

Section 8. Clinical Considerations and Safety Monitoring

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This section presents information on clinical procedures and safety monitoring performed in MTN-028. 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 12.

8.1 Baseline Medical and Menstrual History

The participants' baseline medical and menstrual history is initially collected and documented at the screening visit; and then actively reviewed and updated, as necessary, at the enrollment visit. The purpose of obtaining this information is to:

- Assess and document participant eligibility for the study

- Assess and document the participant’s baseline medical and menstrual conditions and symptoms for comparison with signs, symptoms and conditions that may be identified or reported during follow-up (i.e. adverse event identification)

In order to obtain a complete, accurate, and relevant participant self-reported medical and menstrual history, it will be necessary to ask the participant about significant past medical conditions as well as any current conditions. It is recommended that sites use the MTN-028 Baseline Medical History Questions sheet (Word version available on the MTN-028 web page under *Study Implementation Materials*) in conjunction with the Pre-existing conditions CRF and/or chart notes to guide and document medical history taking. Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing and approach in order to elicit complete and accurate information from the participant. This is especially important with regard to details about severity and frequency of pre-existing conditions.

At the enrollment visit, a participant’s medical and menstrual history should be reviewed and updated as needed. Record the start and stop dates of the participant’s last menstrual period in item 1 of the Pharmacokinetics Specimens—Enrollment CRF. Only record dates of menstrual period bleeding (including expected monthly bleeding on OCPs). If a participant has not had a menses in the past 30 days, mark the ‘none’ box.

The baseline medical and menstrual history should explore in detail any medical conditions or medications that are deemed exclusionary for this study. Refer to protocol section 5.2 and 5.3 for complete listing of study inclusion and exclusion criteria. Further guidance about select clinical eligibility criteria is as follows:

- **History of adverse reactions to any of the components of the study products:** The 3 components of the IVR are the two drugs, VCV (MK-4176) and MK-2048, and ethylene vinyl acetate (EVA) copolymer 28. Women who have a hypersensitivity/allergy to any component of the IVR should not be enrolled. For example, if a potential participant states that she has an allergy to NuvaRing (contains EVA) or Implanon/Nexplanon (contains EVA), she may have an allergy to EVA. However, EVA is generally well-tolerated.
- **Regular use and/or anticipated regular use during the period of study participation of CYP3A inducer(s) and/or inhibitor(s):** Clinical staff should review the list of prohibited CYP3A inducer(s) and/or inhibitors available in SSP section 7 with the participant.
- **Chronic and/or recurrent candidiasis:** defined as 4 or more symptomatic episodes within the past year.
- **PEP/PrEP use for HIV exposure or prevention within 6 months prior to Enrollment:** These criteria are intended to exclude participants who may be high-risk for HIV acquisition or may have an undetectable HIV infection due to PEP or PrEP use. Potential participants that have had an investigational exposure to drugs used for PrEP/PEP may be enrolled as long as other exclusion criteria do not apply (e.g. participation in other investigational studies within the past 60 days.).

8.2 Pre-existing Conditions

Details of all relevant conditions identified during the baseline medical and menstrual history taking at screening should be recorded on the Pre-Existing Conditions CRF. Relevant conditions include (but are not limited to): hospitalizations; surgeries; allergies;

conditions requiring prescription or chronic medication (lasting for more than 2 weeks); and any conditions currently experienced by the participant.

In addition to participant-reported conditions, record the following on the Pre-Existing Conditions CRF:

- Grade 1 and higher lab values
- Medically-relevant physical exam abnormalities
- Pelvic exam abnormal findings
- Any identified STIs

The clinician should record as much information as possible about the severity and frequency of any pre-existing condition in the comments field of the Pre-existing Conditions CRF to best describe the condition at the time the participant enters the study. Severity of each pre-existing condition should be assessed per the DAIDS Female Genital Grading Table for Use in Microbicide Studies (FGGT). If the condition is not listed in the Female Genital Grading Table for Use in Microbicide Studies, 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-028. 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.

At Enrollment, each pre-existing condition entry should be reviewed, updated as needed, and have the status for ‘ongoing at enrollment’ indicated. Note that recurrent chronic conditions should be marked as ‘ongoing’ at enrollment, even if the participant is not currently experiencing an acute event (e.g. intermittent headaches). For severity grading, the highest severity experienced for the condition should be used. In the comments section, note the typical severity for outbreaks/acute episodes of the condition.

Note that any menorrhagia, metrorrhagia, or menometrorrhagia events ongoing at the time of randomization should be marked as “not gradable” on the Pre-existing log CRF. This is because the FGGT grades these bleeding events relative to each participant’s baseline bleeding pattern. In the “Comments” field of the ongoing PRE entry, include text similar to what is in the FGGT row to describe the severity and frequency of the condition.

Any past resolved (not ongoing at the time of randomization) menorrhagia, metrorrhagia, or menometrorrhagia events documented on the PRE CRF should be assigned a grade from 1-4 per the FGGT.

During screening, if a volunteer reports having a history of anaphylactic reactions (such as difficulty in breathing or severe hives after eating peanuts), even if it has happened once before in her lifetime, it is still important for the site clinician to document these events as pre-existing conditions on PRE-1 Log CRF. Record the condition in Item 1 as “allergic reaction to peanuts” and note types of symptoms in the comments field including severity grade (per the ‘acute allergic reaction’ row of the DAIDS toxicity table) when this event occurred. Please see the example below.

In this example, note that the condition is listed as “allergic reaction to peanuts” and the comments field provides a more detailed narrative of signs or symptoms that occurred, e.g. ‘throat swelling or shortness of breath’, and the severity grade.. At the Enrollment Visit, check ‘yes’ for the ‘ongoing at enrollment?’ box and check ‘not gradable’ box (as participant was not experiencing an anaphylaxis event at the time of enrollment). An AE submission for an anaphylactic reaction is required if this same event occurs after enrollment or during the study follow-up.

Pre-existing Conditions		
1. Condition	Onset Date	Staff Initials/Date
← allergic reaction to peanuts	MMM yy [][] [][]	
Comments	Ongoing at Enrollment?	Severity Grade
← throat swelling or shortness of breath	yes no <input checked="" type="checkbox"/> <input type="checkbox"/>	grade not gradable <input type="checkbox"/> <input checked="" type="checkbox"/>

8.3 Follow-up Medical History

It is necessary to update the participants’ medical history at all follow-up clinic 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. Any symptoms reported by the participant should be further probed and evaluated. Study clinicians should follow-up on any ongoing baseline conditions as well as any previously reported adverse events that are continuing.

Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing and approach in order to elicit complete and accurate information from the participant. As an example, follow-up interim history taking could be approached as follows:

- General questions about current health and medications (e.g. How are you feeling today? Any current symptoms, or issues since your last visit? Have you been to your doctor or hospital outside the study clinic since the last time we spoke? Changes to any medications you are currently taking?)
- Targeted gynecological questions (e.g. When was your last menstrual period? Would you say this is typical for you? Have you experienced any gynecologic problems since your last visit, for example, have you been bothered by abnormal discharge, pain, or bleeding?)
- Targeted questions about ongoing pre-existing conditions and previously reported AEs (e.g. At your last visit you reported X was ongoing, how are you feeling now? You reported that you occasionally experience X, have you had any recent episodes?)

If during follow-up a baseline condition resolves or increases in severity or frequency, this update should be documented in chart notes. Such information should not be added to the Pre-Existing Conditions CRF as that form represents a snapshot of the participant’s medical status at baseline. As a reminder, if a condition increases in severity or frequency, this should be reported as a new AE and documented as such (see Section 8.2).

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 new symptoms, illnesses, conditions etc., are reported, and if ongoing conditions remain unchanged, the participant chart should reflect this.

Note that during follow-up, sites should record the start and stop dates of the last vaginal bleeding of any type experienced in item 1 of the respective Pharmacokinetics Specimens CRF. This includes menstrual period bleeding, withdrawal bleeding, or expected breakthrough bleeding experienced while the participant is on Depo, Mirena, or other continuous contraceptive method where a woman does not experience a monthly menstrual period.

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 SSP section 8.11 for further details on AE reporting).

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-028 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, medications taken for pre-exposure (PrEP) or post-exposure prophylaxis (PEP), and herbal and naturopathic preparations. If silver nitrate and/or Monsel solution is used during the collection of cervical biopsies, this should be recorded on the concomitant medications log form.

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 a list of all medications to study visits.

8.5 Prohibited Medications and Practices

Certain medications and practices are contraindicated during MTN-028 study participation because they may be harmful to the participant, impact product safety, confound adverse event determination or impact pharmacokinetic parameters. Prohibited medications and practices for MTN-028 include:

- Receptive intercourse (vaginal, anal, or oral intercourse, finger simulation and the use of sex toys) for duration of study and for 5 days preceding Enrollment, i.e., participants should be sexually abstinent.
- CYP3A inhibitors and CYP3A inducers (see SSP Section 7) with the exception of single dose fluconazole (diflucan) for the treatment of vaginal fungal infections
- Female-to-male transition medications (i.e. cross gender hormonal therapy)
- Non-study vaginal products and other devices. This includes, but is not limited to: spermicides, female condoms, diaphragms, contraceptive intravaginal rings, vaginal medications, menstrual cups, cervical caps, douches, lubricants, and sex toys (e.g., vibrators, dildos, etc.).
- Tampons during the first week of study participation (starting at the enrollment visit) and for 24 hours prior to each clinic visit following enrollment.
- Participation in other research studies involving drugs, medical devices, or vaginal products for the duration of study participation

As outlined in SSP Section 10.2.4, participants will be counseled on avoiding these medications and practices during study participation. Use of any prohibited medications will be recorded on the concomitant medications log CRF and all prohibited medications and practices should be reported to the MTN-028 Management Team. Note that use of prohibited medications will also result in a temporary product hold and the PSRT should be notified (see SSP section 8.10).

NOTE: Use of topical PrEP is not approved by the FDA as a prevention method; therefore it is not available to the general population. If a participant reports its use, the MTN-028 Management Team should be immediately consulted for further guidance as the participant may be co-enrolled in another investigational study. Furthermore, in addition to protocol outlined prohibited medications, study product should be held in response to reported use of PEP or PrEP, and the PSRT should be notified.

8.6 Physical Exam

Protocol Section 7.10 outlines the required physical exam assessments. A comprehensive physical examination is required at Screening and Enrollment. A modified/targeted physical examination (to include at a minimum assessment of general appearance, weight, and vital signs) is required at all other follow-up visits, and at interim visits if 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 Physical Exam CRF will be provided to the site to document the comprehensive physical exam at the Screening and Enrollment Visits and to document the conduct of all targeted physical examinations during follow-up.

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 Pelvic Exam Overview

Pelvic exams are required at all study visits starting with the Screening visit. These exams are necessary to evaluate protocol exclusion criteria, to collect detailed information on baseline vaginal conditions, and to ensure the ongoing safety of study participants during each follow-up visit.

Pelvic exam procedures must be performed in the order shown on the Pelvic Exam checklist and from the area specified on the checklist, if specified (e.g. from the lateral vaginal wall). The order of specimen collection is critical to ensure that first specimens collected do not affect subsequent specimens. Collect specimens away from apparent abnormalities and exclude swabbed areas from subsequent examination. See SSP sections 9.7.8, 9.8.1-9.8.3, and 9.10.1 of this manual for additional details regarding vaginal and cervical samples for PK collection and analysis. The IVR should ideally remain in place during the pelvic exams. There may be instances when inserting the speculum with the ring in place causes discomfort or visually impairs the evaluation; in these instances it is acceptable for the clinician to remove the ring during exams. If applicable, IVR removal and re-insertion during pelvic examination and duration of removal should be documented on the Pelvic Exam Ring Assessment CRF.

Exams During Vaginal Bleeding: Pelvic exams should ideally not be performed if the participant is experiencing vaginal bleeding as this may interfere with visualization of the vagina and cervix, elevate the vaginal pH, affect vaginal PK samples, and complicate interpretation of wet prep findings. However, given the frequency of scheduled exams it is recognized that vaginal bleeding may coincide with some study visits. See below for special circumstances in the event a participant is experiencing her menses or any vaginal bleeding at the time of an exam:

- During screening, if the participant is experiencing any vaginal bleeding, reschedule the exam and associated sample collection to be completed within the 45 day screening window.
- At enrollment, the participant should be rescheduled if any vaginal bleeding is reported or observed on exam. Note per protocol section 7.3, menses should not coincide with a participant's Enrollment visit and ideally Days 1-7; this should be taken into consideration when scheduling enrollment. Every effort should be made to avoid scheduling these visits while participants are on her menses; however, if Days 1-7 study visit take place while participant is on menses, all study procedures and sample collection should continue per participant's comfort level.
- During a scheduled follow-up visit, the pelvic exam and associated sample collection, and vaginal swabs for PK, should still be completed as long as the participant is comfortable. Notify the MTN-028 management team if vaginal bleeding coincides with Days 1-7, or if the participant declines the exam or any sample collection.

- If a participant presents for an interim visit complaining of genital symptoms, perform a pelvic exam to evaluate her symptoms at that time. If she is not comfortable with completing an exam, she should be scheduled to return for a pelvic exam as soon as possible after vaginal bleeding stops.

General Technique:

- Maximize the comfort and privacy of the participant. Position the examination table away from the door or hang a curtain to ensure privacy. Explain what you are doing as you do it. Take as much time as needed to ensure participant comfort and accurate documentation of exam findings.
- 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.
- Use a speculum of appropriate type and size to permit adequate visualization of the vagina and cervix. For most participants, a Graves speculum is preferred to enable visualization of all anatomic areas and tissues. At Screening, record the type and size of the speculum used on the Pelvic Exam Diagrams form for reference at subsequent exams. If during follow-up the speculum type and size changes, site may record the new information on the Pelvic Exam Diagram form. Prior to insertion, ensure that the speculum functions properly and has no rough edges.

8.7.1 Detailed Procedural Instructions for Pelvic Exams

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. While the participant is clothed, explain the procedure to her and answer any questions she may have.

Position the Participant: Drape the participant and establish a comfortable examination position that allows for the perineum and vulva to be inspected. Adjust stirrups and back elevation as needed.

Examine the External Genitalia:

- Do not insert the speculum before examining the external genitalia.
- Relax 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, and perianal area

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, noting any abnormal findings.

Removal of Visual Obstruction: After collection of vaginal and endocervical specimens, any obstruction (e.g., mucus, cellular debris) may be removed using 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. If saline is not available, a swab moistened with water will also suffice.

Examination of the Cervix and Vagina: To complete the naked eye examination of the vagina, slowly withdraw the speculum with the blades moderately open, re-focusing as needed. Alternatively, the speculum may be rotated ninety degrees to allow visualization of the anterior and posterior vaginal walls; retract the speculum away from the cervix and close the blades to rotate.

Perform Bimanual Exam: Required at Screening and Enrollment and when clinically indicated. After completing all of the above-listed tissue examinations and specimen collection and removing the speculum, perform a bimanual exam for adnexal or fundal masses and/or tenderness.

8.7.2 Documentation of Findings

All exam findings (normal and abnormal) should be documented using the non-DataFax Pelvic Exam Diagrams CRF. All abnormal findings must be thoroughly documented (e.g., to include type, size, location, and severity) to ensure appropriate assessment can be provided during the next pelvic exam.

All abnormal findings during screening will be documented on the Pelvic Exam CRF and the Pre-existing Conditions CRF. All abnormal findings identified during follow-up will be documented on the Pelvic Exam CRF and Adverse Experience Log (AE-1) CRF, as appropriate. The results of laboratory test results performed using specimens collected during pelvic exams are recorded on the STI Test Results CRF.

All pelvic exam findings consistent with the “grade 0” column of the FGGT are considered normal. The following also are considered normal:

- anatomic variants
- gland openings
- Nabothian cysts
- mucus retention cysts
- Gartner’s duct cysts
- blood vessel changes other than disruption
- skin tags
- scars
- cervical ectopy

Intrauterine contraceptive device (IUCD) strings may be visible upon exam and are also considered a normal finding. If present, they should be documented on the non-DataFax Pelvic Exam Diagrams form. Sites may determine whether they choose to consistently document the presence of IUCD strings (best practice) or not. It is recommended that if a

participant has an IUCD but the string is not visible upon exam, this be documented and followed up on.

Normally-healing biopsy sites, per clinician’s discretion, including blood expected from the procedure, are considered normal findings. If noted, please document as such on the non-DataFax Pelvic Exam Diagrams form and further information can be added to chart notes. If the biopsy site is not healing normally or there is more blood than expected, per clinician’s discretion, the non-DataFax Pelvic Exam Diagrams form and Pelvic Exam CRF should document the abnormal finding and an AE Log CRF should be completed.

Abnormal findings will be classified according to the state of the epithelium and blood vessels associated with the finding, as follows:

Epithelium

Integrity:

- Intact
- Disrupted:
 - Superficial
 - Deep (complete disruption is considered deep and exposes stroma and possibly blood vessels; a bleeding area is often but not always deep)

Color:

- Normal
- Slightly red
- Red
- White
- Other (includes “pale”)

Blood Vessels

Integrity:

- Intact
- Disrupted

Pelvic exam findings should be documented using terminology corresponding to the FGGT and the study-specific pelvic exam case report forms. For findings in which the finding term marked on the pelvic exam case report form is more specific than the corresponding term on the FGGT, use the more specific term. Figure 8-1 below provides further information to guide and standardize terminology used to describe abnormal pelvic exam findings.

**Figure 8-1
CONRAD/WHO Terminology for Pelvic Exam Findings**

<i>Term</i>	<i>Status of Epithelium</i>	<i>Status of Blood Vessels</i>	<i>Comments</i>
<i>Erythema</i>	<i>Intact</i>	<i>Intact</i>	<i>Distinguished by color (erythema being redder than normal, edema either normal or paler than normal. May be sharp or diffuse.</i>
<i>Edema</i>	<i>Intact</i>	<i>Intact</i>	

Term	Status of Epithelium	Status of Blood Vessels	Comments	
<i>Petechiae</i>	<i>Intact</i>	<i>Disrupted</i>	$\leq 3\text{ mm}$	<i>Color of finding is red or purple.</i>
<i>Ecchymosis</i>	<i>Intact</i>	<i>Disrupted</i>	$> 3\text{ mm}$	
<i>Peeling</i>	<i>Disrupted, superficial</i>	<i>Intact</i>	<i>Fragment of disrupted epithelium may remain attached to the area from which it has peeled off. Generally has well demarcated outline. Underlying epithelium looks normal</i>	
<i>Ulcer</i>	<i>Disrupted, superficial or deep</i>	<i>Intact or disrupted</i>	<i>May include sloughing at base. Generally round or oval with sharply demarcated outline. Superficial ulcers are more accurately called erosions.</i>	
<i>Abrasion</i>	<i>Disrupted, superficial or deep</i>	<i>Intact or disrupted</i>	<i>Distinguished from other findings in this class by diffuse or poorly demarcated outline.</i>	
<i>Laceration</i>	<i>Disrupted, superficial or deep</i>	<i>Intact or disrupted</i>	<i>Sharply demarcated linear finding. Includes fissures. Lacerations appear to be the result of trauma. Fissures appear to be linear “pulling apart” or wearing away of tissue.</i>	

Note: Superficial epithelial disruption does not penetrate into subepithelial tissue. Deep epithelial disruption penetrates into and exposes the subepithelial tissue and possibly blood vessels. If bleeding from the finding is present, the disruption is often but not always deep.

8.9 STI/RTI/UTI Evaluation, Management and Treatment

Clinical and laboratory evaluations are performed in MTN-028 to diagnose the following STIs and RTIs:

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

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): Suspected UTIs may be clinically managed based solely on the presence of symptoms indicative of a possible UTI, including the following:

- 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

Urine dipstick may be performed per site SOP, but sites are expected to send a urine culture for definitive diagnosis when a UTI is suspected. The results of the urine culture do not need to be returned before presumptive treatment, but the results of the culture will influence how the AE is captured. When the participant initially reports symptoms suggestive of a urinary tract infection, capture each symptom as a separate AE. If urine culture results are positive, update the AE CRFs to reflect a single AE for grade 2 Urinary Tract Infection per UTI criteria defined in the FGGT. If urine culture is negative, the AE (s) will remain reported as symptoms only. Record the results of any dipsticks performed on the Safety Laboratory Results CRF; urine culture results must be documented in chart notes and/or other site-specific source documents.

Note that urine dipstick testing is required at screening and Day 28/Visit 9.0. Document results (protein, glucose, LE, and nitrites) on the Safety Laboratory Results CRF. At the screening visit, positive dipstick results do not directly impact eligibility, but abnormal protein and glucose parameters should prompt further evaluation or consideration pending IoR review. Abnormal protein and glucose uncovered at the screening visit should be captured on the Pre-Existing Log CRF. In follow-up, findings of abnormal protein and glucose on the dipstick should be reported on the AE log CRF as indicated. Grade the severity of the urine glucose value according to the "Proteinuria, random collection" row of the Toxicity Table. Note that findings of LE/nitrites are not gradable per the DAIDs toxicity table, and like other non-gradable labs should not be reported as pre-existing conditions or AEs.

STI/RTIs will be treated in accordance with current CDC guidelines available here: <http://www.cdc.gov/std/treatment/> and site SOPs.

When clinically appropriate, investigators should use oral or parenteral medications when at all possible to avoid intravaginal medication use. Observed single dose treatment should be provided whenever possible, per clinician discretion.

8.10 Clinical and Product Use Management

Protocol Section 9 provides detailed guidance on clinical and product use management, including general criteria for product hold and discontinuation (Section 9.3), guidance on product hold and discontinuation in response to observed AEs (Section 9.4), management of other clinical events (Sections 9.5), HIV infection (Sections 9.6), pregnancies (Section 9.7), and early study termination (Section 9.8).

All specifications of protocol Sections 6 and 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. Conditions requiring product hold or permanent discontinuation are summarized in Figure 8-1 below. Flow charts for product

use management are available in the study implementation materials section of the MTN-028 webpage.

The protocol specifies that a hold should be initiated should a participant report prohibited medication use. When possible, treatment options that are not prohibited by the protocol should be pursued; however, clinical management of the participant should be prioritized if alternative treatment is not available. Product use may be resumed when use of the prohibited medication has ended. Consult the PSRT regarding the timeframe for product resumption in the event that a single dose prohibited medication is used. Note that in addition to protocol outlined prohibited medications, study product should be held in response to reported use of PEP or PrEP, and the PSRT should be notified.

Note that per protocol, product should be temporarily held in response to grade 3 unrelated AEs and the PSRT should be notified. Sites are encouraged to request a quick response in the body of the email in these cases, to minimize potential unnecessary time off product.

All clinical and product use management must be fully documented in participant study records. When the PSRT is consulted in relation to clinical and product use management, completed PSRT query forms (including a response from the PSRT) must be printed and filed in participant study records. Unless otherwise specified in protocol section 9, the IoR/designee should immediately consult the PSRT for any product holds, for further guidance on resuming study product, continuing the hold temporarily, or progressing to permanent discontinuation of study product. Product holds and discontinuations must be communicated to site pharmacy staff using the Vaginal Ring Request Slip, as described in Section 7 of this manual. Product holds and discontinuations also must be documented on Product Hold/Discontinuation CRFs.

Following temporary holds or permanent discontinuation from study product, some study procedures will be modified or discontinued. See SSP sections 4.5.5 to 4.5.9 for details.

Figure 8-1
Conditions Requiring Product Hold or Permanent Discontinuation

Condition	Temporary Hold	Permanent Discontinuation
Report of use of prohibited medications and medications to be avoided (including the use of PEP/PrEP) as described in protocol Section 6.6	X	
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.	X*	
Exposure to or acquisition of HIV infection		X
Pregnancy		X
Breastfeeding		X
Grade 3 AE unrelated to Study Product not addressed in Section 9.5	X	
Grade 3 AE related to Study Product not addressed in Section 9.5		X
Grade 4 AE not addressed in Section 9.5 (regardless of relationship)		X

Condition	Temporary Hold	Permanent Discontinuation
Superficial epithelial disruption (abrasion/peeling) which has worsened after re-evaluation in 3-5 days	X	
Deep epithelial disruption (ulceration)	X	
Symptomatic, localized erythema or edema (area <50% of vulvar surface or combined vaginal and cervical surface) which has worsened after re-evaluation in 3-5 days	X	
Asymptomatic, localized erythema or edema (area <50% of vulvar surface or combined vaginal and cervical surface) which has worsened after re-evaluation at the next scheduled visit	X	
Generalized erythema or severe edema (area >50% of vulvar surface or combined vaginal and cervical surface)	X	
Unexpected genital bleeding due to deep epithelial disruption	X	
Vaginal ring has been out for longer than three consecutive days		X
Participant has missed more than three consecutive study visits		X

See Protocol Section 9 for complete guidelines on clinical management and study product holds.
 *After consultation with PSRT, participants may progress to permanent discontinuation from study product.

8.11 Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-028. Please also refer to Section 8 of the MTN-028 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) (DAIDs Toxicity Table)
- Addendum 1, Female Genital Grading Table for Use in Microbicide Studies dated December 2004 (FGGT)
- 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 VCV (MK-4176) IVR and MK-2048A IVR

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.

For MTN-028, the ICH-E6 definition is applied to all participants in all study groups, beginning at the time a participant is randomized through when they terminate from the study. Study staff must document all AEs reported by or observed in study participants,

regardless of severity and presumed relationship to study product on Adverse Experience Log (AE-1) case report forms (CRF).

Ongoing medical conditions, problems, signs, symptoms, and findings identified prior to random assignment are considered pre-existing conditions. Such conditions should be documented on the Pre-Existing Conditions case report form. If a pre-existing condition worsens (increases in severity or frequency) after randomization, the worsened condition is considered an AE. If a pre-existing condition resolves after randomization, but then recurs at a later date, the recurrence is considered an AE.

Each site's SOP for source documentation 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 (SAEs) / Expedited Adverse Events (EAEs)

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

- Results in death,
- Is life-threatening,
 - NOTE: The term "life threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. A grade 4 severity grading on the Toxicity Table does not necessarily mean that an event is life-threatening. For example, when determining whether a grade 4 laboratory event meets the ICH definition of "life threatening", consider the event in the context of any related symptoms the participant may have experienced.*
- Requires in-patient hospitalization or prolongs an existing hospitalization,
 - The following types of hospitalizations are not considered Adverse Events, serious or otherwise:*
 - *Any admission unrelated to an AE (e.g., for labor/delivery)*
 - Admission for diagnosis or therapy of a condition that existed before randomization AND has not increased in severity or frequency since baseline.*
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Important medical events 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 above

ICH guidance (E2A) also states that medical and scientific judgment should be exercised in deciding whether other adverse events not listed above should be considered serious.

SAEs are a subset of all AEs. For each AE identified in MTN-028, an authorized study clinician must determine whether the AE meets the definition of SAE. The Adverse Experience Log CRF includes an item (item 8) to record this determination.

All AEs that meet the definition of “serious” (SAEs), regardless of relationship to study product, are expedited adverse events (EAE). EAEs require additional reporting for rapid review and assessment by DAIDS.

8.11.3 Reporting Adverse Events in an Expedited Manner (EAE Reporting)

Expedited Adverse Events (EAEs) should be reported per the Manual for Expedited Reporting of Adverse Events to DAIDS, version 2.0; January 2010. For MTN-028, the “SAE (Serious Adverse Event) Reporting Category” will be used to report EAEs.

All EAEs must be reported to the DAIDS Regulatory Support Center (RSC) using the internet-based DAIDS Adverse Experience Reporting System (DAERS). All EAEs must be reported within three reporting days of site awareness of the EAE.

All EAEs must also be reported on the AE Log CRF. The AE Log case report form includes an item to record if the AE is also being reported as an EAE. When completing AE Log CRF and DAERS report or EAE form, 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 EAEs submitted to the DAIDS Safety Office will be compared with AE Log CRFs 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. If an EAE that was previously reported to the DAIDS RSC resolves and then later recurs at a level requiring expedited reporting, the second occurrence must be reported as a new EAE report (and a new AE-1 CRF, if not already completed).

8.12 Adverse Event Terminology

Study staff must assign a term or description to all AEs identified in MTN-028. The guidance below should be followed when assigning AE terms/descriptions:

- Whenever possible, a diagnosis should be assigned. Document associated signs and/or symptoms related to a diagnosis in the comments section of the AE Log CRF.
- 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 identified and documented as an individual AE.
- Whenever possible, use specific terms to indicate the anatomical location of the AE (e.g., “vaginal” instead of “genital” or “uterine cervix” instead of “cervical”).
- Use medical terms (e.g. “ulcers” instead of “sores”)
- Ensure correct spelling
- Do not use abbreviations, unless the abbreviations are for accepted laboratory findings (e.g. “AST increased”, “SGOT decreased”)

Procedures per se should not be reported as adverse events; rather the underlying condition which leads to a procedure may be considered an adverse event. Any associated procedures may be considered treatments for the adverse event. For example, while “appendectomy” would not be considered an adverse event, “appendicitis” would, with “appendectomy” documented as a treatment provided for the adverse event. In addition, any event that occurs as a result of a study-related procedure should be recorded as an AE. Specify in AE text description (item 1) if the AE is related to a procedure (iatrogenic). For example, if a participant experiences cervical bleeding that is more than expected as a result of the

cervical biopsy, then “cervical bleeding due to cervical biopsy” should be submitted as an AE. “Cervical bleeding” maps to “Reproductive system and breast disorders” System/Organ Class (SOC) whereas “Cervical bleeding due to biopsy” maps to “Injury, Poisoning, and Procedural Complication” SOC.

Do not include information on relatedness to study product or timing of study product use in the AE term/description if the AE is **not** due to the act of study ring insertion or removal. Limit the AE text to the medical description and anatomical location, when needed. Including text such as “after ring insertion” or “at site of ring placement” affects the way the AE will appear in safety reports.

When reporting AEs which are due to ring removal or insertion, please follow the guidance below:

- If the AE is **due to the act** of study ring insertion or removal, include this information in item 1. For example, use AE text of “pelvic pain due to ring removal” or “vulvar laceration due to ring insertion” rather than just “pelvic pain” or “vulvar laceration.”

It is important to clearly identify in item 1 AEs that are **due to the act** of study ring insertion or removal, as these AEs are assigned unique coding terms within the standardized MedDRA coding system.

If the AE is **not due to the act** of study ring insertion or removal, do not include mention of the ring in item 1 or in the Comments section of the AE log CRF when providing rationale for relationship to study product.

- If text is present in the “Comments” field that the AE is due to the act of ring insertion or removal, this same text needs to be in item 1. If not, this may result in a Clinical Query asking that this information be added to item 1 so that the AE is described completely and accurately.

When reporting an AE that is associated with an underlying condition, include the underlying condition in the AE term or description. For example, if a participant is experiencing pain related to an underlying cancer diagnosis, include the cancer diagnosis in the AE term or description.

8.12.1 Reporting Genital, Genitourinary, and Reproductive System AEs

- Vaginal Discharge: Vaginal discharge by participant report and vaginal discharge as observed by the clinician should be graded per the appropriate rows in the FGGT. The verbatim term from the FGGT should be used to distinguish if vaginal discharge was clinician observed versus participant reported.

** Note – if vaginal discharge is present both by history and on examination, only report the one with the most severe grade. (Grade 3 and 4 vaginal discharge is listed as “NA” in the FGGT.) If they are the same grade, report ‘vaginal discharge by participant report’ as the AE term.

Vaginal bleeding: For MTN-028, the following types of genital bleeding events are reportable as adverse events on an AE Log CRF:

- each new instance of heavy or prolonged menstrual bleeding, intermittent vaginal bleeding, or unexplained infrequent vaginal bleeding (as compared to the participant’s baseline), unless judged to be related to a participant’s contraceptive use
- postcoital bleeding (bleeding associated with sexual intercourse) if not present at baseline

New events of infrequent bleeding during follow-up for unknown reasons or delay of menses for more than one month should be documented on an AE Log CRF using the appropriate term below:

- For missed menses events of 1-3 months in duration, use the term “missed menses”
- For missed menses events of 4-5 months in duration, use the term “oligomenorrhea”
- For missed menses events of 6 months or longer, use the term “amenorrhea”

If the newly-identified bleeding episode is determined to be different from her baseline (i.e. longer, heavier, more/less frequent) and not related to her current contraceptive method, record the episode on an Adverse Experience Log CRF. Grade and term the episode per the applicable “Abnormal Uterine Bleeding Unrelated to Pregnancy” or the “Unexplained Infrequent Bleeding” row of the DAIDS Female Genital Grading Table (menorrhagia, metrorrhagia, or postcoital bleeding). Note that *shorter* than baseline menses is not included in the FGGT, and should not be considered an adverse event.

Note that IVR use can continue in the presence of unexplained genital bleeding per the clinician’s discretion, but ongoing events should be further investigated by a pelvic exam. If evaluation determines bleeding is due to deep epithelial disruption, the IVR should be held per protocol section 9.5.

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.

- Bleeding associated with speculum insertion and/or 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 AE. For example, Monsel’s discharge and/or minimal bleeding related to specimen collection should not be considered an AE. 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.
- If both Menorrhagia and Metrorrhagia are present, a single adverse event should be reported as “Menometrorrhagia” and graded per the Menorrhagia row of the FGGT.
- 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.

STI/RTI

The following terminology should be used only if STI diagnosis is based on clinical evaluation and confirmed, when appropriate/possible, by laboratory result(s). For example, symptomatic bacterial vaginosis and symptomatic vulvovaginal candidiasis should not be reported as AEs based on participant symptoms alone.

- **Bacterial vaginosis**: Only report symptomatic infections that are confirmed with saline wet mount testing and fulfilling Amsel’s criteria (see section 9.7.2 of this manual for definition of criteria) as AEs, using the term “symptomatic bacterial vaginosis.”
- **Candidiasis**: Only report symptomatic infections that are confirmed with KOH wet prep and/or culture as AEs, using the term “vulvovaginal candidiasis.”
- **Chlamydia**: Report all infections using the term “genitourinary chlamydia infection.”
- **Gonorrhea**: Report all infections using the term “genitourinary gonorrhea infection.”
- **Suspected genital herpes outbreaks**: Because herpes testing is not required in MTN-028, each suspected genital herpes outbreak should be reported using the term marked on the Pelvic Exam CRF describing the lesion together with the anatomical location (e.g., vulvar ulceration, vaginal blister).
- **Genital herpes**: Use the criterion for diagnosing genital herpes per the FGGT. Note that laboratory testing is required in order to use the term “genital herpes” for AE reporting. Such testing is not required per protocol and should only be done if clinically indicated. Any new lesion/ulcer observed during the study should be reported as an AE even if it thought to be due to prior herpes diagnosis/infection.
- **Genital warts**: Report all outbreaks of genital warts as AEs, regardless of whether infection with HPV was known to be pre-existing before enrollment/randomization. Report the AE using the term “condyloma” and include the anatomical location of the

warts (e.g., cervical, vaginal, vulvar, perianal). Grade according to the “Condyloma” row of the FGGT.

- **Syphilis:** Per the FGGT, a Grade 2 Syphilis adverse event is defined as a positive treponemal test along with a positive non-treponemal test and no previous treatment OR a four- fold rise in titer on the non-treponemal test after previous treatment regardless of symptoms or non-oral lesions positive by darkfield exam for treponemes. Report all syphilis adverse events, using the term “syphilis infection” (no anatomical location is required when reporting syphilis infections). Contact the MTN-028 PSRT in the event a participant has a positive treponemal test and a negative non-treponemal test as this could represent late latent syphilis.
- **Trichomoniasis:** Report only Grade 2 infections per FGGT, using the term “vaginal trichomoniasis”. Trichomoniasis may be diagnosed by positive wet mount, culture, PCR, rapid Trichomoniasis or other licensed test (excluding Pap smear), showing *T. vaginalis*, regardless of symptoms.

In the absence of a laboratory-confirmed STI or RTI diagnosis, use the term “vulvovaginitis” when 2 or more of the genital/vaginal signs or symptoms listed below are present. Comment on the individual signs/symptoms in the “Comments” field of the AE Log CRF.

- pain
- itching
- erythema
- edema
- rash
- tenderness
- discharge

Similarly, use the term “cervicitis” when 2 or more of the genital/vaginal signs or symptoms listed below are present in the absence of a laboratory-confirmed STI/RTI. Comment on the individual signs/symptoms in the “Comments” field of the AE Log CRF.

- dyspareunia
- erythema
- edema
- tenderness
- discharge

8.12.2 Reporting Abdominal Pain as an AE

When reporting abdominal pain as an AE, pain that is gastrointestinal in nature must be differentiated from pain that is genitourinary or reproductive in nature.

If abdominal pain is assessed as gastrointestinal in nature and no other overarching or unifying diagnosis is available, the term “abdominal pain” or “lower abdominal pain” should be used on item #1 on the AE Log CRF.

If the pain is assessed as genitourinary and a specific anatomic location is known, the term reported on the AE Log CRF should be described as such (i.e., “bladder pain” or “adnexal tenderness”).

If the pain cannot be localized to a specific organ but it believed to be gynecologic in origin it should be described on the AE Log CRF using the term “pelvic pain”

8.12.3 Reporting Laboratory Abnormalities as AEs

If an abnormal laboratory test result is reported as an AE, separate from any clinical diagnosis associated with the result, the type of test performed and the direction of the abnormality should be reported (e.g. elevated ALT). The specific value or the severity grade of the result should not be reported as part of the AE term. Laboratory values that fall outside of a site’s normal range but are below severity grade 1 are not considered AEs. These out of range but below grade 1 values are not documented as pre-existing conditions or adverse events on the PRE-1 CRFs unless requested by the Investigator of Record (IoR) or designee. When assigning severity grades, note that some sites may have normal reference ranges that overlap with the severity grade ranges. Thus, it is possible for a participant to have a result that falls within the site’s normal range, but is still gradable per the Toxicity Table. Assign the severity grade based on the Toxicity Table severity grade ranges, regardless of whether or not the lab result falls within the site’s normal reference range.

The IoR or designee should carefully review all laboratory abnormalities relevant to the participant’s health 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 the source documentation. Results of protocol-specified local laboratory results will also be reported on the Laboratory Result DataFax CRF. Sites should document other results if any, in visit chart note, or in other designated site-specific documents. Through the participant’s study involvement, lab abnormalities that meet the criteria for expedited reporting to DAIDS will be reported separately on the AE Log CRF and reported to DAIDS via the DAERS Reporting System.

8.12.4 HIV and AE Reporting

HIV infection is not included in the DAIDS Toxicity Table, and is not considered an AE for data collection or reporting purposes. Thus, if a participant seroconverts during study participation, HIV infection should not be reported as an AE or written anywhere on an AE Log CRF.

However, primary HIV infection is often symptomatic. If a participant seroconverts and develops one or more signs or symptoms of acute HIV-infection, it is appropriate to report each sign and symptom (e.g. fatigue, pharyngitis) as a separate AE on its own AE log CRF. If item 5 is marked ‘not related’, record ‘due to alternative etiology’ as the rationale in the Comments section of the AE log CRF. Do not write “HIV” or “HIV infection” anywhere on the AE Log CRF.

8.13 Adverse Event Severity Grading

The term severity is used to describe the intensity of an AE. The severity of all AEs identified in MTN-028 must be graded on a five-point scale:

- Grade 1 = Mild
- Grade 2 = Moderate

- Grade 3 = Severe
- Grade 4 = Potentially life-threatening
- Grade 5 = Death

Severity is not the same as seriousness, which is based on the outcome or action associated with an event, as described in Section 8.1.3.

The severity of all AEs identified in MTN-028 will be graded using:

- DAIDS Female Genital Grading Table for Use in Microbicide Studies (FGGT)
- If not identified there, the DAIDS Table for Grading Adult and Pediatric Adverse Events (Toxicity Table), dated December 2004 (Clarification dated August 2009) will be utilized.

The DAIDS Toxicity Tables can be accessed on the DAIDS RSC web site (<http://rsc.tech-res.com/safetyandpharmacovigilance/>).

AEs listed in both the FGGT and the Toxicity Table should be graded according to the FGGT. AEs not listed in the FGGT should be graded according to the Toxicity Table. AEs not listed in the FGGT or the Toxicity Table should be graded according to the “estimating severity grade” row of the Toxicity Table.

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

- Genital petechiae and genital ecchymosis should be considered Grade 1 as neither requires treatment.
- If the severity of an AE falls into more than one grading category on the Toxicity Table, assign the higher of the two grades to the AE.
- If a single AE term is used as a unifying diagnosis to report a cluster of signs and symptoms, and the diagnosis is not specifically listed in the Toxicity Table, assign the AE the highest severity grade among each of the associated signs and symptoms. Record the diagnosis as the AE term and record each associated sign and symptom in the AE Log comments section.
- Seasonal allergies should be graded according to the “Estimating Severity Grade” row of the Toxicity Table (not the “acute systemic allergic reaction” row).
- When grading using the “general infection” row of the Toxicity Table, note that if the condition requires systemic antimicrobial treatment, it must automatically be graded at Grade 2 or higher.
- When the participant initially reports symptoms suggestive of a urinary tract infection, capture each symptom as a separate AE. Once the culture results are available, update the AE CRFs to reflect a single AE for ‘Urinary Tract infection’ if the laboratory evaluation meets UTI criteria defined in the FGGT.
- Grade the severity of the urine glucose value according to the “Proteinuria, random collection” row of the Toxicity Table.
- It is preferable that abnormal Pap smear findings are reported and graded based on results of a biopsy, using the “Intraepithelial Neoplasia by biopsy” row of the FGGT (below). However, if further evaluation of the Pap smear finding is not performed, or is scheduled to be performed at a later date, then abnormal Pap smear findings that represent an increase in severity should be reported as AEs and graded according to the “Pap” row of the FGGT (see below).

Note: Atypical glandular cells (AGC) and AGC-favor neoplastic are not specifically mentioned in the “Pap” row, but should be assigned severity grades 1 and 2, respectively.

If a biopsy is performed at a later date, update the AE-1 CRF to indicate the results of the biopsy (item 1 - AE Diagnosis) and update the severity grade (item 3), as appropriate, per the “Intraepithelial Neoplasia by biopsy” row of the FGGT.

8.14 Adverse Event Relationship Assessment

One of the following relationship categories must be assigned to each AE:

- **Related:** There is a reasonable possibility that the AE may be related to the study product.
- **Not related:** There is not a reasonable possibility that the AE is related to the study product.

When assessing relationship, the study products that should be considered are the two study drugs and the vaginal ring. Any AEs thought to be related to the vaginal ring should be documented as such by choosing “related” and using descriptive text, to indicate that the presumed relationship is with the ring. For example, if the ring stretched the vaginal introitus in the process of insertion and caused a laceration, then the AE should be assessed related to study product and reported as such. However, if the AE cannot be directly attributable to the ring (e.g. fingernail scratch during ring insertion) the AE should be assessed not related to the study product.

Please note that when no other etiology for the event is apparent, the relationship does not automatically default to “related”. There must be at least a reasonable possibility of a causal relationship.

Study staff should provide a reason for their determination of the relationship of the AE to the study product in the “Comments” section of the AE Log CRF. If new information becomes available, the relationship assessment of any AE should be reviewed again and updated as required. When recording an AE that is the result of a study-related procedure, mark the “Relationship to study product” as “Not Related” and provide an explanation in the “Comments” section that the event is a ‘result of a study-related procedure’.

8.15 Adverse Event Outcomes and Follow-Up Information: During Study Participation

All AEs identified in MTN-028 must be followed clinically at each scheduled visit until they resolve (return to baseline) or stabilize (persist at the same severity grade above baseline for 1 month).

At each follow-up visit, an authorized study clinician should review all previously identified ongoing AEs and evaluate and document its current status. Outcomes must also be reported on the AE Log case report form. In many cases, the final outcome of an AE will not be available when the AE Log CRF is first completed and faxed to DataFax. In such cases, the form should be updated when the final outcome becomes available and re-faxed to DataFax at that time.

As noted above, “resolution” of an AE is generally defined as returning to the condition or severity grade that was present at baseline (i.e. at the time of randomization) and

“stabilize” is defined as persistence at a certain severity grade (above baseline) for one month. For clinical events that are AEs, clinical management and follow-up of the AE should proceed per the specifications of section 9 of the protocol. If, however, a clinical AE is not addressed in section 9 of the protocol, at a minimum, follow-up evaluations should be performed at scheduled study visits until resolution or stabilization has been documented. More frequent evaluations may be performed at any time if required to properly monitor and/or manage participant safety, at the discretion of the IoR or designee. It is acceptable for AE follow-up/evaluation to be conducted over the phone, as clinically appropriate.

If an AE increases in severity or frequency (worsens) after it has been reported on an AE Log CRF, it must be reported as a new AE, at the increased severity or frequency, on a new AE Log CRF. In this case, the outcome of the first AE will be documented as “severity/frequency increased” and the new AE page number should be recorded. The outcome date of the first AE and the onset date of the new (worsened) AE will both be the date upon which the severity or frequency increased.

8.16 Adverse Event Outcomes and Follow-Up Information: After Study Termination

All AE Log forms completed for each participant should be reviewed at the Day 35 Final Clinic Visit/Termination visit to confirm they were evaluated by qualified and designated staff, and that the relationship status, AE grade, and outcome are accurately documented in the participant record. For AEs that are ongoing at the termination visit, the status/outcome of the AE should be updated to “continuing at end of study participation” and the AE Log CRF should be re-faxed to DataFax.

A subset of AEs must be followed after a participant's termination visit. AEs that require reassessment after the participant's termination visit include the following:

- AEs that are found to have increased in severity at the termination visit
- AEs deemed related to study product
- All Grade 3 or higher AEs that are ongoing at the termination visit
- SAEs/EAEs

The IoR or designee must establish a clinically appropriate follow-up plan for the AE. At a minimum, the AE must be re-assessed by study staff within 30 days after the termination visit; additional evaluations also may take place at the discretion of the IoR or designee.

For AEs that are continuing at the termination visit but do not meet the criteria above, it is left to the discretion of the IoR or designee as to whether the AE needs to be followed. Sites may notify the Protocol Safety Physicians (mtn028safetymd@mtnstopshiv.org) team for guidance in such situations. The requirements for submission of follow-up information on EAEs are specified in Section 4.3 of the *Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0 dated January 2010)*.

If not resolved or stabilized at the time of reassessment, additional assessments should occur at the following frequency:

- If the study is ongoing, continue to reassess at least once per month while the study is ongoing until resolution/stabilization
- If the entire study has ended (not only participant participation), all AEs requiring reassessment will be re-assessed at least once within 30-60 days after the study end date. The site is to send an informational query regarding the case to the PSRT at the

time of reassessment. The MTN-028 PSRT also may advise on whether any additional follow-up is indicated on a case by case basis.

For AEs that are re-assessed after the termination visit, information on the status of the AE at the time of re-assessment will be recorded in chart notes, and may be communicated to the PSRT, if applicable; however, no updates should be made to any case report forms based on the re-assessments.

8.16.1 Reporting Recurrent Adverse Events

If an AE previously reported on an AE CRF resolves and then recurs at a later date, the second occurrence must be reported as a new AE on a new AE CRF.

8.17 Social Harms

In addition to medical AEs, participants may experience social harms — non-medical adverse consequences — as a result of their participation in the 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. Social harms will also be reported on a Social Impact log CRF. The IoR will report any social harm, in his/her judgment, to be serious or unexpected to the PSRT and IRB according to local requirements. For example, social harms that result in serious adverse events (SAEs) should be considered ‘serious or unexpected’. Social harms that are not SAEs may also be considered serious or unexpected, for example serious threats of physical harm, significant psychological duress, or discontinued provision of food, housing or financial support. Determination of whether a social harm is serious or unexpected is ultimately based on the discretion of the investigator; the MTN-028 PSRT can always be consulted as needed. Study sites may engage their Community Advisory Boards in exploring the social context surrounding instances of social harm.

Prior to study initiation, study staff teams at each site should discuss as a group what issues and problems are most likely to be encountered by participants at their site, and should agree upon how these issues and problems should be handled if reported. Roles and responsibilities should be defined for all staff members, such that each staff member is aware of what actions he/she can appropriately take, and what actions should be referred to other members of the team.

During study implementation, staff teams at each site should continue to discuss actual participant experiences, successful and unsuccessful response strategies, and other lessons learned among themselves and with community representatives. Based on these discussions and lessons learned, procedures for responding to issues and problems should be reassessed and updated as needed throughout 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.
- 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.
- 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.
- If the reported social harm is associated with an AE, report the AE on an AE Log CRF. If the social harm is associated with an AE that meets criteria for expedited reporting to the DAIDS RSC, report it as an EAE. Also report the issue or problem to all IRBs/ECs responsible for oversight of MTN-028, if required per IRB/EC guidelines.
- Consult the Protocol Safety Review Team (PSRT) for further input and guidance as needed. As is the case with medical AEs, data collected on social harms will be monitored by the PSRT.

8.18 Safety Distributions from DAIDS

Study sites may receive product- and safety-related information throughout the period of study implementation. This information will be distributed by DAIDS, through its RSC and/or the MTN Coordinating and Operations Center, and may include:

- Updated Investigators Brochures
- IND Safety Reports
- Other safety memoranda and updates

Each distribution will include a cover memo providing instructions on how the document is to be handled. In all cases, a copy of the distribution must be filed in on-site essential document files. Also in all cases, study staff responsible for clinical oversight of study participants should be made aware of any newly available safety information. In many cases, the distribution will need to be submitted to site IRBs/ECs. Safety distributions do not require IRB/EC approval; however acknowledgement of receipt is desirable. Submission letters/memos for IRB/EC submissions should specify the name and date of all documents submitted.

8.19 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN-028 protocol for a complete description of the participant safety monitoring procedures in place for MTN-028. Section 14 of this manual is a reference for a description of the reports prepared by the MTN SDMC in support of MTN-028 safety monitoring procedures.

Participant safety is of the utmost importance in MTN-028. Primary safety monitoring and safeguarding of individual study participants is the responsibility of study staff, under the direction of the IoR. The IoR and designated study staff also are responsible for submitting case report forms to the MTN SDMC and EAE reports to the DAIDS 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 (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. In addition, Protocol Safety Physicians may contact site staff directly, if needed, for additional clarification of safety data.

- The DAIDS RSC, DAIDS RAB Safety Specialist, and DAIDS PSB Medical Officers will review all EAE Forms received for MTN-028 and follow up on these reports with site staff, the MTN-028 Protocol Team, and drug regulatory authorities when indicated.
- The Protocol Safety Review Team (PSRT) will routinely review safety data reports prepared by the SDMC for the study. The PSRT will meet monthly conference call to discuss cumulative study safety data and any potential safety concerns.
- The MTN Study Monitoring Committee (SMC) also will conduct interim reviews of study progress, including rates of participant accrual and retention, completion of study endpoint assessments, study or lab issues, and in a closed report, safety data by arm of the study. 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 sites in significant ways. These decisions are based on a detailed review of the available study data and careful consideration of ongoing participant safety.

Section Appendix 8-1 MTN-028 Protocol Safety Review Team Plan

Roles and Responsibilities of the PSRT

The roles and responsibilities of the MTN-028 Protocol Safety Review Team (PSRT) are to:

1. 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 and MTN Study Monitoring Committee (SMC) as appropriate.
2. Respond to queries regarding product use management including temporary hold or permanent discontinuation of study product.

The protocol specifies a number of situations in which study product use should be temporarily held, permanently discontinued and/or resumed; designated site staff may implement these holds, discontinuations, and/or resummptions in the absence of consultation with the PSRT. In other situations, however, product use management must be undertaken in consultation with the PSRT. (Protocol Section 9.3 and 9.4)

3. Respond to queries regarding adverse event (AE) assessment, reporting, and/or management.
4. Respond to investigator notification of participant withdrawal from the study
5. Respond to queries regarding study eligibility, participant evaluability, and/or re-joining of study participant's which previously withdrew consent (Protocol Section 9.8)

PSRT Composition

The following individuals comprise the MTN-028 PSRT:

- Albert Liu, Protocol Chair, San Francisco IoR
- Katie Bunge, MTN Protocol Safety Physician
- Devika Singh, MTN Protocol Safety Physician
- Ken Ho, MTN Protocol Safety Physician
- Jeanna Piper, DAIDS Medical Officer (MO)
- Jenny Tseng, SDMC Clinical Affairs Safety Associate (CASA)

Ideally, all members of the PSRT will participate in routine conference calls. At a minimum, the DAIDS Medical Officer (or designee if DAIDS MO is not available), the Protocol Chair, a MTN Safety Physician, must take part in all calls to reach quorum.

If these members are not present, the call may be deferred until the next scheduled call time unless a PSRT member requests an immediate call. MTN LOC (FHI 360) Clinical Research Managers, SDMC Project Managers, Statistical Research Associates, and Site Investigators and study coordinators may attend PSRT calls as observers and/or discussants.

PSRT Communications

A group email address (mtn028psrt@mtnstopshiv.org) will be used to facilitate communication with the PSRT. All PSRT communications will be sent to this email address.

Site consultation with the PSRT will be facilitated using the MTN-028 PSRT Query Form, which is available in the Study Implementation Materials section of the MTN-028 web page. Site staff will email completed query forms to the Protocol Safety Physicians (mtn028safetymd@mtnstopshiv.org) who will work with the PSRT to prepare a consensus response to the query, and then email the final response to the site. This process is expected to occur within three business days. When necessary, site requests for responses within one business day can usually be accommodated. All members of the PSRT are encouraged to review the information provided by the site in the query form and to contribute to the response; however, final determination rests with the Protocol Chair(s).

An emergency safety telephone number (1-412-641-8947) is also available to site staff. This telephone is carried by the Protocol Safety Physicians 24 hours a day, seven days a week. It is intended for use in emergencies only, in which immediate consultation with a Protocol Safety Physician is needed. If the Safety Physician does not answer, a voicemail should be left with the call back number. Questions that can wait for email communication should be handled using the PSRT query process described above.

To document calls made to the emergency safety telephone number, near the time of the call (either before or after) site staff will complete the site section of the MTN-028 Emergency Phone Contact form (available in the Study Implementation Materials section of the MTN-028 web page) and email the form to the Protocol Safety Physicians. Within 24 hours after the call, the responding Protocol Safety Physician will complete the remainder of the form and email the completed version to site staff, copied to the study Management Team.