Section 8. Clinical Considerations and Safety Monitoring

This section presents information on clinical procedures and safety monitoring performed in MTN-014. 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

In order to obtain a complete, accurate, and relevant medical history at screening and enrollment and to assess medical eligibility, it will be necessary to ask the participant about her past medical conditions as well as any conditions she is currently experiencing at the time of the Screening and Enrollment visits. The participants' baseline medical and 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. Information pertaining to the participants' medical history (particularly symptoms, conditions, and diagnoses which occurred in the time since she became sexually active or that affect eligibility) should be obtained.

The baseline medical and menstrual history should explore any medical conditions or medications that are deemed exclusionary for this study. 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 participant's baseline menstrual history, conditions and symptoms for comparison with signs, symptoms and conditions that may be identified or reported during follow-up
- Monitor any potential adverse events during the course of the study

The MTN-014 Baseline Medical History Questions sheet (Word version available on the MTN-014 web page under *Study Implementation Materials*) and the non-DataFax Screening Menstrual History form are recommended source documents for collecting baseline medical history information; however, alternative site-specific history forms may be used.

8.2 Pre-existing Conditions

In order to establish a starting point for each participant's medical status (and also assess medical eligibility), pre-existing conditions will be captured starting at Screening. 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. When collecting past medical history from the participant, ask probing questions in order to collect the most complete and accurate information possible, especially with regard to severity and frequency.

Per the instructions at the top of the questions sheet, relevant items that are marked "yes" on the questions sheet should be recorded on the Pre-existing Conditions CRF.

All participant-reported symptoms, clinical signs (including gradable lab results), diagnoses, and medically relevant chronic conditions will be recorded on 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, Screening and Abbreviated Physical Exam forms, Pelvic and Anorectal Exam forms, Safety Laboratory Results forms, and STI Test Results form. 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 CRF to best describe the condition at the time the participant enters the study. This allows for greater objectiveness in noting any grade increase of the pre-existing condition.

Severity of each condition should be assessed per the DAIDS Female Genital Grading Table for Use in Microbicide Studies and the Rectal Grading Table for Use in Microbicide Studies (Clarification dated May 2012). If the condition is not listed in the Female Genital Grading Table for Use in Microbicide Studies or the Rectal Grading Table for Use in Microbicide Studies (Clarification dated May 2012), 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-014. All conditions noted at screening and enrollment must be graded. The purpose of grading the 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. 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.

8.3 Follow-up Medical History

It is necessary to update the participants' medical history 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 for visits when follow-up medical history is required.

At each visit following Enrollment, it is necessary to record information that has occurred or changed since the participants' last visit. Any symptoms reported by the participant should be further probed and evaluated. Study clinicians should follow-up on baseline symptoms that have not resolved since enrollment (refer to the Pre-existing Conditions CRF) as well as any symptoms listed as "continuing" on an Adverse Event Log CRF. If during follow-up a baseline symptom resolves, you can document the resolution in the "Comments" field of the Pre-existing Conditions CRF. 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.

If during follow-up a condition is identified as being present at baseline and the participant inadvertently did not report it in her baseline medical history, the clinician should add the newly-identified information to the Pre-existing Conditions CRF. A chart note should also be documented to explain why the newly-identified information is recorded on the Pre-existing Conditions CRF retrospectively.

8.4 Concomitant Medications

The MTN-014 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 (including contraceptives), over-the-counter preparations, vitamins and nutritional supplements, recreational drugs and herbal and naturopathic preparations.

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.

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 she 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

Many medications interact and should not be used together, and additionally some medications may alter the parameters that are measured in MTN-014. For this reason, certain medications are contraindicated and should not be used during study participation because it may be harmful to the participant. Prohibited medications and products will be recorded on the Vaginal and Rectal Practices CRF.

The following medications are prohibited and/or restricted during the product use periods and 24 hours prior to each Period Initiation study visit:

- Non study vaginal or rectal preparations and products including, but not limited to: spermicides, female condoms, diaphragms, contraceptive vaginal rings, vaginal medications, menstrual cups, cervical caps (or any other vaginal barrier method), vaginal/rectal douches, enemas, non-study approved lubricants, sex toys (vibrators, dildos, etc.), and tampons.

Participants will also be counseled not to use NSAIDs, aspirin and/or other drugs that are associated with the increased likelihood of bleeding for 72 hours (3 days) prior to and following mucosal biopsy collection. If a participant reports using aspirin or aspirin-containing products and other non-steroidal anti-inflammatory drugs such as ibuprofen (Advil, Motrin) and naproxen (Aleve, Naprosyn) within 72 hours prior to a study visit in which biopsies are obtained, the biopsies may still be collected per IoR discretion but the participant must be counseled regarding potential risks associated with biopsy collection. Documentation of the IoR decision process to continue with biopsy collection should be included in chart notes. If needed, the site may consult the PSRT for guidance.

8.6 Physical Exam

Protocol Section 7.14 outlines the required physical exam assessments. A comprehensive physical examination is required at Screening. A targeted physical examination is required at Period Initiation and Period End Visits. It should also be performed at any other scheduled or interim visit if it is clinically indicated. 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.

The Screening Physical Exam CRF will be provided to the site to document the comprehensive physical exam at the Screening Visit and the Abbreviated Physical Exam CRF will be provided to the site to document the conduct of the targeted physical examination.

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 16. In such situations, the clinician should add the information to the Baseline Medical History Questions Sheet and the Pre-existing Conditions form as well, since the condition was present at the time of enrollment.

8.7 Genital Exams

Pelvic and rectal exams are required at the Screening, Period Initiation and Period End visits. These exams are necessary to evaluate protocol exclusion criteria and to collect detailed information on baseline vaginal and anorectal conditions. Pelvic and rectal exams are also performed to ensure the ongoing safety of study participants and when clinically indicated to evaluate symptoms. Note: although the site should make efforts to schedule follow-up visits during a time she is not experiencing her menses, the site may continue with the pelvic exam if unable to reschedule within the visit window.

Scheduled pelvic and rectal exams should be performed according to the guidance provided in the remainder of this section. Vaginal and rectal exam procedures must be performed in the order shown on the Genital Exam checklist provided on the MTN-014 Study Implementation Materials webpage; however the site may choose to perform the rectal procedures prior to vaginal procedures if needed based on visit flow and availability of clinical staff.

Prior to the Exam:

- Prepare all required equipment; label specimen collection supplies as needed.

- Review documentation of prior exams and other relevant documentation from the current visit and prior visits.

Establish Participant Comfort

- Maximize the comfort and privacy of the participant.
- Explain what you are doing as you do it.
- Use clean hand/dirty hand technique, and/or assistants, to avoid contamination.
- Keep extra gloves available as two hands may be needed at different time points during the exam.
- Consider having an additional person (medical assistance or nurse) present during the examination to ensure participant comfort.

Position the Participant

- Position the participant on her back with her feet resting in stirrups (for the pelvic exam). Position the participant in the left lateral decubitus position (fetal position) with both legs flexed (for the rectal exam).

Examine the External Genitalia:

- Do not insert the speculum before examining the external genitalia.
- 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 without manipulation. Assess for abnormal vaginal and/or cervical discharge and/or blood tinged discharge.

General Technique

- Exams During Menstruation: As much as possible, pelvic exams should not be performed during menses, since the presence of menstrual blood will likely interfere with visualization of the vagina and cervix, elevate the vaginal pH, and complicate interpretation of wet prep findings. Site staff should make every effort to schedule participants for study visits when the participant is not menstruating BUT within the allowable window. If the participant is on her menses and the visit cannot be rescheduled, all PK procedures will be conducted, where applicable. If a participant is menstruating when she presents for an interim visit complaining of genital symptoms, every effort should be made to perform a pelvic exam to evaluate her symptoms at that time. However, if this is not possible the participant should be instructed to return for a pelvic exam as soon as possible after menses.

- Removal of Visual Obstruction: During the pelvic exams after assessment of vaginal pH and collection of vaginal swabs, if necessary remove any obstruction (e.g., mucus, cellular debris) use a large saline-moistened swab (scopette) in a gentle dabbing fashion to remove the obstruction. Avoid twisting or rolling the swab over the surface of epithelium. Do not use a dry swab to remove any obstruction at any time, as this may cause trauma to the epithelium.

Collect Vaginal and Cervical Specimens:

Collect specimens in the order listed on the Genital Exam checklist, located on the MTN-014 Study Implementation Materials webpage. Collect specimens away from apparent abnormalities and exclude swabbed areas from subsequent examination.

Pap Smear: If indicated to confirm eligibility at screening, collect ecto- and endocervical cells for Pap smear. In the event that specimens collected for Pap smear are not evaluable, additional specimens should be collected per local guidance. If inadequate specimens are collected, another screening pelvic exam is required for repeat Pap smear collection and testing. If a second screening pelvic exam is conducted, chart note the exam findings.

CVL for PK, PD and biomarkers:
Collect the CVL for PK, PD and biomarkers as described in the training video available at http://www.mtnstopshiv.org/node/773. Check expiration of sterile saline prior to use and conduct the following procedures:

- Draw 10cc of sterile saline into the 30 mL syringe.
- Carefully insert tip of syringe into the vagina using care not to touch vaginal walls with syringe. With tip of syringe aimed at the cervix, dispense all 10 mL of saline onto the cervix. Gently tilt speculum if necessary to avoid leakage of saline.
- Place tip of a 2ml pipette onto posterior blade of the speculum and draw fluid into pipette, using care not to touch the vagina or cervix.
- Use the 10mL of saline to lavage the cervix, fornices and vaginal walls. Be sure to lavage each sidewall at least twice. Only use the original 10cc of sterile saline. Do not use any additional saline to perform lavage.
- The saline must be in contact with the vaginal vault for at least 1 minute.
- After at least one minute of contact, remove lavage fluid with 30mL syringe and sterile tubing or 2ml pipette.
- Save lavage fluid for analysis. Transfer fluid to 15 mL conical centrifuge tube.

See Section 9 of this manual for additional details on specimen processing and storage.

Vaginal biopsies for PK and gene expression microarray:

The vaginal biopsy will be the last vaginal sample collected. Using forceps, approximately 2-4 mm samples will be taken from two different areas of the vagina. Usually, biopsy of the vagina does not require an anesthetic, although this procedure typically feels like a sharp pinch or a cramp Bleeding may be controlled through a combination of applied pressure, silver nitrate and/ monsel's solution. Each individual biopsy should be obtained before the next one is collected.

Participants should also be informed that they may experience a small amount of bleeding from the vagina 1-2 days following the procedure. If bleeding is reported as being heavier than the participants' usual menstrual period or if the participant experiences a foul odor or a heavier vaginal discharge (more than usual), they should be instructed to contact the study clinic right away. There is a small risk of the biopsy area becoming infected or having bleeding that is heavier than spotting.

All participants will be instructed to abstain from inserting anything into the vagina, including having vaginal sex for 72 hours prior to and following the collection of these samples. Participants will also be counseled to refrain from the use of NSAIDs, aspirin and/or other drugs that are associated with the increased likelihood of bleeding for 72 hours prior to and following mucosal biopsy collection.

Collect Rectal Specimen:

Perianal Examination: A visual exam should be performed during routine scheduled rectal exams. With gloved hands, the clinician should separate the participant's buttocks as far apart as is comfortable for her. Perform a naked eye examination of the perianal area and evaluate any abnormalities including but not limited to hemorrhoids, lesions, warts, lumps, or rashes.

Digital Rectal Examination: A digital rectal exam should be performed during routine rectal exams after each visual inspection. The clinician will perform a digital rectal exam prior to the insertion of the flexible sigmoidoscope for the collection of specimens. The purpose of this exam is two-fold. First, this examination is intended to relax the anal sphincter around the opening of the anus in preparation for the subsequent anoscopy/ flexible sigmoidoscopy and specimen collection. In addition, the examination enables the clinician to assess potential findings such as lumps/areas of discomfort.

The clinician will lubricate a gloved finger with Good Clean Love lubricant provided by the clinic staff. The clinician will then gently and slowly insert a gloved index finger (palmar surface down) into the anus. The clinician should sweep the finger circumferentially around the entire anal/distal rectal surface. Any abnormal findings or unexpected discomfort should be noted on the Anorectal Exam CRF.

Rectal fluid will be collected using either a rectal sponge (for PK, PD and biomarkers) or swab (for GC/CT) that is inserted into the rectum through an anoscope. Using study provided lubricant (Good Clean Love lubricant), the clinician should sparingly lubricate the anoscope prior to insertion. The anoscope with obturator should then be inserted into the anal canal until the anoscope 'wings' touch the anal verge. The clinician should maintain pressure on flange to ensure continued placement of the anoscope and then remove the obturator. Using a lighted instrument (e.g.otoscope or torch) to illuminate the rectum after removing the obturator, the rectal lumen should be visible at the end of the anoscope. The clinician should visually assess the rectum after the anoscope is in place and prior to specimen collection. Following specimen collection, the clinician should assess the anal canal as the anoscope is withdrawn.

Rectal fluid for GC/CT:
The rectal swab for NAAT for GC/CT is required for all participants at Screening.
It is recommended that the GenProbe Transport kit or Cepheid GeneXpert NAAT method be used for collection of this specimen. When using the Gen-Probe Aptima NAAT method, clinicians should use the Gen-Probe Aptima Unisex Swab (blue swab).

Instructions for collection and transport of rectal swabs for GC/CT testing with Gen-Probe:
The clinician/assistant will open the wrapper containing the swab while ensuring the tip of the swab is not touched. Do not place any fluid or lubricant on swab. After removing the obturator, advance the anoscope slightly then insert the GC/CT swab into the proximal rectal lumen that is visible at the end of the anoscope. Rotate it 360 degrees and remove. Fully insert the swab into the transport tube. Carefully snap the swab shaft at the scoreline to fit the tube; use care to avoid splashing of contents. Re-cap tube securely by snapping the cap into place.

Instructions for collection and transport of rectal swabs for GC/CT testing with GeneXpert:
The clinician/assistant will use the Xpert collection swab. The clinician/assistant will open the peel pouch containing the swab. After removing the obturator, advance the anoscope slightly then insert the swab into the proximal rectal lumen that is visible at the end of the anoscope. Rotate it 360 degrees and remove. After specimen collection, put the swab in the transport medium and break the shaft at the painted breakpoint. Re-cap tube securely by snapping the cap into place. Immediately following insertion into the transport tube, elute material from the swab while avoiding foaming by gently shaking or inverting the tube 3-4 times.

Rectal fluid for PK, PD and biomarkers:

Site staff should plan to allot sufficient time to prepare for the rectal sponge procedure.

- Weigh the dry sponge and labeled cryovial and document the weight (pre-weight) on the LDMS Tracking Sheet
- Use the Good Clean Love water-based lubricant to lubricate the anoscope.
- With subject placed in left lateral recumbent position slowly insert the anoscope with obturator in place through the anus and advance the instrument until the flange is flush with the subject's skin. Maintain pressure on flange to ensure continued placement of the anoscope.

- Remove obturator; introduce the sponge (attached to the pipette sponge holder extension: see picture below) through the anoscope into the rectum. Sponges may be collected one at a time or simultaneously.


- Hold (or leave) sponge in place for 2 minutes.
- Disengage sponge from holder (plastic pipette) and discard plastic pipette. Place the sponges back into the original weighed cryovial (by matching the number of the sponge to the tube) and ensure that the cap is fully tightened.
- Record collection time onto the LDMS Tracking Sheet.
- Slowly remove anoscope.
- Weigh sponge and labeled cryovial and document the weight (post-weight) on the LDMS Tracking Sheet

See Section 9 of this manual for additional details on specimen processing and storage.

Coagulation Testing (INR or PT)

Participants must have their blood tested at Screening to determine how quickly their blood clots and if bleeding problems are present to ensure the biopsies are taken safely. Participants with abnormal coagulation test results will be ineligible. Test results will be recorded on the local lab results report and documented in chart notes. The values listed below are exclusionary for enrollment:

- International Normalized Ratio (INR): >1.5x site laboratory ULN (Grade 1)
- Prothrombin Time (PT): >1.25x site laboratory ULN (Grade 1)

Enema:

Prior to each rectal biopsy procedure and sigmoidoscopy, each participant will have a rectal enema performed. In the event the enema does not provide instructions for use, the following procedures should be performed:

- Fill enema bottle with 125 mL (about 4 ounces) of sterile normal (0.9%) saline, if not pre-packaged.
- Have participant rotate onto her left-hand side with right knee bent.
- If enema bottle is not pre-lubricated, apply a small amount of Good Clean Love water-based lubricant. (DO NOT USE Surgilube or other chlorhexidine containing lubricants)

- Gently insert the tip of the enema bottle into the anus.
- Slowly instill the solution into the rectum.
- After holding the fluid in the rectum for about 3-5 minutes, ask the participant to expel the enema fluid into a restroom toilet.

No other special preparation, including dietary, is needed before having these specimens collected. Participants may follow their regular daily routine and eat/drink as they normally would prior to arriving to the visit. Participants should be instructed not to douche or take any laxatives to cleanse the rectum prior to biopsy collection as any required cleansing procedures will be conducted in clinic. Such practices may change the cells in the rectum, which must be left undisturbed in order to get an accurate sampling.

Rectal biopsies for PK, gene expression microarray, histology and proteomics:

Preparation for the sigmoidoscopy should begin at the time of preparation of the rectal sponge. Site staff should check to ensure the sigmoidoscope light is switched on, suction is on, and air flow is working. With the participant in the left lateral decubitus position, the sigmoidoscope tip is lubricated with Good Clean Love lubricant and gently inserted to ~15 cm from the anal verge. Introduce endoscopic 'jumbo' forceps into the sigmoidoscope channel and commence mucosal specimen collection at ~15 cm from the anal verge. The forceps need to be washed (dipped) in water between every biopsy. Forceps measuring approximately 3.7 mm with a 3.3 mm jaw will be required in order to obtain a 15 mg biopsy. Each individual biopsy should be obtained before the next one is collected.

Following tissue collection, participant vital signs should be obtained and documented and any abnormal findings should be further evaluated.

Participants should also be informed that they may experience a small amount of bleeding from the rectum (noticeable when wiping after a bowel movement) for 2 to 3 days following the procedure. Excessive bleeding is not expected. In the unlikely event excessive bleeding occurs, it is likely to be noticed when having a bowel movement or when wiping following a bowel movement. If the participant experiences large blood clots, signs of infection, or life-threatening event, they should be referred for assessment at emergency department of nearest hospital. All participants in the biopsy subset will be instructed to abstain from inserting anything into the rectum, including having anal sex for 72 hours prior to and following the collection of these samples. Participants will also be counseled to refrain from the use of NSAIDs, aspirin and/or other drugs that are associated with the increased likelihood of bleeding for 72 hours prior to and following mucosal biopsy collection.

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 Pelvic Exam Diagrams (non-DataFax) form, the Pelvic Exam CRF and the Anorectal Exam CRF.

Additionally, abnormal findings are documented on the Pre-existing Conditions CRF (at Screening and updated 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 and the Rectal Grading Table for Use in Microbicide Studies (Clarification dated May 2012).

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
- cervical ectopy
- 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

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, including contraceptive related bleeding is unexpected, and therefore an AE. This may include unusually heavy or prolonged menses, as well as non-menstrual bleeding different from baseline. Note: Shorter menses than reported at baseline is not considered a change in baseline bleeding pattern for the purposes of adverse event reporting.

Genital bleeding during pregnancy prior to the onset of labor (regardless of trimester) will be graded as follows:

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Spotting or bleeding less than menses	Bleeding like menses or heavier, no intervention indicated	Profuse bleeding with dizziness or orthostatic hypotension, transfusion indicated	Potentially life-threatening bleeding and/or shock

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 genital 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" or the "Unexplained Infrequent Bleeding" row of the DAIDS Female Genital Grading Table. Note: no AE should be reported if the change in bleeding pattern is due to contraception. In addition, a late menses should be graded according to the "Unexplained infrequent bleeding" row 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 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 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, this event should be recorded as "postcoital bleeding" and graded per the "Postcoital Bleeding" row of the DAIDS Female Genital Grading Table.

8.9 STI/RTI/UTI Evaluation and Management

Clinical and laboratory evaluations are performed in MTN-014 to diagnose the following STIs and RTIs:

- Bacterial vaginosis (BV)
- Candidiasis
- Chlamydia infection
- Gonorrhea infection
- Syphilis infection
- Trichomoniasis

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): UTIs may be diagnosed based solely on the presence of symptoms indicative of a possible UTI and graded per the infection row of the DAIDS Toxicity Table. The following symptoms are considered indicative of a possible UTI:

- Frequent urge to urinate
- Passage of only a small volume of urine
- Pain and burning during urination
- Lower abdominal pain and/or uncomfortable pressure above the pubic bone
- Milky/cloudy, reddish, or bloody urine

Other methods of diagnosis (ie urine culture or dipstick) may be performed per site standard of care per site SOP. Results must be documented in chart notes and/or on other site-specific source documents. If the UTI is diagnosed by signs and symptoms, grade the AE per the general "Infection" row of the DAIDS Toxicity Table. If other methods are used to diagnosis the UTI, such as a urinalysis or culture, the UTI should be graded per the UTI row of the FGGT if criteria are fulfilled. The term UTI should be the AE term utilized for the diagnosis based on clinical signs and symptoms regardless of laboratory confirmation.

8.9.1 STI/RTI Treatment

STI/RTIs will be treated in accordance with current World Health Organization (WHO) guidelines which can be accessed at: http://www.who.int/reproductivehealth/topics/rtis/evidence/en/index.html.

8.10 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
- Pregnancy or breastfeeding
- Report of use of post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP)

Participants will be temporarily discontinued from product use if they are 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), product use may continue regardless of relationship. If the IoR/designee opts to temporarily hold study product, the PSRT must be notified. In the event of a Grade 2 laboratory test result, follow up testing should be performed at scheduled study visits, at a minimum, until resolution or stabilization has been documented. More frequent testing may be performed at any time if required to properly monitor and/or manage participant safety, at the discretion of the IoR/designee.

If a participant develops a Grade 3 or 4 AE regardless of relationship to the study product, product use must be temporarily held. The PSRT must be consulted to determine if the participant may continue to use product. The IoR/designee must consult the PSRT and continue the temporary product hold until a recommendation is obtained from the PSRT. If product use is resumed and the same AE recurs at the same grade level, product must be permanently discontinued.

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-014 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 Management Slip. Any clinician-initiated product hold or permanent discontinuation must be documented on Clinical Product Hold/Discontinuation Log form.

8.11 Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-014. Please also refer to Section 8 of the MTN-014 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)
- Addendum 1, Female Genital Grading Table for Use in Microbicide Studies dated December 2004
- Addendum 3, Rectal Grading Table for Use in Microbicide Studies, (Clarification dated May 2012)
- 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

8.11.1 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-014 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 participants in MTN-014, the following subset of AEs are reportable on case report forms if they are reported by or observed in enrolled participants:

- All Grade 2 and higher AEs
- Grade 1 genitourinary and rectal AEs as reported by or observed in enrolled study participants, regardless of presumed relationship to study product.

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. Non-genitourinary Grade 1 AEs should be documented in chart notes. 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.

8.11.2 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-014, 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.

8.11.3 Adverse Events Requiring Expedited Reporting

For MTN-014 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.

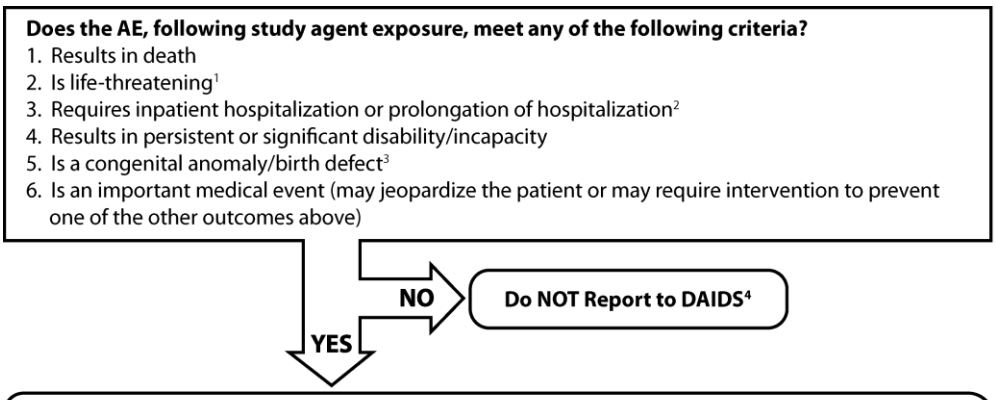
If the site cannot use DAERS to report an AE on an expedited basis, the AE must be documented on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form) and submitted as specified by the DAIDS Manual for Expedited Reporting of AEs. This form may be found on the Regulatory Support Center (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-014



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

"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.

8.12 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).

8.13 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 DAIDS Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 dated December 2004) and Rectal Grading Table for Use in Microbicide Studies (Addendum 3, Clarification dated May 2012) 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 those 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 3 will be the grading scales utilized. If there is ever an AE that could be evaluated using both the Rectal Grading Table and the Female Genital Table, contact the MTN-014 PSRT for guidance on which table to utilize.. 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 Female or Rectal Grading tables, the DAIDS Toxicity Table, or in the protocol, the site is 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

8.14 Adverse Event Relationship Assessment

For each AE identified in MTN-014, 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-014 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)

Note: When assessing an AE's relationship to study product (AE Log CRF item 4), the site clinician should only consider the most recent study product regimen the participant used prior to the AE onset date. If an AE onset date falls during a washout period, the site clinician should assess the AE's relationship to the study product used during the last completed period in which the participant received study product.

8.15 Follow-up Documentation of Adverse Events

All AEs identified in MTN-014 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.

8.16 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 Safety Phone/Termination call which occurs approximately 7 days following the Period 2 End/Final Clinic visit, item 6 ("Status/Outcome") of the AE Log form should be updated to "Continuing at end of study participation". 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. The site 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, the site 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.

8.17 Reporting Recurrent Adverse Events

If 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.

8.18 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 harms occur, study staff should fully document the issues or problems and make every effort to facilitate their resolution as described in this section. Ongoing social harms should be followed up on until they have resolved, it has been determined that they will not be resolved, or it is the end of the study.

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 her thoughts on what can/should be done to address the problem, including what she 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 her to develop a plan to try to address the problem. Document the plan in signed and dated chart notes.

- Develop a strategy agreed upon with the participant, to address the problem. 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-014 Protocol Safety Review Team (PSRT) for further input and guidance as needed.

8.19 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN-014 protocol for a complete description of the participant safety monitoring procedures in place for MTN-014. Also refer to Section 13 of this manual for a description of the reports prepared by the MTN SDMC in support of MTN-014 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-014 and follow up on these reports with site staff, the MTN-014 Protocol Team, and drug regulatory authorities when indicated.

- The MTN-014 Protocol Safety Review Team (PSRT) will routinely review safety data reports prepared for MTN-014 by the MTN SDMC. The PSRT will meet via conference call to discuss the accumulating study safety data and any potential safety concerns (see 8.21.1 below 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.

8.20 MTN-014 Protocol Safety Review Team (PSRT)

8.20.1 Roles and Responsibilities of the PSRT

Per the MTN-014 protocol, the roles and responsibilities of the MTN-014 Protocol Safety Review Team (PSRT) are to:

- Conduct regular reviews of standardized study safety data reports.
    - Once the SDMC begins receiving follow-up safety data, the PSRT will convene via regularly scheduled monthly conference calls. 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 Protocol Team or SMC as appropriate.
- Respond to notifications, requests and/or queries regarding:
    - product use management

- *Note: The protocol specifies situations in which study product use should be temporarily held, permanently discontinued and/or resumed. Site staff will implement these holds, discontinuations, and/or resumptions in the absence of required consultation with the PSRT. In other situations, however, product use must be managed in accordance with PSRT consultation.*
  - adverse event (AE) assessment, reporting, and management
  - participant withdrawal from the study
  - participant study eligibility

8.20.2 PSRT Composition

The following individuals currently comprise the MTN-014 PSRT:

- Gonasagrie Nair, Protocol Chair
- Jessica Justman, Protocol Co-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
- Yevgeny Grigoriev, 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-014 Protocol Chair or Co-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 Laboratory Center representative, and Co-Sponsors also may attend calls as observers.

8.20.3 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).

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.

8.20.4 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

mtn014safetymd@mtnstopshiv.org. All safety data summary reports from the SDMC will be distributed via mtn014psrt@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-014 Protocol Chair and/or Co-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-014 Protocol Chair and/or Co-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.

Appendix 8-1
PSRT Query Form

SITE AND PARTIPANT INFORMATION			
Site Name:		Query Date:	
Staff Name:		Staff Email Address:	
Participant ID:		Participant Age:	

REASON FOR QUERY
☐ Request for consultation on clinical/laboratory evaluations related to eligibility determination
☐ Request for consultation on clinical/laboratory evaluations related to study product management ☐ Should study product be continued? ☐ Should study product be temporarily held? ☐ Should study product be permanently discontinued? ☐ Should study product be resumed?
☐ Request for consultation on AE management ☐ Yes. Complete Section A and B, as appropriate ☐ No. Skip to Narrative Summary

Current Study Product Regimen:	☐ Vaginal Dosing ☐ Rectal Dosing

☐ Other: Please Describe

ADVERSE EVENT (AE) INFORMATION: SECTION A	
Primary AE of Concern:	
Onset Date:	
Severity Grade at Onset:	☐ Grade 1 Mild ☐ Grade 2 Moderate ☐ Grade 3 Severe ☐ Grade 4 Potentially Life-Threatening ☐ Grade 5 Death
Relatedness to Study Product:	☐ Related ☐ Not Related
Relatedness to Study Procedure:	☐ Yes. Record etiology or explanation in the Narrative Summary section. ☐ No
Current Study Product Administration:	☐ Not Applicable ☐ Continuing ☐ Temporarily Held, as of (DD-MMM-YY) ☐ Permanently Discontinued, as of (DD-MMM-YY)
Has this AE been reported on a SCHARP AE Log form?	☐ Yes ☐ No
Has this AE been reported as an SAE/EAE?	☐ Yes ☐ No
Has this AE been evaluated more than once?	☐ Yes. Complete Section B ☐ No. Skip to Narrative Summary

ADVERSE EVENT (AE) RE-ASSESSMENT INFORMATION: SECTION B	
Date of Most Recent Evaluation:	
Status of AE at Most Recent Evaluation:	☐ Continuing, stabilized (severity grade unchanged) ☐ Continuing, improving → severity grade decreased to: ☐ Continuing, worsening → severity grade increased to: ☐ Resolved

NARRATIVE SUMMARY
Describe the sequence of the signs and/or symptoms, relevant past medical history, diagnosis, intervention and/or treatment, relevant lab tests and results and current status of participant:
Proposed course of action:

End of Form for Site Staff. Email completed form to the MTN-014 Protocol Safety Physicians mtn014safetmd@mtnstopshiv.org If an email response is not received from the PSRT within 3 business days, re-contact the Protocol Safety Physicians, copying the following distribution list (mtn014mgmt@mtnstopshiv.org) for assistance.

PSRT USE ONLY	
PSRT Responding Member Name:	
PSRT Response Date:	
PSRT Comments:	
Query Outcome ☐ Not Applicable ☐ Approved ☐ Not Approved	