Section 8. Clinical Considerations and Safety Monitoring

This section presents information on clinical procedures and safety monitoring performed in MTN-011. Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in Section 9. Instructions for completing data collection forms associated with clinical procedures are provided in Section 10.

8.1 Baseline Medical History

The female and male participants' baseline medical history, and the female participant's menstrual history, is initially collected and documented at the screening visit. It is then actively reviewed and updated, as necessary, at the enrollment visit and follow-up visits.

The baseline medical and/or menstrual history should explore any medical conditions or medications that are deemed exclusionary for this study for both female and male participants. The purpose of obtaining this information during screening and enrollment is to:

- Assess and document participant eligibility for the study
- Assess and document the participant's baseline medical conditions and symptoms for comparison with signs, symptoms and conditions that may be identified or reported during follow-up
- Assess and document the female participant's baseline menstrual history, conditions and symptoms for comparison with signs, symptoms and conditions that may be identified or reported during follow-up
    - Note: Dysmenorrhea causing greater than minimal interference with usual social and functional activities *or* the need for non-narcotic medications is considered a Grade 2 event per the DAIDS Female Genital Grading Table. Female participants are excluded from enrolling in the study if at the time of enrollment; she is experiencing a Grade 2 or higher genital sign and/or symptom. However, if her menses is complete at the time of enrollment, her dysmenorrhea should be considered an inactive ongoing condition and listed on the Pre-existing Conditions form. She is eligible to enroll and any increase in severity of dysmenorrhea during follow-up would be considered an adverse event.
- Monitor any potential adverse events during the course of the study

The MTN-011 Baseline Medical History Questions sheet (Word version available on the MTN-011 web page under *Study Implementation Materials*) and the non-DataFax Screening Menstrual History forms are recommended source documents for collecting baseline medical history information; however, alternative site-specific history forms may be used. That is, a site may create its own source documentation.

Per the instructions at the top of the questions sheet, for female participants record relevant items which are marked "yes" on the Pre-existing Conditions CRF. Pre-existing conditions for male participants will be documented on the MTN-011 Pre-existing Conditions Tracker. Ask probing questions to the participant in order to collect the most complete and accurate information possible, especially with regard to severity and frequency. Assess and record the current severity of the condition per the DAIDS Female/Male Genital Grading Table for Use in Microbicide Studies (F/MGGT). If the condition is not listed in the F/MGGT, refer to the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events (hereafter referred to as the "DAIDS Toxicity Table"). See Section 8.14 for further clarifications, guidelines, and tips for severity grading in MTN-011.

8.2 Pre-existing Conditions

All ongoing medical conditions, problems, signs, symptoms and abnormal findings that are observed and/or reported at the time of enrollment are considered pre-existing conditions.

For all female participants enrolled in the study, all ongoing conditions recorded as pre-existing are to be thoroughly source documented and transcribed onto the Pre-existing Conditions CRF. This form is to be completed at the Enrollment Visit based on all screening and enrollment source documents including, but not limited to, the Baseline Medical History Questions Sheet, Physical Exam form, Pelvic Exam form, Laboratory Results form, and STI Test Results form.

All pre-existing conditions noted at screening and enrollment must be graded. The purpose of grading a pre-existing condition is to determine whether abnormal conditions, symptoms, signs and findings identified during follow-up are adverse events (AEs). By definition, pre-existing conditions are present prior to or at enrollment and are, therefore, not considered AEs. However, new conditions identified during follow-up that were not present at enrollment, and pre-existing conditions that increase in severity (increase to a higher grade) or frequency during follow-up, are considered AEs. Therefore, the clinician should record as much information as possible about the severity and frequency of any pre-existing condition in source documents as well as in the comments field of the Pre-existing Conditions form to best describe the condition at study entry. This allows for greater objectiveness in noting any grade increase of the pre-existing condition.

8.3 Follow-up Medical History

It is necessary to update the female and male participants' medical histories at follow-up clinic visits (and any interim visits) to determine whether previously reported conditions remain ongoing and whether new symptoms, illnesses, conditions, etc. have occurred since the last medical history was performed. See protocol Section 7 and SSP Section 5 for visits when follow-up medical history is required. At each post-enrollment visit it is only necessary to record information that has occurred or changed (in severity or frequency) since the previous visit. Review of the medical history must be documented; this can be done in chart notes or in a site-specific tool if desired. If no symptoms, illnesses, conditions etc., are reported, the participant chart should reflect this.

All newly-identified participant-reported symptoms and conditions, that meet the definition of a reportable AE per protocol section 8, will be documented on the Adverse Experience Log (AE-1) CRF. See Section 8.12 below for details regarding AE documentation.

8.4 Concomitant Medications

The MTN-011 protocol requires site staff to document all medications taken by study participants beginning at screening and continuing throughout the duration of the study. This includes any preventive medications and treatments (e.g., allergy shots, flu shots, and other vaccinations), prescriptions, over-the-counter preparations, vitamins and nutritional supplements, recreational drugs and herbal and naturopathic preparations. For female and male participants, all medications (including contraceptives), drugs, supplements and preparations will be recorded on the Concomitant Medications Log.

It is helpful to ascertain the baseline medication information in the context of the baseline medical history. Site staff should ask open-ended questions to elicit participant report of current medications, and use the information obtained in the medical history to probe for additional medications that the participant may otherwise forget to report. For example, if the participant reports headaches as part of his medical history, but does not spontaneously list any medications taken for headaches; ask if s/he takes any medications for headaches. Similarly, if a participant reports taking a medication for a condition that he inadvertently did not report when providing medical history information, add the condition to the baseline medical history source document.

At follow-up visits, or during an interim visit, retrieve the participant's previously completed Concomitant Medications Log form, record any new medications provided to the participant by study staff, and actively ask the participant whether s/he is still taking all previously-recorded medications, at the same dose and frequency. Also actively ask whether the participant has taken any new medications since the last medical history was taken. Add all new information to the form in log fashion, using additional form pages as needed. To help ensure accurate reporting of concomitant medications information, participants should be encouraged to bring all medications to study visits.

8.5 Prohibited Medications and Products

For MTN-011 the following medications are prohibited from use during the study:

- Female participants only: Systemic immune modulators, e.g. oral steroids for asthma. Note: Occasional or intermittent use of inhaled steroids and topical (not vaginal but skin) steroids are not considered systemic immune modulators and are permitted. If the female participant reports chronic use of inhaled steroids, this would indicate severe asthma and they should be excluded from study participation
- Genitally-applied preparations and products, e.g. tampons, lubricants/spermicides, and douching, 72 hours prior to each follow-up visit. Group 2 female participants are prohibited from these practices while dosing with gel at home.

If a participant reports using a prohibited medication during the study, this must be recorded on the Concomitant Medications Log. Per protocol section 9.3, if the female participant reports use of a systemic immune modulator, the participant will be permanently discontinued from study product use.

8.6 Physical Exam

A physical exam is completed for female and male participants at required study visits per protocol Section 7. It should also be performed at Interim Visits if it is clinically indicated. At all scheduled time points, physical exams should include the assessments listed in protocol section 7.10 and repeated below. Site clinicians may use their discretion to determine whether or not to conduct a more comprehensive physical exam in response to reported symptoms or illnesses present at the time of the exam.

Following is a list of required physical exam components:

- General appearance~
- Vital Signs
    - Temperature
    - Pulse
    - Blood pressure
    - Respirations
- Genitourinary
- Height*
- Weight*
- Heart*
- Lungs*
- Abdomen*
- Extremities*
- Skin*
- Other components as indicated by participant symptoms

* May be omitted after the screening visit

~The genitourinary physical exam requirement is an assessment of any genitourinary symptoms the participant may or may not be experiencing. Site staff are not required to complete a full genital exam for a genitourinary assessment unless required at a particular visit per protocol, of if symptoms indicate a more thorough exam is needed.

The Physical Exam form for female participants and the Physical Exam – Male form (non-DataFax) are the recommended source documents for recording physical exam findings. The participant's weight should be documented on the applicable Physical Exam form. In addition, for female participants, the participant's weight should be documented on the Pharmacokinetics CRF when applicable.

For female participants who enroll in the study, ongoing abnormal physical exam findings (that are not exclusionary) identified at the Screening and Enrollment Visits and ongoing at the time of enrollment should be recorded on the Pre-existing Conditions form. Abnormal findings found during physical exams performed during follow-up should be documented and/or reported as described below in Section 8.12.

Physical exams may identify additional baseline medical information that participants inadvertently do not report in their baseline medical history. For example, the clinician may identify a skin condition during the physical exam and upon further inquiry learn that the participant has had this intermittent chronic condition since age 15. In such situations, the clinician should add the newly identified information to the Baseline Medical History Questions Sheet and the Pre-existing Conditions form (or female participants) as well, since the condition was present at the time of enrollment.

8.7 Pelvic Exams

Pelvic exams are required at the Screening, Enrollment, and applicable follow-up visits per protocol Section 7. It should also be performed at regularly scheduled visits or interim visits if clinically indicated. Although sites should make efforts to schedule follow-up visits so that the participant is not experiencing menses during pelvic exams, the sites may continue with the pelvic exam if there is no other option.

Scheduled pelvic exams should be performed according to the guidance provided in the remainder of this section. Exam procedures must be performed in the order shown on the exam checklist provided on the MTN-011 Study Implementation Materials webpage. Pelvic exams performed at non-scheduled visits (e.g. interim visits or in response to symptoms) should be targeted to symptoms and staff are not required to complete all components of the complete pelvic exam.

Prior to the Exam: Prepare all required equipment, supplies, and paperwork; label specimen collection supplies as needed. Review documentation of prior exams and other relevant documentation from the current visit and prior visits.

Examine the External Genitalia:

- Do not insert the speculum before examining the external genitalia.
- Spread the participant's knees as far apart as is comfortable for her.
- Palpate the inguinal lymph nodes to assess for enlargement and/or tenderness.
- Perform naked eye examination of the external genitalia including the perineum, perianal area, and the epithelial lining of the introitus.

Examine the Cervix and Vagina:

- The speculum may be lubricated with warm water if needed. No other lubricant may be used. Gently insert the speculum and open it once past the pelvic floor muscles, using gentle downward pressure, so as to avoid trauma while enabling visualization of the cervical face and upper vagina.

- If the cervix is poorly visualized, to avoid iatrogenic injury, remove the speculum and use a gloved finger (lubricated with warm water if needed) to establish the position of the cervix. Then re-insert the speculum.

- Perform naked eye exam of the cervix and vagina.

- Assess for cervical ectopy.

Collect Vaginal and Cervical Specimens:

Collect specimens in the order listed on the pelvic exam checklists and per SSP Section 9.8, 9.9, 9.10. Collect specimens away from apparent abnormalities and exclude swabbed areas from subsequent examination.

Collect Rectal Specimen:

- Rectal sponge: site staff should prepare for the rectal sponge procedure with sufficient time prior to the collection of the rectal sponge specimen through the anoscope. See Section 9.13 of this manual for further details on procedure and storage.

Document all exam findings — both normal and abnormal — on the Pelvic Exam Diagrams (non-DataFax) CRF. Screening Visit, Enrollment Visit, and protocol-required follow-up pelvic exams are documented on the non-DataFax Pelvic Exam Diagrams form and the Pelvic Exam CRF. Clinically-indicated pelvic exams done on the same day as a required pelvic exam (e.g. Visit 3a for Group 1) are documented on the non-DataFax Pelvic Exam Diagrams form and the Pelvic Exam – Clinically-indicated CRF.

Additionally, abnormal findings are documented on the Pre-existing Conditions CRF (at Enrollment), and on the Adverse Experience Log if applicable (at follow-up). Supplemental information may also be recorded in chart notes or on other designated source documents as needed. Source documentation for abnormal findings should include the severity grade of the finding, assessed per the Female Genital Grading Table.

All pelvic exam findings consistent with the "grade 0" column of the Female Genital Grading Table are considered normal. The following also are considered normal:

- anatomic variants
- gland openings
- Nabothian cysts
- mucus retention cysts
- Gartner's duct cysts
- atrophic changes
- blood vessel changes other than disruption
- skin tags
- scars
- expected menstrual and non-menstrual bleeding

Note: Following biopsy collection, the female participants should be advised to avoid sex until vaginal spotting or bleeding stops. As a general suggestion, female participants should delay intercourse for a minimum of 5 days.

8.8 Genital Bleeding Assessment

For purposes of this protocol, genital bleeding consistent with a participant's baseline bleeding pattern is considered expected. All bleeding occurring during follow-up that is different from the participant's baseline bleeding pattern is unexpected, and therefore an AE. This may include unusually heavy or prolonged menses, as well as non-menstrual bleeding different from baseline.

Genital bleeding other than menstrual bleeding, often referred to as intermenstrual bleeding (IMB), is a common occurrence among reproductive age women, and often is of physiologic or benign etiology. Some women normally experience mid-cycle bleeding or pre-menstrual bleeding. IMB is common in hormonal contraceptive users, particularly new and/or inconsistent users. IMB also may be associated with traumatic injury to the cervicovaginal epithelium (e.g., due to speculum insertion, product insertion, sexual activity).

Participant Reports and Clinician Assessment of Genital Bleeding

Participants will be counseled to report all occurrences of genital bleeding other than usual menstrual bleeding to study staff as soon as possible after identification of the bleeding. At each study visit, clinicians will obtain interval medical/menstrual history information from participants, including active ascertainment of whether any genitourinary symptoms including genital bleeding were experienced since the last study visit.

Study participants will undergo pelvic exams at scheduled time points, as well as to evaluate any participant report of bleeding that is different from baseline. The assessment of genital bleeding should begin by determining whether the bleeding (menstrual or non-menstrual) is consistent with baseline bleeding patterns.

If the newly-identified bleeding episode is determined to be different from her baseline bleeding pattern (i.e. longer, heavier, more/less frequent), record the episode on an Adverse Experience Log CRF. Grade the episode per the "Abnormal Uterine Bleeding Unrelated to Pregnancy" rows of the DAIDS Female Genital Grading Table.

When reporting genital bleeding events, reference should be made to the points below, which standardize the terminology that should be used at all sites when reporting AEs involving genital bleeding.

- Cervical bleeding associated with speculum insertion and/or cervical specimen collection judged to be within the range of normal according to the clinical judgment of the IoR or designee is not considered to be an adverse event. If the bleeding exceeds the amount considered normal by the clinician, it should be considered an AE and should be documented and reported if applicable using the term cervical friability. The severity of cervical friability should be graded per the cervical edema and friability row of the DAIDS Female Genital Grading Table.

- Bleeding that is associated with an observed abnormal pelvic exam finding should be considered an AE and should be documented and reported if applicable using the term associated with the exam finding, with the anatomical location noted. For example, if a vaginal laceration is observed on exam, with blood emanating from the finding, the term vaginal laceration should be used to document the AE. The fact that blood or bleeding was present should be documented on the Pelvic Exam Diagrams form and the pelvic exam case report form, and may also be noted in the comments section of the Adverse Experience Log CRF, but the term metrorrhagia should not be used to document the AE.

- Non-menstrual bleeding that is not associated with an observed pelvic exam finding, i.e., for which no abnormal source of blood or bleeding is observed on exam, should be considered an AE and should be documented and reported if applicable using the term metrorrhagia. This term refers to bleeding of variable amounts occurring between regular menstrual periods and should be used to report non-menstrual bleeding such as spotting between menses, ovulation bleeding, and breakthrough bleeding. This term should also be used to report blood-tinged discharge and blood observed in the vagina with no identified source.

- If a participant reports genital bleeding after sexual intercourse, you will report this event as "postcoital bleeding" and grade it per the "Postcoital Bleeding" row of the DAIDS Female Genital Grading Table.

8.9 Male Genital Exams

Male genital exams are required at the Screening, Enrollment, and applicable follow-up visits per protocol section 7. They should include the assessments listed in protocol section 7.10 and repeated below.

General inspection via naked eye and, if necessary, a hand-held magnifying glass of the following:

- Entire penile surface
    - Internal and external foreskin (if present)
    - Shaft
    - Glans
    - Urethral meatus
- Scrotum
- Inguinal lymph nodes

The Genital Exam – Male form (non-DataFax) is the recommended source document for recording genital exam findings at screening, enrollment, and applicable follow-up visits. For participants who enroll in the study, abnormal genital exam findings (that are not exclusionary) identified at the Screening and Enrollment Visits and ongoing at the time of enrollment should be on the MTN-011 Pre-existing Conditions Tracker. Abnormal findings found during genital exams performed during follow-up should be documented and/or reported as described below in Section 8.12.

8.9.1 Semen Sample Collection

At the screening visit, male participants will provide a semen specimen, obtained by masturbation. Male participants will be provided with a container labeled with the appropriate SCHARP provided PTID label. Please see SSP Section 9.12 for detailed instructions.

8.10 STI/RTI/UTI Evaluation and Management

Clinical and laboratory evaluations are performed in MTN-011 to diagnose Urinary Tract Infections and the following STIs and RTIs:

- Chlamydia infection
- Gonorrhea infection
- Syphilis infection
- Hepatitis B

Infections should be considered "symptomatic" when a participant self-reports or complains of symptoms associated with the infection. Symptoms should not be confused with "signs" of infection that may be observed during clinical examinations performed by study staff.

Urinary tract infections (UTIs) will be diagnosed based on the presence of symptoms and a urine culture.

In addition to required STI testing during study follow-up; couples that return to the study clinic for a visit more than 42 days past their last study visit must be tested for HIV, GC/CT, and

Syphilis. Negative results for both the male and female partner must be obtained prior to dispensing gel and continuing with study procedures.

Any participant diagnosed with an STI or RTI requiring treatment, during the screening process will be ineligible for the study. If the participant is diagnosed with a UTI, they may still enroll in the study once treatment is completed and symptoms have resolved. If the participant is diagnosed with an RTI, following treatment and resolution of symptoms, they may rescreen for the study (one re-screen permitted). If the participant is diagnosed with an STI, they may only rescreen for the study 6 months after the diagnosis, per inclusion criteria #2a, assuming treatment is complete and symptoms have resolved. For enrolled participants, STI/RTI/UTIs diagnosed during follow-up are considered AEs that must be documented, reported and clinically managed. Acquisition of an STI during follow-up will result in permanent discontinuation of study product. If the participant acquires a UTI or RTI, the participant will be referred for treatment and the visit will be rescheduled after treatment is complete and symptoms have resolved.

Genital herpes and genital warts are non-curable STIs and are handled differently from the curable STI/RTIs. Genital herpes and genital warts are associated with chronic viral infections — HSV-2 and HPV — and periodic symptomatic outbreaks — genital ulcers and genital warts. Reporting of these conditions as pre-existing conditions and/or AEs should be handled as follows:

- If infection with HSV-2 or HPV is known to have occurred before randomization, the infection is considered a pre-existing condition: record on the Pre-existing Conditions case report form.

- For HPV, genital warts present at any time before randomization are considered a pre-existing condition; record on the Pre-existing Conditions case report form.

- An outbreak that occurs after randomization that has increased in severity, frequency, or duration, as compared to her baseline condition, is considered an AE. Document and report as an AE.

8.10.1 STI/RTI Treatment

STIs/RTIs will be treated per current CDC guidelines, which can be accessed at:

http://www.cdc.gov/std/treatment/2010/default.htm

In day-to-day practice, the CDC guidelines should be referenced to obtain complete information on treatment regimens, contraindications, etc. To optimize cure rates, directly observed single dose treatment regimens should be provided whenever possible.

8.11 Clinical and Product Use Management

Protocol Section 9 provides detailed guidance on clinical and product use management, including general criteria for permanent discontinuation of product (Section 9.3), guidance on discontinuation in response to observed AEs (Section 9.4), and management of other clinical events (Sections 9.5).

Participants will be permanently discontinued from product use for any of the following reasons:

- Indeterminate or positive HIV-1 test
- Acquisition of STI
- Male or female participant self-report of non-monogomy
- Pregnancy
- Report of use of PEP for possible HIV-1 exposure
- Report of PrEP for HIV prevention
- Reported use of systemic immune modulators, female only (prohibited concomitant medications as per Section 6.9)
- Participant is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use according to the judgment of the IoR/designee

If a participant develops a Grade 1 or 2 AE, as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (clarification dated August 2009), regardless of relationship to study product may continue product use. If the IoR/designee opts to temporarily hold study product, the PSRT must be notified.

If a participant develops a Grade 3 AE that is judged by the IoR/designee to be unrelated to study product, s/he may continue product use. If the IoR/designee opts to hold study product, the PSRT will be notified. For participants who develop a Grade 3 AE that is judged by the IoR/designee to be related to product, the PSRT must be consulted to determine if the participant may continue to use product. The IoR/designee would temporary hold study product while awaiting a decision from the PSRT. Assuming product use continues, the IoR/designee must follow-up on this event (unless a different management plan has been devised in consultation with the PSRT):

- Reevaluate the participant at least weekly up to 2 weeks
- Consult the PSRT if the adverse event has not improved to less than or equal to Grade 2 within 2 weeks

If a participant develops a Grade 4 AE, regardless of relationship to study product, s/he should have the study product temporarily held. The IoR/designee must consult the PSRT and continue the temporary product hold until a recommendation is obtained from the PSRT.

All specifications of protocol Section 9 must be followed; IoRs are encouraged to consult the PSRT with any questions related to proper interpretation of the protocol and proper management of study product use in particular.

Following permanent discontinuation from study product, PK/PD specimens should be collected at the next scheduled visit and then discontinued thereafter. Contact the MTN-011 Management Team and MTN-011 PSRT with any questions related to product discontinuation and procedure completion.

All clinical and product use management must be fully documented in participant study records. When the PSRT is consulted, completed PSRT query forms (including a response from the PSRT) must be printed and filed in participant study records. Permanent discontinuations must be communicated to site pharmacy staff using the Study Product Request Slip. Any clinician-initiated product hold or permanent discontinuation must be documented on Product Hold/Discontinuation Log form.

8.12 Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-011. Please also refer to Section 8 of the MTN-011 Protocol and the following resources relevant to AE assessment and reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004, (Clarification Dated August 2009)
- Female Genital Grading Table for Use in Microbicide Studies (Addendum 1)
- Male Genital Grading Table for Use in Microbicide Studies (Addendum 2)
- Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0, January 2010
- DAERS Reference Guide for Site Reporters and Study Physicians
- Investigators Brochure for Tenofovir gel

8.12.1 Adverse Events

The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (ICH-E6) defines an adverse event (AE) as any untoward medical occurrence in a clinical research participant administered an investigational product and that does not necessarily have a causal relationship with the investigational product. As such, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

The MTN-011 protocol specifies that any untoward medical occurrence experienced by a participant after enrollment, which begins when the investigator signs-off of the eligibility checklist, per site SOP, is considered an AE, regardless of the study group to which the participant is assigned.

For all female and male participants in MTN-011, the following subset of AEs are reportable on case report forms if they are reported by or observed in enrolled participants:

- All genital, genitourinary, and reproductive system AEs
    - Fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths) will not be reported as AEs. However, untoward maternal conditions that either result in or result from fetal losses are reported as reproductive system AEs
    - Genital bleeding clinically assessed to be expected is not an AE
- All AEs of severity Grade 2 or higher
- All serious AEs, as defined by the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice
- All AEs that result in permanent discontinuation of study product use
- All laboratory test abnormalities specified in the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004(clarification August 2009), that are not otherwise associated with a reported clinical AE
- AEs that do not meet the above-listed criteria but do meet expedited reporting requirements per Section 8.4 below

That means that the above AEs should be recorded on the Adverse Experience (AE) Log CRF (See Section 10) and the form should be faxed to the MTN Statistical and Data Management Center (SDMC) via DataFax. Each site's SOP for source documentation (See Section 3) should define the extent to which the AE Log CRF will be used as a source document. Site-specific delegation of duties documentation should designate study staff authorized by the Investigator of Record (IoR) to complete AE Log forms. Regardless of who initially completes these forms, a clinician listed on the site's FDA Form 1572 should review them to ensure the accuracy of the data reported and to help maintain consistency of reporting across clinicians.

8.12.2 Serious Adverse Events

ICH-E6 defines a serious adverse event (SAE) as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or may require intervention to prevent one of the outcomes listed in the definition above

SAEs are a subset of all AEs. For each AE identified in MTN-011, an authorized study clinician must determine whether the AE meets the definition of SAE, listed above. The Adverse Experience Log case report form includes an item (item 8) to record whether the AE is also an SAE.

8.12.3 Adverse Events Requiring Expedited Reporting

For MTN-011 all SAEs will be reported to DAIDS in an expedited manner.
This includes all SAEs occurring following enrollment through the participant's final study contact, regardless of the relationship to the study agents (see Figure 8-1).

Expedited AE reports must be made to the DAIDS Regulatory Support Center (RSC) Safety Office, also known as the DAIDS Safety Office, via the online DAIDS Adverse Event Reporting System (DAERS). If a report needs to be modified or updated, or a report submitted in error needs to be withdrawn, this can also be done through DAERS. For questions about DAERS, contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov or from within the DAERS application itself. Information about DAERS is also available on the RSC website at http://rsc.tech-res.com. All SAEs will be reported via DAERS Reporting System within three (3) reporting days of site awareness (the site's recognition that the event fulfills the criteria for expedited reporting) to the DAIDS Safety Office according to the procedures specified in the DAIDS Manual for Expedited Reporting of AEs.

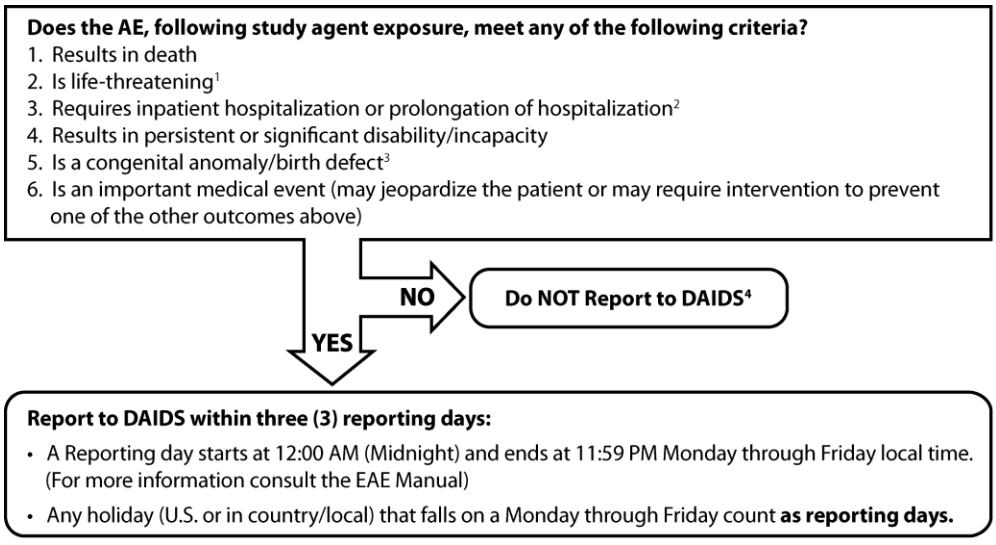
If the site cannot use DAERS to report an AE on an expedited basis, the AE must be documented on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form) and submitted as specified by the DAIDS Manual for Expedited Reporting of AEs. This form may be found on the Regulatory Support Center (RSC) website at http://rsc.tech-res.com.

For questions or other communications regarding expedited reporting of AEs, see below.

Website:	http://rsc.tech-res.com
Office Phone:	301-897-1709 or toll free in the US: 800-537-9979
Office Fax:	301-897-1710 or toll free in the US: 800-275-7619
Office Email:	DAIDSRSCSafetyOffice@tech-res.com
Office Hours:	Monday through Friday, 8:30 AM to 5:00 PM ET

The AE Log case report form includes an item (item 9) to record if the AE is also being reported as an EAE. When completing AE Log CRFs and DAERS report, study clinicians should carefully review all documentation of the event to ensure accuracy, completeness and consistency. All AE descriptions and details (e.g., onset date, severity grade, relationship to study product) must be recorded consistently across all documents. All expedited AE reports submitted to the DAIDS Safety Office will be compared with AE Log forms received at the MTN SDMC to ensure that all reports that should have been received by both DAIDS Safety Office and the SDMC have been received and that the details recorded on each form are consistent.

Figure 8-1
Expedited Adverse Event Reporting Requirements for MTN-011



Contact Information for the DAIDS Safety Office:
Website: http://rcc.tech-res.com • **E-mail:** RCCSafetyOffice@tech-res.com
Office Phone: 1-800-537-9979 (U.S. only) or +1-301-897-1709 • **Fax:** 1-800-275-7619 (U.S. only) or +1-301-897-1710
(Office Phone and Fax are accessible 24 hours per day)
Mailing Address: DAIDS Safety Office 6500 Rock Spring Drive, Suite 650, Bethesda, MD 20817

[1] "Life-threatening" refers to an event in which the patient was at risk of death at the time of the event. It does NOT refer to an event that hypothetically might have caused death if it were more severe.

[2] Per the ICH SAE definition, hospitalization is NOT an adverse event (AE), but is an outcome of the event. **DO NOT REPORT**: Any admission unrelated to an AE (e.g., for standard labor/delivery, cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep); protocol-specified admission (e.g., for a procedure required by protocol); admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) **and** has not increased in severity or frequency as

judged by the clinical investigator. (**NOTE**: A new AIDS-defining event in a subject already known to be HIV-infected would be considered an increase in severity of a pre-existing condition [HIV infection] and **would be** reportable.)

[3] Clinically insignificant physical findings at birth, including those regarded as normal variants, do NOT meet reporting criteria. If a clinically significant anomaly is reported, all findings (including those of no individual significance) should be included in the same report. For example, do NOT report an isolated finding of polydactyly (extra fingers or toes) or Mongolian spot in an infant. But if either finding occurred with a major cardiac defect, report all findings in the SAE Report.

[4] Please ensure that any other protocol-specific reporting requirements are met.

8.13 Adverse Event Terminology

Both the Adverse Experience Log case report form and the DAERS report require site staff to assign a term or description to each AE. Whenever possible, a single diagnosis should be reported, rather than a cluster of signs and/or symptoms. When it is not possible to identify a single diagnosis to describe a cluster of signs and/or symptoms, each individual sign and symptom must be reported as an individual AE. When relevant, an anatomical location should be included in the term or description.

Further tips and guidelines for assigning AE terms are as follows: use medical terms whenever possible, use correct spelling for all terms, and do not use abbreviations. Additional instructions on completion of AE Log forms can be found in Section 10 (both on the back of the AE Log form and in Section 10).

8.14 Adverse Event Severity

The term severity is described as the intensity of an AE (that is, the grade or level for a specific event such as mild, moderate, severe, or potentially life-threatening). Importantly, severity is not the same as seriousness, which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning (ICH E2A).

The current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (clarification dated August 2009), Addenda 1 (Female Genital Table for Use in Microbicide Studies) and 2 (Male Genital Grading Table for Use in Microbicide Studies) will be the primary tools for grading adverse events for this protocol, except that asymptomatic BV will not be a reportable AE. Adverse events not included in that table will be graded by the DAIDS AE Grading Table, Version 1.0 December 2004 (Clarification dated August 2009). In cases where an AE is covered in multiple tables, Addenda 1 and 2 (F/MGGT) will be the grading scales utilized for women and men, respectively. The grading tables are available at:

http://rsc.tech-res.com/safetyandpharmacovigilance/default.aspx

There are 5 severity grades that can be assigned to AEs, which are defined as follows:

Grade 1 = Mild
Grade 2 = Moderate
Grade 3 = Severe
Grade 4 = Potentially Life-threatening
Grade 5 = Death

Further clarifications, tips and guidelines for grading the severity of AEs are as follows:

- For the grading of clinical AEs not specified in the F/MGGT, the DAIDS Toxicity Table, or in the protocol, sites are to use the 'Estimating Severity Grade' on page 3 of the of the DAIDS Toxicity Table
- If the severity of an AE could fall under either one of two grades (e.g., the severity could be a grade 2 or a 3), the higher of the two grades should be assigned
- If a single AE term is used as a unifying diagnosis to report a cluster of signs and symptoms, assign the highest severity grade of each of the signs and symptoms to the AE
- Seasonal allergies should be graded according to the 'Estimating Severity Grade' row of the DAIDS Toxicity Table

8.15 Adverse Event Relationship Assessment

For each AE indentified in MTN-011, the study clinician must assess the relationship of the AE to the study product, based on the temporal relationship of AE onset to study drug administration, the pharmacology of the study product and his/her clinical judgment. When assessing relationship, the study products in MTN-011 that should be considered are tenofovir gel and the study applicator. The categories of relatedness that will be used to assess the relationship of all AEs to study product are:

- Related: There is a reasonable possibility that the AE may be related to the study agent(s)

- Not related: There is not a reasonable possibility that the AE is related to the study agent(s)

8.16 Follow-up Documentation of Adverse Events

All AEs identified in MTN-011 must be followed clinically until the AE resolves (returns to baseline) or stabilizes. "Stabilization" is defined as continuing at the same severity grade for 1 month. In addition to performing protocol-specified assessments, at each visit, an authorized study clinician should review all previously reported ongoing AEs to evaluate and document in the participant's chart notes the current status.

A new Adverse Experience Log CRF is NOT required when submitting follow-up information for a previously reported AE. Rather, the existing CRF is updated and resubmitted. However, if an AE increases in severity or frequency, it must be reported as a new AE on a new AE Log form. The onset date on the AE Log form will be the date that the severity or frequency increased. Note that a decrease in severity should not be reported as a new AE. For additional instructions, see Section 10.

Likewise, any ongoing SAE that increases in severity to a higher grade than previously reported must be reported again as a new report in DAERS. Ongoing events that improve, but are not resolved and subsequently increase in severity to the same or lower severity grade than previously reported do not have to be reported again to the DAIDS Safety Office.

The requirements for submission of follow-up information on AEs reported to DAIDS are specified in Section 4 of the Manual for Expedited Reporting of Adverse Events to DAIDS

(Version 2.0 dated January 2010). As specified therein, for the circumstances listed below regarding an AE reported to DAIDS, the site is required to submit an updated report to DAIDS as soon as significant additional information becomes available. Requirements include:

- An updated report documenting the stable or resolved outcome of the AE, unless the initial report included a final outcome
- Any change in the assessment of the severity grade of the AE or the relationship between the AE and the study agent
- Additional significant information on a previously reported AE (e.g., cause of death, results of re-challenge with the study agent).

Note: if information regarding an AE reported to DAIDS is updated, the corresponding AE Log case report form should also be updated and resubmitted if any data recorded on the AE Log form has been updated.

8.17 Outcome of Adverse Events, Review of AE Reports, and Clinician Assessment

The site must follow the progress of each reported adverse event and record eventual outcomes in source documentation. In many cases the final outcome of an AE will not be available when the AE Log form is first completed and faxed to SCHARP DataFax. In such cases, the AE Log form should be updated when the final outcome becomes available. If the AE is still continuing at the time of the Final Clinic Visit, item 6 ("Status/Outcome") of the AE Log form should be updated to "Continuing at end of study participation". Any AE continuing at the Final Clinic Visit should be followed clinically until resolution (return to baseline) or stabilizes. "Stabilization" is defined as continuing at the same severity grade for 1 month following study exit. The Investigator will determine the appropriate follow-up plan for monitoring ongoing AEs at the end of the study and may consult the PSRT for guidance as needed. Clinical management and follow-up after the participant exits the study should be documented in chart notes only (the AE Log form should not be updated once the participant has terminated from the study).

The Investigator or designee should carefully review all laboratory abnormalities relevant to the participant's health available since the last visit to identify any adverse events or health problems. Documentation of this review is required by initialing and dating each page of lab results.

The severity of all lab abnormalities will be graded and recorded in source documentation. Results of protocol-specified local laboratory results will also be reported on the Laboratory Result form and if applicable, an Adverse Experience Log form. Sites should document other results if any, in visit chart notes, or in other designated site-specific documents. If any non-protocol-specified lab abnormalities meet AE criteria, these will also need to be reported on an AE Log form. Through the participant's study involvement, lab abnormalities that meet the criteria for expedited reporting to DAIDS must also be reported to DAIDS via the DAERS Reporting System.

A study clinician listed on the FDA Form 1572 must assess each participant and record the details of all adverse events in the source documentation and complete or carefully review the information transcribed onto the AE Log CRF. S/he must also review and verify the data on the DAERS report for accuracy and completeness. This physician makes the site's final assessment of the relationship between the study product and the adverse event. S/he must electronically sign the completed DAERS report. If necessary, to meet timely reporting requirements, sites can submit an expedited adverse event report without a completed signature page. However, the

completed signature page, and necessary corrections or additions, must be submitted within the next 3 reporting days.

8.18 Reporting Recurrent Adverse Events

In the rare occurrence that a resolved adverse event that was previously reported on the AE Log form later recurs, the AE is considered a new adverse event and a new AE Log form must be completed.

Likewise, if a resolved AE that was previously reported to DAIDS later recurs at a level requiring expedited reporting, the AE must be reported as a new EAE Report to the DAIDS Safety Office.

8.19 Social Harms

In addition to medical adverse events, participants may experience social harms – any non-medical adverse consequence experienced as a result of a person's participation in a study. For example, participants could experience difficulties in their personal relationships with partners, family members, and friends. They also could experience stigma or discrimination from family members and members of their community.

In the event that any social harm occurs, study staff should fully document the issues or problems and make every effort to facilitate their resolution as described in this section. There is no CRF for the reporting of social harms. However, in addition to documenting the social harm in the source files, the Investigator of Record will report any social harm, in his/her judgment, to be serious or unexpected to the IRB on at least an annual basis. Study sites may engage their Community Advisory Boards in exploring the social context surrounding instances of social harm.

The following are suggested strategies for responding to social harms that may be adapted and tailored to best meet participant needs at each site:

- When first responding to an issue or problem, actively listen to the participant's description of the problem and ask questions to elicit as much detail as possible about the problem, including the participant's perception of the severity of the problem. Record all pertinent details in signed and dated chart notes. Also report the issue or problem to all responsible IRBs, if required per IRB guidelines.

- Ask the participant to articulate his thoughts on what can/should be done to address the problem, including what he would like study staff to do in response to the problem (if anything).

- Discuss with the participant any additional or alternative strategies that you might suggest to address the problem and collaborate with him to develop a plan to try to address the problem. Document the plan in signed and dated chart notes.

- Take all possible action to try to address the problem, per the plan agreed upon with the participant. Document all action taken, and outcomes thereof, in signed and dated chart notes.

- As with medical AEs, follow all problems to resolution or return to baseline.

- Provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem.

- Consult the MTN-011 Protocol Safety Review Team (PSRT) for further input and guidance as needed.

8.20 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN-011 protocol for a complete description of the participant safety monitoring procedures in place for MTN-011. Also refer to Section 14 of this manual for a description of the reports prepared by the MTN SDMC in support of MTN-011 safety monitoring procedures.

Participant safety is of utmost concern. Primary safety monitoring and safeguarding of individual study participants is the responsibility of study site staff, under the direction of the IoR. The IoR and designated site staff also are responsible for submitting case report forms to the MTN SDMC and expedited AE reports to the DAIDS Safety Office, such that relevant safety data are available in a timely manner for other study-specific safety monitoring procedures, as follows:

- Clinical Affairs staff at the MTN SDMC will review clinic and laboratory data received at the SDMC and apply clinical data quality control notes (clinical queries) to data requiring confirmation, clarification, or further follow-up by site staff. These queries will be issued to site staff for resolution on an ongoing basis throughout the period of study implementation.

- The DAIDS Medical Officer and CONRAD Medical Officer will review all DAERS reports received for MTN-011 and follow up on these reports with site staff, the MTN-011 Protocol Team, and drug regulatory authorities when indicated.

- The MTN-011 Protocol Safety Review Team (PSRT) will routinely review safety data reports prepared for MTN-011 by the MTN SDMC. The PSRT will meet via conference call to discuss the accumulating study safety data and any potential safety concerns (See Section Appendix I for more details).

Management of permanently discontinuing study product relative to the occurrence of toxicities must follow the standard toxicity management procedures. Site staff should seek the advice and counsel of the PSRT on these matters.

8.21 MTN-011 Protocol Safety Review Team (PSRT)

8.21.1 Roles and Responsibilities of the PSRT

Per the MTN-011 protocol, the roles and responsibilities of the MTN-011 Protocol Safety Review Team (PSRT) are to:

1. Conduct regular reviews of standardized study safety data reports. Once the SDMC begins receiving study follow-up safety data, the PSRT will convene via regularly scheduled monthly conference calls. Thereafter, the frequency of calls may be adjusted throughout the period of study implementation as agreed upon by the PSRT. Should any

safety concerns be identified by the PSRT, these will be referred to the MTN Study Monitoring Committee (SMC).

2. Respond to Investigator queries regarding early termination of study participation. The site IoR should consult the PSRT when he/she decides to withdraw a participant from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures.

3. Respond to Investigator queries regarding study eligibility and general AE management and reporting (not necessarily related to product use).

4. Respond to Investigator queries regarding rescheduling visits and resupplying study gel in the event the couple does not adhere to study procedures

8.21.2 PSRT Composition

The following individuals currently comprise the MTN-011 PSRT:

- Betsy Herold, Protocol Chair
- Jeanna Piper, DAIDS Medical Officer
- Jill Schwartz, CONRAD Medical Director
- Katherine Bunge, MTN Safety Physician
- Ken Ho, MTN Safety Physician
- Devika Singh, MTN Safety Physician
- Jill Zeller, SDMC Clinical Affairs Safety Associate

Ideally all of the above-listed PSRT members will take part in routine PSRT conference calls; however a quorum of at least three members, the MTN-011 Protocol Chair, DAIDS Medical Officer (or designee) and one of the MTN Safety Physicians, must take part in all calls.

If a quorum is not present, the call may be deferred until the next scheduled call time unless a quorum member requests a more immediate call.

The MTN CORE (FHI 360) Clinical Research Manager, and the SDMC (SCHARP) Project Manager, also will participate in PSRT calls and reviews. The DAIDS PSB Program Officer(s), MTN CORE Pharmacist, MTN Network Lab representative, and Co-Sponsors also may attend calls as observers.

8.21.3 Routine Safety Data Summary Reports: Content, Format and Frequency

The SDMC will generate and distribute standard safety data reports to the PSRT via e-mail within a week prior to each PSRT conference call. Tabulations will be generated for all study participants combined (i.e., across all study regimen groups).

Reports will include summary information regarding the number and frequency of events organized by body system (using MedDRA terms) and severity, and will include information on relatedness to study product.

During PSRT conference calls, the DAIDS Medical Officer will summarize any additional DAERS reports received at the DAIDS Safety Office after the cut-off date for inclusion in the SDMC PSRT report.

8.21.4 PSRT Communication

An email distribution list will be used to facilitate communication with the PSRT. Site queries and communications with the PSRT should be sent via email to mtn011safetymd@mtnstopshiv.org. All safety data summary reports from the SDMC will be distributed via mtn011psrt@mtnstopshiv.org.

A standard PSRT query form (Appendix I) will be used to elicit sufficient information to allow the PSRT to make an informed determination and respond to each query. To ensure a timely PSRT response, the MTN-011 Protocol Chair, MTN Safety Physicians and DAIDS Medical Officer have ultimate responsibility for providing a final response to the query (via email) within three business days after receipt of the query (unless a more urgent response is requested by the site). All members of the PSRT are encouraged to review the information provided by the site and to offer their advice; however final determination rests with the MTN-011 Protocol Chair, MTN Safety Physicians and the DAIDS Medical Officer on behalf of the PSRT.

In the event that the protocol team or PSRT has serious safety concerns, the protocol team or PSRT will request a review of the data by the MTN Study Monitoring Committee (SMC). While site staff are not typically involved in these reviews, site staff should be aware that the SMC may make recommendations to DAIDS and/or the MTN leadership that could affect the study and study sites in significant ways. These decisions are based on detailed review of the available study data and careful consideration of ongoing participant safety and study viability.

Section Appendix 8-I
MTN-011 Protocol Safety Review Team Query Form

Instructions: Email completed form to MTN Safety Physicians: mtn011safetymd@mtnstopshiv.org

IMPORTANT: Complete all required fields so the PSRT has all information needed to respond to your query.

Site: **Query Date (dd-MMM-yy):**
Completed by: **Email address:**

PTID: **Participant Age** (in years):
Gender: **Last Visit**:
Study Group (1 or 2):

Reason for query:
- ☐ Product use consultation:
  - ☐ Should use of study product be temporarily discontinued?
  - ☐ Should use of study product be permanently discontinued?
  - ☐ Should use of study product be resumed?
- ☐ Request for consultation on AE management
- ☐ Request to withdraw participant from the study
- ☐ Other, specify:

Is this query a request for the PSRT to consult on an adverse event (AE)?
☐ Yes → continue completing this page
☐ No → skip to Comments on page 2

Primary AE of concern:

AE onset date (dd-MMM-yy): **AE severity grade at onset:**

Relatedness to study product:
☐ Related
☐ Not related

Current study product administration:
☐ No change
☐ On hold
☐ Permanently discontinued
☐ Not applicable

Has this AE been reported on a SCHARP AE Log form?
☐ Yes
☐ No

Has this AE been reported as an EAE?
☐ Yes
☐ No

Has this AE been assessed more than once?
☐ Yes
☐ No → skip to Comments on page 2

Date of most recent assessment (dd-MMM-yy):

Status of AE at most recent assessment:
☐ Continuing, stabilized (severity grade unchanged)
☐ Continuing, improving → severity grade decreased to
☐ Continuing, worsening → severity grade increased to
☐ Resolved

Comments: Provide additional details relevant to this query. If product use has been held, include date of last reported product use prior to the hold (per participant report).

End of Form for Site Staff. Email completed form to the MTN-011 Protocol Safety Physicians, mtn011safetymd@mtnstopshiv.org. If an email response is not received from the PSRT within 3 business days, re-contact the Protocol Safety Physicians, copying the study management team (mtn011mgmt@mtnstopshiv.org), for assistance as soon as possible.

FOR PSRT USE ONLY — PROVIDE RESPONSE TO QUERY HERE

PSRT Responding Member:
PSRT Response Date (dd-MMM-yy):

Query Outcome:
☐ Approved
☐ Not approved
☐ Not applicable

PSRT Comments: