

**SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:**

MTN-015

DAIDS Protocol #:10529

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

**THE AMENDED PROTOCOL IS IDENTIFIED AS:
Version 2.0/May 3, 2013**

Information/Instructions to Study Sites

The information contained in this protocol amendment impacts the MTN-015 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. IRB approval is required before implementation of the modifications contained in this amendment. All IRB requirements must be followed.

Please file this Summary of Changes, Version 2.0 of the protocol and all associated IRB correspondence in your essential documents files for MTN-015

Summary of Revisions

This amendment incorporates previously issued Clarification Memos and Letter of Amendments. To ease in the review process, all revisions, including Clarification Memos and Letters of Amendment and new revisions are displayed below without distinction. A summary of revisions is provided below:

- The cover page has been revised to include all funding agencies for the study
- The Protocol Team Roster is updated to reflect current members. The roster format is also modified to list members by affiliation.
- The list of Abbreviations and Acronyms has been updated
- An Investigator Signature form has been added
- The study objectives and endpoints are modified to be more concise and improve clarity
- The endpoints were modified to reflect the changes in the objectives and were expanded upon to allow for planned analyses related to the Primary and Secondary Objectives
- The background section is updated to include additional and up-to-date information regarding clinical studies of HIV-1 seroconversion. Related sections have been updated accordingly

- The eligibility criteria are updated to reflect standardized MTN protocol language
- In Section 7, *Study Procedures*, the formatting and organization has been revised. The study procedures are comprehensively listed in table format. Appendix I, *Schedule of Study Visits and Evaluations*, and the Sample Informed Consent documents are updated accordingly
- Section 10, *Statistical Considerations*, is modified to reflect the revised study objectives and endpoints, power estimates, clarify study blinding and the oversight of the Interim Study Review (ISR) Committee instead of the Data and Safety Monitoring Board (DSMB), and data analysis
- Section 12, *Clinical Site Monitoring*, has been revised to include all authorized representatives allowed to inspect study-related documentation
- Section 13, *Human Subjects Protection*, is updated to reflect DAIDS Protocol Registration template language
- Section 14, *Publication Policy*, is updated to more accurately describe the DAIDS/NIAID and MTN publication policy
- Appendix V: *Sample Informed Consent (Screening and Enrollment)*, has been updated to reflect study procedures and revised to enhance participant understanding of the trial
- The Sample Informed Consent document (Storage and Future Testing of Specimens section) is revised to include checkboxes for participants to indicate whether or not they agree to long-term specimen storage under *Can my private health information and samples collected by this study be used for future studies?* Also, minor revisions have been made to the *Signatures* page
- Other minor updates, corrections, and clarifications are incorporated

Rationale

The primary purpose of this full version amendment is to clarify that participants will remain on-study for a minimum of 12 months after HIV-1 seroconversion and that follow-up may continue as funding permits or as determined by MTN leadership. The overall scientific priorities, study design, study population, sample size, and the study visit schedule remain consistent with Version 1.0. Modifications throughout the protocol, including updates to the introduction, reorganization of the study procedures, and updates to the statistical considerations section have been incorporated. In addition, several edits were incorporated to align Version 2.0 with the current MTN Protocol Template and current DAIDS guidance and templates. Text within the objectives was modified to be more concise and to improve clarity. The endpoints were also modified to reflect the changes in the objectives and were expanded upon to allow for planned analyses related to the primary and secondary objectives.

The proposed revisions enhance the scientific merit of MTN-015 that the integrity of the data generated is reinforced and ensures that the proper safeguards for participant safety remain intact.

Implementation

This amendment is now official MTN-015 protocol documentation. Prior to implementing the revisions listed below, MTN-015 study sites will submit this Summary of Changes and protocol Version 2.0 to all relevant regulatory authorities and IRBs/ECs.

Upon receipt of all regulatory and IRB approvals and completion of protocol registration procedures, the protocol modifications listed below will be implemented. With exceptions to modifications to the Protocol Team Roster, detailed modifications of the protocol text are indicated by ~~strike through~~ (for deletions) and **bold** (for additions). Unless otherwise stated section numbers reflect the current version of the protocol.

Detailed Listing of Revisions New to Version 2.0

1. Protocol Cover Page, appropriate funding agencies have been added, the grant number has been updated, and the protocol chair's information has been modified:

**Sponsored by
Funding Agencies:**

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

Grant #:

~~4-U01-5UM1~~ AI068633-0407

Protocol Chair:

Sharon A. Riddler, MD, MPH
University Of Pittsburgh
~~MTN-CORE~~

2. The *List of Abbreviations and Acronyms* has been updated:

HSV-2	Herpes Simplex Virus—Type II
NAAT	Nucleic Acid Amplification Testing
RCC	Regulatory Compliance Center
PrEP	pre-exposure prophylaxis
RE	regulatory entity
RSC	Regulatory Support Center
SDA	strand displacement assay

3. The Protocol Team Roster is updated to reflect current Protocol Team members and contact information:

The following individuals are added to the Protocol Team Roster:

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4. An Investigator Signature Form has been added to the Protocol:

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

5. Protocol Summary:

Sample Size: Approximately 500 ~~women participants~~ **(estimated minimum 165, with 138 available for the evaluation of the primary objective)**

Study Population: ~~Women~~**Participants** who have HIV-1 seroconversion during participation in microbicide trials

Study Duration: ~~Until May 31st, 2013, with possibility of extension~~ **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 the ~~plasma HIV-1 RNA level twelve~~ **disease progression 12** months after ~~HIV-1 post~~ seroconversion among ~~antiretroviral treatment (ART) naïve~~ participants assigned to an active ~~microbicial or chemoprophylactic~~ agent compared to **placebo/control** participants.

Secondary Objectives:

- ~~To characterize the trajectory of CD4+ T-cell counts after~~ **To compare HIV-1 disease progression post** seroconversion among ~~antiretroviral treatment naïve~~ participants assigned to an active ~~microbicial or chemoprophylactic~~ agent compared to **placebo/control** participants **over the total duration of follow-up.**
- To compare the ~~plasma HIV-1 RNA level six months after HIV-1 seroconversion among~~ **virologic and immunologic responses following initiation of** antiretroviral ~~treatment naïve~~ **therapy among** participants assigned to an active ~~microbicial or chemoprophylactic~~ agent compared to **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.**
- ~~To evaluate the virologic response to initiation of antiretroviral therapy among participants assigned to an active microbicial or chemoprophylactic agent compared to control participants in microbicide trials and by study specific analysis (for larger trials including current and future trials).~~
- ~~The proportion with HIV-1 RNA less than 50 copies/mL six months, twelve months, and twenty-four months following initiation of antiretroviral therapy the CD4+ T-cell response~~

~~to initiation of antiretroviral therapy in participants after seroconversion in microbicide trials.~~

- ~~• The CD4+ T-cell increase six months, twelve months, and twenty-four months following initiation of antiretroviral therapy, at the time of virologic failure (HIV-1 RNA >200 copies/mL at or after six months of antiretroviral therapy) in participants assigned to an active microbicide or chemoprophylactic agent compared to control in microbicide trials and by study specific analysis (for larger trials including current and future trials).~~
- ~~• To describe HIV-1 related (WHO Stage II) and AIDS-defining (WHO Stage III and IV) clinical events and deaths (from any cause) occurring among seroconverters with and without antiretroviral therapy.~~
- ~~• To compare the rate of HIV-1 disease progression among participants assigned to an active microbicide or chemoprophylactic agent compared to control.~~
- ~~• To describe post-seroconversion changes in sexual behaviors and partnership status of women who seroconvert during participation in microbicide trials.~~
- ~~• To provide a repository of specimens from women who have HIV-1 seroconversion during participation in microbicide trials that can be used for future analyses.~~

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 among participants assigned to an active microbicide or chemoprophylactic agent compared to control participants. drug resistance mutations in plasma and cervical lavage fluid using more **both standard and** sensitive methods (which may include modified ultrasensitive assays of plasma HIV RNA) in studyin specific subgroups of seroconverters.~~
6. Section 1.2, *Funding Agencies, Sponsor Monitor Identification*, has been revised to include updated funders and their contact information:

~~Sponsor:~~ **Funding Agencies:**

**US Division of AIDS (DAIDS)/National Institute of Allergy and Infectious Diseases (NIAID)
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7. Section 1.3, *Medical Officer*:

1.3 ~~Medical Officers~~**Officer**

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8. Section 1.4, *Site Investigators*, was removed:

~~1.4. Site Investigators~~

~~Site Investigators: See Appendix II~~

9. Section 1.5, *Network Laboratory*:

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~~Site Laboratories: See Appendix III~~

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11. Section 1.8, *Study Operations*:

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12. Section 2.1, *HIV/AIDS Prevention and Microbicides*:

~~According to UNAIDS, approximately 40 million people worldwide were living with HIV in 2006.~~ **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 ~~topical microbicides.~~ **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) ~~will include Phase I, II and IIIa safety trials of new compounds as well as larger, Phase IIb and III randomized trials.~~ The variety of potential compounds is broad and includes agents with and without specific HIV-1 inhibitory activity. Trials conducted by the MTN will include ~~both topical microbicides and~~ **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. ~~There~~ **However, there will, however,** be new HIV-1 infections among study participants and, ultimately, users of microbicides and ~~chemoprophylaxis.~~ **oral PrEP.** It is essential to monitor these HIV-1 seroconverters ~~in order~~ to better understand the impact of microbicides or chemoprophylaxis on the natural history of HIV-1 infection in those who become infected or are unknowingly already infected while receiving a product. The potential alteration of the clinical course of HIV-1 infection among users of microbicides or ~~chemoprophylaxis~~ **oral PrEP** may be beneficial or harmful for the exposed individuals. For example, it is possible that the use of a ~~topical microbicide or chemoprophylactic agent~~ **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 ~~women~~ **individuals**, who are infected, despite the use of ~~topical microbicides or oral chemoprophylaxis~~ **PrEP**, will have a lower viral set-point and subsequent slower progression of HIV disease.

A major concern is the possibility that ~~topical microbicides or oral chemoprophylaxis~~ **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 ~~women~~ **individuals** who become infected while using ~~topical or oral 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 in North America and Western Europe South Africa,** approximately 40~~<~~**5%** of all new infections are attributed to viruses that contain at least one drug resistance mutation ~~but there are no data yet regarding the incidence of resistance among recipients of single or dual drug chemoprophylaxis or microbicides.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 ~~women~~ **individuals** who unknowingly are already HIV-infected. This may be less of a concern with respect to topically applied products with ~~little~~ **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.^{v, vi, vii} ~~Risky.~~⁵⁻⁷ **Therefore, risky** sexual behavior soon after infection ~~therefore~~ 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.^{8, 9} 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 infection¹⁰⁻¹² Among serodiscordant couples, the risk of HIV transmission was found to be seven times higher during the first five months after seroconversion as compared to later stages of infection when measured prospectively.~~v~~ ~~Clearly, accumulating.~~⁵ **Accumulating** biological and modeling data suggest that transmission from individuals in the acute and early stages of HIV disease represent a major contribution to continuing the HIV epidemics. What is not known is how effective early detection of new infection and counseling may be ~~to~~in reducing such transmission. ~~Women~~**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.

13. Section 2.2.2, *Rationale*:

Evaluation of the effect of ~~topical~~ microbicides or oral ~~chemoprophylaxis~~**PrEP** use on the natural history of HIV-1 infection is essential for the development of guidance for the use of ~~such~~**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 ~~microbicide~~**MTN** study participants who become HIV-infected during product use. Careful monitoring of ~~topical~~ microbicide and oral ~~chemoprophylaxis~~**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 ~~HPTN-059~~ **are other trials of efficacy** are considered MTN studies from which participants in ~~MTN-015~~ **will** may be drawn. In addition, studies investigating both ~~topical~~ microbicides and oral ~~chemoprophylaxis~~**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 ~~women~~**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. ~~This protocol will also include storage of biologic samples to allow further characterization of virologic and immune parameters among subsets of participants using a nested case control approach.~~

Individuals recently HIV infected often have high viral loads and may be highly infectious.~~v, vi, vii~~⁵⁻⁷ 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.~~v~~.¹³ Possible mediators of such behavior change include dynamics of partnerships and disclosure. Observation of individuals with recent HIV-1 infection over time can provide information critical to secondary

prevention. Many HIV positive individuals in Africa do disclose their status, with rates as high as 92% reported in one South African study. ~~xiii However, there is also.~~¹³ **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. ~~Moreover, even among the individuals in whom high disclosure was observed there was also considerable delayed disclosure (15% greater than a year) or non-disclosure (21%) to partners.~~¹⁴ ~~Women who have participated in~~ **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 ~~among women~~ in this unique situation to reduce transmission is important to describe and may help future counseling programs for HIV positive ~~women~~ **individuals** in developing countries. Describing the pattern of behavior change among newly HIV infected ~~women~~ **individuals** in comparison to ~~women~~ **those** who are negative or chronically infected (from HPTN 035 and other datasets), will inform counseling strategies to reduce further HIV infection.

14. Section 3.1, *Primary Objective*:

- To compare ~~the plasma HIV-1 RNA level twelve~~ **disease progression 12** months after ~~HIV-1 post~~ seroconversion among antiretroviral treatment (ART) naïve participants assigned to an active ~~microbical or chemoprophylactic~~ agent compared to **placebo/control** participants.

15. Section 3.2, *Secondary Objectives*:

- ~~To characterize the trajectory of CD4+ T-cell counts after HIV-1~~ **To compare HIV disease progression post** seroconversion among antiretroviral treatment naïve participants assigned to an active ~~microbical or chemoprophylactic~~ agent compared to **placebo/control** participants **over the total duration of follow-up.**
- To compare ~~the plasma HIV-1 RNA level six months after HIV-1 seroconversion among~~ **virologic and immunologic responses following initiation of** antiretroviral ~~treatment naïve~~ **therapy among** participants assigned to an active ~~microbical or chemoprophylactic~~ agent compared to **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.**
- ~~To evaluate the virologic response to initiation of antiretroviral therapy among participants assigned to an active microbical or chemoprophylactic agent compared to control participants in microbicide trials and by study specific analysis (for larger trials including current and future trials).~~
- ~~The proportion with HIV-1 RNA less than 50 copies/mL six months, twelve months, and twenty-four months following initiation of antiretroviral therapy~~

- ~~To describe the CD4+ T-cell response to initiation of antiretroviral therapy in participants after seroconversion in microbicide trials.~~
- ~~The CD4+ T-cell increase six months, twelve months, and twenty four months following initiation of antiretroviral therapy, at the time of virologic failure (HIV-1 RNA >200 copies/mL at or after six months of antiretroviral therapy) in participants assigned to an active microbicide or chemoprophylactic agent compared to control in microbicide trials and by study specific analysis (for larger trials including current and future trials).~~
- ~~To describe HIV-1 related (WHO Stage II) and AIDS-defining (WHO Stage III and IV) clinical events and deaths (from any cause) occurring among seroconverters with and without antiretroviral therapy.~~
- ~~To compare the rate of HIV disease progression among participants assigned to an active microbicide or chemoprophylactic agent compared to control.~~
- ~~To describe post-seroconversion changes in sexual behaviors and partnership status of women who seroconvert during participation in microbicide trials.~~
- ~~To provide a repository of specimens from women who have HIV-1 seroconversion during participation in microbicide trials that can be used for future analyses.~~

16. Section 3.3, *Exploratory Objective*, was added condensing secondary objective text:

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 among participants assigned to an active microbicide or chemoprophylactic agent compared to control participants. ~~To evaluate the prevalence and persistence of HIV drug resistance mutations in plasma and cervical lavage fluid using more~~ **both standard and** sensitive methods (which may include modified ultrasensitive assays of plasma HIV RNA) in studyin specific subgroups of seroconverters.

17. Section 4.1, *Identification of Study Design*, the first, second, third, and fourth paragraphs have been revised:

MTN-015 is a multi-site, prospective observational cohort study. Potential participants will be offered enrollment in MTN-015 following identification of HIV-1 seroconversion in the parent trial (the trial from which they were **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.

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

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

18. Section 4.2, *Description of Study Population*:

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

19. Section 4.5, *Expected Duration of Participation*:

~~The expected duration of participation for an individual participant is~~ **At a minimum, participants will remain on-study up until May 31st, 2013. 12 months (approximately 1 year) after the HIV-1 seroconversion identification date. Follow-up may continue as funding permits or as determined by the MTN Executive Committee.** ~~Study sites are listed in Appendix III leadership.~~

20. Section 4.6, *Sites* has been removed.

21. Section 5.0, *Study Population*:

The study population will consist of ~~female~~ participants who are identified as infected with HIV-1 during participation in microbicide clinical trials who meet the eligibility criteria listed below. Potential participants will be recruited for MTN-015 as soon as possible after identification of HIV-1 seroconversion; however, there is no time limit for MTN-015 enrollment after identification of seroconversion. ~~With assistance from the SDMC, the Site PI or designee will identify participants who seroconvert during participation in parent microbicide trials.~~

22. Section 5.1, *Selection of the Study Population*, paragraphs under *Composition* and *Recruitment* have been modified:

Composition

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

Recruitment

Study site staff will recruit potentially eligible study participants. For microbicide trial participants who seroconvert prior to activation of MTN-015, study staff will retrospectively contact the participants for possible enrollment in MTN-015, unless the participants have refused further contact with study staff. For microbicide trial participants who seroconvert after activation of MTN-015, study staff will ~~prospectively~~ contact the participants for possible enrollment in MTN-015 ~~at the time of identified seroconversion.~~ **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.

23. Section 5.2, *Inclusion Criteria*:

~~Women~~**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 ~~(including HPTN 035 and HPTN 059)~~, **based on local laboratory testing and** according to the HIV testing algorithm of the parent MTN trial.
2. Able and willing to provide ~~independent~~ written informed consent to participate in the study.

24. Section 5.3, *Exclusion Criteria*:

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

25. Section 7, *Study Procedures*, the first and second paragraphs have been revised and a fourth paragraph has been added:

Information is provided below and in Appendix 4I on when each study procedure is to be performed. ~~Screening and~~ 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 completed if needed to complete all required procedures. If a participant is being followed in her parent trial, site staff will make every effort to may schedule and complete MTN-015 visits on the same day as parent protocol visits. Completion of the parent MTN protocol visit should take priority if time or other factors do not allow efficient for both study visits to be completed on the same day. **site staff and participants.**

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 www.mtnstopshiv.org for additional information.

26. Section 7.0, *Study Procedures*, component titles have been updated for consistency.

27. Section 7.0, *Study Procedures*, has been reorganized for clarity and precision. Sections 7.1 through 7.6 and Tables 1-6, have been updated accordingly:

7.1 Screening and/Enrollment Visit

Table 1: Screening and/Enrollment Visit

Screening and/Enrollment Visit	
Component	Procedure/Analysis
Administrative: Screening	<ul style="list-style-type: none"> - Review Parent Study Records to Confirm HIV-1 Seroconversion
Administrative: Enrollment	<ul style="list-style-type: none"> - Update Collect Demographics
Clinical	<ul style="list-style-type: none"> - Concomitant Medications Assessment, including Assessment of Antiretroviral Use (past and current) - *Antiretroviral Treatment Record - Complete Physical Exam (See Appendix IVII) - Gynecologic Exam (See Appendix IVII) - *Provide Available Test Results - *Treatment or Referral*
Behavioral	<ul style="list-style-type: none"> - Baseline Behavioral Questionnaire - *ART Adherence Questionnaire*
Urine	<ul style="list-style-type: none"> - SDANAAT for Chlamydia and Gonorrhea
Blood	<ul style="list-style-type: none"> - Plasma - HIV-1 Genotypic Resistance Testing ▲ - HSV-2 Antibody (site lab, regional lab, or MTN NL, archived plasma) - HIV ELISA and Western Blot (MTN NL, archived serum)** - HIV Serology (2 rapid tests) - Contact Management Team if both are not positive

	<ul style="list-style-type: none"> - Peripheral Blood Mononuclear Cells (PBMC)
Pelvic Samples	<ul style="list-style-type: none"> = Testing for Wet Mount for Bacterial Vaginosis (BV), and Candida, and* - Testing for Trichomonas - [†]Pap Smear at Selected Sites[†] - Vaginal Swabs - Cervicovaginal Lavage
Specimens for Storage	<ul style="list-style-type: none"> = Vaginal Swabs = Cervicovaginal Lavage = Plasma = Serum = Peripheral Blood Mononuclear Cells (PBMC)

~~Specimens for Storage Serum Peripheral Blood Mononuclear Cells (PBMC)~~

~~*If indicated, **If not previously confirmed in a Network Laboratory, † PAP smears should be done at 6 month intervals in the first year after seroconversion, and then annually if the initial tests are negative. ◇ At sites with capacity. ▲ Will be processed at the discretion of MTN NL.~~

Section 7.2, *Follow-up Visits*, the first, second, and third bullets and last paragraph have been revised

- Participants who have not initiated use of ART at the time of enrollment in MTN-015 will follow the schedule based on the date of identification of seroconversion, which is described in Section 7.2.1. On this schedule, follow-up visits occur at Months 1, 3, and 6 after the date of identification of seroconversion, and every 6 months thereafter. Participants may enroll anytime after seroconversion. Following the enrollment **Screening and Enrollment** visit, the subsequent **follow-up** visits will be scheduled according to the seroconversion date ~~(for. For example, a participant who enrolls 43 months after seroconversion would have a secondmiss her Month 1 and Month 3 Post-Seroconversion Visits, and would complete her Month 6 Post-Seroconversion Visit as her first follow-up visit at 6 months after seroconversion (2 months after enrollment) and-. 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 ~~specified above~~, visits may be completed at any time during allowable visit windows. For both the non-ART and

ART visit schedules, the allowable visit windows are contiguous and extend from the midpoint of one visit interval to the midpoint of the next visit interval. For example, the Month 24 visit window ~~extends from~~ **begins mid-way between the Month 21 through 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.

Section 7.2.2, *Visits for non-ART Participants*, Table 2: *Month 1 and Month 3 Post-Seroconversion Visits*, and Table 3: *Month 6 and Q6 Months Post-Seroconversion Visits*, has been modified:

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

Month 1 and Month 3 Post-Seroconversion Visits	
Component	Procedure/Analysis
Clinical	<ul style="list-style-type: none"> - TargetedComplete Physical Exam (See Appendix II) - Gynecologic Exam (See Appendix II) - *Provide Available Test Results - *Treatment or Referral*
Behavioral	<ul style="list-style-type: none"> - Follow-up Behavioral Questionnaire (at Month 3 Post-Seroconversion-Only) - Social Harms Assessment (at Month 3 Post-Seroconversion-Only)
Urine	<ul style="list-style-type: none"> - *Qualitative hCG - *SDA-NAAT for Chlamydia and Gonorrhea*
Blood	<ul style="list-style-type: none"> - *Syphilis Serology* - Complete Blood Count (at Month 3 Post-Seroconversion-Only) - Liver and Renal Function (at Month 3 Post-Seroconversion-Only) - Plasma - PBMC Collection◇
Pelvic Samples	<ul style="list-style-type: none"> - *Vaginal pH* - Wet MountTesting for BV, Candida*, and - Testing for Trichomonas - *† Pap Smear at Selected Sites*† - Vaginal Swabs - Cervicovaginal Lavage
Specimens for Storage	<ul style="list-style-type: none"> - Vaginal Swabs - Cervicovaginal Lavage - Plasma - PBMC

*If indicated; †PAP smears should be done at 6 month intervals in the first year after seroconversion, and then annually if the initial tests are negative. ◇ **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
Clinical	<ul style="list-style-type: none"> - Targeted Complete Physical Exam (See Appendix II) - Gynecologic Exam (See Appendix II) - *Provide Available Test Results - *Treatment or Referral*
Urine	<ul style="list-style-type: none"> - *Qualitative hCG* - *SDA-NAAT for Chlamydia and Gonorrhea*
Blood	<ul style="list-style-type: none"> - */** Syphilis Serology (annually)*/** - Plasma - PBMC Collection◇
Pelvic Samples	<ul style="list-style-type: none"> - */** Vaginal pH*/** - *Vaginal pH* - *Wet Mount Testing for BV, and Candida*, and - Testing for Trichomonas*/** - */† Pap Smear at Selected Sites (annually)*/† - Vaginal Swabs - Cervicovaginal Lavage
Specimens for Storage	<ul style="list-style-type: none"> - Vaginal Swabs - Cervicovaginal Lavage - Plasma - PBMC

*If indicated; **/***Urine SDANAAT for Chlamydia and Gonorrhea, Syphilis Serology, Vaginal pH, and ~~Wet Mount~~ **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.**

Section 7.2.4, *Follow-Up Visits for Participants after ART Initiation*, Tables 4 and 5 have been revised:

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
Clinical	<ul style="list-style-type: none"> - Targeted Complete Physical Exam (See Appendix II) - Gynecologic Exam (See Appendix II) - *Provide Available Test Results - *Treatment or Referral*
Behavioral	<ul style="list-style-type: none"> - Follow-up Behavioral Questionnaire (Month 3 only) - If ART is begun more than 24 months after identification of seroconversion, then the Follow-up Behavioral Questionnaire is omitted at post-ART visits.

Week 2, Month 1, and Month 3 After Initiation of ART	
Component	Procedure/Analysis
	<ul style="list-style-type: none"> - ART Adherence Questionnaire (Month 3 only) - Social Harms Assessment (Month 3 only)
Urine	<ul style="list-style-type: none"> - *Qualitative hCG* - *SDANAAT for Chlamydia and Gonorrhea*
Blood	<ul style="list-style-type: none"> - *Syphilis Serology* - *Complete Blood Count* - *Liver and Renal Function Tests* - *HIV-1 Genotypic Resistance Testing (at NL)* - Plasma - PBMC (Week 2 and Month 3 only)◇
Pelvic Samples	<ul style="list-style-type: none"> - *Vaginal pH* - *Wet Mount Testing for BV, and Candida*, and - Testing for Trichomonas* - *[†] Pap Smear at Selected Sites*[†] - Vaginal Swabs (Month 1 and 3 only) - Cervicovaginal Lavage (Month 1 and 3 only)
Specimens for Storage	<ul style="list-style-type: none"> = Vaginal Swabs = Cervicovaginal Lavage (Month 3 only) = Plasma = PBMC (Week 2 and Month 3 only)

*If indicated; [†]PAP smears should be done at 6 month intervals in the first year after seroconversion, and then annually if the initial tests are negative. ◇ **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
Clinical Assessments	<ul style="list-style-type: none"> - TargetedComplete Physical Exam (See Appendix II) - Gynecologic Exam (See Appendix II) - *Provide Available Test Results - *Treatment or Referral*
Behavioral Assessments	<ul style="list-style-type: none"> - Follow-up Behavioral Questionnaire (Month 12 and Month 24 only) = If ART is begun more than 24 months after identification of seroconversion, then the Follow-up Behavioral Questionnaire is omitted at post-ART visits. - ART Adherence Questionnaire
Urine	<ul style="list-style-type: none"> - *Qualitative hCG* - */**SDANAAT for Chlamydia and Gonorrhea (annually)*/**
Blood	<ul style="list-style-type: none"> - */**Syphilis Serology (annually)*/**

Month 6 and Q6 Months Visits After Initiation of ART	
Component	Procedure/Analysis
	<ul style="list-style-type: none"> - *HIV-1 Genotypic Resistance Testing* (at NL) - Plasma - PBMC collection◊
Pelvic Samples	<ul style="list-style-type: none"> - */**Vaginal pH*/** - *Wet Mount Testing for BV, Candida* and - Testing for Trichomonas*/** - */† Pap Smear at Selected Sites(annually)*/† - Vaginal Swabs - Cervicovaginal Lavage
Specimens for Storage	<ul style="list-style-type: none"> = Vaginal Swabs = Cervicovaginal Lavage = Plasma = PBMC

*If indicated; **Urine SDNAAT for Chlamydia and Gonorrhea, Syphilis Serology, Vaginal pH, and Wet Mount 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.

Section 7.2.5, *Final/Early Termination Visit – All Participants*, and Table 6 have been modified:

7.2.5 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
Clinical	<ul style="list-style-type: none"> - *Antiretroviral Treatment Record* - TargetedComplete Physical Exam (See Appendix II) - Gynecologic Exam (See Appendix II) - *Provide Available Test Results - *Treatment or Referral*
Behavioral	<ul style="list-style-type: none"> - * 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)* = (ART track participants only)
Urine	<ul style="list-style-type: none"> - SDA NAAT for Chlamydia and Gonorrhea
Blood	<ul style="list-style-type: none"> - HIV-1 Genotypic Resistance Testing* - Plasma - PBMC Collection◊

Pelvic Samples	<ul style="list-style-type: none"> - *Wet Mount Testing for BV, and Candida*, and - Testing for Trichomonas - *† Pap Smear at Selected Sites*† - Vaginal Swabs - Cervicovaginal Lavage
Specimens for Storage	<ul style="list-style-type: none"> = Vaginal Swabs = Cervicovaginal Lavage = Plasma = PBMC

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

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

Section 7.3, *Interim Visits:*

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

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

All interim contacts, study procedures, and visits will be documented in participants' study records and ~~when needed,~~ **on applicable case report forms (CRFs) when applicable.**

Section 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 who do not report with~~ **past or current use of ART at enrollment, behavioral questionnaires will not include questions on, an ART adherence, and will be performed at 3, 12, and 24 months post seroconversion. For participants on ART, behavioral questionnaires will be performed at 3, 12, and 24 months post initiation of ART and an adherence questionnaire will be completed at Month 3, Month 6, and every 6 months thereafter as outlined in Section 7.1 and 7.2.** All behavioral evaluations, ~~as well as and ART adherence questionnaires, including the Social Harms Assessment~~ **social harms questionnaire**, will be available in the MTN-015 Study-Specific Procedures Manual at <http://www.mtnstopshiv.org>.

Section 7.5, *Specimen Collection*:

Each study site will adhere to the standards of good clinical laboratory practice, the HPTN-MTN Network ~~current~~ **DAIDS Good Clinical Laboratory Manual** (available at www.mtnstopshiv.org), ~~DAIDS Laboratory Requirements~~ (available at <http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Labs/>), ~~the~~ **Practice Standards**, MTN-015 Study-Specific Procedures Manual (available at <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 (LDMS). **In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-draw specimens.**

Section 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 ~~SDNA~~ **AAT** method will test urine for Chlamydia and ~~gonorrhoea~~ **Gonorrhoea**.

Blood Samples

~~Study site staff will collect blood samples for the~~ **The** following testing at the local laboratory ~~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 ~~wet mount~~ testing for bacterial vaginosis, candidiasis and trichomoniasis will be conducted at the sites by clinical and/or laboratory staff who have established proficiency in these procedures per MTN policies and procedures.

Section 7.5.2, *Regional Laboratory Specimens* section was deleted:

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

Section 7.5.3, *Network Laboratory Specimens* first two paragraphs deleted:

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

~~Network laboratory (storage) specimens must be collected for MTN-015 as required. Except for HIV-1 seroconversion plasma from the parent trial, sites may not use specimens collected or stored for another trial as stored specimens for MTN-015.~~

Vaginal Swabs

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

Cervicovaginal Lavage

Testing on cervicovaginal lavage samples ~~will~~**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.

Serum

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

Plasma

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

Urine

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

Section 7.6, *Specimen Handling*:

Specimens will be handled in accordance with ~~Requirements~~**current requirements** for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials

~~<http://www3.niaid.nih.gov/research/resources/DAIDSCLINRsrch/Labs/>.~~

(<http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/labpolicy.pdf>)

28. Section 8, *Assessment of Safety*, the third, fourth, fifth, and sixth paragraphs have been revised. Paragraphs seven and eight have been deleted:

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

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

MTN-015 Summary of Changes

May 3, 2013

From Version 1.0 to Version 2.0

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 ~~a minimum of every 6 months~~ **regular intervals** per any applicable DAIDS requirements.

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

- ~~Possibly related: unanticipated~~ **Related: There is a reasonable possibility that the problem and may be related to** study participation/procedures are reasonably
- **Not Related: There is not a reasonable possibility that the problem is** related in time, and the unanticipated problem could be explained equally well by causes other than ~~to~~ study participation/procedures.

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

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

29. Section 9.1, *HIV-1 Infection*, the fourth and fifth sentences have been revised:

Some of the research sites are part of health care institutions that provide HIV-1 care and support, and can refer ~~women~~ **participants** to those services. Other sites have established referral agreements with programs to expand access to antiretroviral therapy, ~~such as those funded by the US President's Emergency Plan for AIDS Relief (PEPFAR).~~

30. Section 9.2, *Reproductive Tract Infection*, the first sentence have been revised:

Participants who are diagnosed with a sexually transmitted infection (STI) or other reproductive tract infection (RTI) will be provided treatment in accordance with current World Health Organization (WHO) guidelines, ~~free of charge.~~

31. Section 9.3, *Pregnancy*, a final sentence has been added to indicate that outcomes will be ascertained on participants until the end of their study participation.

Participants will be contacted to collect the outcome of pregnancies until the end of their study participation.

32. Section 9.4, *Provision of Test Results*, the following sentences have been added after the second sentence:

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.

33. Section 9.5, *Criteria for Discontinuation of Study Participation*, the last sentence has been revised:

Participants will be asked to complete a final/early termination study visit.

34. Section 10.1, *Overview and General Design*:

This is a prospective **observational** cohort study of seroconverters identified in microbicide trials. ~~Currently, 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 come~~ **eligible for MTN-015 (however, these subjects may be excluded from two trials: HPTN-035 and HPTN-059. The 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) in HPTN-035 is 192 for two MTN protocols. In MTN-003, the expected number of HIV seroconversions was 217, while the expected number of HIV endpoints in HPTN-059 is much smaller (0 to 2 seroconverters only). 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 at ~~192~~ **using the parent protocol with the lower number of anticipated events (120 events).**

35. Section 10.2.1 Primary Endpoint:

~~Virologic Response~~ **HIV-1 disease progression 12 months post seroconversion.**

Consistent with the primary study objective, ~~plasma HIV-1 RNA~~ **disease progression 12 months after identification of HIV-1 post seroconversion will be the primary endpoint. Comparison of the 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 12 months after HIV-1 seroconversion between active microbicides seroconversion and 12 months post seroconversion will be compared between active agent and placebo/control groups is.**
- **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 primary objective event guidelines differ).

- **HIV-1 related and AIDS-defining events.** The occurrence and frequency of this study 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.

36. Section 10.2.2, *Secondary Endpoints:*

- ~~Immunologic response. (CD4+ T cell count). CD4+ T cell counts at Weeks 0 and 2, Months 1, 3, 6 and every 6 months thereafter. Time from seroconversion to immunologic failure will be compared between active microbicide and placebo/control groups. Immunologic failure is defined as two consecutive measurements of CD4+ T-cell count within or below the range of 200-250 cells/mm³, or the development of an AIDS defining illness.~~
- **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-seroconversion. In addition, genital HIV shedding and genital health may also be assessed.
- ~~Virologic and immunologic responses (CD4+ T-cell count) after initiation of ART. CD4+ T-cell count and blood plasma HIV-1 RNA levels and CD4+ T-cell count trajectories will be assessed over time after initiation of ART. Time from initiation of ART to immunologic and virologic failure. virologic failure will be compared between active agent and placebo/control groups. In addition, the proportion of participants with a suppressed HIV-1 related and AIDS-defining events. Occurrence and frequency of HIV-1 related and AIDS-defining events. Time from enrollment to time of first AIDS-defining event or death.~~ **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, ~~and occurrence of social harms.~~ 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.

37. Section 10.2.3, *Exploratory Endpoint*, was added:

10.2.3 Exploratory Endpoint

- To evaluate the prevalence and persistence of HIV~~HIV-1 genotypic~~-1 **drug resistance mutations and drug resistant virus**. ~~Prevalence of HIV-1 genotypic mutations over time and drug resistant HIV-1 virus in plasma and/or genital tract. Proportions specimens using both standard and more sensitive methods in specific subgroups of infected participants acquiring a drug resistant HIV-1 virus seroconverters.~~

38. Section 10.4, *Sample Size*, in the original protocol has been omitted.

39. Section 10.3, *Power Estimates*, and Table 7: *Power Calculation for Primary Endpoint* have been revised. Also, Figure 1: *Estimates of the Mean Difference Detectable with 80% Power* has been added.

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 ~~within and between person components of variance~~ **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 ~~around the viral set point~~ **in our population**. The between person variance component is 0.52 (\log_{10} copies²/ml²) and the within person variance component is 0.096 (\log_{10} copies²/ml²).¹⁵

In the HPTN-035~~MTN-020~~ trial, we expect ~~192~~**120** seroconverters: ~~128~~**86** in the placebo-gel and /control groups~~group~~ and ~~64~~**34** in the PRO2000 and BufferGel groups ~~dapivirine group~~ (*assuming an effectiveness of 50% for both active microbicides. This breakdown between groups is conservative since the true effectiveness will most likely be lower. Effectiveness that is lower than 50% will slightly improve the power of this study since the numbers between the active microbicide and placebo/control groups would be more balanced.* **60%**). However, not all of these ~~192~~**seroconverters** will be available for the evaluation of the primary endpoint at one year after seroconversion since:

~~By the time this study is in the field, several newly-infected participants will have seroconverted more than one year ago. We estimate this number to be around 20 such that we will have 172 eligible seroconverters for the evaluation of the primary objective. Newly-infected women may have elected to terminate from the parent study and/or do not wish to enroll in this study and/or have been lost to follow-up in the parent study. Of the 172~~**120** eligible ~~women~~**participants**, we estimate that ~~45~~**20%** of the ~~women~~**participants** eligible for this study will not enroll ~~due and an additional 5% will be lost to one of the above reasons~~**follow-up**.

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

Therefore we anticipate that ~~13891~~ **9265** seroconverters (~~9265~~ from the placebo and /control groups and ~~4626~~ **4626** from the active ~~microbicide groups~~ **group**, assuming that the active ~~microbicides~~ **product reduces** HIV acquisition by ~~50~~ **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 ~~microbicide~~ and placebo/control groups.

Table 7: Power Calculation for Primary Endpoint

Power to detect the indicated difference in log ₁₀ HIV RNA (viral set point) between active microbicide and placebo/control groups assuming 4626 and 9265 individuals in those groups, respectively. The two-sided α level is 0.05.			
	Difference in log ₁₀ plasma HIV RNA (viral set point) at 12 months between active microbicide and placebo/control groups		
No. obs/person	0.3	0.4	0.5
Power	41%	66%	84%
1	56%	80%	94%
2	59%	83%	96%
3	61%	84%	96%
4	61%	85%	96%

Thus, we have ~~80~~ **84%** power to detect a difference of ~~0.45~~ **0.45** log₁₀ copies/ml in viral ~~set point~~ **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. ~~Due to the relatively low within-person variation in viral load, multiple measurements on an individual do not produce a significant increase in power. As mentioned above, if the effectiveness of the active microbicides~~ **product** is smaller than ~~50~~ **60%**, then the power in this study would slightly increase since the numbers between the comparison groups would be more balanced.

~~From the available data and a poll of the site investigators currently conducting HPTN-035, we believe the number of women initiating ART in the first 6-12 months after seroconversion will be very low, less than 10%. Given that the primary analysis will be restricted to seroconverters that have not initiated ART in the first 12 months of seroconversion, the power of the study will decrease slightly. Assuming that 10% of seroconverters will initiate ART within the first 12 months, the study will have at least 76% power to detect a difference of 0.4 log₁₀ copies/ml in viral set point at one year. 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.~~

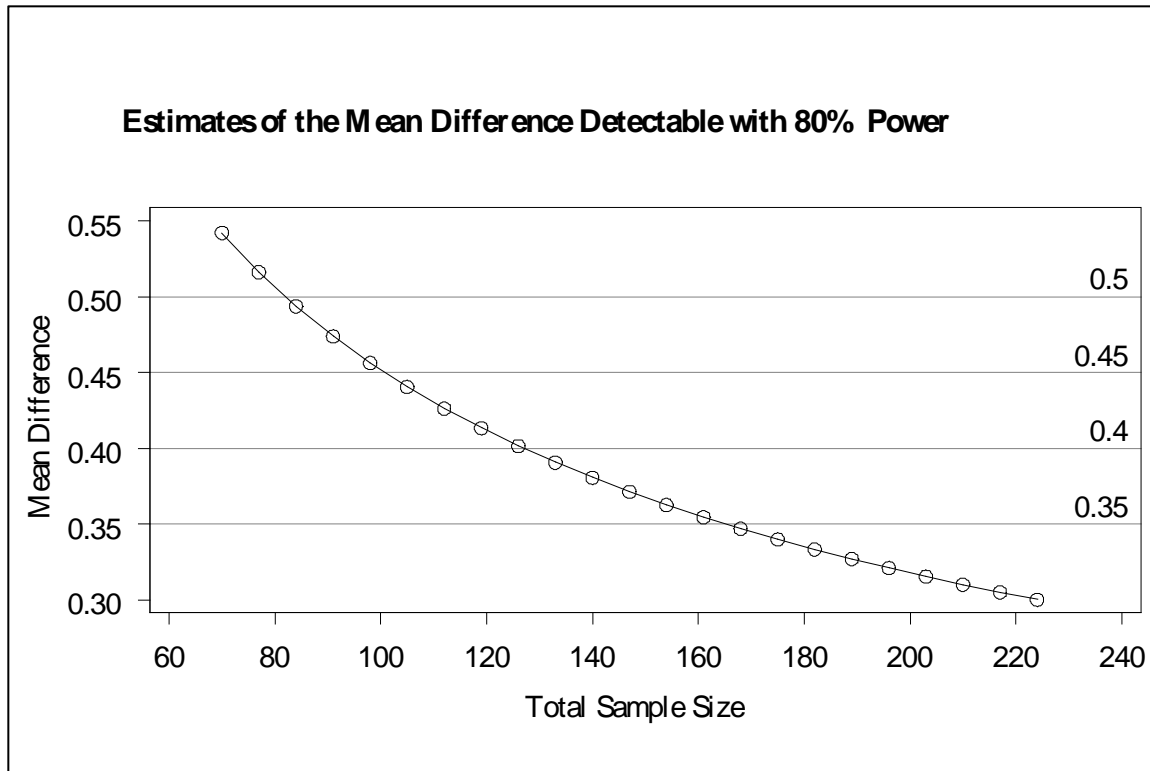


Figure 1: Estimates of the Mean Difference Detectable with 80% Power

40. Section 10.4, *Blinding*:

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

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

There are no circumstances under which it is expected that unblinding will be necessary for the provision of medical treatment or to otherwise protect the safety of study participants. **If event that** an Investigator feels that specific product knowledge is necessary to protect participant safety, the Investigator will notify the Protocol Chair, Protocol Biostatistician, and DAIDS Medical Officer (or designees) to consider and jointly rule upon the request. **while the parent protocol is still blinded, they should follow the processes outlined in the parent protocol for early unblinding.**

41. Section 10.5, *Participant Accrual and Retention*:

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

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.

42. Section 10.6.1, *Interim Study Review Committee*, modification have been made to the section title and after the first paragraph:

10.6.1 Interim Study Monitoring Review (ISR) Committee ~~(SMC)~~

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

~~Once The MTN SMC 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 interim reviews of study progress (blinded with regard to treatment assignment), including rates of participant accrual, retention, the completion of primary and main secondary endpoint assessments, and study or lab issues. endpoints. These reviews will take place are anticipated to occur approximately every 4-6 months, or as needed. annually following the first review. At the time of these reviews, or at any other time, the SMC ISR may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. The SMC 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.

43. Section 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 of the seroconverters will include calculation of the mean and median CD4+ T-cell count and log-transformed viral load by active microbicide and placebo/control groups— 12 months following seroconversion. A simple t-test can will be used to compare log-transformed viral load levels 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 these two groups. However, cautionseroconversion 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) ~~found~~**observed**. Although the ~~overall active microbicide and placebo/control groups should be comparable at baseline (in the parent study) due to randomization, individuals who seroconvert in the active microbicide group~~**arm** may not be comparable to individuals who seroconvert in the placebo/control ~~group~~**arm**. Approaches described by Gilbert et al, Biometrics, 2003 will be used for isolating the effect of an intervention on post-seroconversion outcomes. Furthermore, the primary analysis will be restricted.¹⁶

The frequency of HIV-related and AIDS defining events and ART initiation will be assessed using descriptive statistics. Time-to-seroconverters that have not initiated ART in the 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 12 months after seroconversion 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.

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

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

Secondary Analyses

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

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

~~generally, GEE (Generalized Estimating Equation) methods and robust variance estimates will be used to evaluate group.~~

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-1 transmission such as sexual intercourse without a condom, the frequency of sexual intercourse, and the numbers of sexual partners, and partnership status and dynamics will be measured over time among women participants in this study and compared. 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 women HIV negative participants in ongoing microbicide trials (including parent trials) who are HIV-1 negative and to large household surveys of women individuals (Demographic Health Surveys) in the same countries as the women in this study are located from the same country. Finally, descriptive statistics will be used to summarize the occurrence of reported social harms over the duration of follow-up.~~

44. Section 11.2, *Source Documents and Access to Source Data/Documents*:

~~Source documents and access to~~**All study sites will maintain** source data/documents will be maintained in accordance with the Requirements for Source Documentation in current DAIDS Funded and/or Sponsored Clinical Trials. ~~policies.~~

~~(<http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Default.asp>)~~

(<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 ~~two~~**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, ~~site~~**protocol** registration documents ~~and reports, correspondence,~~ informed consent forms, ~~and notations of all contacts~~**contact** with the participant, **case report forms, and other study related correspondence.**

45. Section 11.3, *Quality Control and Quality Assurance*:

~~Quality~~ **All study sites will conduct quality control and quality assurance procedures for MTN-015 will be performed in accordance with Requirements for Clinical Quality Management Plans at current DAIDS Funded and/or Supported Clinical Research Sites policies.**

(<http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/qmppolicy.pdf>)

46. Section 11.4, Study Coordination in Version 1.0, has been deleted:

~~Study implementation will be directed by this protocol and further guided by the Study Specific Procedures Manual provided by Family Health International, the Statistical Center for HIV/AIDS Research & Prevention (SCHARP), and the MTN Network Laboratory.~~

47. Section 12, *Clinical Site Monitoring*, the last paragraph has been revised:

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the MTN CORE, MTN Network Laboratory, Family Health International, SCHARP, NIAIDSDMC, 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.

48. Section 13.1, *Institutional Review Boards*:

Each participating institution ~~institution~~ **study site** is responsible for assuring that this protocol and the associated informed consent documents and study-related documents are reviewed by ~~an Ethics Committee (EC) or Institutional Review Board (IRB)~~ **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.

49. Section 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 Each study site will complete protocol registration with the DAIDS Regulatory Compliance Center (RCC) Protocol Registration Office. For additional information, refer to the protocol registration documents located at <http://rcc.tech-res.com/forms.htm>. Protocol registration must occur as a condition for site-specific study activation; no participants may be screened or enrolled in this study prior to obtaining protocol registration approval and completing all other study activation requirements. MTN CORE staff will notify each study site when all activation requirements have been met by issuing a site-specific study activation notice. Study implementation may not be initiated until the activation notice is issued.~~

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

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.

50. Section 13.3, *Risk/Benefit Statement*, the first paragraph, *Risks*, the third sentence has been modified, and the second paragraph, *Benefits*, the first, second, and fourth sentences have been modified:

Risks

[...] Disclosure of STI status may cause sadness or depression in ~~volunteers~~**participants**. [...]

Benefits

Participation in this study may provide no direct benefit to ~~volunteers~~**participants**. Some ~~volunteers~~**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. [...] They will be provided STI treatment in accordance with current WHO guidelines ~~free of charge~~, and will be offered STI testing and treatment for their partners.

51. Sections 13.4, *Informed Consent Process*, the second sentence in the first paragraph, the third sentence in the second paragraph, and the third and fourth paragraphs have been revised:

[...] In obtaining and documenting informed consent, the investigators and their designees will comply with applicable local and ~~domestic~~**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.

[...] Each study site is responsible for developing study informed consent forms for local use, based on the templates in Appendices ~~VII~~ and ~~VIII~~ that describe the purpose of screening and of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. [...]

Prior to the beginning of the trial, site investigators will have the IRBs'/ECs' written approval/~~favorable opinion~~ of the protocol, informed consent forms, and any other study-related information to be provided to participants. This study does not plan to enroll children under 18-**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.~~Listed study investigators and/or their designees.~~ **Trained study staff** will obtain informed consent from potential study participants. ~~The investigators~~**Study staff** will keep research participants fully informed of any new information that could affect their willingness to continue study participation.

~~In addition to the informed consent forms, Protocol Team members have worked with study staff and community representatives to develop locally appropriate information materials about the study and a standardized approach to the informed consent process to be implemented at all study sites, which is detailed in the study-specific procedures manual. The process and materials were tested prior to study start-up to ensure cultural appropriateness at each site. The informed consent process covers all elements of informed consent required by research regulations. In addition, the process specifically addresses the following topics of import to this study:~~

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

52. Section 13.5, *Participant Confidentiality*, the second sentence in the first paragraph has been revised and the fourth and sixth sentences in the second paragraph have been omitted:

[...] Each study site will ~~establish a standard operating procedure for~~**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. [...]

[...] ~~All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number.~~

[...] ~~Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.~~

53. Section 13.6.1, *Pregnant Participants*, the second sentence has been revised:

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 to prevent Maternal-to-Child Transmission **for PMTCT** of HIV-1.

54. Section 14, *Publication Policy*, has been modified:

DAIDS/NIAID and MTN policies will govern publication of the results of this study. ~~Any presentation, abstract, or manuscript will be submitted by the Investigator to the MTN Manuscript Review Committee and DAIDS for review prior to submission.~~

55. 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)						
Review Parent Study Records (Confirm HIV-1 Seroconversion)	X						
Eligibility Determination	X (SCR)						
Assign Participant ID	X (ENR)						
Update Locator Information	X (ENR)	X	X	X	X	X	X
Update 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						

Targeted 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 and & Mo. 24)	≅X (Mo. 3 Post-ART Initiation)	≅X (Mo. 12 and & Mo. 24 Post-ART Initiation)	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							
Approx. Total Blood Volume Collected (mL)	83	72	77	77	72	77	77
Urine Qualitative hCG	X	▲X	▲X	▲	▲	▲	X
Urine SDANAAT 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) <i>(Will be processed at the discretion of MTN NL)</i>	X				▲	▲	▲
HIV ELISA and Western Blot	▲						
HSV-2 Serology (using archived plasma)	X						
Vaginal pH	X	▲	▲	▲ (Annual)	▲	▲ (Annual)	X
Wet Mount Testing for BV, Candida, Trichomonas	X	▲	▲	▲ (Annual)	▲	▲ (Annual)	X
Testing for BV and Candida	▲	▲	▲	▲	▲	▲	▲
PAP Smear at Selected Sites	X†	▲▲/▲/†	▲▲/†	▲ (▲/†)	▲▲/†	▲▲/†	▲▲/†
Specimens for Storage							

Vaginal Swabs	X	X	X	X	XX (Mo. 1 & Mo. 3)	X	X
Cervicovaginal Lavage	X	X	X	X	X (Mo. 1 & Mo. 3)	X	X
Plasma	X	X	X	X	X	X	X
Serum	X						
PBMC	X	X	X	X	X (Wk. 2 and Mo. 3)	X	X

X=protocol-defined procedure; ▲=performed as indicated; †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.

56. Appendix II: *Sites and Site Investigators*, and Appendix III: *Site Laboratories*, has been omitted.

57. Appendix IV: *Physical Exam and Gynecologic Exam Components*, is now Appendix II and the following text has been revised:

APPENDIX II: PHYSICAL EXAM AND GYNECOLOGIC EXAM COMPONENTS

[...]

Targeted Physical Exam

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

[...]

58. Appendix V: *WHO Criteria for HIV Staging Events*, in Version 1.0 is now Appendix III and the following modifications have been made:

APPENDIX III: WHO CRITERIA FOR HIV STAGING EVENTS

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

59. Appendix VI: *Hematology, Liver and Renal Function*, is now Appendix IV:

APPENDIX IV: HEMATOLOGY, LIVER AND RENAL FUNCTION

60. Appendix VII: *Sample Informed Consent (Screening and Enrollment)*, is now Appendix V:

APPENDIX V: SAMPLE INFORMED CONSENT (SCREENING AND ENROLLMENT)

Introduction, first paragraph:

MTN-015 is a long-term research study of ~~women~~**participants** who have become infected with the human immunodeficiency virus (HIV) while taking part in a ~~microbicide~~**MTN** study. You are

MTN-015 Summary of Changes
May 3, 2013
From Version 1.0 to Version 2.0

being asked to take part in this study because you have become infected with HIV during a ~~microbicide~~MTN study. HIV is the virus that causes AIDS.

Why Is This Study Being Done? In the first and last sentence the word *women* has been changed to *participants*.

The main purpose of this study is to see if using a microbicide affects the health of ~~women~~**participants** after they become infected with HIV. [...] The study will also look at possible microbicide effects on other aspects of health such as illnesses that ~~women~~**participants** may get after HIV infection.

What Do I Have To Do If I Am In This Study? The first sentence has been deleted and the fifth sentence has been revised. The second paragraph has been revised and the last paragraph has been added.

~~This study is planned to continue until the year 2013.~~ [...] **Some if you agree, some** of these samples also will be stored for later testing.

If you are still taking part in your ~~microbicide~~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, the first and last paragraphs have been modified. The fourth, fifth, sixth, seventh and tenth bullets have been revised. Also, and the following text has been removed.

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 2X hours-].** The study clinician will review **and access** the records from your ~~microbicide~~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.** [...]

- 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 ~~will be stored for later testing.~~ **The laterand** testing of your vaginal fluids will be ~~done in~~**performed for research purposes only, you will not be made aware of the United States.** ~~results of these tests as they are not relevant for your care.~~ *[For selected sites only:* Study staff also ~~will~~**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 about 6 tablespoons or ~~[blood [SITES TO INSERT LOCAL EQUIVALENT] of blood.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 and herpes. These are infections. **Syphilis is an infection** passed during sex.
[...]
- 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.**
- ~~[INSERT THE FOLLOWING LANGUAGE IF REQUIRED BY SITE IRB/EC] About four and a half tablespoons or [INSERT LOCAL EQUIVALENT] of this blood would be used only for storage and future research-related testing.~~

~~Some of your test results will be available during the visit, and will be given to you at that time. Most other tests will take about two weeks. The tests for herpes and for resistance to HIV medications will take 2-3 months.~~

[...]

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.**

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

Follow-Up Visits (Months 1, 3, 6 and every 6 months), the first, second, and third sentences of the second paragraph have been revised. The second, fifth, and sixth bullet and last paragraph have been modified.

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 4X hour(s)]**). You will answer questions like at the Screening/Enrollment Visit ~~and~~, **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. [...]

- [For selected sites only:] Tests for abnormalities that could mean you have cervical cancer, or that could lead to cervical cancer.
- ~~Tests~~**Other tests** of the HIV virus and your immune system that will be done in the United States.
- ~~[INSERT THE FOLLOWING LANGUAGE IF REQUIRED BY SITE IRB/EC] A little more than four tablespoons or [INSERT LOCAL EQUIVALENT] of this blood would be used only~~**performed** for storage and future research-related testing- **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 ~~in the United States~~**for research purposes** will not be given to you unless they are important to your health.

Visits after Starting Medicine for HIV, the last sentence of the paragraph now reads:

[Sites to insert the anticipated amount of time the study visits will take: These visits will take about 1 and ½ hours.X hour(s)].

Final Visit, now reads:

You will be asked to complete a final visit at the end of the study, or if you choose to leave the study before it ends. ~~This visit~~**[Sites to insert the anticipated amount of time the study visits will take: These visits will take about 4X hour-and(s)].** **Procedures** will include the same types of questions, exams, and tests as the other follow-up visits.

Any Time During The Study, the following sentence has been added to the end of the second paragraph:

In addition, study staff may have to collect samples from you again if there are any problems.

Any Time During The Study, the following text has been removed:

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

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

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

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

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

How Many Women Will Be In this Study? The word *women* has been changed to *participants*.

How Many ~~Women~~Participants Will Be In this Study?

~~Up to~~ **About 500 women****participants** will take part in this study.

How Long Will I be In This Study?, now reads:

You will be in this study ~~until~~**for a minimum of 12 months after you have found out the year 2013 results of your HIV test, but you may stay in the study longer if the study is still being done at this clinic**

Risks of Blood Draws, now reads:

When your blood is taken, you ~~also~~ may feel discomfort or pain. You may feel dizzy or lightheaded. You may have a bruise, swelling, or infection where the needle goes into your arm.

Other Possible Risks, has the following sentence added after the second sentence:

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

Possible Risks to Your Privacy, the following paragraphs have been removed:

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

Risks Related to Stored Samples:

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

Are There Risks Related To Pregnancy?, the last sentence has been modified:

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

What About Confidentiality?, section now includes Office of Human Research Protection (OHRP) as an entity that may review study records:

[...]

Your study records may be reviewed by:

[...]

- **Office of Human Research Protection (OHRP)**

[...]

What Are The Costs To Me?, section has been updated to include information about the costs associated with STI treatment as this may vary by site:

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.]

APPENDIX VIII: *SAMPLE INFORMED CONSENT (STORAGE AND FUTURE TESTING OF SPECIMENS)* has been removed. The following text has been added and/or removed to *Can my private health information and samples collected by this study be used for future studies?*, in order to explain storage of samples and future testing and the signing of the informed consent form. Also, the *Signatures* page has been revised and organized for clarity:

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

You may have biological specimens, such as blood, vaginal, urine 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. ~~[SITE INSERT THE FOLLOWING TEXT RELATED TO STORAGE AND FUTURE TESTING OF SAMPLES IF NOT USING A SEPARATE INFORMED CONSENT FORM FOR STORAGE AND FUTURE TESTING OF SAMPLES]~~ By writing your initials or making your mark in the spaces below, you may also agree to long-term storage of your leftover samples.

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

~~_____Blood~~

~~_____~~

~~_____Vaginal fluid~~

~~OR~~

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

61. The protocol title, version number and date are updated throughout the protocol document.
62. Correction of minor editorial and typographical edits and updates are made throughout the protocol document.