

SUMMARY OF CHANGES

INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:

MTN-003

DAIDS Protocol #:10622

Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

Version 1.0/22 May 2008

THE AMENDED PROTOCOL IS IDENTIFIED AS:

Version 2.0 / December 31, 2010

IND#: 55,690

Information/Instructions to Study Sites

The information contained in this protocol amendment impacts the MTN-003 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. IRB/EC approval is required before implementation of the modifications contained in this amendment. All IRB/EC requirements must be followed.

Issuance of this amendment requires preparation of revised informed consent forms. These forms must be labeled with protocol Version 2.0 and must be used when obtaining informed consent for screening, enrollment, and specimen storage for future research testing, after obtaining IRB/EC approval of the amendment. All previously enrolled study participants will be re-consented with the revised informed consent forms.

Please file this Summary of Changes, Version 2.0 of the protocol and all associated IRB correspondence in your essential documents files for MTN-003.

The Division of AIDS Regulatory Affairs Branch will submit this amendment to the United States Food and Drug Administration for inclusion in IND application #55,690.

Rationale

The primary rationale for this protocol amendment is the need to update the sample size and expected length of follow-up on study product, with relevant updates to statistical considerations. These changes, initiated by the NIAID Vaccine and Prevention Data and Safety Monitoring Board provide greater assurance of answering the primary effectiveness objective by buffering against the possibility of falling HIV incidence rates during the trial. **NOTE: these changes are not expected to increase the total length**

of study duration, which is currently anticipated to complete follow-up as originally planned, in mid-2012.

Summary of Major Revisions and Justification

This amendment incorporates two previously issued Clarification Memos and two Letters of Amendment:

Clarification Memos

- Clarification Memo #01, dated 27 May 2009
- Clarification Memo #02, dated 25 August 2009

Letters of Amendment

- Letter of Amendment #01, dated 31 March 2009
- Letter of Amendment #02, dated 26 March 2010

Further revisions are listed below, some of which affect previously modified sections of the protocol.

- The sample size and expected length of follow-up on study product have been increased, with relevant updates to statistical considerations, to provide greater assurance of answering the primary effectiveness objective, even in the presence of any lower than expected HIV incidence during the trial.
- An exploratory objective on HSV-1 and HSV-2 acquisition is added to the study, in response to recent findings of CAPRISA 004.
- Results of recent relevant studies, including CAPRISA 004 and iPrEx, have been added to the protocol.
- The list of risks and benefits has been modified, to reflect updates to study product package inserts and Investigator Brochures.
- The upper limit of participant age has been expanded, to reflect site input on local populations at risk.
- The burden of expected procedures for HIV seroconverters has been lessened, to ensure that procedures are directly related to study questions.
- The laboratory quality assurance procedures for HIV endpoint determination have been updated, to further decrease the possibility of false positive and false negative HIV endpoints in the trial.
- Language regarding AE reporting and protocol registration have been updated, to reflect updates to DAIDS policies.
- Clinical management guidance for serum transaminase, serum creatinine, serum phosphate, urine protein, and urine glucose results has been modified to increase input from the Protocol Safety Review Team and further the likelihood of clinically relevant product holds.
- Corresponding updates to the sample informed consent documents have been made.

Summary of Changes

General Updates

- Updated title page, table of contents, team roster, acronyms, protocol summary, web links, and references.
- Renumbered sections and tables as needed.
- Minor corrections made to grammar, spelling, and formatting.

Section 1: KEY ROLES

- Revisions were made to Sponsor and Co-sponsor contact information.

Section 2: INTRODUCTION

- Throughout the Introduction, revisions were made to include relevant results from HPTN 035, MDP 301, CAPRISA 004, iPrEx, a recent study performed in macaques, CONRAD A04-095, and MTN-002.
- In Sections 2.8.1 and 2.8.2, data on pregnancy outcomes from the Antiretroviral Pregnancy Registry were updated for 2010.
- In Section 2.9, tables summarizing clinical studies of tenofovir for HIV prevention were updated and reformatted for clarity.
- In Section 2.10.2, a paragraph was added on Mental Health.
- In Section 2.10.2, a paragraph was added on the new exploratory objective related to herpes simplex virus.

Section 3: OBJECTIVES

- An exploratory objective was added to assess the incidence of HSV-1 and HSV-2 seroconversion in study product arms.

Section 4: STUDY DESIGN

- In Section 4.1, the identification of study design was updated to note anticipated enrollment of 5,000 participants, and expected monthly follow-up visits for a period of 12 – 36 months.
- In Section 4.4, time to complete accrual was modified to indicate approximately 24 months.
- In Section 4.6, maximum length of study product use was modified to indicate 36 months.

Section 5: STUDY POPULATION

- In Section 5.2, first criterion, the upper age limit for eligible participants was increased to 45 years old.
- In Section 5.3, first criterion, sub-bullet (e), text was modified to indicate that PEP provision is for HIV exposure, rather than infection.
- In Section 5.3, second criterion, notes following the criterion were updated to indicate that dipstick retesting is allowable in cases where results are attributable to urinary tract infection or menses, according to the judgment of the IoR/designee, and that serum creatinine results below the site limit of normal will be repeated during the Screening period.

Section 6: STUDY PRODUCT

- In Section 6.7, first paragraph, it was clarified that there will be no attempt to reconcile study product counts and self-reported data, as both measures will be considered in the interpretation of study results by the protocol team.

Section 7: STUDY PROCEDURES

- In Section 7.2.2, a note was made to remind study sites to repeat creatinine levels below the site lower limit of normal during the Screening period.
- In Sections 7.3.2 and 7.3.3, it was clarified that during Screening 2, vaginal fluid swabs are tested for BV and candidiasis only in cases where participants are symptomatic.
- The title of Section 7.4 was clarified to reflect that the bulleted list of procedures includes those for final screening and confirmation of eligibility.
- In Section 7.4.1, the first sub-bullet of the fourth bullet was clarified to indicate that PEP provision is for HIV exposure, rather than infection.
- In Section 7.4.1, a new sub-bullet was added to the last bullet to indicate that informed consent for enrollment may precede final confirmation of eligibility if doing so will decrease participant burden, and if this approach is included in an approved site SOP.
- In Section 7.4.4, it was clarified that BV and candidiasis testing are done if indicated to confirm eligibility on day of enrollment.
- In Section 7.5.2, under the fourth bullet, second, seventh, eighth and tenth sub-bullets respectively, reminders were inserted that assessment of vaginal pH, vaginal fluid swab for storage for biomarker analyses, endocervical swab for biomarker analyses, and bimanual exam are performed at all pelvic exams during follow-up, scheduled and unscheduled.

- In Sections 7.5.2 and 7.5.3, it was clarified that during follow-up, vaginal fluid swabs are tested for BV and candidiasis only in cases where participants are symptomatic.
- In Section 7.5.3, a final bullet was added to the list of laboratory procedures to indicate that HSV testing will be performed on plasma archive specimens, if indicated per instructions from Network Laboratory
- In Section 7.6, language from LoA #01 was omitted and replaced with new language to specify which behavioral questions will be omitted for participants not exposed to study product during the time frame in question (product adherence, study product sharing, and assessment of partner's reaction to product use).
- In Section 7.6.1, the list of procedures that will not occur for participants who become infected with HIV was clarified and supplemented to include:
 - ACASI surveys
 - Last dose recall
 - Vaginal fluid swabs for dried smear for Gram stain assessment at MTN NL
 - Complete blood count with differential and platelets, following a final test 8 weeks after initiation of product hold
 - Phosphate, creatinine, AST and ALT, following a final test 8 weeks after initiation of product hold
 - Dipstick urinalysis for protein and glucose, following a final test 8 weeks after initiation of product hold
 - Plasma archive at Quarterly Visits and PUEV
 - Scheduled VOICE Termination Visit
- In Section 7.6.1, HBsAb testing was omitted from the list of procedures to be performed for participants who delay or decline enrollment in MTN-015, as HBsAb testing will still be performed for these participants, regardless of enrollment in MTN-015, but at 1-2 months following the completion of the vaccine series. This change was further reflected in Appendix I of the protocol, and the Sample Informed Consent for Enrollment.
- In Section 7.6.1, the HIV resistance testing to be performed was modified to indicate “sensitive”, rather than “specialized” testing, for consistency with other locations in the protocol.
- In Section 7.11, Local, Regional, or Network Laboratory sub-section, tests for HSV-1 and HSV-2 antibodies were added.
- In Section 7.11, Network Laboratories sub-section, the HIV resistance testing to be performed was modified to indicate “sensitive”, rather than “specialized” testing, for consistency with other locations in the protocol.
- In Section 7.12, the quality assurance procedures to be used by the Network Laboratory for primary HIV endpoint determination were modified, to further decrease the possibility of false positives and false negatives among primary endpoints. Specifically, The NL will test Study Entry, PUEV, and scheduled

Termination Visit specimens from a 10 percent random sample of participants enrolled at each site for evidence of HIV infection using FDA-licensed tests. If any false-negative local laboratory results are identified, the NL will test the respective Study Entry, PUEV and scheduled Termination Visit specimens from all enrolled participants from that Clinical Research Site. Additionally, the NL will test the Study Entry and Seroconversion specimens from all study participants identified by the local laboratories as having become infected with HIV during the study follow-up period. The NL will also test matched Study Entry and Follow-Up specimens from a random sample of uninfected participants (equal to the number of seroconversions). Study Entry specimens are collected at participants' Enrollment Visits. Seroconversion specimens are collected at the time of specimen collection for confirmatory HIV testing, i.e., when Sample 2 in Appendix III is obtained. All specimens will be tested for evidence of HIV infection using FDA-licensed tests. For seroconverters, Study Entry specimens also will be tested by RNA PCR.

Section 8: ASSESSMENT OF SAFETY

- In Section 8.2, the definition of an AE was modified to indicate that an AE is defined as any untoward medical occurrence in a clinical research participant, from the time of randomization through when she terminates from the study; it does not necessarily have a causal relationship with the investigational product.
- In Section 8.2, under the first bullet, an additional sub-bullet was inserted to clarify that genital bleeding clinically assessed to be expected is not an AE.
- In Section 8.2, the sixth bullet was modified to refer to laboratory test abnormalities specified in the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004, that are not otherwise associated with a reported clinical AE
- In Section 8.2, seventh paragraph, it was clarified that at a minimum, an SAE/EAE (rather than AE) must be re-assessed by study staff 30 days after the participant's study exit visit; additional evaluations also may take place at the discretion of the IoR/designee.
- At the end of Section 8.2 and within Section 8.3, new template language from DAIDS was added to reflect changes to required expedited reporting of adverse events.

Section 9: CLINICAL MANAGEMENT

- In Section 9.3, a reminder was inserted (via a new first bullet) to hold study product upon the occurrence of a reactive rapid HIV test and the bullet related to use of PEP was modified to indicate that PEP provision is for HIV exposure, rather than infection.
- In Section 9.4, under Grade 3 events, clarification was provided regarding PSRT consultation for study product management.

- In Section 9.5.2, under AST and/or ALT elevations, Oral Study Product, Grade 3, PSRT consultation replaced automatic permanent discontinuation of study product.
- In Section 9.5.2, under AST and/or ALT elevations, Oral Study Product, Grade 4, the clinical management was re-organized into events Related to Study Product and Events Not Related to Study Product. For events Related to Study Product, PSRT consultation was inserted prior to permanent discontinuation of study product. Follow-up with repeat AST and ALT testing was modified to allow for an alternate schedule, based on the clinical judgment of the IoR/designee. For Grade 4 events Not Related to Study Product, the IoR/designee must temporarily hold study product and repeat the ALT and AST as soon as possible (at most within 1 week) and consult the PSRT. The participant should then be followed weekly or as clinically indicated until levels are Grade ≤ 1 , at which point, with concurrence from the PSRT, study product may be resumed. If following a Grade 4 event(s) not related to study product the participant resumes oral study product, but has one or more events (AST and/or ALT) at a Grade ≥ 3 level, the IoR/designee must perform the following:
 - Place a temporary hold on oral study product
 - Offer symptomatic treatment (if appropriate)
 - Order any clinically relevant laboratory analyses (per judgment of the IoR/designee)
 - Consult the PSRT for further guidance on continuing the temporary hold or progressing to permanent discontinuation of the oral study product.
- In Section 9.5.3, first paragraph, it was clarified that the most recent creatinine level drawn during the Screening period is used as the BL. Following a product hold for a creatinine increase of greater than or equal to 1.5 x BL, the creatinine should be repeated as soon as possible (at most within 1 week). Product use may be resumed when the creatinine level improves to ≤ 1.3 x BL, in consultation with the PSRT. If product use is resumed and the creatinine level increases to ≥ 1.5 X BL, the IoR/designee must consult the PSRT for further guidance on continuing the product hold temporarily, or progressing to permanent discontinuation.
- In Section 9.5.4, PSRT consultation is added for further study product management for participants who fail to undergo confirmatory testing of creatinine clearance within the specified time frame.
- In Section 9.5.6, clinical management guidance for hypophosphatemia was modified to organize repeat laboratory testing and product use management around clear, discrete ranges for phosphate results, as follows:
 - **ORAL STUDY PRODUCT**
Phosphate ≥ 2.0 mg/dL
 Unless other product hold requirements apply, study product should not be held. There is no need to recheck phosphate level before the next scheduled phosphate test.

Phosphate 1.4 mg/dL-1.9 mg/dL

Unless other product hold requirements apply, study product should not be held. Participants should be reminded to eat a phosphate rich diet. There is no need to recheck phosphate level before the next scheduled phosphate test.

Phosphate 1.0 mg/dL-1.3 mg/dL

Unless other product hold requirements apply, study product should not be held. Participants should be reminded to eat a phosphate rich diet and may be offered a two week course of phosphate supplements at the discretion of the IoR/designee.

Phosphate level should be rechecked at the next scheduled study visit.

If the phosphate is ≥ 2.0 mg/dL on recheck, guidance noted above should be followed (Phosphate ≥ 2.0 mg/dL).

If phosphate level is between 1.0 and 1.9 mg/dL on recheck, the participant should be reminded to eat a phosphate rich diet and may be offered a two week course of phosphate supplements at the discretion of the IoR/designee. Phosphate level should be rechecked at the next scheduled study visit.

If the phosphate level is < 1.0 mg/dL on recheck, the guidance noted below should be followed (Phosphate < 1.0 mg/dL).

Phosphate < 1.0 mg/dL

A temporary product hold should be implemented. Participants should be advised to eat a phosphate rich diet and may receive a two week course of phosphate supplements at the discretion of the IoR/designee. The phosphate test should be repeated within 2 weeks of the receipt of the results. If improvement to ≥ 1.0 mg/dL cannot be documented within two weeks, the product hold should continue and the PSRT should be consulted.

If improvement to ≥ 1.0 mg/dL is documented within two weeks, product may be resumed and guidance above followed, depending on the phosphate level result.

- In Section 9.6, ORAL STUDY PRODUCT, the clinical management of proteinuria was clarified to reflect recent recommendations from the protocol team's nephrologist:

Proteinuria is assessed by urine dipstick. A finding of proteinuria greater than trace should prompt serum creatinine and phosphate testing on the day of detection. A finding of 1+ proteinuria requires a repeat urine dipstick 1-2 weeks after the initial proteinuria detection. Proteinuria of 2+ or greater does not need to be confirmed at a separate visit.

ORAL STUDY PRODUCT

The IoR/designee should temporarily hold oral study product in the following circumstances:

- In the presence of 1+ proteinuria, oral study product should be held only if serum creatinine or phosphorus results obtained at the time of detection of proteinuria meet hold criteria (Sections 9.5.3 and 9.5.6). Detection of 1+ proteinuria alone should not lead to product hold.
- Detection of 2+ proteinuria. Oral study product should be held until results of serum creatinine and phosphorus results obtained at the time of proteinuria detection are available. Product hold should continue if hold criteria outlined for serum creatinine or phosphorus are met. If neither value meets criteria for study product hold, oral study product should be resumed.
- Detection of 3+ or greater proteinuria at any visit. Oral study product should be held and the PSRT should be consulted regarding further testing and product management.

Assuming no other hold criteria apply, in cases of oral study product hold based on proteinuria (i.e., 3+ or higher proteinuria), product use may be resumed following the resolution of proteinuria to < 2+, and once oral product restart has been approved by the PSRT. If product use is resumed (after a hold in the setting of 3+ or higher proteinuria), and proteinuria increases to 2+ or greater, product use must be held, and the PSRT consulted.

- In Section 9.7, the clinical management of glycosuria was modified to reflect recent recommendations from the protocol team's nephrologist:

Glycosuria is assessed by urine dipstick. A finding of 1+ glycosuria should be confirmed with a second urine dipstick performed no earlier than one week but no later than 2 weeks after detection of the first 1+ glycosuria. Glycosuria of 2+ or greater does not need to be confirmed at a separate visit.

ORAL STUDY PRODUCT

The IoR/designee should temporarily hold oral study product and test serum creatinine and phosphorus in the presence of confirmed 1+ glycosuria or any single level of glycosuria $\geq 2+$. The PSRT must be consulted for further guidance regarding management of oral study product.

- Section 9.11, first paragraph, is clarified to refer to hepatitis B infection, for consistency with the rest of the text therein.
- Section 9.12, second paragraph, is corrected to remove "permanent" as a descriptor for discontinuation, as the protocol allows for resumption of study product among participants who report cessation of breastfeeding.

Section 10: STATISTICAL CONSIDERATIONS

- In Section 10.1, the first paragraph has updated the number of participants to 5,000.

- In Section 10.1, second paragraph, the second sentence has been updated to reflect the maximum length of time a participant may be on product, now 36 months, rather than 33. This change primarily affects participants enrolled at the beginning of the study.
- In Section 10.4, Sample Size and Power Calculations, Primary effectiveness endpoint subsection, the heading rows of the tables are modified for clarity.
- In Section 10.4, Primary safety endpoint subsection, first paragraph, text was modified to correct the number of person-years (1800 rather than 1420) and the (hazard) rate ratio that may be detected under current assumption, and resulting from changes to the maximum time of follow-up on study:

For this analysis, a safety and toxicity endpoint is defined as the occurrence of the primary safety endpoint described in Section 10.2. Assuming that each candidate product will be compared separately to its corresponding placebo, a 5% significance level for a two-sided test (i.e., a 2.5 % false positive rate), 1800 p-y of follow-up per arm (see Section 10.5), and a pooled (pooled across active and placebo) safety and toxicity rate of 10% (i.e., 10 safety and toxicity endpoints per 100 p-y), the study has 90% power to detect a (hazard) rate ratio of $\leq 71\%$. This corresponds to safety and toxicity rates in placebo and active arms of 8 and 12 per 100 p-y, respectively. Table 9 displays the statistical power achieved for different safety and toxicity rates and (hazard) rate ratios.

- In Section 10.4, in the Primary Safety Endpoint subsection, old Table 8 (new Table 9) was modified to reflect updated power calculations.

Table 1: Statistical Power by Safety/Toxicity Rate and Hazard Rate Ratio

Safety/Toxicity Rate (per 100 p-y) (pooled over active and placebo)	Hazard Rate Ratio (placebo over active)						
	0.50	0.55	0.60	0.65	0.70	0.75	0.80
2.5%	90.8%	80.9%	67.8%	53.3%	39.4%	27.6%	18.4%
5.0%	99.6%	98.0%	92.9%	82.4%	66.7%	48.8%	32.2%
7.5%	100.0%	99.8%	98.7%	94.3%	83.4%	65.7%	45.0%
10.0%	100.0%	100.0%	99.8%	98.3%	92.3%	77.9%	56.2%
12.5%	100.0%	100.0%	100.0%	99.5%	96.6%	86.2%	65.8%
15.0%	100.0%	100.0%	100.0%	99.9%	98.6%	91.7%	73.7%
17.5%	100.0%	100.0%	100.0%	100.0%	99.4%	95.1%	80.0%
20.0%	100.0%	100.0%	100.0%	100.0%	99.8%	97.1%	84.9%
22.5%	100.0%	100.0%	100.0%	100.0%	99.9%	98.4%	88.8%
25.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.1%	91.7%
27.5%	100.0%	100.0%	100.0%	100.0%	100.0%	99.5%	93.9%
30.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.7%	95.6%
32.5%	100.0%	100.0%	100.0%	100.0%	100.0%	99.8%	96.8%

- In Section 10.5, first paragraph, the first sentence is modified to reflect the new accrual target (5,000).
- In Section 10.5, third paragraph, the text was modified to reflect the maximum time on follow-up (36 months).
- In Section 10.5, seventh and eighth paragraphs, the numbers of person-years of follow-up (now 1800) and the number of expected incident HIV infections (now 235) were updated. Estimates were also updated for the anticipated average baseline HIV rate in the placebo arm (now lower, 3.89%) and the anticipated average HIV rate for the entire trial (now lower, 2.61%), assuming 55% effectiveness for all three active products (2.82% and 2.46% for the topical and oral arms, respectively). The Lead Statistician has also updated the levels of seroincidence that could be tolerated in cases where an increase in length of follow-up was needed. Under updated assumptions, an increase in sample size by 20% at each study site would yield an increase of about 50% in p-y which would allow an average annual baseline HIV seroincidence rate as low as of 2.5% per 100 p-y (compared to the slightly conservative assumption of 3.89%). The selection of sites for VOICE is based on a demonstrated baseline HIV rate of at least 3.00%. Given that the protocol team has achieved high retention of participants in trials with long follow-up, the follow-up could be increased by an additional 6 months which would yield a total increase of about 80% in p-y. The resulting total number of p-y allows an average annual baseline HIV seroincidence rate as low as of 2.0% which is well below of what is currently observed in the VOICE participating sites.
- In Section 10.8.1, second paragraph, first and second sentence the target HIV rate was modified to 2.61% for the entire trial.
- In Section 10.8.3, Delayed Seroconversions subsection, fourth paragraph, first through third sentences, numbers of events and proportions were updated to reflect changes in seroincidence assumptions for the trial.

Section 11: DATA HANDLING AND RECORDKEEPING

- No new changes were made, other than updates to web links listed in Sections 11.2 and 11.3.

Section 12: CLINICAL SITE MONITORING

- No new changes were made other than an update to the web link listed in Section 12.

Section 13: HUMAN SUBJECTS PROTECTIONS

- In Section 13.2, the entire section was updated to reflect updates to DAIDS policy and corresponding template language for Protocol Registration.

- In Section 13.4.1, first paragraph, first sentence, it is clarified that phlebotomy may lead to greater than expected bleeding, as well as risks previously listed.
- In Section 13.4.1, Oral TDF Tablet, depression and generalized weakness were added as possible risks, as well as possible damage to the liver.
- Section 13.4.1, now also lists bone pain and bone changes such as thinning or softening which may increase the risk of breakage as a possible risk for Oral TDF Tablet.
- At the end of Section 13.4.1, Tenofovir 1% Gel, a new fourth paragraph was added:

In CAPRISA 004, there were no serious adverse events deemed related to the use of study product. No renal disorders were observed in the study. Mild, self-limiting diarrhea was more common among women who used tenofovir gel (16.9 percent) compared to women who used the placebo gel (11.0 percent). No tenofovir resistance was observed among the women who became infected with HIV in the tenofovir group. No increase in hepatic flares was observed in participants infected with the hepatitis B virus. There were no safety concerns in the 54 pregnancies observed in the trial.

- In Section 13.5, first paragraph, text was modified to clarify that separate informed consent forms will be used for all substudies and any ancillary studies.

Section 14: PUBLICATION POLICY

- In Section 14, first paragraph, text was modified to reflect that separate Clinical Trial Agreements were executed for this study (one with each study co-sponsor).

Section 15: APPENDICES

APPENDIX I

- In the SCHEDULE OF STUDY VISITS AND EVALUATIONS, the schedule for physical exam was changed to indicate that physical exam at Termination will be done as indicated.
- In the notes below the SCHEDULE OF STUDY VISITS AND EVALUATIONS, the frequency of serum chemistries was corrected for consistency with other areas of the protocol. For hepatitis B susceptible participants randomized to oral study product who do not receive hepatitis B vaccination, HBsAg additionally is checked annually and 6 months after PUEV; serum chemistries are checked 6 months (rather than 3 and 6 months) after PUEV.
- In the Schedule of Post HIV-1 Seroconversion Laboratory Procedures, time since completion of hepatitis B vaccine series was corrected to 1-2 months (rather than 6 months).

- A new sub-section on HSV Laboratory Procedures was added to note that at study end, HSV antibody testing will be performed on plasma archive specimens upon instructions from the MTN NL.

APPENDIX III

- In the ALGORITHM FOR HIV ANTIBODY TESTING (FOLLOW-UP AND PRIMARY ENDPOINT DETERMINATION), a note was added for participants whose Sample 1 Western Blots are found to be indeterminate or negative. In such cases, site staff must consult the MTN Network Lab and continue with algorithm.

APPENDIX IV

- In the ALGORITHM FOR MANAGEMENT OF HEPATITIS B SEROLOGIC ASSAYS ASSESSED AT SCREENING, the box at bottom left, beginning with the word “Vaccinate” was modified to indicate that vaccination may proceed at times 0, 1, and 6 months, or according to local guidelines.

APPENDIX V

- In the SAMPLE INFORMED CONSENT FORM (SCREENING), first paragraph, the final sentence was updated to reflect the new number of women (5,000) anticipated to be enrolled.
- In YOUR PARTICIPATION IS VOLUNTARY, new information relevant to MTN-003 study products is added to the end of the section:

Recently, results became available from two studies. Each study had at least one product that is being tested in VOICE.

The CAPRISA 004 study was done to find out if tenofovir gel could protect women from getting HIV, and to test the gel’s safety. The results of CAPRISA 004 showed that women who received tenofovir gel had a lower risk of getting HIV during the trial, compared to women who received placebo gel. Placebo gel is a gel that looks and feels like tenofovir gel, but does not contain tenofovir. Tenofovir gel also showed some protection against new cases of herpes. Additional studies of tenofovir gel are needed to see if similar results are seen for more women from different areas, and for women who use the gel daily, instead of before and after sex. Tenofovir gel used daily in VOICE could be more effective, less effective, or the same, compared to gel used before and after sex in CAPRISA. We will give you more information about CAPRISA 004 if you request it.

The iPrEx study was done to see if Truvada tablets could protect men who have sex with men from getting HIV and to test the tablets’ safety. The results of iPrEx showed Truvada tablets were safe when taken daily by men who have sex with men. Men who took Truvada tablets in iPrEx had a lower risk of getting HIV than men who used placebo tablets. Placebo tablets are tablets that look and feel like

Truvada tablets, but do not contain Truvada. The safety and effectiveness in preventing HIV of Truvada tablets used daily by women is not yet known. The study products in VOICE could be more effective, less effective, or the same for women, compared to Truvada tablets taken daily by men who have sex with men. We will give you more information about iPrEx if you request it.

- Throughout the sample informed consent, language was modified to encourage sites to insert updated estimates for length of procedures.
- In PROCEDURES, optional new text was added under Visit 3 for sites that will use this approach to reduce the number of blood draws performed on a single day.

[For selected sites only: You may be offered the option to sign the other consent form for further participation in VOICE before we have all of your screening test results. This would give us permission to do final blood tests for screening and the first set of blood tests for participants who enroll in VOICE from one blood draw instead of two. We will give you more information about this if you request it.]

- In the Risks of Blood Draws subsection, first paragraph, text was modified to clarify that most women do not experience dizziness or faint due to blood draw. This paragraph was also modified to include more than expected bleeding as a possible risk of blood draw.
- Under the COSTS TO YOU subsection, first paragraph, language is clarified regarding the free nature of treatment for sexually transmitted infections other than HIV.

APPENDIX VI

- In the SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT), PURPOSE OF THE STUDY subsection, the expected number of participants was updated (5,000), as well as the anticipated end of the study (currently expected to end in mid-2012), and the total length of time for individual participation (now 14 to 38 months, depending on timing of enrollment).
- Under STUDY GROUPS, first sentence, it was clarified that randomization to a study group will only occur for eligible participants.
- Under STUDY GROUPS, Tablet Groups, language was changed to remind participants to bring all tablets and bottles left from a previous visit to the next visit, including any empty bottles.
- Under STUDY PROCEDURES, third paragraph, text was added to inform participants that if they are in the tablet group, they may also have tests for hepatitis B and the health of their liver, about six months after they finish taking tablets during the study.

- Under STUDY PROCEDURES, in the sub-section on the end of product visit, it was clarified that participants stay in the study for about 8 weeks after their scheduled end of study product use.
- At the end of STUDY PROCEDURES, a new sub-section is added to describe herpes testing:

At the end of the VOICE study:

- Your blood samples (ones you already had drawn during study visits, not new ones) will be tested to see if you got a new herpes infection during the time that you were in the study. You will get the results of your herpes testing after the tests are completed, which may take several months. It is important to let us know how to stay in touch with you after the end of the study.
- In the If you become infected with HIV subsection, second paragraph, second sentence, text was added to inform participants that resistance testing will be done on specimens found to confirm HIV test results, and that results of this testing will be provided to participants if needed for medical care.
- In the If you become infected with HIV subsection, fifth paragraph, a correction was made to the number of months (one to two months, rather than six) after hepatitis vaccine series that blood would be tested for hepatitis B antibody.
- In RISKS AND/OR DISCOMFORTS, second and third bullets, text was modified to clarify that most women do not experience dizziness or faint due to blood draw. This section was also modified to include more than expected bleeding as a possible risk of blood draw.
- In the RISKS AND/OR DISCOMFORTS, Gel groups subsection, a fifth bullet (Diarrhea) was added.
- In the RISKS AND/OR DISCOMFORTS, Tablet groups subsection, the eighth bullet was updated to indicate Depression, rather than Anxiety.
- In the RISKS AND/OR DISCOMFORTS, Tablet groups subsection, under the list of potentially serious but rare side effects, it was clarified that inflammation or swelling and possible damage can occur to the liver, as well as the pancreas. This is not a new risk, but rather a clarification of the existing language in this sub-section referring to “liver function problems”.
- In the NEW INFORMATION subsection, results of the CAPRISA 004 and iPrEx studies are added:

Recently, results became available from two studies. Each study had at least one product that is being tested in VOICE.

The CAPRISA 004 study was done to find out if tenofovir gel could protect women from getting HIV, and to test the gel’s safety. The results of CAPRISA 004 showed that women who received tenofovir gel had a lower risk of getting HIV during the trial, compared to women who received placebo gel. Tenofovir gel also showed some protection against new cases of herpes. Additional studies of tenofovir gel are needed to see if similar results are seen for more women

from different areas, and for women who use the gel daily, instead of before and after sex. Tenofovir gel used daily in VOICE could be more effective, less effective, or the same, compared to gel used before and after sex in CAPRISA. We will give you more information about CAPRISA 004 if you request it.

The iPrEx study was done to see if Truvada tablets could protect men who have sex with men from getting HIV and to test the tablets' safety. The results of iPrEx showed Truvada tablets were safe when taken daily by men who have sex with men. Men who took Truvada tablets in iPrEx had a lower risk of getting HIV than men who used placebo tablets. The safety and effectiveness in preventing HIV of Truvada tablets used daily by women is not yet known. The study products in VOICE could be more effective, less effective, or the same for women, compared to Truvada tablets taken daily by men who have sex with men. We will give you more information about iPrEx if you request it.

- In the COSTS TO YOU subsection, first paragraph, second sentence, language is clarified regarding the free nature of treatment for sexually transmitted infection, other than HIV.

APPENDIX VII

- In the SAMPLE INFORMED CONSENT (STORAGE AND FUTURE TESTING OF SPECIMENS), INTRODUCTION, a third sentence is added to define what is meant by "vaginal fluid".
- In the HOW WILL MY BLOOD AND VAGINAL FLUID BE STORED? Subsection, text describing facilities for stored specimens is added to clarify that there is not one single designated specimen repository.