MTN-015

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

A Study of the Microbicide Trials Network

Funding Agencies:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
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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
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
NAAT	Nucleic Acid Amplification Testing
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.
PrEP	pre-exposure prophylaxis
RE	regulatory entity
RNA	ribonucleic acid
RSC	Regulatory Support Center
RTI	reproductive tract infection
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
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

INVESTIGATOR SIGNATURE FORM

Version 2.0
May 3, 2013

A Study of the Microbicide Trials Network (MTN)

Sponsored by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
US National Institute of Mental Health
US National Institutes of Health

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Investigator of Record Agreement which I have also signed. I agree to maintain all study documentation for a minimum of three years after the study is closed, unless otherwise specified by the Division of AIDS (DAIDS) or the Microbicide Trials Network (MTN) Coordinating and Operations Center. Publication of the results of this study will be governed by MTN policies. Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee for review prior to submission and will be made available to DAIDS.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

_____
Name of Investigator of Record

_____ _____
Signature of Investigator of Record Date

MTN-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 participants
Study Population:	Participants 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:	At a minimum, participants will remain on-study up until 12 months (approximately 1 year) after the HIV-1 seroconversion identification date. Follow-up may continue as funding permits or as determined by MTN leadership.

Primary Objective:

- To compare HIV disease progression 12 months post seroconversion among participants assigned to an active agent compared to placebo/control participants.

Secondary Objectives:

- To compare HIV disease progression post seroconversion among participants assigned to an active agent compared to placebo/control participants over the total duration of follow-up.

- To compare virologic and immunologic responses following initiation of antiretroviral therapy among participants assigned to an active agent versus placebo/control participants.

- To compare the HIV-1 drug resistance profile, among antiretroviral therapy recipients at the time of virologic failure in participants assigned to an active agent versus placebo/control participants.

- To describe post seroconversion changes in sexual behaviors and partnership status of participants.

Exploratory Objective:

- To evaluate the prevalence and persistence of HIV-1 drug resistance mutations in plasma and/or genital tract specimens after HIV-1 seroconversion using both standard and sensitive methods in specific subgroups of seroconverters.

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: May 3, 2013

1.2. Funding Agencies, Sponsor and Monitor Identification

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2. INTRODUCTION

2.1. HIV/AIDS Prevention and Microbicides

According to Joint United Nations Programme on HIV/AIDS (UNAIDS), approximately 34 million people worldwide were living with HIV in 2011.[1] In sub-Saharan Africa, women account for 58% of people living with HIV, demonstrating a need for HIV prevention in this at-risk population.[1] 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[2], 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 microbicides, including vaginal gel, film, and ring formulations.[3] Microbicide clinical trials in HIV-negative participants conducted by the NIH-funded Microbicide Trials Network (MTN) include Phase I, II and IIa 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 microbicides administered using various formulations (film, gel, ring), as well as orally administered antiretroviral agents (also referred to as chemoprophylaxis or pre-exposure prophylaxis [PrEP]).

The primary goal of a microbicide is to prevent acquisition of HIV-1 infection. However, there will be new HIV-1 infections among study participants and, ultimately, users of microbicides and oral PrEP. It is essential to monitor these HIV-1 seroconverters 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 oral PrEP may be beneficial or harmful for the exposed individuals. For example, it is possible that the use of a microbicides or oral PrEP will result in a lower inoculum of infecting viral strain. By this mechanism or others not yet understood, it is possible that individuals, who are infected, despite the use of microbicides or oral PrEP, will have a lower viral set-point and subsequent slower progression of HIV disease.

A major concern is the possibility that microbicides or oral PrEP 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 individuals who become infected while using antiretroviral agents for HIV-1 prevention 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 or dapivirine. Currently in South Africa, approximately <5% of all new infections are attributed to viruses that contain at least one drug resistance mutation.[4] Data also suggests that there is a high prevalence of NNRTI-resistance, which is consistent with single-dose nevirapine.[5] There is also the

potential for selection of drug resistance in individuals who unknowingly are already HIV-infected. This may be less of a concern with respect to topically applied products with minimal 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.[6-8] Therefore, risky sexual behavior soon after infection carries a 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.[9, 10] 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.[11-13] 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.[6] 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 in reducing such transmission. Participants 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 microbicides or oral PrEP use on the natural history of HIV-1 infection is essential for the development of guidance for the use of these 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 MTN study participants who become HIV-infected during product use. Careful monitoring of microbicide and oral PrEP 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 1-3 months). For the purposes of MTN-015, HIV Prevention Trials Network (HPTN) 035, MTN-003, MTN-020 and other trials of efficacy are considered MTN studies from which participants may be drawn. In addition, studies

investigating both microbicides and oral PrEP 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 participants 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 parent study participation will be eligible for enrollment into this protocol regardless of the specific product or placebo or the route of administration.

Individuals recently HIV infected often have high viral loads and may be highly infectious.[6-8] 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.[14] 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.[14] Conversely, there is 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.[15] Participants of microbicides trials may have different responses to disclosure as their trial participation may have been known by a partner. The pattern of behavior change in this unique situation to reduce transmission is important to describe and may help future counseling programs for HIV positive individuals in developing countries. Describing the pattern of behavior change among newly HIV infected individuals in comparison to those 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 HIV disease progression 12 months post seroconversion among participants assigned to an active agent compared to placebo/control participants.

3.2. Secondary Objectives

- To compare HIV disease progression post seroconversion among participants assigned to an active agent compared to placebo/control participants over the total duration of follow-up.

- To compare virologic and immunologic responses following initiation of antiretroviral therapy among participants assigned to an active agent versus placebo/control participants.

- To compare the HIV-1 drug resistance profile, among antiretroviral therapy recipients at the time of virologic failure in participants assigned to an active agent versus placebo/control participants.

- To describe post seroconversion changes in sexual behaviors and partnership status of participants.

3.3. Exploratory Objective

- To evaluate the prevalence and persistence of HIV-1 drug resistance mutations in plasma and/or genital tract specimens after HIV-1 seroconversion using both standard and sensitive methods in specific subgroups of seroconverters.

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 in which HIV-1 seroconversion was 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, unless specified by MTN leadership. 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 prevention of mother-to-child transmission (PMTCT) will not constitute initiation of ART for purposes of this study.

MTN 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. MTN 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.

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, and will be offered STI testing and treatment for their partners.

4.2. Description of Study Population

The study population will consist of participants who are identified as infected with HIV-1 during participation in MTN clinical trials who meet the MTN-015 eligibility criteria in Sections 5.2 and 5.3.

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

At a minimum, participants will remain on-study up until 12 months (approximately 1 year) after the HIV-1 seroconversion identification date. Follow-up may continue as funding permits or as determined by MTN leadership.

5. STUDY POPULATION

The study population will consist of 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.

5.1. Selection of the Study Population

Composition
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 contact the participants for possible enrollment in MTN-015 once seroconversion has been confirmed by local laboratory testing. 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

Participants 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, based on local laboratory testing and according to the HIV testing algorithm of the parent MTN trial.

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

5.3. Exclusion Criterion

Participants 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 I on when each study procedure is to be performed. Screening/Enrollment Visit 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 needed to complete all required procedures. If a participant is being followed in her parent trial, site staff may schedule and complete MTN-015 visits on the same day as parent protocol visits if efficient for site staff and participants.

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.

Procedures and documented results from the parent MTN study may be utilized for MTN-015, if the procedure(s) was performed/sample(s) was collected in the visit window and within the past 30 days provided that the test kit, laboratory and/or specified clinical assessments, and method of data collection are the same in both studies. See MTN-015 Study-Specific Procedures Manual at http://www.mtnstopshiv.org for additional information.

7.1. Screening/Enrollment Visit

Table 1: Screening/Enrollment Visit

Screening/Enrollment Visit	
Component	**Procedure/Analysis**
Administrative: Screening	– Informed Consent – Eligibility Determination
Administrative: Enrollment	– Assign Participant ID – Update Locator Information – Collect Demographics – Schedule Next Visit – Reimbursement
Clinical	– Update Medical History – Record Clinical Events – Acute Seroconversion Assessment – Concomitant Medications Assessment, including Assessment of Antiretroviral Use (past and current) – Complete Physical Exam (See Appendix II) – Gynecologic Exam (See Appendix II) – Provide Available Test Results – Treatment or Referral*
Behavioral	– Baseline Behavioral Questionnaire – ART Adherence Questionnaire* – STI Risk Reduction and Contraception Counseling – HIV Secondary Prevention Counseling – Provision of Condoms
Urine	– Qualitative hCG – NAAT for Chlamydia and Gonorrhea
Blood	– Complete Blood Count – Liver and Renal Function Tests – Syphilis Serology – CD4+ T-Cell Count – Plasma HIV-1 RNA – Plasma – HIV-1 Genotypic Resistance Testing ▲ – HIV Serology (2 rapid tests) o *Contact Management Team if both are not positive* – Peripheral Blood Mononuclear Cells (PBMC) Collection ◊
Pelvic Samples	– Vaginal pH – Testing for Bacterial Vaginosis (BV) and Candida* – Testing for Trichomonas – Pap Smear at Selected Sites† – Vaginal Swabs – Cervicovaginal Lavage

*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. ◊ At sites with capacity. ▲Will be processed at the discretion of MTN NL.

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 Screening and Enrollment visit, subsequent follow-up visits will be scheduled according to the seroconversion date. For example, a participant who enrolls 3 months after seroconversion would miss her Month 1 and Month 3 Post-Seroconversion Visits, and would complete her Month 6 Post-Seroconversion Visit as her first follow-up visit. She would then complete follow-up visits every 6 months thereafter.

- 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. For example, a participant who enrolls 3 months after initiation of ART would miss her Week 2, Month 1, Month 3 post-ART follow-up visits and would complete her Month 6 post-ART visit as her first follow-up visit. She would then complete follow-up visits every 6 months thereafter.

- Participants who initiate use of ART during follow-up in MTN-015 will initially 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, 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 begins mid-way between the Month 18 and Month 24 target dates and ends mid-way between the Month 24 and Month 30 target dates. 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 – Complete Physical Exam (See Appendix II) – Gynecologic Exam (See Appendix II) – Provide Available Test Results – Treatment or Referral*
Behavioral	– Follow-up Behavioral Questionnaire (Month 3 Only) – Social Harms Assessment (Month 3 Only) – Provision of Condoms
Urine	– Qualitative hCG – NAAT for Chlamydia and Gonorrhea*
Blood	– Plasma HIV-1 RNA – CD4+ T-Cell Count – Syphilis Serology* – Complete Blood Count (Month 3 Only) – Liver and Renal Function (Month 3 Only) – Plasma – PBMC Collection ◊
Pelvic Samples	– Vaginal pH* – Testing for BV and Candida* – Testing for Trichomonas* – Pap Smear at Selected Sites*/† – Vaginal Swabs – Cervicovaginal Lavage

*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. ◊ At sites with capacity.

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 – Complete Physical Exam (See Appendix II) – Gynecologic Exam (See Appendix II) – Provide Available Test Results – Treatment or Referral*
Behavioral	– Follow-up Behavioral Questionnaire (Month 12 and 24 only) – Social Harms Assessment – STI Risk Reduction and Contraception Counseling – HIV-1 Secondary Prevention Counseling – Provision of Condoms
Urine	– Qualitative hCG* – NAAT for Chlamydia and Gonorrhea (annually)*/**
Blood	– Plasma HIV-1 RNA – CD4+ T-Cell Count – Complete Blood Count – Liver and Renal Function – Syphilis Serology (annually)*/** – Plasma – PBMC Collection◊
Pelvic Samples	– Vaginal pH*/** – Testing for BV and Candida* – Testing for Trichomonas*/** – Pap Smear at Select Sites*/† – Vaginal Swabs – Cervicovaginal Lavage

*If indicated; */**Urine NAAT for Chlamydia and Gonorrhea, Syphilis Serology, Vaginal pH, and testing for Trichomonas 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. ◊ At sites with capacity.

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 – Complete Physical Exam (See Appendix II) – Gynecologic Exam (See Appendix II) – Provide Available Test Results – Treatment or Referral*
Behavioral	– Follow-up Behavioral Questionnaire (Month 3 only) – ART Adherence Questionnaire (Month 3 only) – Social Harms Assessment (Month 3 only) – Provision of Condoms
Urine	– Qualitative hCG* – NAAT 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 Testing* – Plasma – PBMC Collection (Week 2 and Month 3 only) ◊
Pelvic Samples	– Vaginal pH* – Testing for BV and Candida* – Testing for Trichomonas* – Pap Smear at Selected Sites*/† – Vaginal Swabs (Month 1 and 3 only) – Cervicovaginal Lavage (Month 1 and 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. ◊ At sites with capacity.

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	– Update Locator Information – Schedule Next Visit – Reimbursement
Clinical	– Update Medical History – Update Clinical Events – Concomitant Medications Assessment – Antiretroviral Treatment Record – Complete Physical Exam (See Appendix II) – Gynecologic Exam (See Appendix II) – Provide Available Test Results – Treatment or Referral*
Behavioral	– Follow-up Behavioral Questionnaire (Month 12 and Month 24 only) – ART Adherence Questionnaire – Social Harms Assessment – STI Risk Reduction and Contraception Counseling – HIV-1 Secondary Prevention Counseling – Provision of Condoms
Urine	– Qualitative hCG* – NAAT 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 Testing* – Plasma – PBMC Collection◊
Pelvic Samples	– Vaginal pH*/** – Testing for BV and Candida* – Testing for Trichomonas*/** – Pap Smear at Selected Sites*/† – Vaginal Swabs – Cervicovaginal Lavage

*If indicated; */**Urine NAAT for Chlamydia and Gonorrhea, Syphilis Serology, Vaginal pH, and testing for Trichomonas 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. ◊ At sites with capacity.

7.2.3. Final/Early Termination Visit – All Participants

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

Table 6: Final/Early Termination Visit

Final Visit	
Component	**Procedure/Analysis**
Administrative	– Update Locator Information – Reimbursement
Clinical	– Update Medical History – Update Clinical Events – Concomitant Medications Assessment – Antiretroviral Treatment Record* – Complete Physical Exam (See Appendix II) – Gynecologic Exam (See Appendix II) – Provide Available Test Results – Treatment or Referral*
Behavioral	– ART Adherence Questionnaire* – Follow-up Behavioral Questionnaire (To be complete only if the visit occurs at Non-ART Month 3, 12, 24 or ART Month 3, 12, 24) – Social Harms Assessment – HIV-1 Secondary Prevention Counseling – STI Risk Reduction and Contraception Counseling – Provision of Condoms
Urine	– Qualitative hCG – NAAT for Chlamydia and Gonorrhea
Blood	– Plasma HIV-1 RNA – CD4+ T-Cell Count – Complete Blood Count – Liver and Renal Function Tests – Syphilis Serology – HIV-1 Genotypic Resistance Testing* – Plasma – PBMC Collection◊
Pelvic Samples	– Vaginal pH – Testing for BV and Candida* – Testing for Trichomonas – Pap Smear at Selected Sites*/† – Vaginal Swabs – Cervicovaginal Lavage

*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. ◊ At sites with capacity.

7.3. Interim Visits

Interim visits may be performed at any time during the study. All interim contacts, study procedures, and visits will be documented in participants' study records and/or on case report forms (CRFs), when applicable.

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 and will be completed as outlined in Section 7.1 and 7.2. For participants with past or current use of ART, an ART adherence questionnaire will be completed as outlined in Section 7.1 and 7.2. All behavioral and ART adherence questionnaires, including the social harms questionnaire, will be available in the MTN-015 Study-Specific Procedures Manual at http://www.mtnstopshiv.org.

7.5. Specimen Collection

Each study site will adhere to the current DAIDS Good Clinical Laboratory Practice Standards, MTN-015 Study Specific Procedures Manual (http://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. In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-draw specimens.

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, provided that the sample(s) were collected within the past 30 days. See MTN-015 Study-Specific Procedures Manual at http://www.mtnstopshiv.org for additional information.

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

Blood Samples
The following blood tests will be performed locally: CD4+ T-cell counts, plasma HIV-1 RNA, complete blood count (see Appendix IV), liver and renal function tests (see Appendix IV), HIV serology and syphilis serology.

Pelvic Samples
Vaginal pH testing and 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. Network Laboratory Specimens

Vaginal Swabs
Testing on vaginal swabs may include vaginal flora proteomics, markers of inflammation, viral DNA (HPV/HSV/HIV) load determination, and sexual exposure (Y chromosome).

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

Plasma
Testing on plasma will include standard genotypic resistance testing, allele-specific polymerase chain reaction (PCR) for relevant drug resistance codons and single genome sequencing.

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

7.6. Specimen Handling

Specimens will be handled in accordance with current requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials. (http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/labpolicy.pdf)

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 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 according to individual IRB requirements, 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 and/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 regular intervals per any applicable DAIDS requirements.

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

- Related: There is a reasonable possibility that the problem may be related to study participation

- Not Related: There is not a reasonable possibility that the problem is related to study participation

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 participants to those services. Other sites have established referral agreements with programs to expand access to antiretroviral therapy. 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. 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. Participants will be contacted to collect the outcome of pregnancies until the end of their study participation.

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. To maintain blinding of product assignments, HIV resistance test results will not be routinely available during ongoing parent randomized trials. The site clinician will determine if resistance test results are needed for an individual participant's ongoing medical care and can request that these results be provided. 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/early termination study visit.

10. STATISTICAL CONSIDERATIONS

10.1 Overview and General Design

This is a prospective observational cohort study of seroconverters identified in microbicide trials. MTN 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). Analyses will generally be conducted by the parent protocol to assess the effect of active microbicidal or chemoprophylactic agents used in the protocol on HIV disease progression. At the time this protocol was written, information was available on the targeted number of seroconverters (i.e., HIV endpoints) for two MTN protocols. In MTN-003, the expected number of HIV seroconversions was 217, while the expected number of HIV seroconversion in MTN-020 is 120. Given that it is difficult to anticipate the number of seroconverters generated by future MTN trials, we will conservatively estimate the available sample size using the parent protocol with the lower number of anticipated events (120 events).

10.2 Study Endpoints

10.2.1 Primary Endpoint

HIV-1 disease progression 12 months post seroconversion.
Consistent with the primary study objective, HIV disease progression 12 months post seroconversion will be compared among participants assigned to an active agent compared to placebo/control participants. HIV disease progression will be evaluated based on the following factors:

- **Virologic response.** The trajectory of blood plasma HIV-1 RNA level between seroconversion and 12 months post seroconversion will be compared between active agent and placebo/control groups.

- **CD4+ T cell count response.** The CD4+ T cell count trajectory between seroconversion and 12 months post seroconversion will be assessed. Time from seroconversion to having a CD4+ T-cell count below the threshold for initiation of combination ART will be compared between active agent and placebo/control groups. Analyses will be conducted using both local and WHO guidelines for ART initiation (in the event guidelines differ).

- **HIV-1 related and AIDS-defining events**. The occurrence and frequency of HIV-1 related and AIDS-defining events will be assessed. Time from enrollment to time of first AIDS-defining event or death not due to trauma will be compared between active agent and placebo/control groups.

- **Initiation of combination antiretroviral therapy (ART).** The frequency of initiation of ART will be assessed (excluding single-antiretroviral, dual-antiretroviral, or combination ART initiated exclusively for prevention of mother-to-child transmission of HIV-1). Time from seroconversion to initiation of ART will be compared between active agent and placebo/control groups.

In addition, a composite HIV disease progression end point will be constructed, defined as the first occurrence of a CD4 T-cell count below the threshold for initiation of ART, initiation of ART, or death not due to trauma. Time from seroconversion to the composite HIV disease progression outcome will be compared between active agent and placebo/control groups

10.2.2 Secondary Endpoints

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

- **HIV-1 disease progression post seroconversion.** The same factors evaluated in the primary objective will also be evaluated over the duration of follow-up post-serconversion. In addition, genital HIV shedding and genital health may also be assessed.

- **Virologic and immunologic responses (CD4+ T-cell count) after initiation of ART.** Blood plasma HIV-1 RNA and CD4+ T-cell count trajectories will be assessed over time after initiation of ART. Time from initiation of ART to virologic failure will be compared between active agent and placebo/control groups. In addition, the proportion of participants with a suppressed HIV-1 viral load following initiation of ART.

- **HIV-1 drug resistant virus.** Prevalence of drug resistant HIV-1 virus in plasma and genital tract specimens at the time of virologic failure. Among participants with virologic failure, the drug resistance profile and proportion of participants with drug resistant HIV-1 virus will be compared between active agent and placebo/control groups.

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

10.2.3 Exploratory Endpoint

- To evaluate the prevalence and persistence of HIV-1 drug resistance mutations in plasma and/or genital tract specimens using both standard and more sensitive methods in specific subgroups of seroconverters.

10.3 Power Estimates

Preliminary data from the University of Washington/Fred Hutchinson Cancer Research Center (UW/FHCRC) Primary Infection Clinic was used to estimate the variability in $\log_{10}$ HIV RNA 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 in our population. The between person variance component is 0.52 ($\log_{10}$ copies^2/ml^2).[16]

In the MTN-020 trial, we expect 120 seroconverters: 86 in the placebo/control group and 34 in the dapivirine group (assuming an effectiveness of 60%). However, not all seroconverters will be available for the evaluation of the primary endpoint since newly-infected participants 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 120 eligible participants, we estimate that 20% of the participants eligible for this study will not enroll and an additional 5% will be lost to follow-up.

Therefore, we anticipate that 91 seroconverters (65 from the placebo/control groups and 26 from the active group, assuming that the active product reduces HIV acquisition by 60%) 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 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 and placebo/control groups assuming 26 and 65 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 and placebo/control groups		
	0.3	0.4	0.5
Power	41%	66%	84%

Thus, we have 84% power to detect a difference of 0.5 $\log_{10}$ copies/ml in viral load 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. If the effectiveness of the active product is smaller than 60%, then the power in this study would slightly increase since the numbers between the comparison groups would be more balanced.

In the event that the number of participants from the MTN-020 parent protocol enrolled on MTN-015 differs from the estimates above, the following table shows estimates of the power for varying sample sizes. These estimates will also apply for other parent protocols enrolling participants in MTN-015. This plot estimates that the active arm has 2.5 times the number of participants as the control arm, similar to what we expect in MTN-020.

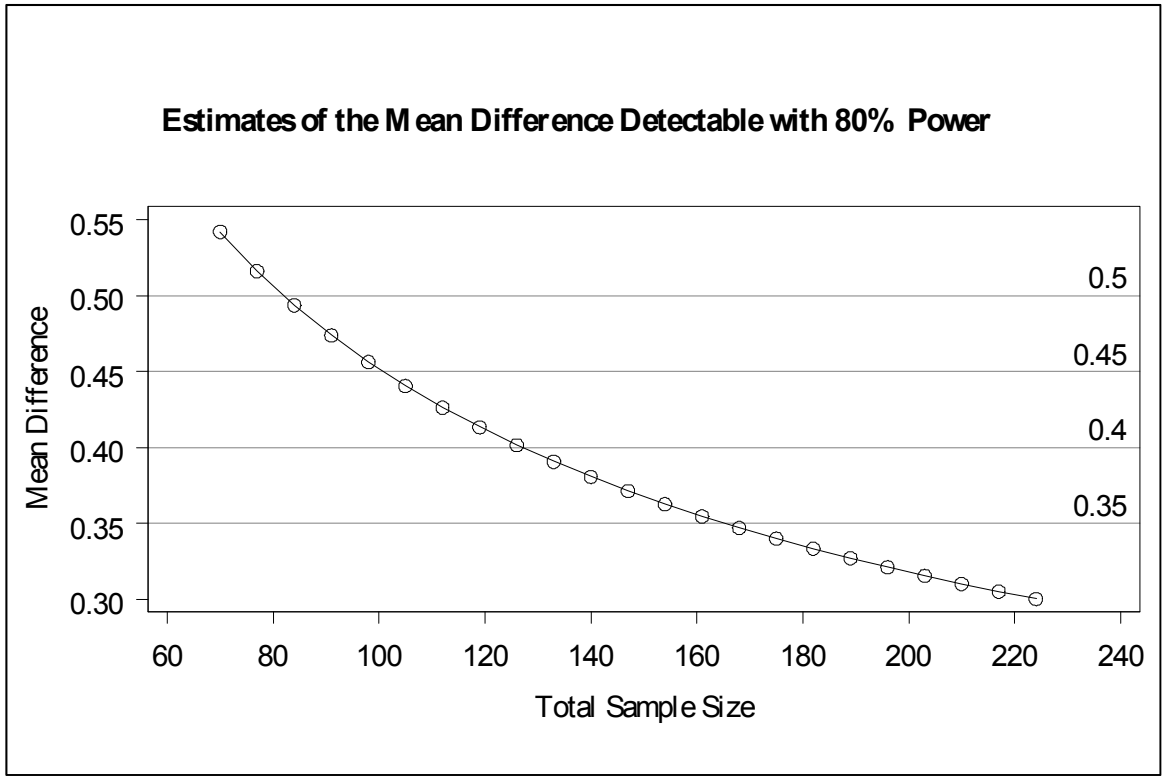

Figure 1: Estimates of the Mean Difference Detectable with 80% Power

10.4 Blinding

Blinding/unblinding processes will be dictated by the parent study protocols. In the event that an Investigator feels that specific product knowledge is necessary to protect participant safety while the parent protocol is still blinded, they should follow the processes outlined in the parent protocol for early unblinding.

10.5 Participant Accrual and Retention

All seroconverters identified at sites participating in MTN-015 will be recruited into 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 Interim Study Review (ISR) Committee

No Data and Safety Monitoring Board (DSMB) oversight is planned for this observational study.

Once results from a parent study are unblinded and analyzed, the Interim Study Review (ISR) Committee will review MTN-015 participant's safety/disease progression. In addition, this small group will assess the study conduct with regard to the completion of primary and main secondary endpoints. These reviews are anticipated to occur approximately annually following the first review. At the time of these reviews, or at any other time, the ISR may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. The ISR may consider recommending termination of this study if recruitment and retention are lower than targeted, or if study data quality is poor.

Additional details regarding the ISR are provided in the MTN Manual of Operational Procedures at http://www.mtnstopshiv.org.

The MTN-015 protocol team leadership will routinely monitor study conduct and progress, see the MTN-015 SSP for additional details.

10.6.2 Data Analysis

In most cases, the analyses will be stratified by parent protocol. However, when appropriate analyses combining data from multiple protocols may be conducted.

Primary Analyses

Descriptive analyses will include calculation of the mean and median CD4+ T-cell count and log-transformed viral load by active and placebo/control groups 12 months following seroconversion. A t-test will be used to compare CD4+ T-cell count and viral load by arm at the 12 month visit among participants stratified by ART use. The trajectory of CD4+ T-cell count and log-transformed viral load over multiple visits between seroconversion and 12 months post-seroconversion will be assessed using both unadjusted and adjusted linear mixed effect models. Participants will be censored following initiation of ART. Caution must be exercised in the interpretation of any difference (or lack of difference) observed. Although the active and placebo/control groups should be comparable at baseline (in the parent study) due to randomization, individuals who seroconvert in the active arm may not be comparable to individuals who seroconvert in the placebo/control arm. Approaches described by Gilbert et al, Biometrics, 2003 will be used for isolating the effect of an intervention on post-seroconversion outcomes.[17]

The frequency of HIV-related and AIDS defining events and ART initiation will be assessed using descriptive statistics. Time-to-event analyses using Kaplan-Meier survival curves, a stratified log-rank test, and Cox proportional hazards models will be performed to assess the effect of parent protocol treatment (active versus placebo/control) on time from seroconversion to having a CD4+ count below the threshold for initiation of ART, first AIDS-defining illness and initiation of ART, each assessed as separate outcomes. A composite HIV disease progression end point will be constructed, defined as the first occurrence of a CD4+ T-cell count below the threshold for initiation of ART, AIDS-defining illness, initiation of ART, or death not due to trauma. Time from seroconversion to the composite HIV disease progression outcome will be compared between active and placebo/control groups.

Secondary Analyses

The same methods used to assess the primary endpoint will be used to assess HIV-1 disease progression over the entire duration of follow-up.

Among participants who initiate ART, viral load and CD4 count trajectories will be assessed over time following initiation of ART using linear mixed effects models. Time from initiation of ART to virologic failure will be compared between active and placebo/control groups using the same time-to-event methods described for the primary analysis. In addition, time-to-event methods will be used to assess time from ART initiation to HIV-1 viral load suppression between active and placebo/control groups.

Among participants who experience virologic failure, descriptive statistics will be used to compare the prevalence and profile of HIV-1 drug resistance virus in plasma and genital tract specimens between active and placebo/control groups.

Data on behaviors that are associated with HIV transmission such as sexual intercourse without a condom, the frequency of sexual intercourse, the numbers of sexual partners, and partnership status and dynamics will be measured over time among participants in this study. The effect of depression, interpersonal violence and HIV disclosure patterns on such behaviors will be assessed. In addition to these within participant analyses, exploratory analyses will compare these behaviors to the same behaviors reported by HIV negative participants in ongoing microbicide trials and to large household surveys of individuals (Demographic Health Surveys) from the same country. Finally, descriptive statistics will be used to summarize the occurrence of reported social harms over the duration of follow-up.

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

All study sites will maintain source data/documents in accordance with current DAIDS policies.(http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Default.aspx)

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 three years after study closure. Study records will not be destroyed prior to receiving approval for record destruction from DAIDS. Applicable records include essential and source documents, protocol registration documents, informed consent forms, all contact with the participant, case report forms, and other study related correspondence.

11.3 Quality Control and Quality Assurance

All study sites will conduct quality control and quality assurance procedures in accordance with current DAIDS policies.
(http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/qmppolicy.pdf)

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 SDMC, MTN NL, NIAID, OHRP, IRBs, 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 study site is responsible for assuring that this protocol and the associated informed consent documents and study-related documents are reviewed by its responsible IRBs/ECs 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

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) *WILL NOT* be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS

PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) *WILL NOT* be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

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 participants. 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 participants. Some participants 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, 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 US

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 Appendix V 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 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 years of age.

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 and/or designees. Trained study staff will obtain informed consent from potential study participants. Study staff will keep research participants fully informed of any new information that could affect their willingness to continue study participation.

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 ensure confidentiality protection that reflects the local study implementation plan (e.g., whether community-based visits will be conducted) and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them. In addition to local considerations, the protections described below will be implemented at all sites.

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. Data collection, process, and administrative forms, laboratory specimens, and other reports will be identified by a coded number only to maintain participant confidentiality. All local databases will be secured with password-protected access systems. 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 and counseling, including treatment for PMTCT 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/NIAID and MTN policies will govern publication of the results of this study.

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(SCR)						
Eligibility Determination	X(SCR)						
Assign Participant ID	X(ENR)						
Update Locator Information	X(ENR)	X	X	X	X	X	X
Collect Demographics	X(ENR)						
Schedule Next Visit	X(ENR)	X	X	X	X	X	
Reimbursement	X(ENR)	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 (at baseline Assessment of Antiretroviral Use will be assessed)	X	X	X	X	X	X	X
Antiretroviral Treatment Record					X	X	▲
Provide Available Test Results	X	X	X	X	X	X	X
Treatment or Referral	▲	▲	▲	▲	▲	▲	▲
Complete Physical Exam	X	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 & 24)	X (Mo. 3)	X (Mo. 12 & 24)	X (Mo. 3, 12 & 24)
ART 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 (Mo.3)	X	X
Provision of Condoms	X	X	X	X	X	X	X
Laboratory Procedures							
Urine Qualitative hCG	X	X	X	▲	▲	▲	X
Urine NAAT 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
Plasma	X	X	X	X	X	X	X
HIV serology (Two rapids performed at SCR/ENR. Contact NL if both are not positive)	X						
PBMC	◊	◊	◊	◊	◊ (Wk. 2 & Mo. 3)	◊	◊
HIV-1 Genotypic Resistance Test (at NL) (*Will be processed at the discretion of MTN NL)*	X				▲	▲	▲
Vaginal pH	X	▲	▲	▲ (Annual)	▲	▲ (Annual)	X
Testing for Trichomonas	X	▲	▲	▲ (Annual)	▲	▲ (Annual)	X
Testing for BV and Candida	▲	▲	▲	▲	▲	▲	▲
PAP Smear at Selected Sites	†	▲/†	▲/†	▲/†	▲/†	▲/†	▲/†

Vaginal Swabs	X	X	X	X	X (Mo.1 & Mo. 3)	X	X
Cervicovaginal Lavage	X	X	X	X	X (Mo.1 & Mo. 3)	X	X

X=protocol-defined procedure; ▲=performed as 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. ◊ Collected at sites with capacity.

APPENDIX II: 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

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 III: WHO CRITERIA FOR HIV STAGING EVENTS

For current WHO criteria for HIV staging events please go to http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf. The link to the WHO criteria for HIV staging events is current as of the protocol version date shown in the footer. Future updates to these criteria will be adopted as appropriate.

APPENDIX IV: 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 V: SAMPLE INFORMED CONSENT (SCREENING AND ENROLLMENT)

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

Version 2.0
May 3, 2013

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 participants who have become infected with the human immunodeficiency virus (HIV) while taking part in a MTN study. You are being asked to take part in this study because you have become infected with HIV during a MTN 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 participants 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 participants may get after HIV infection.

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

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. If you agree, 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 MTN study, you can stay in that study and be in this study at the same time.

After you have signed the informed consent, some of the procedures listed below may be removed if they were done within the past 30 days as part of the parent study. Clinicians and/or study staff may look at your records from the parent study at enrollment and at follow-up visits, as needed.

Screening/Enrollment Visit:

This visit will continue today after you read, discuss and sign or make your mark on this form. [Sites to insert the anticipated amount of time the study visits will take: It will take about X hours]. The study clinician will review and access the records from your MTN study to make sure you meet the requirements for this study. Then you will be asked some questions. Some of these questions may be asked via computer. The study staff will show you how to use the computer. 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 vaginal swabs and testing of your vaginal fluids will be performed for research purposes only, you will not be made aware of the results of these tests as they are not relevant for your care.
- [For selected sites only: Study staff also may 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 blood [SITES TO INSERT XXmL]. This blood will be used for:
    - Tests to reconfirm your HIV status. You must receive HIV test results to be in this study. Even though HIV testing was already done in your microbicide trial, study staff will perform additional tests to reconfirm that you are eligible to be in this study. In some cases your HIV status may not be confirmed right away and additional testing may be required. Your test result will be told to you [sites to add expected timeframe]. If you need to, you can talk with the study staff about the meaning of your tests and feelings you may have about the results. If the test shows that you do not have HIV, you cannot join this study. We will refer you to

available sources of medical care and inform you if there are other studies you may be eligible for.

- Tests for syphilis. Syphilis is an infection 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. The resistance testing may not need to be performed if you have recent results from the MTN study you were taking part in.

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. It is important to know that results of tests that are done for research purposes only will not be routinely provided to you or your doctor unless they are important for 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 [Sites to insert the anticipated amount of time the study visits will take: about X hour(s)]. You will answer questions like at the Screening/Enrollment Visit, again some of these questions may be asked via computer. Study staff will also ask 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.
- Other tests of HIV virus and your immune system that will be performed for research purposes

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 for research purposes 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. [Sites to insert the anticipated amount of time the study visits will take: These visits will take about X hour(s)].

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. [Sites to insert the anticipated amount of time the study visits will take: These visits will take about X hour(s)]. Procedures 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. In addition, study staff may have to collect samples from you again if there are any problems.

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.

How Many Participants Will Be In this Study?
About 500 participants will take part in this study.

How Long Will I be In This Study?
You will be in this study for a minimum of 12 months after you have found out the results of your HIV test, but you may stay in the study longer if the study is still being done at this clinic.

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 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. Learning that you have an infection passed through sex may cause you sadness or depression. 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.

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. If you are still enrolled in this study when the outcome of your pregnancy occurs, study staff will ask you a few questions about the outcome.

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 [LOCAL 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
- Office of Human Research Protection (OHRP)
- [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.
[SITES TO SPECIFY COSTS ASSOCIATED WITH TREATMENT OF STIs, IF ANY.]

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]

Can my private health information and samples collected by this study be used for future studies?

You may have biological specimens, such as blood, urine, vaginal, and cervical samples, left over after we have done all of the study-related testing after your study visits. We would like to ask your permission to store these samples and health data related to these samples for use in future studies. This health information may include personal facts about you such as your race, ethnicity, sex, medical conditions and your age range. If you agree, your samples and related health data will be stored safely and securely so that only approved researchers will have access to the samples. [*Non-US site(s) storage plans*: At some point in the future, or after your study participation is complete, some of these samples may be stored outside of your country.] Some employees of the facilities will need to have access to your samples to store them and keep track of where they are, but these people will not have information that directly identifies you. You can still enroll in this study if you decide not to have these samples stored for future studies. If you do not want the samples stored, we will destroy the leftover specimens. Any future studies that may be done will also be approved by an IRB/EC. *[Sites to specify institutional policy:]* There is no time limit on how long your samples or health data will be stored or when these leftover specimens may be tested. If at any time you decide not to allow for the storage and future testing of your samples, your extra samples will be destroyed.

Risks Related to Stored Samples:

If you choose to have leftover samples stored and collected solely for this purpose, 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.

_____ I agree to allow my biological specimens and health
Initials & Date data to be used in future research studies.

_____ I do not agree to allow my biological specimens and
Initials & Date health data to be used in future research studies.

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.

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

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