LETTER OF AMENDMENT #01 TO:

MTN-008
DAIDS Document ID 10805

Expanded Safety Investigation of Tenofovir 1% Gel in Pregnancy and Lactation
Version 1.0/29 March 2010
IND # 55,690

Letter of Amendment Date: November 23, 2010

Instructions to Study Sites from the Division of AIDS

The following information impacts the MTN-008 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. This must be approved by your IRB/EC before implementation. The following information impacts the sample informed consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this Letter of Amendment (LoA).

Summary of Revisions and Rationale

The primary reason for this LoA is to update the protocol and informed consent documents with information regarding the results of CAPRISA 004. This LoA does not impact the overall design and study visit schedule for MTN-008. This LoA provides updates/clarification on the following items:

1. Protocol Team Roster
2. Results of the CAPRISA 004 study and related changes to the sample informed consent forms
3. The accrual plan
4. Intent of the protocol eligibility criteria
5. Procedures, particularly updates to data collection methods for behavioral assessments
6. Expedited adverse event reporting requirements and protocol registration procedures, to reflect recent updates to requirements and template language from the US NIH Division of AIDS (DAIDS)
7. Referrals for mothers found to be HIV-infected during study participation, including corresponding updates to sample informed consent forms, to reflect the Protocol Team's response to comments from US FDA
8. Other minor updates to acronyms and web links

Implementation

Upon receiving final IRB/EC and any other applicable Regulatory Entity (RE) approval(s) for this LoA, sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. Sites will not be able to implement this LOA until they have received an LOA registration notification from the DAIDS PRO. A copy of the DAIDS PRO LoA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

Except for modifications to the Protocol Team Roster, text to be deleted is generally noted by ~~strikethrough~~ and text to be added is noted below in **bold**. Tables appear truncated below to highlight components with modifications. Sections 8.4 and 13.2 are replaced in their entirety by new language.

Detailed Listing of Revisions

1. The Protocol Team Roster is updated.

   The following new members of the Protocol Team have been added to the Protocol Team Roster:

Cheryl Cokley
Community Program Associate
FHI
P.O. Box 13950
Research Triangle Park, NC 27709 USA
Phone: 919-544-7040 Ext. 11359
Fax: 919-544-0207
Email: ccokley@fhi.org

Devika Singh, MD, MPH
Protocol Safety Physician
Box 359927, Department of Global Health, ICRC
325 Ninth Ave.
Seattle, WA 98104 USA
Phone: 206-744-8311
Fax: 206-520-3831
Email: dsingh@u.washington.edu

The following individual is deleted from the Protocol Team Roster: Mala Shah.

2. The results of CAPRISA 004 and their impact on the risk benefit ratio for study participation are added to the protocol and sample informed consent documents.

In Section 2.8, *Other Clinical Studies of Tenofovir for HIV Prevention*, text related to CAPRISA 004 (as an ongoing study) is deleted from Table 2, and study results are added below the table:

Table 1: Studies of Tenofovir 1% Gel

Location	Sponsor	Population	Design
~~South Africa~~	~~CAPRISA~~	~~Sexually active women~~	~~Phase 2B, two-arm, randomized placebo controlled, coitally dependent~~

The Centre for the AIDS Program of Research in South Africa (CAPRISA) recently reported results of a trial (CAPRISA 004, NCT00441298) which assessed effectiveness and safety of the same investigational product in MTN-008, tenofovir 1% vaginal gel, for the prevention of HIV acquisition in sexually active women. Results of this Phase 2B trial conducted among nearly 900 women in South Africa demonstrated that tenofovir 1% vaginal gel was associated with a 39% decrease in new HIV infections (p=0.017). Of note, there was also a 51% decrease in new herpes simplex virus type 2 (HSV-2) infections among the tenofovir gel users (p=0.003). Although tenofovir gel was associated with mild diarrhea, no significant safety concerns were seen.

The overall pregnancy rate was 4.0/100 women-years: 3.2/100 women-years in the tenofovir arm and 4.7/100 women-years in the placebo arm (*P* = 0.183). At time of analysis, there were six ongoing pregnancies, and 58.3% of the remaining 48 had resulted in a full-term live birth. There were no significant differences in pregnancy outcomes by arm, and no congenital anomalies.

In Section 13.3.1, *Risks*, third paragraph, one sentence is added to the end of the paragraph:

CAPRISA 004 found that 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).

In Section 13.3.2, *Benefits*, the following edits are made:

~~Participation in this study likely will have no direct benefit to participants, yet the participant may appreciate the opportunity to contribute to the body of knowledge in the field of microbicide research.~~ **Section 2.8 describes the reduction in HIV and HSV-2 acquisition observed in CAPRISA 004. As HSV-2 is a commonly acquired sexually transmitted infection in the MTN-008 study population, with potential devastating effects on neonates, the anti-HSV-2 activity of tenofovir 1% vaginal gel observed in CAPRISA 004 holds forth the prospect of a potential benefit for MTN-008 participants. Further research is anticipated to test whether CAPRISA 004 results will be confirmed.**

In APPENDIX VI: SAMPLE INFORMED CONSENT DOCUMENT FOR PREGNANCY COHORT – MOTHERS AND INFANTS (ENROLLMENT), the following edits are made to RISKS AND/OR DISCOMFORTS, second paragraph, and BENEFITS:

It is possible you could have side effects from the gel. Some, but not all, women who used tenofovir gel in other studies have had:

- Dryness, itching, burning feeling, or pain in the genital area
- Vaginal yeast infection
- Discharge from the vagina
- **Diarrhea**

BENEFITS
You and your baby may get no direct benefit from being in this study. You or others may benefit in the future from information learned in this study. You may also get some personal satisfaction from taking part in HIV research.

A study of about 900 non-pregnant women in South Africa called CAPRISA 004 was done to see if tenofovir gel used before and after sex was safe and whether it could protect women from getting HIV infection. This study found that women in the tenofovir gel group were 39% less likely to get HIV and about half as likely to get a new (very first) herpes simplex virus infection, compared to those in the placebo group. No significant safety problems were seen. This study did not test the impact of the gel on repeat herpes "breakouts". More research is planned to see if CAPRISA 004 results will be confirmed.

In APPENDIX VII: CONSENT DOCUMENT FOR LACTATION COHORT ENROLLMENT), the following edits are made to RISKS AND/OR DISCOMFORTS, third paragraph, and BENEFITS:

It is possible you could have side effects from the gel. Some, but not all, women who used tenofovir gel in other studies have had:
- Dryness, itching, burning feeling, or pain in the genital area
- Vaginal yeast infection
- Discharge from the vagina
- **Diarrhea**

BENEFITS
You may get no direct benefit from being in this study. You or others may benefit in the future from information learned in this study. You may also get some personal satisfaction from taking part in HIV research.

A study of about 900 non-pregnant women in South Africa called CAPRISA 004 was done to see if tenofovir gel used before and after sex was safe and whether it could protect women from getting HIV infection. This study found that women in the tenofovir gel group were 39% less likely to get HIV and about half as likely to get a new (very first) herpes virus infection, compared to those in the placebo group. No significant safety problems were seen. This study did not test the impact of the gel on repeat herpes "breakouts". More research is planned to see if CAPRISA 004 results will be confirmed.

3. Throughout the protocol, the accrual plan is updated to indicate the revised site projections of 2-4 enrollments per month and accrual period of approximately 20 months.

   In the Protocol Summary, under Study Duration:

   Approximately ~~16~~ **20** total months for planned accrual and study duration for Pregnancy and Lactation Cohorts

   In Section 4.4, *Time to Complete Accrual*:

   Accrual is expected to be completed in approximately ~~14~~ **20** months.

   In Section 10.5, *Participant Accrual, Randomization, Follow-up and Retention*:

   The Pregnancy Cohort and Lactation Cohort will be recruited simultaneously. The study site is expected to enroll approximately **2-**4 participants per month. Therefore, accrual is anticipated to take

approximately 6**-10** months for Pregnancy Cohort 1, **1**2 months for the Lactation Cohort, and an additional 6**-10** months for Pregnancy Cohort 2.

In APPENDIX VI: SAMPLE INFORMED CONSENT DOCUMENT FOR PREGNANCY COHORT – MOTHERS AND INFANTS (ENROLLMENT), Purpose of the Study, 6th paragraph:

It may take up to about ~~14~~ **20** months to enroll all participants.

In Appendix VII: SAMPLE INFORMED CONSENT DOCUMENT FOR LACTATION COHORT (ENROLLMENT):

It may take up to about ~~14~~ **20** months to enroll all participants.

4. The intent of eligibility criteria listed in Section 5 STUDY POPULATION is clarified.

   In Section 5.3, *Pregnancy Cohort Exclusion Criteria: Mothers*, the sixth criterion is edited:

   6. Clinically apparent Grade 2 or higher pelvic exam finding (observed by study staff) **at the Enrollment Visit**

   In Section 5.4, *Lactation Cohort Inclusion Criteria: Mothers*, the sixth criterion is edited.

   6. **At Enrollment, ~~C~~c**urrently primarily breastfeeding a single healthy infant between the ages of 4 and 26 weeks (inclusive) according to guidelines specified in the MTN-008 SSP Manual

   In Section 5.5, *Lactation Cohort Exclusion Criteria: Mothers*, the seventh and ninth criteria are clarified.

   7. By participant report or review of medical record, in the 8 weeks prior to ~~Day 0~~**Enrollment**, STI, including Chlamydia, gonorrhea, and/or trichomonasis

   9. ~~On pelvic exam~~**At Enrollment**, any of the following findings:
      a. Incomplete postpartum involution of the uterus
      b. Clinically apparent Grade 2 or higher pelvic exam finding (observed by study staff)

   In Section 5.6, *Lactation Cohort Inclusion Criteria: Infants*, text is edited as follows:

   3. Between the ages of 4 and 26 weeks (inclusive) **at both Screening and Enrollment**

5. Edits are made to procedures in Section 7 STUDY PROCEDURES.

   In introductory text for Section 7, 1st paragraph, the following text is added to the end of the paragraph:

   Coital log data are collected via CASI. Product use data are collected via home dosing log (transcribed to CRF) and CASI.

   In introductory text for Section 7, 4th paragraph, a clarification is made:

   A participant who is not administered ~~any~~ study gel **on Day 0** will not **be dispensed study product or** complete subsequent scheduled laboratory procedures or assessments of adherence/behavior.

   In Section 7.2, Screening *Visit: Pregnancy and Lactation Cohort*, the first sentence is clarified:

   A Screening Visit may take place up to 4 weeks prior to the Enrollment Visit (Day 0)~~ in the Pregnancy Cohort~~. **Attention should be paid to the eligibility window for infants, in terms of their age at Enrollment**.

   In Section 7.3, *Enrollment Visit: Pregnancy and Lactation Cohorts*, plasma archive is added to Table 11: Enrollment Visit: Pregnancy and Lactation Cohorts, Laboratory, for mothers in both cohorts:

Administrative, Behavioral, and Regulatory	• Informed consent for enrollment • Locator information • Eligibility confirmation • Randomization • Baseline acceptability questionnaire • Coital log • Adherence counseling • Reimbursement • Schedule follow-up visits/calls • Disclosure of available test results* • Provision of condoms and panty liners* • **Education/distribution for home dosing log**	• Informed consent for enrollment • Locator information • Eligibility confirmation • Baseline acceptability questionnaire • Coital log • Adherence counseling • Participant education on collection of 2 breast milk samples at home (target 4 hours post dosing on two different days when study product was inserted) • Supplies for breast milk collection • Reimbursement • Schedule follow-up visits/calls • Disclosure of available test results* • Provision of condoms and panty liners* • **Education/distribution for home dosing and milk logs**	• Eligibility confirmation
Laboratory	• CBC with differential (pre-gel) • **Plasma archive** • Maternal blood tenofovir level (pre-gel, 1, 2, 4, 6, and 8 hours) • Flow cytometry (pre-gel)*** • PBMCs*** • Vaginal pH • Vaginal and cervical biomarkers • Quantitative vaginal culture • Gram stain • Wet prep* • Trichomonas* • Herpes culture*	• Urine HCG • CBC with differential (pre-gel) • **Plasma archive** • Maternal blood tenofovir levels (pre-gel, 1, 2, 4, 6, and 8 hours) • Flow cytometry (pre-gel)*** • PBMCs*** • Breast milk tenofovir level (target pre-gel, 2,4,6 hours) • Vaginal pH • Vaginal and cervical biomarkers • Quantitative vaginal culture • Gram stain • Wet prep* • Trichomonas test* • Herpes culture*	

In Section 7.4, *Day 1 and Day 3 Phone Calls: Pregnancy and Lactation Cohorts*, Table 12, text is updated.

Table 12: Day 1 and Day 3 Phone Calls: Pregnancy and Lactation Cohorts

Day 1 and Day 3 Phone Calls: Pregnancy and Lactation Cohorts	
Component	Procedure/Analysis
Administrative, Behavioral, and Regulatory	• Update locator information • Schedule study visit* • ~~Brief adherence assessment~~ • Adherence counseling
Clinical	Collect AEs for mothers and infants (if born)

* if indicated

In Section 7.5, *Day 6 Visit: Pregnancy and Lactation Cohorts*, clarifications and minor formatting edits are made to Table 13: *Day 6 Visit: Pregnancy and Lactation Cohorts*.

Day 6 Visit: Pregnancy and Lactation Cohorts			
Component	Pregnancy Cohort Procedure/Analysis (Mothers)	Lactation Cohort Procedure/Analysis (Mothers)	Lactation Cohort: Procedure/Analysis (-Infants)
Clinical and Study Product	• Medical history • Concomitant medications • Targeted physical exam • Pelvic exam • Vaginal and cervical swabs • Urine collection* • Single dose of study gel to be administered by IoR/designee at clinic • Insert saline lock**	• Medical history • Concomitant medications • Targeted physical exam • Pelvic exam • Vaginal and cervical swabs • Urine collection~~*~~ • Single dose of study gel administered by IoR/designee at clinic • Insert saline lock**	• Medical history • **Feeding history** • Concomitant medications • Collect AEs • Blood collection via heelstick (target 6 hours <u>following maternal dosing</u>) **+**

	• Blood collection at PK time points (target pre-gel and 1, 2, 4, 6, and 8 hours) • Collect AEs • Collect unused study gel • Disclosure of results*	• Blood collection at PK time points (target pre-gel and 1, 2, 4, 6, and 8 hours) • Breast milk collection (target pre-dose and 2,4, 6 hours) • Collect AEs • Collect unused study gel • Disclosure of results*	
Laboratory	• ~~Cervical NAAT for~~ GC/CT* • CBC with differential (pre-gel) • Serum creatinine • AST and ALT • HIV serology* • HBsAg* • Maternal blood tenofovir level (target pre-gel, 1, 2, 4, 6, and 8 hours) • Flow cytometry (pre-gel)*** • PBMCs*** • Vaginal pH • Vaginal/cervical biomarkers • Quantitative vaginal culture • Vaginal Gram stain • Trichomonas test* • Wet prep* • Herpes culture*	• ~~Cervical NAAT for~~ GC/CT* • **Urine HCG** • CBC with differential (pre-gel) • Serum creatinine • AST and ALT • HIV serology* • HBsAg* • Maternal blood tenofovir level (target pre-gel, 1, 2, 4, 6, and 8 hours) • Breast milk tenofovir levels (target pre-dose and 2,4, 6 hours) • Flow cytometry (pre-gel)*** • PBMCs*** • Vaginal pH • Vaginal/cervical biomarkers • Quantitative vaginal culture • Vaginal Gram stain • Trichomonas test* • Wet prep* • Herpes culture*	• Blood tenofovir levels **+**

*if indicated ** if applicable *** if site capacity allows

+ Optimally, blood is drawn about 1-4 hours following start time for a nursing session. While it is anticipated that all infants would nurse during this interval, infant blood draw/tenofovir levels would not be performed for infants who did not nurse after maternal dosing and before departure from this visit.

In Section 7.6, *Day 14 Phone Call: Pregnancy and Lactation Cohorts*, collection of interim medical history and concomitant medications for mothers and infants is added to Table 14.

Clinical	• **Record interim medical history for mothers and infants (if born)** • **Record concomitant medications for mothers and infants (if born)** • Record AEs for mothers and infants (if born)

In Section 7.8, *Delivery Visit (Pregnancy Cohort only)*, minor edits are made to Table 16.

Clinical	• Cord blood collection • Blood collection (Mothers, single time point when cord blood is taken) • Collect AEs for mothers and infants • Targeted physical exam (Mothers)* • **Record concomitant medications for mothers and infants (if born)**
Laboratory	• Cord blood tenofovir level • CBC **with differential***** • Maternal blood tenofovir level • Flow cytometry*** • PBMCs***

*As needed, e.g., to evaluate a reported AE *** if site capacity allows

In Section 7.9, *Post-Delivery Assessment (Pregnancy Cohort only)*, minor edits are made to Table 17.

Post-Delivery Assessment: Pregnancy Cohort	
Component	**Procedure/Analysis**
Administrative, Behavioral, and Regulatory	• Update locator information • Reimbursement
Clinical	• **Medical history** • Collect AEs for mothers and infants

In Section 7.10, *Interim Visit*, minor edits are made to Table 18.

Interim Visit			
Component	**Pregnancy Cohort: Procedure/Analysis (Mothers)**	**Lactation Cohort: Procedure/Analysis (Mothers)**	**Pregnancy and Lactation Cohort: Infants**
Clinical	• **Update medical history*** • Update concomitant medications • Update AEs • Perform targeted physical exam* • Perform pelvic exam* • Vaginal swabs* • Cervical swabs* • Urine collection* • Blood collection* • Chart review* • Treatment for RTI/UTI* • Disclosure of available results*	• **Update medical history*** • Update concomitant medications • Update AEs • Perform targeted physical exam* • Perform pelvic exam* • Vaginal swabs* • Cervical swabs* • Urine collection* • Blood collection* • Treatment for RTI/UTI or mastitis* • Disclosure of available results*	• Update AEs • Blood collection via heelstick* (Lactation Cohort only)
Laboratory	• ~~Cervical NAAT for~~ GC/CT* • Serum creatinine* • AST and ALT* • HIV serology* • HBsAg* • Vaginal pH* • Trichomonas test* • Wet prep* • Herpes culture*	• ~~Cervical NAAT for~~ GC/CT* • Serum creatinine* • AST and ALT* • HIV serology* • HBsAg* • Vaginal pH* • Trichomonas test* • Wet prep* • Herpes culture*	

In Section 7.12, *Pharmacokinetic Measures*, procedures for mothers and infants are clarified.

Edits are made to Table 19: *Overview of Study Regimen and Pharmacokinetic (PK) Procedures*.

PK measurements (mothers in Lactation Cohort)	Breast milk (target **pre-gel,** 2, 4, and 6 hours post-dose)		
PK measurements (infants in Lactation Cohort)	Infant blood (target 6 hours <u>following maternal dosing</u>)	Infant blood (target 6 hours <u>following maternal dosing</u>)**+**	

+ Optimally, blood will be drawn about 1-4 hours following the start time for a nursing session. While the study team anticipates that all infants would nurse during this interval, infant blood draw and blood tenofovir levels would not be performed if the infant did not nurse following maternal dosing and prior to final departure from the study visit.

In Section 7.14.1, Local Laboratory, first paragraph, 10th bullet, the following edit is made:

- C~~ervical NAAT for c~~hlamydia and gonorrhea

In Section 7.18, *Behavioral Assessments*, 2nd paragraph, 3rd sentence, text is modified:

Participants will be asked questions about sexual behavior and intravaginal practice history, ~~and about~~ their attitudes towards the physical properties of the gel, **and** their attitudes and perceptions about using gel during pregnancy and lactation~~, and other acceptability measures of the gel related to the sexual partner(s), sexual pleasure attributes, etc~~.

In Section 10.6.2, *Data Analysis*, Adherence, Acceptability, and Sexual Behavior, second sentence, text is updated:

Self-reported adherence to product use will be measured ~~at 3 time points~~ through ~~clinician~~ **CASI** interview ~~(Day 1 and Day 3 Phone Calls; Day 6 Visit),~~ and through self-completed retrospective product log (Day 6 Visit).

Appendices I, VI and VII are modified to reflect the changes noted above.

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

PREGNANCY									
	SCR Visit	ENR Visit (Day 0)	Day 1 and Day 3 Calls	Day 6 Visit	Day 14 Call	Del. Call	Del.	Post-Del.	Interim
ADMINISTRATIVE, BEHAVIORAL, AND REGULATORY									
Adherence Assessment			~~X~~	X					
Education/Distribution for Logs		**X**							
CLINICAL									
Medical History	X	X		X	**X**			X	▲
Concomitant Medications	X	X		X	**X**		**X**	**X**	X
LABORATORY									
~~Cervical NAAT for~~ GC/CT	X			▲					▲
Plasma Archive		**X**							

LACTATION COHORT						
	SCR Visit	ENR Visit Day 0	Day 1 and Day 3 Calls	Day 6 Visit	Day 14 Call	Interim
ADMINISTRATIVE, BEHAVIORAL, AND REGULATORY						
Education/Distribution for Logs		**X**				
CLINICAL						
Disclosure of Available Test Results	X	▲		~~▲~~**X**		▲
Urine Collection	X	X		~~▲~~**X**		▲
Medical History		X		X	**X**	▲
Concomitant Medications		X		X	**X**	X
LABORATORY						
~~Cervical NAAT for~~ GC/CT	X			▲		▲
Plasma Archive		**X**				
Urine HCG	X	X		**X**		

Pregnancy Cohort: Infants			
	Delivery Visit	Post-Delivery	Interim
Clinical			
Concomitant Medications		**X**	

Lactation Cohort: Infants						
	SCR Visit	ENR Visit Day 0	Day 1 and Day 3 Calls	Day 6 Visit	Day 14 Call	Interim
Clinical						
Feeding History				**X**		
Medical History	X	X	X	X	**X**	
Concomitant Medications	X	X	X	X	**X**	

▲ *If indicated*

In APPENDIX VI: SAMPLE INFORMED CONSENT DOCUMENT FOR PREGNANCY COHORT – MOTHERS AND INFANTS (ENROLLMENT), STUDY PROCEDURES, 3rd paragraph, 3rd bullet:

- Give blood] [site to insert amount] to check the health of your blood, liver and kidneys**; some of this blood will be saved, and may also be tested for HIV, if you have a positive HIV test while you are in the study**

In APPENDIX VII: CONSENT DOCUMENT FOR LACTATION COHORT (ENROLLMENT), Study Procedures, 3rd paragraph, 4th bullet:

- Give urine for a pregnancy test ~~(Day 0 only)~~

In STUDY PROCEDURES, 5th paragraph, a bullet is added to the list of procedures:

- Hear about how to write down information at home on your baby's feeding, when you used your study gel, and when you collected your milk samples, and turn in this information to study staff

6. In Section 8, ASSESSMENT OF SAFETY and Section 13, HUMAN SUBJECT PROTECTIONS, language is modified to reflect recent updates to guidance from DAIDS.

   The following will replace Section 8.4, *Expedited Adverse Event Reporting Requirements*:

8.4 Expedited Adverse Event Reporting

8.4.1 Expedited Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/. The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself. Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.

The study agents for which expedited reporting are required are:

For mothers

- **Tenofovir 1% gel**
- **HEC placebo gel (Pregnancy Cohort)**
- **Study gel applicator**

For infants (for maternal exposure to study gel)

- **Tenofovir 1% gel**
- **HEC placebo gel (Pregnancy Cohort)**

8.4.2 Grading Severity of Events

The most current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) is used and is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/. Hypertensive disorders of pregnancy will be graded according to the parameters provided in this protocol.

8.4.3 Expedited AE Reporting Period

The expedited AE reporting period for this study is the entire study duration for each individual participant (from study enrollment until study completion or discontinuation of the participant from study participation for any reason). After the protocol-defined AE reporting period, unless otherwise noted, only SUSARs as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

The following will replace Section 13.2, *Protocol Registration*:

13.2 Protocol Registration

Initial Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent forms approved, as appropriate, by their local IRB/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 RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received. Site-

specific ICFs will be reviewed by the DAIDS PRO, and sites will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Registration for any Future Amendments

Upon receiving final IRB and any other applicable RE (regulatory entity) 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* be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files. For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

MTN CORE FHI staff will notify the study site when all activation requirements have been met by issuing a site-specific study activation notice. Study implementation may not be initiated until the activation notice is issued. The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chairs and DAIDS Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB and the RCC prior to implementing the amendment.

7. In Section 13.9.2, *Care for Participants Identified as HIV-Infected*, the second sentence in the paragraph is clarified. Corresponding updates are made to the Sample Informed Consents.

   In compliance with local regulations and in accordance with site SOPs, study staff will refer participants found to be HIV-infected to available sources of medical and psychological care, social support, and local research studies for HIV-infected women **and their infants**.

   In Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING – PREGNANCY COHORT), under BENEFITS, the fifth sentence is updated:

   If you are infected with HIV, you will be referred for medical care, counseling, and other available services**, including research studies for HIV-infected women and their infants**.

   In Appendix V, SAMPLE INFORMED CONSENT FORM (SCREENING – LACTATION COHORT), under BENEFITS, the fifth sentence is updated:

   If you are infected with HIV, you will be referred for medical care, counseling, and other available services**, including research studies for HIV-infected women and their infants**.

8. Other minor updates include the following: Regulatory Compliance Center (RCC) is now Regulatory Support Center (RSC) and Family Health International is now FHI throughout the protocol.

   The *List of Abbreviations and Acronyms* is updated:

   ~~FHI Family Health International~~
   ~~RCC Regulatory Compliance Center~~
   RE regulatory entity
   RSC Regulatory Support Center

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