent will be obtained from all potential study participants prior to the initiation of any study-related procedures. In obtaining and documenting informed consent, the investigators and their designees will comply with applicable local and 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 DAIDS Standard Operating Procedure for Source Documentation. Participants are provided with copies of the informed consent forms if they are willing to receive them. Each study site is responsible for developing study informed consent forms for local use, based on the templates in Appendices VII and VIII that describe the purpose of screening and of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. Each study site also is responsible for translating the template forms into local languages, and verifying the accuracy of the translation by performing an independent back-translation.

Prior to the beginning of the trial, site investigators will have the IRBs'/ECs' 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.

In addition to the informed consent forms, Protocol Team members have worked with study staff and community representatives to develop locally-appropriate information materials about the study and a standardized approach to the informed consent process to be implemented at all study sites, which is detailed in the study-specific procedures manual. The process and materials were tested prior to study start-up to ensure cultural appropriateness at each site. 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 to do if such risks are experienced).
- The potential social harms associated with study participation (and what to do if such harms are experienced).
- The real yet limited benefits of study participation.
- The distinction between research and clinical care.
- The right to withdraw from the study at any time.

13.5. Participant Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Each study site will establish a standard operating procedure for confidentiality protection that reflects the local study implementation plan (e.g., whether community-based visits will be conducted) and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them. In addition to local considerations, the protections described below will be implemented at all sites.

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. Data collection, process, and administrative forms, laboratory specimens, and other reports will be identified by a coded number only to maintain participant confidentiality. All 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 will apply for a Certificate of Confidentiality from the US Department of Health and Human Services that will be applicable for this study. This Certificate protects study staff from being compelled to disclose study-related information by any US Federal, State or local civil, criminal, administrative, legislative or other proceedings. It thus serves to protect the identity and privacy of study participants. Since the Certificate cannot be enforced outside of the US, however, it will apply only to US site staff and participants.

13.6. Special Populations

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

13.6.1 Pregnant Participants

Pregnant participants will not be excluded from participation in this natural history cohort study. Participants who are pregnant at Enrollment or at any time during the study follow up will be referred to local obstetric/gynecologic providers for pregnancy options counseling, including treatment to prevent Maternal-to-Child Transmission of HIV-1. Pelvic exams, the collection of pelvic specimens, and

blood draws may be deferred or reduced during pregnancy at the discretion of the site investigator.

13.6.2 Children

The NIH Policy on Inclusion of Children defines a child as an individual under the age of 21 years. The intent of the NIH policy is to provide the opportunity for children to participate in research studies when there is a sound scientific rationale for including them, and their participation benefits children and is appropriate under existing Federal guidelines. Thus, children must be included in NIH conducted or supported clinical research unless there are scientific and ethical reasons not to include them. This study will enroll eligible participants aged 18 to 21 years that are able to provide written informed consent.

13.6.3 Prisoners

MTN-015 does not meet the criteria for prisoner participation per US 45 Code of Federal Regulations (CFR) 46.306 (a)(2)(D). MTN-015 is not suitable for further reviews by local IRBs/ECs for the inclusion of prisoners.

13.7. Incentives

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

13.8. Communicable Disease Reporting

Study staff will comply with all applicable local requirements to report communicable diseases 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-1-Related Care

According to site standard operating procedures (SOPs), study staff will refer participants to available sources of medical (including ART) and psychological care, social support, and local clinical trials for HIV-1-infected participants.

13.10. Study Discontinuation

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

14. PUBLICATION POLICY

DAIDS and MTN policies 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 and DAIDS for review prior to submission.

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

	Screening and Enrollment	Month 1 Post-Seroconversion	Month 3 Post - Seroconversion	Mo. 6/Q6 Mo. Post-Seroconversion	Week 2, Month 1, Month 3 Post-ART Initiation	Month 6 and Q6 Months Visits After Initiation of ART	Final Visit
Administrative Procedures							
Informed Consent	X						
Review Parent Study Records (Confirm HIV-1 Seroconversion)	X						
Eligibility Determination	X						
Assign Participant ID	X						
Update Locator Information	X	X	X	X	X	X	X
Update Demographics	X						
Schedule Next Visit	X	X	X	X	X	X	
Reimbursement	X	X	X	X	X	X	X
Clinical							
Record/Update Medical History and Clinical Events	X	X	X	X	X	X	X
Acute Seroconversion Assessment	X						
Concomitant Medications Assessment	X	X	X	X	X	X	X
Antiretroviral Treatment Record	▲				X	X	▲
Provide Test Results	▲	▲	▲	▲	▲	▲	▲
Treatment or Referral	▲	▲	▲	▲	▲	▲	▲
Complete Physical Exam	X						
Targeted Physical Exam		X	X	X	X	X	X
Gynecologic Exam	X	X	X	X	X	X	X
Behavioral							
Baseline Behavioral Questionnaire	X						
Follow-Up Behavioral Questionnaire			X	X (Mo. 12 and Mo. 24)	*X (Mo. 3 Post-ART Initiation)	*X (Mo. 12 and Mo. 24 Post-ART Initiation)	
Adherence Questionnaire	▲				X Mo 3	X	▲
STI Risk Reduction/Contraception Counseling	X			X		X	X
HIV-1 Secondary Prevention Counseling	X			X		X	X
Social Harms Assessment			X	X	X	X	X
Provision of Condoms	X	X	X	X	X	X	X
Laboratory Procedures							
Approx. Total Blood Volume Collected (mL)	83	72	77	77	72	77	77
Urine Qualitative hCG	X	▲	▲	▲	▲	▲	X
Urine SDA for Chlamydia, GC	X	▲	▲	▲ (Annual)	▲	▲ (Annual)	X
CBC, Liver and Renal Function	X		X	X	▲	X	X
Syphilis Serology	X	▲	▲	▲ (Annual)	▲	▲ (Annual)	X
CD4+ T-Cell Count	X	X	X	X	X	X	X
Plasma HIV-1 RNA	X	X	X	X	X	X	X
HIV-1 Genotypic Resistance Test (at NL)	X				▲	▲	
HIV ELISA and Western Blot	▲						
HSV-2 Serology (using archived plasma)	X						
Vaginal pH	X	▲	▲	▲ (Annual)	▲	▲ (Annual)	X
Wet Mount for BV, Candida, Trichomonas	X	▲	▲	▲ (Annual)	▲	▲ (Annual)	X
PAP Smear at Selected Sites	X	▲	▲	▲ (Annual)	▲	▲ (Annual)	▲
Specimens for Storage							
Vaginal Swabs	X	X	X	X	X	X	X
Cervicovaginal Lavage	X	X	X	X	X (Mo. 3)	X	X
Plasma	X	X	X	X	X	X	X
Serum	X						
PBMC	X	X	X	X	X (Wk. 2 and Mo. 3)	X	X

X=protocol-defined procedure; ▲=performed as indicated; *If ART is begun more than 24 months after identification of seroconversion, then the Follow-Up Behavioral Questionnaire is omitted at post-ART visits.

APPENDIX II: SITES AND SITE INVESTIGATORS

- Lisa Maslankowski, University of Pennsylvania, Philadelphia, Pennsylvania, USA
- Bonus Makanani and Newton Kumwenda, Queen Elizabeth Central Hospital, Blantyre, Malawi
- Francis Martinson, Lilongwe Central Hospital, Lilongwe, Malawi
- Muzala Kapina, Kamwala Health Centre, Lusaka, Zambia
- Mike Chirenje, and Tsitsi Magure, University of Zimbabwe Obstetrics and Gynaecology Research Clinic at Spilhaus Zimbabwe
- Mike Chirenje and Tsitsi Magure, Seke South Clinic (Chitungwiza), Chitungwiza, Zimbabwe
- Gita Ramjee, Medical Research Council-Hlabisa, Hlabisa, South Africa
- Gita Ramjee, R.K. Khan Hospital, Chatsworth, South Africa
- Smita N. Joshi, Jehangir Hospital - NARI Clinic, Pune, India
- Craig Hoesley, University of Alabama at Birmingham, Birmingham, Alabama, USA
- Jessica Justman, Bronx-Lebanon Hospital Center, New York, New York, USA
- Sharon A. Riddler, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
- Michael Lederman, Case Western Reserve University, Cleveland, Ohio, USA
- Laura Guay, Makerere University, Kampala, Uganda
- David Coetzee, University of Cape Town, Cape Town, South Africa

APPENDIX III: SITE LABORATORIES

Site Laboratory:
National AIDS Research Institute
Plot No. 73, G Block
M.I.D.C. Bhosari
Pune, Maharashtra 411 026
India

Site Laboratory:
University of Alabama Hospital Lab
619 South 19th Street
Birmingham, Alabama 35233-1924
USA

Site Laboratory:
UAB Div of Infectious Diseases Lab
THT 220 1900 University Boulevard
Birmingham, Alabama 35294
USA

Site Laboratory:
LabCorp
Raritan Facility
69 First Avenue
Raritan, NJ 08869
USA

Site Laboratory:
CIDRZ Central Laboratory
Kalingalinga District Clinic
Off Alick Nkhata Road
Kalingalinga
Post Office Box 34681
Lusaka
Zambia

Site Laboratory:
Children's Hospital of Philadelphia
Abramson Research Center 1204K
34th Street and Civic Center Boulevard
Philadelphia, PA 19104
USA

Site Laboratory:
Queen Elizabeth Central Hospital
P.O. Box 1131
Chipatala Avenue
Blantyre, Malawi

Site Laboratory:	Tidziwe Centre Lilongwe Central Hospital 100 Mzimba Road Lilongwe, Malawi
Site Laboratory:	UZ-UCSF Collaborative Research Programme in Women's Health 15 Phillips Avenue Harare, Zimbabwe
Site Laboratory:	Lancet 102 Lancet Medical Centre 74 Lorne Street Durban, South Africa
Site Laboratory:	Lancet (BARC) First Floor, Napier House Napier Road, Richmond Johannesburg, South Africa
Site Laboratory:	Empangeni Garden Hospital Suite 8, 1st Floor Consulting Blocks Corner of Ukula and Biyela Street Empangeni, South Africa
Site Laboratory:	Department of Cytology Nkosi Albert Luthuli Central Hospital 800 Bellair Road Mayville, 4091 South Africa
Site Laboratory:	MU-JHU Research Collaboration Lab IDIL at New Mulago Hospital Complex P.O. Box 22418, Kampala, Uganda

APPENDIX IV: PHYSICAL EXAM AND GYNECOLOGIC EXAM COMPONENTS

Complete Physical Exam

- Vital signs
    - Temperature
    - Pulse
    - Blood pressure
- Height
- Weight
- General appearance
- Skin
- Head and neck
- Lungs
- Heart
- Abdomen

Targeted Physical Exam

- Vital signs
    - Temperature
    - Pulse
    - Blood pressure
- Weight
- Other components as indicated by participant symptoms

Gynecologic Exam

- Vulva
- Perianal area
- Speculum exam
    - Vagina (including vaginal discharge)
    - Cervix (including cervical discharge)
- Bimanual exam
    - Cervix
    - Uterus
    - Adnexae
- Inguinal area
    - Lymph nodes

APPENDIX V: WHO CRITERIA FOR HIV STAGING EVENTS

These criteria are current as of the protocol version date shown in the footer. Future updates to these criteria will be adopted as appropriate.

CRITERIA FOR HIV STAGING EVENTS
Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Clinical stage 1		
Asymptomatic	No HIV-related symptoms reported and no signs on examination	Not applicable
Persistent generalized lymphadenopathy	Painless enlarged lymph nodes >1 cm in two or more non-contiguous sites (excluding inguinal) in the absence of known cause and persisting for three months or more	Histology
Clinical stage 2		
Unexplained moderate weight loss (<10% of body weight)	Reported unexplained involuntary weight loss in pregnancy failure to gain weight	Documented weight loss <10% of body weight
Recurrent upper respiratory tract infections (current event plus one or more in last six-month period)	Symptom complex, such as unilateral face pain with nasal discharge (sinusitis), painful inflamed eardrum (otitis media) or tonsillopharyngitis without features of viral infection (such as coryza or cough)	Laboratory studies where available, such as culture of suitable body fluid
Herpes zoster	Painful vesicular rash in dermatomal distribution of a nerve supply, does not cross the midline	Clinical diagnosis
Angular cheilitis	Splits or cracks at the angle of the mouth not due to iron or vitamin deficiency, usually respond to antifungal treatment	Clinical diagnosis

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Recurrent oral ulceration (two or more episodes in last six months)	Aphthous ulceration, typically painful with a halo of inflammation and a yellow-grey pseudomembrane	Clinical diagnosis
Papular pruritic eruption	Papular pruritic lesions, often with marked post-inflammatory pigmentation	Clinical diagnosis
Seborrhoeic dermatitis	Itchy scaly skin condition, particularly affecting hairy areas (scalp, axillae, upper trunk and groin)	Clinical diagnosis
Fungal nail infection	Paronychia (painful red and swollen nail bed) or onycholysis (separation of the nail from the nail bed) of the fingernails (white discoloration – especially involving proximal part of nail plate – with thickening and separation of the nail from the nail bed)	Fungal culture of the nail or nail plate material
Clinical stage 3		
Unexplained severe weight loss (more than 10% of body weight)	Reported unexplained involuntary weight loss (>10% of body weight) and visible thinning of face, waist and extremities with obvious wasting or body mass index <18.5 kg/m2; in pregnancy, the weight loss may be masked	Documented loss of more than 10% of body weight

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Unexplained chronic diarrhoea for longer than one month	Chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month	Three or more stools observed and documented as unformed, and two or more stool tests reveal no pathogens
Unexplained persistent fever (intermittent or constant and lasting for longer than one month)	Fever or night sweats for more than one month, either intermittent or constant with reported lack of response to antibiotics or antimalarial agents, without other obvious foci of disease reported or found on examination; malaria must be excluded in malarious areas	Documented fever >37.5°C with negative blood culture, negative Ziehl-Nielsen stain, negative malaria slide, normal or unchanged chest X-ray and no other obvious focus of infection
Persistant oral candidiasis	Persistent or recurring creamy white curd-like plaques that can be scraped off (pseudomembranous) or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form)	Clinical diagnosis
Oral hairy leukoplakia	Fine white small linear or corrugated lesions on lateral borders of the tongue that do not scrape off	Clinical diagnosis

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Pulmonary tuberculosis (current)	Chronic symptoms: (lasting at least 2–3 weeks) cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats. PLUS EITHER positive sputum smear OR negative sputum smear AND compatible chest radiograph (including but not restricted to upper lobe infiltrates, caritation, pulmonary fibrosist shrinkage. No evidence of extrapulmonary diseas	Isolation of *M. Tuberculosis* on sputum culture or histology of lung biopsy (with compatible symptoms)
Severe bacterial infection (such as pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia and severe pelvic inflammatory disease)	Fever accompanied by specific symptoms or signs that localize infection and response to appropriate antibiotic	Isolation of bacteria from appropriate clinical specimens (usually sterile sites)
Acute necrotizing ulcerative gingivitis or necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour and rapid loss of bone and/or soft tissue	Clinical diagnosis

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 10^9 per litre) or chronic (more than one month) thrombocytopaenia (<50 × 10^9 per litre)	Not presumptive clinical diagnosis	Diagnosed on laboratory testing and not explained by other non-HIV conditions; not responding to standard therapy with haematinics, antimalarial agents or anthelmintic agents as outlined in relevant national treatment guidelines, WHO Integrated Management of Childhood Illness guidelines or other relevant guidelines
Clinical stage 4		
HIV wasting syndrome	Unexplained involuntary weight loss (>10% baseline body weight), with obvious wasting or body mass index <18.5 PLUS EITHER unexplained chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month OR reports of fever or night sweats for more than one month without other cause and lack of response to antibiotics or antimalarial agents; malaria must be excluded in malarious areas	Documented weight loss (>10% of body weight) PLUS EITHER two or more unformed stools negative for pathogens OR documented temperature of >37.5°C with no other cause of disease, negative blood culture, negative malaria slide and normal or unchanged chest X-ray

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Pneumocystis pneumonia	Dyspnoea on exertion or nonproductive cough of recent onset (within the past three months), tachypnoea and fever AND Chest X-ray evidence of diffuse bilateral interstitial infiltrates AND No evidence of bacterial pneumonia; bilateral crepitations on auscultation with or without reduced air entry	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage or histology of lung tissue
Recurrent bacterial pneumonia (this episode plus one or more episodes in last six months)	Current episode plus one or more previous episodes in the past six months; acute onset (<2 weeks) of severe symptoms (such as fever, cough, dyspnoea, and chest pain) PLUS new consolidation on clinical examination or chest X-ray; response to antibiotics	Positive culture or antigen test of a compatible organism
Chronic herpes simplex virus infection (orolabial, genital or anorectal) of more than one month or visceral infection of any duration	Painful, progressive anogenital or orolabial ulceration; lesions caused by recurrence of herpes simplex virus infection and reported for more than one month. History of previous episodes. Visceral herpes simplex virus requires definitive diagnosis	Positive culture or DNA (by polymerase chain reaction) of herpes simplex virus or compatible cytology or histology

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Oesophageal candidiasis	Recent onset of retrosternal pain or difficulty on swallowing (food and fluids) together with oral Candidasis	Macroscopic appearance at endoscopy or bronchoscopy, or by microscopy or histology
Extrapulmonary tuberculosis	Systemic illness (such as fever, night sweats, weakness and weight loss). Other evidence for extrapulmonary or disseminated tuberculosis varies by site: Pleural, pericardia, peritoneal involvement, meningitis, mediastinal or abdominal lymphadenopathy or ostetis Discrete peripheral lymph node *Mycobacterium* tuberculosis infection (especially cervical) is considered a less severe form of extrapulmonary tuberculosis	*M. tuberculosis* isolation or compatible histology from appropriate site or radiological evidence of miliary TB (diffuse uniformly distributed small miliary shadows or micronodules on chest X-ray).
Kaposi sarcoma	Typical gross appearance in skin or oropharynx of persistent, initially flat, patches with a pink or violaceous colour, skin lesions that usually develop into plaques or nodules	Macroscopic appearance at endoscopy or bronchoscopy, or by histology

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Cytomegalovirus disease (other than liver, spleen or lymph node)	Retinitis only: may be diagnosed by experienced clinicians. Typical eye lesions on fundoscopic examination: discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis	Compatible histology or cytomegalovirus demonstrated in cerebrospinal fluid by culture or DNA (by polymerase chain reaction)
Central nervous system toxoplasmosis	Recent onset of a focal nervous system abnormality consistent with intracranial disease or reduced level of consciousness AND response within 10 days to specific therapy	Positive serum toxoplasma antibody AND (if available) single or multiple intracranial mass lesion on neuroimaging (computed tomography or magnetic resonance imaging)
HIV encephalopathy	Disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks or months in the absence of a concurrent illness or condition other than HIV infection that might explain the findings	Diagnosis of exclusion: and (if available) neuroimaging (computed tomography or magnetic resonance imaging)
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy	Isolation of *Cryptococcus neoformans* from extrapulmonary site or positive cryptococcal antigen test on cerebrospinal fluid or blood

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Disseminated non-tuberculous mycobacteria infection	No presumptive clinical diagnosis	Diagnosed by finding atypical mycobacterial species from stool, blood, body fluid or other body tissue, excluding the lungs
Progressive multifocal leukoencephalopathy	No presumptive clinical diagnosis	Progressive nervous system disorder (cognitive dysfunction, gait/speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuro-imaging or positive polyomavirus JC polymerase chain reaction on cerebrospinal fluid
Chronic cryptosporidiosis (with diarrhoea lasting more than one month)	No presumptive clinical diagnosis	Cysts identified on modified Ziehl-Nielsen stain microscopic examination of unformed stool
Chronic isosporiasis	No presumptive clinical diagnosis	Identification of *Isospora*
Disseminated mycosis (coccidiomycosis or histoplasmosis)	No presumptive clinical diagnosis	Histology, antigen detection or culture from clinical specimen or blood culture
Recurrent non-typhoid *Salmonella* bacteraemia	No presumptive clinical diagnosis	Blood culture
Lymphoma (cerebral or B-cell non-Hodgkin)	No presumptive clinical diagnosis	Histology of relevant specimen or, for central nervous system tumours, neuroimaging techniques
Invasive cervical carcinoma	No presumptive clinical diagnosis	Histology or cytology

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Atypical disseminated leishmaniasis	No presumptive clinical diagnosis	Diagnosed by histology (amastigotes visualized) or culture from any appropriate clinical specimen
Symptometic HIV-associated nephropathy	No presumptive clinical diagnosis	Renal biopsy
Symptometic HIV-associated cardiomyopathy	No presumptive clinical diagnosis	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography

APPENDIX VI: HEMATOLOGY, LIVER AND RENAL FUNCTION

Hematology	Hemoglobin Red blood cells Mean corpuscular volume Platelets White blood cell count Differential WBC (% and absolute count) Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Liver and Renal Function Tests	Total bilirubin AST (SGOT) ALT (SGPT) Alkaline phosphatase Creatinine

APPENDIX VII: SAMPLE INFORMED CONSENT (SCREENING AND ENROLLMENT)

MTN-015
An Observational Cohort Study of Women following HIV-1 Seroconversion in Microbicide Trials

Final Version 1.0
June 19, 2007

PRINCIPAL INVESTIGATOR: **[insert]**
PHONE: **[insert]**
Short Title for the Study: **MTN HIV-1 Seroconverter Study**

Introduction

MTN-015 is a long-term research study of women who have become infected with the human immunodeficiency virus (HIV) while taking part in a microbicide study. You are being asked to take part in this study because you have become infected with HIV during a microbicide study. HIV is the virus that causes AIDS.

This study is being paid for by the United States National Institutes of Health. The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR].

Before you decide whether to take part 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 take part in this study, you will be asked to sign or make your mark on 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 using a microbicide affects the health of women after they become infected with HIV. For example, the study will look at whether using a microbicide at the time of HIV infection affects the amount of HIV in the blood after infection. The study will also look at possible microbicide effects on other aspects of health such as illnesses that women may get after HIV infection.

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

This study is planned to continue until the year 2013. If you decide to take part in this study, you will be asked to come back for study visits for as long as the study is going on. At study visits, you will answer questions, have physical exams, and give blood, urine, and fluids from your vagina for laboratory tests. Condoms will be given to you at every visit. Some of these samples also will be stored for later testing. This later testing will take place in the United States and will be done for research purposes only. Your samples will not be sold or used to make products that could be sold.

The visits you will have in this study are described in detail below.

If you are still taking part in your microbicide study, you can stay in that study and be in this study at the same time.

Screening/Enrollment Visit:

This visit will continue today after you read, discuss and sign or make your mark on this form. It will take about 2 hours. The study clinician will review the records from your microbicide study to make sure you meet the requirements for this study. Then you will be asked some questions. The questions will be about you, where you live, your health, medicines you take, and your sexual practices. You also will:

- Talk with study staff about HIV, infections passed during sex, ways to avoid getting these infections and passing them to someone else.
- Receive condoms.
- Give urine to test for pregnancy, gonorrhea, and chlamydia. Gonorrhea and chlamydia are infections passed during sex.
- Have a physical exam, including an exam of your genital area and inside your vagina. During the exam, study staff will pour about 1 tablespoon [INSERT LOCAL EQUIVALENT] of sterile water in your vagina and then collect and store the water for later testing. Study staff also will collect fluid from your vagina with a swab. Some swabs will be used to test for infections. These infections are called trichomoniasis, candidiasis, and bacterial vaginosis. Other swabs will be stored for later testing. The later testing of your vaginal fluids will be done in the United States.
- [*For selected sites only:* Study staff also will collect samples from your cervix to test for abnormalities that could mean you have cervical cancer, or that could lead to cervical cancer. This test is called a “Pap test.” It takes about [x] weeks before Pap test results are available. We will give you the results as soon as they are available.

- Give about 6 tablespoons or [INSERT LOCAL EQUIVALENT] of blood. This blood will be used for:
  - Tests for syphilis and herpes. These are infections passed during sex.
  - Tests to check on the overall health of your blood, liver and kidneys.
  - Tests of the amount of HIV in your blood and your CD4+ T-cell count. The CD4+ T-cell count is a test that measures the amount of damage HIV has done to your immune system. The immune system is the part of the body that fights off germs and infections.
  - Other tests of the HIV virus and your immune system that will be done in the United States. These tests include a test (resistance test) of whether the HIV virus has any resistance to medications used to treat HIV.
  - [INSERT THE FOLLOWING LANGUAGE IF REQUIRED BY SITE IRB/EC] About four and a half tablespoons or [INSERT LOCAL EQUIVALENT] of this blood would be used only for storage and future research-related testing.

Some of your test results will be available during the visit, and will be given to you at that time. Most other tests will take about two weeks. The tests for herpes and for resistance to HIV medications will take 2-3 months. Study staff will make arrangements to give your results to you when they are ready.

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. Study staff also will be available to talk with other doctors that you see for your medical care. Because the results of study tests may help other doctors make the best medical choices for you, study staff will give the results of your study tests to your other doctors, if you wish and with your permission.

Some tests of your blood and vaginal fluid done in the United States will be done at different times during the study, or after the study is completed. The results of these tests will not be given to you unless they are important to your health.

Follow Up Visits (Months 1, 3, 6 and every 6 months):

These visits will take place 1, 3, and 6 months after you become infected with HIV, and then every 6 months thereafter. You may skip some of these visits depending on when you became infected with HIV and when you join the study.

These visits will be similar to the Screening/Enrollment Visit, but will take less time (about 1 hour). You will answer questions like at the Screening/Enrollment Visit and about whether being in this study has caused you any problems. You will hear about how to lower your chances of getting an infection passed through sex, how to avoid pregnancy (if you are trying to avoid pregnancy), and how to lower chances of passing HIV infection to other people. You will have a physical exam including an exam of your genital area and inside your vagina, and give blood, urine, and fluids from your vagina for tests. Most of the following tests will be done at these visits:

- Tests for infections passed during sex.
- [For selected sites only: Tests for abnormalities that could mean you have cervical cancer, or that could lead to cervical cancer.
- Tests to check on the overall health of your blood, liver and kidneys.
- Tests of the amount of HIV in your blood and your CD4+ T-cell count.
- Tests of the HIV virus and your immune system that will be done in the United States.
    - [INSERT THE FOLLOWING LANGUAGE IF REQUIRED BY SITE IRB/EC] A little more than four tablespoons or [INSERT LOCAL EQUIVALENT] of this blood would be used only for storage and future research-related testing.

Study staff will arrange to give you your test results when they are ready. They also will give your results to your doctor, with your permission. The results of tests done in the United States will not be given to you unless they are important to your health.

Visits after Starting Medicine for HIV

The medicines used to treat HIV infection are called "antiretroviral therapy" or "ART." If you are taking ART when you join the study, or start taking ART while in the study, you will have study visits 2 weeks, 1 month, 3 months, and 6 months after your start taking ART, and then every 6 months thereafter. You will have these visits **instead of** the visits that are in the section before called "Follow Up Visits." These visits will be very similar to the follow-up visits described above, with the same types of questions, exams, and tests. The study staff will ask you about what kind of ART you are taking and how often you take it. If the study staff thinks it is necessary, you may have a resistance test done at one or more of these visits. You will receive counseling on how to lower your chances of getting an infection passed through sex, how to avoid pregnancy (if you are trying to avoid pregnancy) and how to lower chances of passing HIV infection to other people. These visits will take about 1 and ½ hours.

Final Visit:

You will be asked to complete a final visit at the end of the study, or if you choose to leave the study before it ends. This visit will take about 1 hour and will include the same types of questions, exams, and tests as the other follow-up visits.

Any Time During The Study:
At any time in the study, if you or the study staff think that you may have become pregnant, you will give urine for a pregnancy test. Also, if you are having health problems that may be caused by infections passed during sex, you will:

- Have an exam of your genital area and inside your vagina
- Give blood or urine to test for infections passed during sex
- Get treatment if you need it
- Be offered testing and treatment for your partner

You are asked to tell the study staff about any medical problems you have during the study, especially infections or other illnesses that might be related to HIV infection. You also can contact the study staff between regular visits to report these problems. The study staff will examine you as necessary and either provide or refer you for medical care that you may need.

You are also asked to tell the study staff if you start taking any ART medications.

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

[SITE INSERT THE FOLLOWING TEXT RELATED TO STORAGE AND FUTURE TESTING OF SAMPLES IF NOT USING A SEPARATE INFORMED CONSENT FORM FOR STORAGE AND FUTURE TESTING OF SAMPLES]

Samples Leftover at the End of the Study:
Once all the testing listed above is done for this study, some of your blood and vaginal fluid may be leftover. We would like to use the leftover samples for future testing that is not a part of this study. The testing that would be done in the future would be related to HIV only. Some of the testing may include genetic testing. An Institutional Review Board or Ethics Committee, which watches over the safety and rights of research participants, must approve any research studies using your samples. There is no time limit on how long these samples will be stored.

If you agree to have these samples stored for future research, they will be stored safely and securely in a storage facility in the United States. Only the people who work at the facility and approved researchers will have access to your samples. The people who work at the facility will not have any information that identifies you. The approved researchers may be given information about you

such as your age and sex, but they will not be given your name or any other information that identifies you.

At the end of this consent form you will indicate whether you agree to storage and future testing of your leftover samples. You can choose not to have your samples stored and still be in this study. If you do not agree to have your samples stored, your samples will be destroyed once all the testing for this study has been completed.

If you agree to have your samples stored for future testing, you can change your mind at any time. You let us know that you changed your mind by writing a letter to or telling a study staff member at the study site [SITE INSERT CONTACT INFORMATION]. Your samples will then be destroyed.

How Many Women Will Be In this Study?
Up to 500 women will take part in this study.

How Long Will I be In This Study?
You will be in this study until the year 2013.

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.
- You are not able to keep appointments for study visits.
- 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, you also 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.

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 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.

[SITE INSERT THE FOLLOWING TEXT RELATED TO STORAGE AND FUTURE TESTING OF SAMPLES IF NOT USING A SEPARATE INFORMED CONSENT FORM FOR STORAGE AND FUTURE TESTING OF SAMPLES]

Risks Related to Stored Samples:

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

Are There Risks Related To Pregnancy?

There are no special risks related to pregnancy for this study. Study staff will talk with you about options for preventing pregnancy. This study does not provide care related to pregnancy, delivery of a baby, or care for babies. If you become pregnant, study staff will refer you to any services you and your baby may need. You will not have genital exams for the study while you are pregnant if you are also having any vaginal bleeding or spotting, or symptoms of labor. Study staff also will ask you a few questions about the outcome of your pregnancy.

What are the Benefits of This Study?

You may 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 and counseling related to HIV and other infections passed during sex.
- Treatment for infections passed during sex (including treatment for your partners).
- Exam and laboratory tests, including tests that may help your doctor with treatment of your HIV infection.
- Referrals to medical care and other services you may need.

There are no direct benefits to you if you agree to allow your blood and/or vaginal fluid to be stored for possible future testing. The benefit of doing research on stored samples includes learning more about HIV infection and its prevention.

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 HIV.

What Other Choices Do I Have Besides This Study?

You do not have to participate in this study. [SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE: There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about. You can also talk to your doctor about other choices that may be available to you.]

What About Confidentiality?

Efforts will be made to keep your personal information confidential. However, we cannot guarantee absolute confidentiality. Any publication of this study will not use your name or identify you personally.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE:]
[LOCAL/STATE/NATIONAL] regulations require study staff to report the names of people who test positive for other infections passed during sex to the [LOCAL HEALTH AUTHORITY]. Outreach workers from the [health authority] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [HEALTH AUTHORITY]. [LOCAL/STATE/NATIONAL] regulations require study staff to report the names of people who harm themselves or others, including children, to the [LOCAL HEALTH AUTHORITY].

Your study records may be reviewed by:

- United States National Institutes of Health
- [INSERT applicable local authorities, e.g., Ministry of Health, medicine control authority]
- [INSERT names of applicable site IRBs/ECs]
- Study staff
- Study monitors

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

What Are The Costs To Me?
There is no cost to you for study visits, exams, laboratory tests, or other procedures.

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 [SUCH AS CHILD CARE, TRAVEL, LOSS OF WORK TIME – SITES TO COMPLETE].

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. However, you or your 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 injuries. You will not be giving up any of your legal rights by signing this consent form.
[SITES TO SPECIFY INSTITUTIONAL POLICY]

What Are My Rights?
Taking part in this study is completely voluntary. You may choose not to take part or to leave the study at any time. You will be treated the same no matter what you decide. If you choose not to take part 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:
[SITE INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]
[SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

For questions about your rights as a research participant, contact:
[SITE INSERT NAME OR TITLE OF PERSON ON THE INSTITUTIONAL REVIEW BOARD (IRB) OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE] [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

SIGNATURES
[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB]

If you have read the informed consent, or had it read and explained to you, and all your questions have been answered, and you agree to take part in this study, please sign your name or make your mark below. [SITE INSERT THE FOLLOWING TEXT RELATED TO STORAGE AND FUTURE TESTING OF SAMPLES IF NOT USING A SEPARATE INFORMED CONSENT FORM FOR STORAGE AND FUTURE TESTING OF SAMPLES] By writing your initials or making your mark in the spaces below, you may also agree to long-term storage of your leftover samples.

I agree to allow the following leftover samples to be stored for future testing:

____Blood

____Vaginal fluid

OR

____I do not agree to allow any of my leftover samples to be stored for future testing.

_____	_____
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

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

MTN-015
An Observational Cohort Study of Women following HIV-1 Seroconversion in Microbicide Trials

Final Version 1.0
June 19, 2007

PRINCIPAL INVESTIGATOR: **[insert]**
PHONE: **[insert]**
Short Title for the Study: **MTN HIV-1 Seroconverter Study**

INTRODUCTION

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

HOW WILL YOU GET THE SAMPLES FROM ME?

You are being asked to agree to have blood, cervical fluid, and vaginal fluid taken, tested and stored as part of the MTN-015 study. During the study, your stored samples may be tested to check on your health. The research doctors would like to keep any blood and vaginal fluid that is left over, after the MTN-015 study is done, to use for research in the future. If you agree to this, no additional samples will be taken from you. Only leftover samples will be kept and used for future research.

HOW WILL YOU USE MY SAMPLES?

Your samples may be used to look for evidence of your body's response to HIV or other infections (such as examining cells, proteins, and other chemicals in your body). Tests may also include examining your genes (DNA), since they might affect your response to disease in important ways. Your genes might make you more or less susceptible to becoming infected, affect your responses to infection, or make your responses to treatment stronger or weaker. No other kinds of genetic test will be done by anyone on your stored specimens without first explaining the test to you and getting your permission.

The researchers do not plan to contact you or your regular doctor with any results from tests done on your stored samples. This is because research tests

are often done with experimental procedures, so the results from one research study are generally not useful for making decisions on managing your health. Should a situation come up where the researchers believe that one of the test results would provide important information for your health, the researchers will notify your study doctor and your study doctor will try to contact you. If you wish to be contacted with this type of test result, you must give the study doctor or nurse any change to your address and/or phone number. If you want your regular doctor to be told about this type of test result, you must provide the study doctor or nurse with your regular doctor's name, address and phone number. Your samples will not be sold or used directly to produce products that can be sold for profit.

Research studies using your samples will be reviewed by the National Institutes of Health, and Ethics Committee, and a special committee at the researcher's institution (an Institutional Review Board).

HOW LONG WILL YOU KEEP MY SAMPLES?

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

HOW WILL MY SAMPLES BE STORED?

Your samples will be stored in the United States at special facilities that are designed to store samples safely and securely. The storage facilities are designed so that only approved researchers will have access to the samples. Some employees of the storage facilities will need to have some access to your samples to store them and to keep track of where they are, but these people will not have information that directly identifies you. An Institutional Review Board will oversee the storage facilities to protect you and other research volunteers from harm.

DOES STORAGE OF MY SAMPLES BENEFIT ME?

There are no direct benefits to you. The benefit of doing research on stored samples includes learning more about HIV infection and its prevention.

WHAT ARE THE RISKS?

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

WHAT ABOUT CONFIDENTIALITY?

To keep your information private, your samples will be labeled with a code that can only be traced back to your research clinic. Your personal information (name, address, phone number) will be protected by the research clinic. When

researchers are given your stored samples to study they will not be given your personal information. The results of future tests will not be included in your health records. Also, any publication of the research will not use your name or identify you personally.

The research staff will do everything they can to protect your privacy. Every effort will be made to keep your personal information confidential, but absolute confidentiality cannot be guaranteed.

People who may review your records include:

- the United States National Institutes of Health (NIH)
- [insert applicable local authorities, e.g., Ministry of Health]
- [insert names of applicable IRBs/ECs]
- study staff
- study monitors, and their designees

WHAT ARE MY RIGHTS?

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

WHAT DO I DO IF I HAVE QUESTIONS?

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

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

SIGNATURE PAGE
[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB]

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

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness Name (print)	Witness Signature and Date

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