

Section 10. Clinical Considerations

This section presents information on the clinical procedures performed in MTN 001. Further clinical considerations related to participant safety monitoring and adverse event reporting are provided in Section 11. Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in Section 12. Instructions for completing data collection forms associated with clinical procedures are provided in Section 13.

10.1 Baseline Medical/Menstrual/Genitourinary History and Ascertainment of Concomitant Medications

A focused baseline medical/menstrual/genitourinary history is obtained from potential study participants at the Screening and Enrollment Visits. Medications used by the participant are also ascertained and documented at this time. Any updated information is obtained at all follow-up visits. The purpose for obtaining this information during screening and enrollment is to:

- Assess and document participant eligibility for the study
- Assess and document the participants' baseline medical conditions and symptoms, for comparison with signs, symptoms, and conditions that may be identified or reported during follow-up
- Monitor any potential AEs associated with the use of the product during the course of the study

10.1.1 Focused Baseline Medical/Menstrual/Genitourinary/Genitourinary History

The non-DataFax MTN 001 Baseline Medical and Menstrual History form is a recommended source document for collecting pertinent baseline medical/menstrual history data. This form will be available to sites via Word format upon request. Sites may adapt the form for local use, taking into consideration local methods of capturing medical and menstrual history information. Alternative site-specific history forms also may be used.

The Baseline Medical and Menstrual History form is initially completed at the Screening Visit. It is reviewed and updated at the participant's Enrollment Visit in order to capture any medical events occurring between the Screening and Enrollment visits. In addition, at the Enrollment Visit, the Baseline Genital Symptoms form is administered to the participant. This form is used to collect data on genitourinary symptoms, including intermenstrual bleeding/spotting, that the participant reports experiencing since her last Screening Visit.

For enrolled participants, all baseline conditions identified as ongoing at the time of the Enrollment Visit are documented on the (DataFax) Pre-existing Conditions form. This includes ongoing medical conditions captured in Section E of the Baseline Medical and Menstrual History form as well as any ongoing genital symptoms recorded on the Baseline Genital Symptoms form. Recurring and/or chronic conditions are considered ongoing whether or not they are present/active at baseline (e.g. headaches, asthma).

When obtaining a focused baseline medical/menstrual history for MTN 001, it is not necessary to document the participant's lifetime medical history. Rather, focus on conditions and symptoms that were experienced since the participant became sexually active. Probe for the most accurate information available on the participant's current health and reproductive status vis-à-vis the reported history. Several additional guidelines are presented below:

- Use the list of questions in Section D of the MTN 001 Baseline Medical and Menstrual History form to probe for conditions/symptoms the participant may have experienced.
- Record symptoms, illnesses, allergies, and medical procedures (this is included as item "t" in Section D of the MTN 001 Baseline Medical and Menstrual History form).
- Record both chronic and acute conditions, as well as both ongoing and resolved conditions.
- For menstrual history, document the details of the participant's usual menstrual cycle and flow. Also enter the first and last day of the participant's last menstrual period, and the average number of bleeding days (e.g., 3-5 days) she experiences during her regular menses. Note the participant's age of menarche and any menstrual problems she may have, such as irregular menses, amenorrhea, menorrhagia, etc. Document the type and severity of any usual menstrual symptoms. See Section A of the MTN 001 Baseline Medical and Menstrual History form.
- Document any usual or typical non-menstrual genital bleeding patterns experienced by the participant. This includes any breakthrough genital bleeding/spotting associated with the participant's contraceptive use. Include the frequency of bleeding, the average duration, type of flow (e.g. light, moderate, or heavy) and any associated symptoms (this is included as item "s" in Section D of the MTN 001 Baseline Medical and Menstrual History form).
- Explore whether the participant has experienced (or continues to experience) any type of sexual trauma (item "v" in Section D of MTN 001 Baseline Medical and Menstrual History form).
- For reproductive history, record the number, date, and outcome of each of the participant's pregnancies, (see Section B of the MTN 001 Baseline Medical and Menstrual History form) as well as any gynecologic and obstetrical procedures/surgeries (item "t" in Section D of MTN 001 Baseline Medical and Menstrual History form).
- At the Screening Visit, record the participant's history of contraceptive use (see Section C of the MTN 001 Baseline Medical and Menstrual History form). Review and update this section at the Enrollment Visit, and transcribe the participant's current family planning methods onto the Family Planning Methods case report form. If applicable, enter details of the participant's current contraceptive method on the Concomitant Medications Log form. Per Section 5 of the study protocol, spermicides, diaphragms, sponges, and contraceptive vaginal rings should not be used during participation in MTN 001. Participants who report current use of these contraceptive products and devices during screening are ineligible for participation in the study. If the participant reports use of any of these contraceptive products at the Enrollment Visit, she is not eligible for the study. If the participant is interested, refer the participant to family planning services for provision of alternative methods prior to enrollment in the study.

- Document medications currently taken for all ongoing conditions, including usual menstrual symptoms, on the Concomitant Medications Log form, as described in Section 10.1.2.

Site clinicians are encouraged to use their clinical experience and judgment — together with any advice available from Community Advisory Board members or others — to determine the best phrasing in the local language to elicit complete and accurate history information from study participants.

10.1.2 Initial Ascertainment of Concomitant Medications

The MTN 001 protocol requires documentation of all medications taken by study participants beginning at the Screening Visit and continuing throughout follow-up. For purposes of this study, medications include all of the following, regardless of route of administration:

- Prescription and “over-the counter” medications and preparations
- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations
- Recreational drugs

The Concomitant Medications Log form may be used as a source document for collecting information on participants’ use of medications. When recording the route of medications/preparations that are applied intravaginally, mark the box labeled “VAG”. When recording the route of medications/preparations that are applied rectally, mark the box “REC.”

It is recommended that study clinicians ascertain participants’ baseline medication information in the context of obtaining the baseline medical/menstrual history. In addition to asking open-ended questions to elicit participant report of current medications, use the information obtained in the medical/menstrual history to probe for additional medications that the participant may forget to report. For example, if the participant reports recurrent headaches as part of her medical history, but does not spontaneously list any medications taken for headaches; ask her if she takes any medications for the headaches. Similarly, if a participant reports taking a medication for a condition that she inadvertently did not report when providing medical history information, add the condition to the Baseline Medical History form and Pre-existing Conditions form as appropriate.

10.1.3 Pre-existing Conditions

As noted above, a key purpose of conducting the baseline medical/menstrual history — as well as the physical exam and screening pelvic exam described below — is to document participants’ baseline medical conditions, for comparison with signs, symptoms, and conditions that may be identified or reported at subsequent scheduled or interval study visits. For MTN 001, all ongoing medical conditions, problems, signs, symptoms, and (abnormal) findings that are observed and/or reported *at enrollment* are considered pre-existing conditions. Such conditions should be documented per the screening and enrollment visit guidance provided in Sections 4 and 7 of this manual, as well as in the remainder of this section.

For participants who enroll in the study, all ongoing medical/laboratory conditions observed and/or reported at the Enrollment Visit should be reported on the Pre-existing Conditions form. This case report form is completed at the Enrollment Visit, based on all other screening and enrollment source documents, including the Baseline Medical and Menstrual History form, Baseline Genital Symptoms form, Physical Exam form, Screening and Enrollment Pelvic Exam form, all screening laboratory results, chart notes, and any other site-specific source documents. Once the participant is enrolled in the study, any ongoing symptoms at the time of enrollment will be recorded in the Follow-up Medical History Log. This log will facilitate the review of participant's symptom(s) during follow-up.

As is described in greater detail in Section 11, the Pre-existing Conditions form serves as the “starting point” from which study clinicians must determine whether medical conditions, problems, signs, symptoms, and other abnormal findings identified or reported during follow-up are adverse events (AEs). By definition, pre-existing conditions are present at the time of randomization/enrollment in the study and are therefore not considered AEs. However, if a pre-existing condition resolves after randomization, but then recurs at a later date, the recurrence is considered an AE. New conditions identified during follow-up that were not present at the time of enrollment/randomization, and any pre-existing conditions that increase in severity or frequency during follow-up, are also considered AEs. With this in mind, when completing the source documents listed above, as well as the Pre-existing Conditions form, study clinicians should document as much detail as possible about the severity and frequency of each pre-existing condition. When completing the Pre-existing Conditions case report form, it is recommended that this information be recorded in the “Comments” section for each condition.

10.2 Interval Medical/Menstrual/Genitourinary History and Updating of Concomitant Medications

For enrolled participants, an interval medical/menstrual/genitourinary history and update of concomitant medications is obtained at each scheduled follow-up visit. This procedure also is performed at interim visits. The purpose of these procedures is to determine whether participants have experienced any new illnesses, symptoms, etc., since the last study visit. An interval medical/menstrual/genitourinary history also should be performed at interim visits to obtain updated information on previously reported adverse events when applicable.

10.2.1 Interval Medical/Menstrual/Genitourinary History

The non-DataFax Follow-up Medical History Log form is a recommended source document for collecting interval medical/menstrual history data. This form is used to track any symptom reported by the participant that are ongoing at the Enrollment Visit through follow-up.

At each follow-up visit, site staff should actively review the Follow-up Medical History Log and review any conditions that are ongoing (that is, conditions that do not have an “outcome date” recorded on the form). If the condition has resolved, record the outcome date. If the condition has not resolved, leave the outcome date blank and inquire about the condition the next time an interval medical history is performed. Once all ongoing conditions on the Follow-up Medical History form have been reviewed, ask the participant an open-ended question such as “What, if any, other symptoms or health problems have you had since your last visit?” to complete the history. Add new conditions to the log form as needed. Additionally, the interviewer-administered Follow-up Genital Symptoms form, a source document, will be used to document in the study database any genitourinary symptoms experienced by the participant since her last interval medical history.

See Section 10.5 below for more information on assessing participant reports of genital bleeding.

Site clinicians are encouraged to use their clinical experience and judgment — together with any advice available from Community Advisory Board members or others — to determine the best phrasing in the local language to elicit complete and accurate follow-up information from study participants.

10.2.2 Updating of Concomitant Medications Information

At each visit retrieve the participant's Concomitant Medications Log, record any new medications taken by the participant, and actively inquire as to whether the participant is still taking medications listed previously, at the same dose and frequency. Also actively inquire as to whether the participant has begun taking any new medications since her last visit, including medications obtained outside the study (not provided by the study staff). To further probe for updates, if the participant reports any intercurrent illnesses, symptoms, etc., since her last visit, inquire as to whether she took any medications for these. Add all new information to the form in log fashion, using additional form pages as needed. Similarly, if a participant reports taking a new medication for a condition that she inadvertently did not report when providing interval medical/menstrual history information, add the condition to the Follow-up Medical History log, and Pre-existing Conditions form (if present at enrollment).

10.3 Physical Exams

A physical exam is required at the Screening, Enrollment, and all Follow-up Clinic Visits with the exception of the Week 21 visit. Site clinicians may use their discretion to determine whether or not to conduct a more complete physical exam, in response to reported symptoms or illnesses present at the time of the exam. Following is a list of the required physical exam components.

- Height (may be omitted after the Enrollment Visit)
- Weight
- Vital signs
 - Temperature
 - Pulse
 - Blood pressure
- General appearance
- Abdomen

The non-DataFax Physical Exam form is a recommended source document for recording physical exam findings. For participants who enroll in the study, abnormal physical exam findings identified at the Enrollment Visit also are recorded on the Pre-existing Conditions form.

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

10.4 Pelvic Exams

Pelvic exams are performed in MTN 001 for purposes of determining eligibility and identifying study safety information. As such, they are critical to ensure the ongoing safety of study participants. Pelvic exams are performed at Screening, Enrollment and all scheduled Follow-up Clinic Visits with the exception of the Week 21 Visit, per the schedule in protocol Section 7. Pelvic exams also are performed when clinically indicated to evaluate genital symptoms.

Pelvic exams are performed, and findings classified, according to the CONRAD/World Health Organization (WHO) Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004 (available at www.conrad.org), and the remainder of this section. Exam procedures must be performed in the order shown on the exam checklists in Section 7 of this manual. All procedures listed on the exam checklists should be performed during routinely scheduled exams. When additional exams are performed to assess genital symptoms, only clinically indicated procedures should be performed. As indicated in greater detail below, exam findings are reported on the following forms provided by the MTN SDMC:

- Screening and Enrollment Pelvic Exam (SPE-1)
- Follow-up Pelvic Exam (FPE-1)
- Pelvic Exam Diagrams (non Datafax form)
- Pelvic Laboratory Results (PLR-1)
- Follow-up Medical History Log

For participants who enroll in the study, abnormal exam findings identified at the Enrollment Visit (that are not exclusionary per the study eligibility criteria) also are recorded on the Pre-existing Conditions form.

10.4.1 Overview

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 assure 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 to adjust equipment.

For each area examined, i.e., the external genitalia, cervix, and vagina, first perform a naked eye 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. Prior to insertion, ensure that the speculum functions properly and has no rough edges. The speculum may be lubricated with warm water if needed. No other lubricant may be used.

Record the length and axis of the vagina, position of the cervix, and type and size of speculum during the participant's first pelvic examination (e.g., on the exam checklist or Pelvic Exam Diagrams form). This information can then be reviewed prior to subsequent exams to reduce the risk of iatrogenic injury.

Lavage and Removal of Visual Obstruction: During the pelvic exams at the Screening Visit, Mid-Study-Period Visits (3, 10, and 17 Week), and Study Period 2 and 3 Start Visits (7 and 14 Week), after assessment of vaginal pH and collection of vaginal swabs, if necessary remove any obstruction (e.g., mucus, cellular debris) by lavage with sterile, isotonic, non-bacteriostatic saline. Avoid contact between the pipette and the epithelium. The lateral fornices may be lavaged without manipulation by directing the stream into them. Aspirate the fluid with the tip of the pipette against the inner surface of the posterior blade of the speculum. Do not lavage prior to assessing pH and collecting swabs for wet prep.

If lavage does not adequately remove the obstruction, 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.

The lavage for removal of visual obstruction will not be conducted during the pelvic exams performed at the Enrollment Visit and at End of Study Period Visits (6, 13, and 20 Week). At these visits, participants will undergo PK procedures (see Protocol section 7), where cervicovaginal lavage (CVL) will be collected to evaluate vaginal flora proteomics, markers of inflammation, and tenofovir levels. Procedures for collection of PK samples are described in Section 10.8. Do not collect CVL samples prior to assessing pH and collecting swabs for wet prep.

Specimen Collection: Perform specimen collection during each exam in the sequence specified on the pelvic exam checklists (see Section 7 of this manual).

Documentation of Findings: Document all exam findings — both normal and abnormal — on the Pelvic Exam Diagrams form. Document abnormal findings only on the appropriate pelvic exam form case report form. Both the Screening Pelvic Exam form and the Follow-up Pelvic Exam forms are recommended source documents for recording relevant descriptors and details of abnormal findings. However, supplemental information may be recorded on the Pelvic Exam Diagrams form, in chart notes, and/or on other source documents. For participants who enroll in the study, abnormal exam findings identified at the Screening Visit (that are not exclusionary per the study eligibility criteria) also are recorded on the Pre-existing Conditions form. See Section 10.4.3 for detailed instructions on classifying and documenting exam findings.

10.4.2 Detailed Procedural Instructions

Note: As much as possible, study-specific 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. This is especially important during the “end of study period” visits when PK procedures are required. If the participant is on her menses and the visit cannot be rescheduled, all PK procedures will be conducted, including collection of CVL samples, and cytobrush and vaginal biopsy 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.

Note: See Section 6 of this manual for procedural modifications to be followed with pregnant participants.

Prior to the Exam: Prepare all required equipment, supplies, and paperwork. Verify that all equipment is in good working order. Review documentation of prior exams (if any) and other relevant documentation from the current visit and prior visits. While the participant is clothed, explain the procedure and equipment to her and answer any questions she may have.

Position the Participant: Establish a comfortable examination position for the participant that allows for the perineum and vulva to be inspected. Adjust stirrups and back elevation as needed. Provide socks if the room is cold; provide a fan for the participant’s face if the room is warm. Drape the participant and point out distractions such as photos on the ceiling or music if available.

Examine the External Genitalia:

- Do not insert the speculum prior to examining the external genitalia.
- Spread the participant’s knees as far apart as is comfortable for her.
- Palpate the inguinal lymph nodes to assess for enlargement and/or tenderness.
- Perform naked eye examination of the external genitalia including the perineum, perianal area, and the epithelial lining of the introitus.
- Note all findings on the Pelvic Exam Diagrams form. Further document abnormal findings on the appropriate pelvic exam case report form.

Examine the Cervix:

- 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 without manipulation, observing the general state of the cervix, the size and shape of the cervical os, and any other findings.
- Assess cervical ectopy.
- Assess for homogeneous discharge. Record outcome on the Pelvic Laboratory Results form. If any abnormal vaginal or cervical discharge and/or blood-tinged discharge are also present, document the discharge on the Pelvic Exam Diagrams and on the appropriate pelvic exam form (Screening and Enrollment Pelvic Exam form or the Follow-up Pelvic Exam form).
- Vaginal fluids are collected via swab and then swabbed onto the pH strip (instead of inserting the pH strip into the vagina). Avoid contact with cervical mucus, which has a high pH. Match the resulting color of the pH strip to the color scale provided with the strips to determine the pH value. Record the pH on the Pelvic Laboratory Results form.
- Collect vaginal fluids via (dry) swab for wet prep as required by the visit. Collect fluids from the lateral vaginal wall, away from any apparent abnormalities. See Section 12 of this manual for detailed wet prep slide preparation and assessment procedures.

Wet prep slides are to be read by local laboratory or site research staff, and results should be recorded on the Pelvic Laboratory Results form.

- If needed, lavage the cervix and vagina as described in Section 10.4.1 and complete naked eye exam (except for visits requiring PK sample collection).
- Note all findings (variants of normal and abnormal) on the non-DataFax Pelvic Exam Diagrams form. See the variants of normal in section 10.4.3 below. Further document abnormal findings on the appropriate pelvic exam case report form.

Examine the Vagina: To examine the rest 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. Note all findings on the Pelvic Exam Diagrams form. Further document abnormal findings on the appropriate pelvic exam case report form.

Collect Genital Ulcer Swabs: If local standard of care, if any genital ulcers are observed during follow-up, swab the base of the ulcer for HSV-2 culture per local laboratory specifications. Document specimen collection on the Follow-up Pelvic Exam form. See Section 12 of this manual for further instructions for proper swab handling and storage prior to testing at the MTN Network Laboratory.

Collect Pap Smear: A Pap smear is required at the Screening Visit if there is no documentation of a normal result in the form of a written report within the 12 calendar months prior to screening. If no such documentation exists, collect ecto- and endo-cervical cytobrush specimens after completing all naked eye examinations. Document specimen collection on the Pelvic Laboratory Results form and transcribe results, once they become available, to that same form. Participants with abnormal results will not be eligible for the study. Pap smears will be reported as per the 2001 Bethesda System and will be presumed normal in the absence of intra-epithelial lesion or malignancy.

Perform Bimanual Exam (if clinically indicated): After completing all tissue examinations and specimen collection, close the speculum blades, gently remove the speculum, and perform bimanual exam for adnexal or fundal masses and/or tenderness.

NOTE: At the End of Study Period, the bimanual exam will be done after all PK samples have been collected.

10.4.3 Documentation of Findings

Document all exam findings, both variants of normal and abnormal, on the Pelvic Exam Diagrams form.

The following findings are considered normal:

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

Per the CONRAD/WHO Manual, 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 considered deep)

Color:

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

Blood Vessels

Integrity:

- Intact
- Disrupted

Figure 10-1 provides information to guide and standardize terminology used to describe abnormal pelvic exam findings. Examining clinicians also are encouraged to consult the Photo Atlas for Microbicide Evaluation developed by Bollen, Kilmarx, and Wiwatwongwana (MOPH-US CDC Collaboration, 2007) for further examples of terminology applied to pelvic exam findings in microbicide studies.

The Screening and Enrollment Pelvic Exam form, and the Follow-up Pelvic Exam form are recommended source documents for recording relevant descriptors and details of abnormal findings; however supplemental information may be recorded on the Pelvic Exam Diagrams form, in chart notes, and/or on other source documents. Iatrogenic findings such as those caused by speculum trauma should be included among the “abnormal” findings documented for the exam, with notations added to source documents and case report forms to specify the cause of the finding.

Figure 10-1
CONRAD/WHO Terminology for Pelvic Exam Findings

Term	Status of Epithelium	Status of Blood Vessels	Comments	
Erythema	Intact	Intact	Distinguished by color (erythema being redder than normal, edema either normal or paler than normal, and grossly white findings being white). Grossly white findings are sharply demarcated whereas edema and erythema may be sharp or diffuse.	
Edema	Intact	Intact		
Grossly white finding	Intact	Intact		
Petechiae	Intact	Disrupted	≤ 3 mm	Color of finding is red or purple.
Ecchymosis	Intact	Disrupted	> 3 mm	
Peeling	Disrupted, superficial	Intact	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	
Ulcer	Disrupted, superficial or deep	Intact or disrupted	May include sloughing at base. Generally round or oval with sharply demarcated outline. Superficial ulcers are more accurately called erosions.	
Abrasion	Disrupted, superficial or deep	Intact or disrupted	Distinguished from other findings in this class by diffuse or poorly demarcated outline.	
Laceration	Disrupted, superficial or deep	Intact or disrupted	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.	

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 considered deep.

10.5 Genital Bleeding Assessment

Genital bleeding other than menstrual bleeding, often referred to as “intermenstrual bleeding” or “IMB” is a common occurrence among reproductive age women, and often is of physiologic or benign etiology. Some women normally experience mid-cycle bleeding or pre-menstrual bleeding. IMB is common in oral contraceptive users, particularly new and/or inconsistent users. Use of intrauterine contraceptive devices, smoking, and chlamydia infection have been identified as risk factors for IMB, and IMB may be associated with genital tract pathology such as cancer or polyps. IMB also may be associated with traumatic injury to the cervicovaginal epithelium (e.g., due to speculum insertion, product applicator insertion, sexual activity).

Background rates of IMB in the general population are not known with precision. In a recent survey of HIV-negative and HIV-positive women, 12 percent and 11 percent respectively reported IMB in the last six months. In clinical trials of oral contraceptives, IMB rates have ranged from five percent to over 50 percent. The high variability in IMB rates seen in these studies is likely due to different methods of data collection and reporting as well as cultural factors. Regardless, since oral contraceptive trials generally are not placebo controlled, it is difficult to assess how rates reported in those trials compare to background rates in the general population.

Similar to observations in contraceptive trials, variable rates of IMB have been observed in Phase I microbicide trials, many of which have not included a control group. While IMB has been reported in microbicide trials, IMB has not been associated with anemia or hemodynamic instability in those trials. The main concern raised by observation of IMB in microbicide trials is that candidate microbicides that are associated with increased rates of IMB may increase, rather than decrease, the user’s risk of HIV infection, presumably by disrupting the cervicovaginal epithelium and blood vessels. Increased rates of IMB also might affect the microbicide’s acceptability.

The MTN 001 Protocol Team has carefully considered the potential risks that may be associated with IMB and has developed procedures to evaluate, monitor, and report on genital bleeding throughout the course of the study. These procedures are described below and several possible genital bleeding assessment scenarios are presented in Appendix 10-1.

10.5.1 Genital Bleeding Assessment for Pregnant Participants

The remainder of this section provides procedural instructions and guidance for assessment of genital bleeding among non-pregnant participants. If a pregnant participant reports genital bleeding, study staff will clinically manage the participant per local practice standards for pregnancy. In particular, study staff will refer the participant to a qualified clinician for further evaluation, care, and treatment; pelvic exams may be performed by qualified clinicians unless contraindicated. Study staff will document the bleeding event and all follow-up actions in the participant's study records.

When reporting the event as an AE, it is not expected that a term such as “intermenstrual bleeding” or “metrorrhagia” will be used to describe the AE. Rather clinically appropriate terminology reflecting the cause or source of the bleeding (e.g., “threatened abortion”) should be used, if possible, and the bleeding itself should be graded according to the “First trimester bleeding”, “Second/third trimester bleeding”, or “Postpartum hemorrhage” row of the Female Genital Toxicity Table as appropriate. Any questions related to genital bleeding assessment or AE reporting for pregnant participants should be submitted to the MTN 001 PSRT as described in Section 11.

10.5.2 Participant Reports of Genital Bleeding

As part of the MTN 001 informed consent and enrollment process, study participants will be counseled to report all occurrences of genital bleeding — other than usual menstrual bleeding — to the study site as soon as possible after identification of the bleeding. Study staff will provide site contact information to each participant upon enrollment. Thereafter, at each study follow-up visit, contact information will be reiterated and active reporting of genital symptoms including unexpected menstrual bleeding and unexpected non-menstrual genital bleeding will be emphasized.

As described in Section 10.2, 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. Any changes in participants' use of concomitant medications, including contraceptives and topical and intravaginal medications/preparations, also will be actively ascertained. Reports of genital bleeding should be recorded on the Baseline Genital Symptoms form (at enrollment) or on the Follow-up Genital Symptoms form (for follow-up visits).

10.5.3 Clinician Assessment of Genital Bleeding

Study participants will undergo pelvic exams at the Screening Visit, Enrollment and at every Follow-up Visit, with the exception of the 21-Week Visit, thereafter. Pelvic exams also will be performed to evaluate any participant report of unexpected menstrual bleeding and/or unexpected non-menstrual genital bleeding. Pelvic examinations will be performed and documented as described in Section 10.4.

Figures 10-2a and 10-2b outline the genital bleeding assessment and reporting procedures that will be followed at all sites during follow-up. As shown in the figures, the sequence of procedures will differ depending on whether genital bleeding is first reported by the participant or first observed on pelvic exam. The Genital Bleeding Assessment form (see Section 13) will be used at all sites to guide and document clinicians' assessment of both participant-reported genital bleeding and clinician-observed genital bleeding when applicable (see more below). The Genital Bleeding Assessment form guides clinicians to collect and consider information on the many factors that may contribute to the observation of genital bleeding, to help determine whether the bleeding may be related to product use, or whether it may be more likely attributable to another cause. These factors include:

- Early onset of menses
- Use of hormonal contraceptive methods
- Use of intrauterine contraceptive devices
- Missed oral contraceptive pills or injections
- Sexual activity/trauma
- Trauma associated with insertion of study product or other vaginal preparations
- Trauma associated with pelvic exam procedures
- Sexually transmitted or reproductive tract infections/outbreaks
- Epithelial and/or blood vessel disruption observed on pelvic exam
- Other pathology observed on pelvic exam (e.g., polyps, carcinoma)

Assessment of genital bleeding should begin by determining whether the bleeding is *expected* or *unexpected*, and then proceed to determining whether the bleeding is *menstrual* or *non-menstrual*. Expectedness will be determined based on the participant's baseline medical/menstrual history (e.g., whether she reports genital bleeding as a pre-existing condition) as well as any other relevant factors such as hormonal contraceptive use. If a participant reports bleeding consistent in amount and duration with her baseline menstrual history, or that is consistent with use of her hormonal contraceptive method, the bleeding will be considered *expected*. In particular, intermenstrual genital bleeding occurring within the first three months of initiating a hormonal contraceptive method will be considered expected, unless the study clinician determines that the bleeding is inconsistent with bleeding patterns usually associated with that method. Lochia also will be considered expected.

A pelvic exam must be performed to evaluate all episodes of unexpected genital bleeding. Pelvic exams are not required to evaluate expected bleeding events; however, such exams may be performed at the discretion of the IoR or designee.

During follow-up, the Genital Bleeding Assessment form must be completed for participants who:

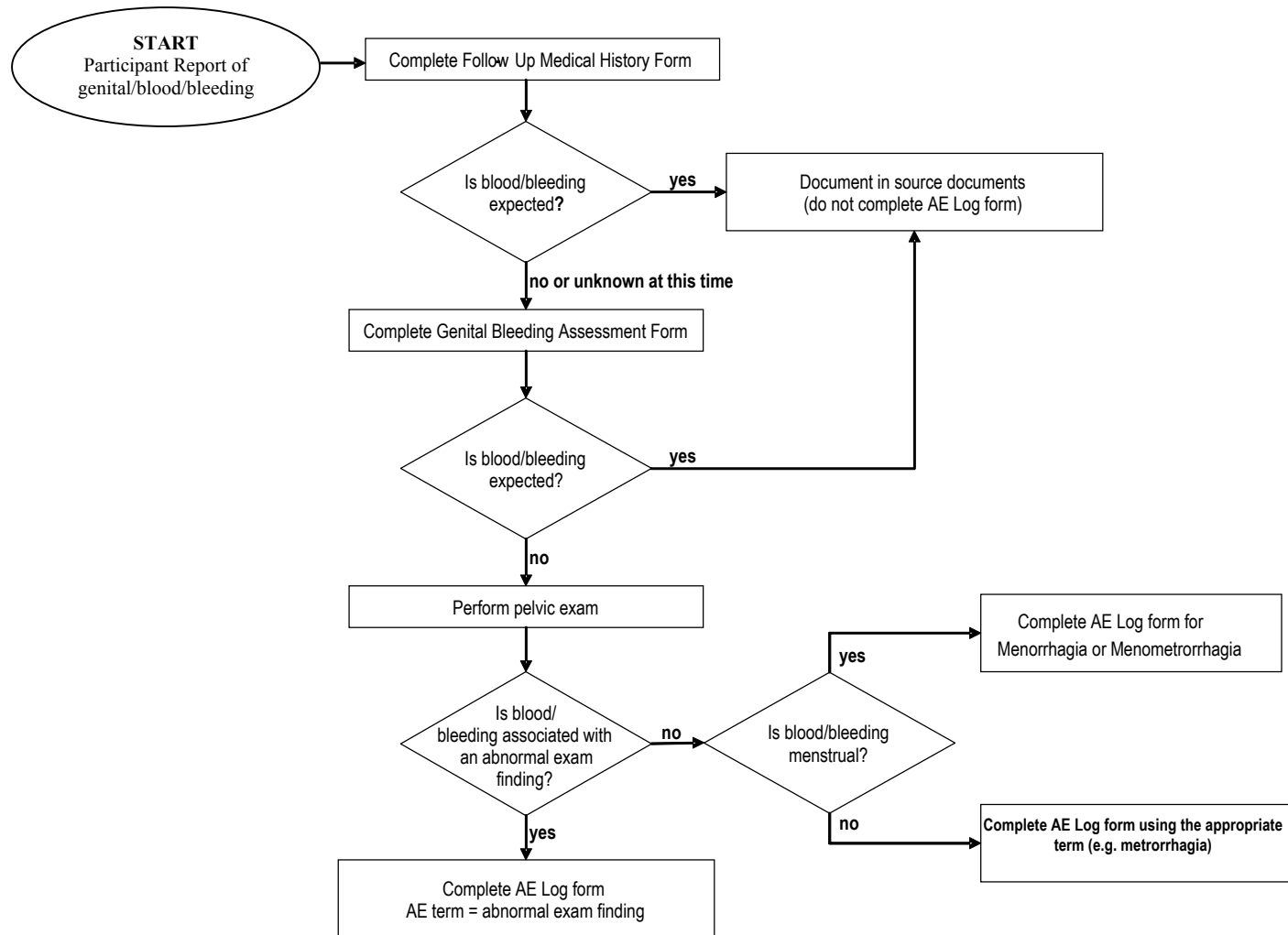
- Self-report genital bleeding other than their normal menses, unless the bleeding is determined to be expected before completing the form
- Do not self-report genital bleeding, but have genital blood/bleeding observed on pelvic exam that is not associated with an abnormal exam finding (e.g., laceration).

The Genital Bleeding Assessment form is not required to be completed for participants who:

- Self-report genital bleeding that is determined to be expected prior to completion of the form

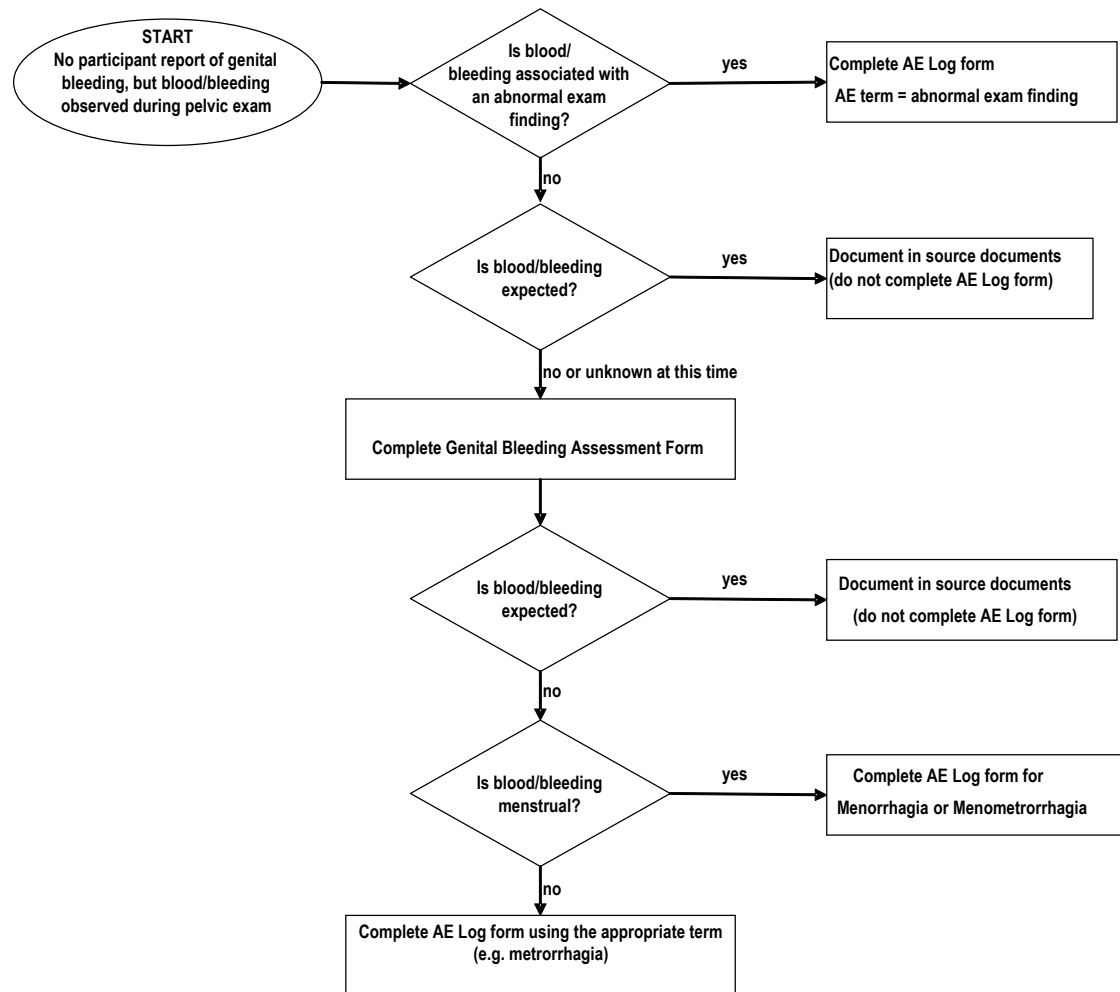
- Do not self-report genital bleeding but have genital blood/bleeding observed on pelvic exam that is associated with an abnormal exam finding.
- Do not self-report genital bleeding but have genital blood/bleeding observed on pelvic exam that is determined to be menstrual bleeding before completing the form.

Figure 10-2a
Overview of Assessment and Reporting Procedures for Genital Bleeding in MTN 001 — Beginning with Participant Report of Bleeding



Note: This algorithm is followed for non-pregnant participants only (see Section 10.5) and does not apply to genital hemorrhage. See Section 10.5.4 for more information on terminology and severity grading for adverse events (AEs) involving genital bleeding.

Figure 10-2b
Overview of Assessment and Reporting Procedures for Genital Bleeding in MTN 001 — Beginning with Clinical Observation of Blood/Bleeding



Note: This algorithm is followed for non-pregnant participants only (see Section 10.5) and does not apply to genital hemorrhage. See Section 10.5.4 for more information on terminology and severity grading for adverse events (AEs) involving genital bleeding.

10.5.4 Documentation of Genital Bleeding

Participants' prior history of menstrual and non-menstrual genital bleeding will be documented on the non-DataFax Baseline Medical History form and on the Pre-existing Conditions case report form, if applicable.

All cases of participant-reported genital bleeding occurring between usual menstrual periods will be documented on the Baseline Genital Symptoms form (at enrollment) or the Follow-up Genital Symptoms form (at follow-up visits). The non-DataFax Pelvic Exam Diagrams form is used to record all pelvic exam findings, both normal and abnormal. This means that all clinically observed genital blood/bleeding, whether expected, unexpected, menstrual, or non-menstrual, should be documented on the non-DataFax Pelvic Exam Diagrams form. In contrast, the Screening and Enrollment Pelvic Exam form and Follow-up Pelvic Exam form are used to record only abnormal pelvic exam findings. This means that only unexpected menstrual bleeding (excluding early menses) and unexpected non-menstrual bleeding should be recorded on these forms. In addition, certain episodes of genital bleeding will be documented on the Genital Bleeding Assessment form, as specified in Section 10.5.3 above.

All episodes of unexpected menstrual bleeding and unexpected non-menstrual genital bleeding — whether participant-reported or clinician-observed or both — will be considered adverse events (AEs) that must be documented on Adverse Experience Log case report forms.

Detailed information on AE reporting is provided in Section 11, however when reporting genital bleeding events, reference also should be made to the nine points below, which standardize the terminology that should be used at all sites when reporting AEs involving genital bleeding.

- Expected menstrual bleeding should not be reported as an AE. “Early menses” also should not be reported as an AE. Although clinical judgment will be required to determine whether any genital bleeding event may be due to early menses, as a general guideline, menses occurring more than two days prior to the participant’s usual menstrual cycle should be considered early menses. It is recognized, however, that it may not be possible to make a real-time diagnosis of early menses, based on the information available when first documenting a genital bleeding event. For example, the event could be reported on the first day of bleeding and it may not be known at that time whether a full menstrual period will follow. When information needed for a real time diagnosis of early menses is not available, study clinicians should initially report the event using a term other than “early menses” and then review the event after its final outcome has been ascertained and to determine whether it should be re-categorized as “early menses.”
- Unexpected menstrual bleeding (i.e., menstrual bleeding that is heavier in volume or of longer duration than the participant’s usual menses), should be reported as an AE using the following AE terms:
 - Menorrhagia: prolonged (more than seven days) or excessive (more than 80 mL) uterine bleeding
 - Menometrorrhagia: prolonged uterine bleeding occurring at irregular intervals

Grade these AEs per the “Menorrhagia” row of the Female Genital Toxicity Table.

- Expected non-menstrual bleeding should not be reported as an AE. This may include a small amount of cervical bleeding that can occur with speculum insertion or specimen collection, provided the IoR or designee deems the amount of bleeding to be within the range of normal. If the cervical bleeding observed with speculum insertion or specimen collection exceeds that which is expected, in the opinion of the IoR or designee, then the cervical bleeding should be recorded as an AE of “cervical friability”, and graded according to the “Cervical edema and friability” row of the Female Genital Toxicity Table.
- Unexpected non-menstrual bleeding that is associated with an observed abnormal pelvic exam finding should be reported as an AE using the term associated with the exam finding, with the anatomical location noted. For example, if a laceration is observed on exam, with blood emanating from the finding, the term “laceration” should be used to describe the AE. The fact that blood or bleeding was present also will be documented on the Pelvic Exam Diagrams form and the Pelvic Exam case report form, and may be noted in the Comments section of the Adverse Experience Log form, but the term “metrorrhagia” (“intermenstrual bleeding”) should not be used to describe the AE.
- Unexpected non-menstrual bleeding that is not associated with an observed pelvic exam finding, i.e., for which no abnormal source of blood or bleeding is observed on exam, should be reported as an AE using the term “metrorrhagia.” This term refers to bleeding of variable amounts occurring between regular menstrual periods and should be used to report all types of unexpected non-menstrual bleeding such as prolonged or excessive uterine bleeding, spotting between menses, ovulation bleeding, vaginal spotting, and breakthrough bleeding. This term also should be used to report blood-tinged discharge and blood observed in the vagina with no identified source. Grade these AEs per the “Metrorrhagia” row in the Female Genital Toxicity Table.
- In cases with bleeding that qualifies as both menorrhagia and metrorrhagia, it should be labeled menometrorrhagia, but will be graded based on the menorrhagia component. For example, if a participant experiences genital bleeding at irregular intervals that is heavier than her usual menses, you will report the event as “menometrorrhagia” and grade per the “Menorrhagia” row in the Female Genital Toxicity Table.
- If a participant reports genital bleeding after sexual intercourse, you will report this event as “postcoital bleeding” and grade it per the “Postcoital Bleeding” row of the Female Genital Toxicity Table.

- Genital Hemorrhage should be reported as an AE; however, the term genital hemorrhage should not be used to describe the AE. When reporting genital hemorrhage, a specific location must be specified. To report uterine hemorrhage, the term “uterine hemorrhage” will be used to describe the AE and graded per the menorrhagia row in the Female Genital Toxicity Table. In the event that a participant experiences a non uterine genital hemorrhage, the specific location of the hemorrhage needs to be included and the term to be used to describe the AE should be the underlying cause of the condition. For example, if the hemorrhage is caused by trauma in the vagina, then it should be graded per the "Vaginal abrasions or lacerations" row, which is graded by extent of laceration not by degree of bleeding.

10.6 STI/RTI Management

Clinical and laboratory evaluations are performed throughout the course of MTN 001 to diagnose the following sexually transmitted diseases and other reproductive tract infections (STIs/RTIs):

- Bacterial vaginosis (BV)
- Candidiasis (any species)
- Chlamydia infection
- Genital ulcer disease
- Gonorrhea infection
- Syphilis infection
- Trichomoniasis

Signs and symptoms commonly associated with the above-listed infections are presented in Figure 10-3. 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 evaluations performed by study staff.

Figure 10-3
Signs and Symptoms Commonly Associated with STIs/RTIs

STI/RTI	Common Signs and Symptoms
Bacterial vaginosis	Excessive or malodorous discharge is a common finding. Other signs and symptoms include erythema, edema, and pruritis of the external genitalia.
Candidiasis	Clinical presentation varies from no signs or symptoms to erythema, edema, and pruritis of the external genitalia. Symptoms and signs alone do not distinguish the microbial etiology.
Chancroid	The combination of painful ulcer and tender inguinal adenopathy, symptoms occurring in one third patients, suggests a diagnosis of chancroid; when accompanied by suppurative inguinal adenopathy, these signs are almost pathognomonic.
Chlamydia infection	Many infections are asymptomatic and probably chronic. Mucopurulent discharge may not be recognized by the patient or may not be perceived as abnormal.
Genital herpes	Single or multiple vesicles, which usually are pruritic can appear anywhere on the genitalia. Vesicles spontaneously rupture to form shallow ulcers that may be very painful. Lesions spontaneously resolve with minimal scarring.
Gonorrhea infection	Women may have abnormal vaginal discharge, abnormal menses, or dysuria, or most commonly are asymptomatic. Pharyngeal gonorrhea can produce symptoms of pharyngitis.
Syphilis infection — primary	The classical chancre is a painless indurated ulcer located at the site of exposure.
Syphilis infection — secondary	Patients may have a highly variable skin rash, mucous patches, condylomatalata (fleshy, moist tissue growths), lymphadenopathy, alopecia, or other signs.
Syphilis infection — latent	Patients are without clinical signs of infection.

Figure 10-3
Signs and Symptoms Commonly Associated with STIs/RTIs

STI/RTI	Common Signs and Symptoms
Trichomoniasis	Excessive, frothy, diffuse, yellow-green discharge is common, although clinical presentation varies from no signs or symptoms to erythema, edema, and pruritis of the external genitalia. Dysuria and dyspareunia are also frequent. The type of symptoms or signs alone do not distinguish the microbial etiology.
Pelvic Inflammatory Disease (PID)	Patients must meet three criteria for PID: symptoms and exam findings of lower abdominal pain and tenderness, cervical motion tenderness, and adnexal tenderness. Additionally patients may present with fever, abnormal cervical or vaginal discharge, and cervicitis.
Cervical or Vaginal Warts	Patients usually present with a painless cauliflower lesion(s), sessile or on a stalk. Patients usually present with a painless cauliflower lesion(s), sessile or on a stalk.

Adapted from: *Contraceptive Technology* (18th Revised Edition, 2004); Chapter 8: Reproductive Tract Infections; Alphabetic Catalog of Reproductive Tract Infections; pages 201-218.

10.6.1 STI/RTI Treatment

STIs/RTIs will be treated in accordance with current WHO Guidelines for the Management of Sexually Transmitted Infections. WHO guidelines can be found at:

http://www.who.int/reproductive-health/publications/mngt_stis/guidelines_mngt_stis.pdf.

Should updated guidelines be issued by the WHO during the study, the updated guidelines will then be followed.

Note: Neither asymptomatic bacterial vaginosis nor asymptomatic vaginal candidiasis require treatment per WHO guidelines. These conditions will not be reported as an AE for this protocol

Figure 10-4 summarizes the WHO treatment guidelines for each of the conditions listed above. In day-to-day practice, the WHO guidelines — or local site treatment guidelines based on the WHO guidelines — should be referenced to obtain complete information on treatment regimens, contraindications, etc. To optimize cure rates, and thereby optimize the validity of study endpoint data, directly observed single dose treatment regimens should be provided whenever possible.

Figure 10-4
(2003) WHO Guidelines for the Management of Sexually Transmitted Infections
for STI/RTI Diagnosed in MTN 001

STI/RTI	WHO Sexually Transmitted Infections Treatment Guidelines
Bacterial vaginosis	<p><u>For symptomatic patients only.</u> Recommended:</p> <ul style="list-style-type: none"> • Metronidazole, 400 mg or 500 mg orally, twice daily for 7 days <p>Alternative:</p> <ul style="list-style-type: none"> • Metronidazole, 2 g orally, as a single dose • Clindamycin 2% vaginal cream, 5 g intravaginally, at bedtime for 7 days • Metronidazole 0.75% gel, 5 g intravaginally, twice daily for 5 days • Clindamycin, 300 mg orally, twice daily for 7 days
Candidiasis	<p><u>For symptomatic patients only.</u> Recommended:</p> <ul style="list-style-type: none"> • Miconazole or clotrimazole, 200 mg intravaginally, daily for 3 days • Clotrimazole, 500 mg intravaginally, as a single dose • Fluconazole, 150 mg orally, as a single dose <p>Alternative:</p> <ul style="list-style-type: none"> • Nystatin, 100 000 IU intravaginally, daily for 14 days
Chlamydia infection (uncomplicated anogenital infection)	<p>Recommended:</p> <ul style="list-style-type: none"> • Doxycycline, 100 mg orally, twice daily for 7 days • Azithromycin, 1 g orally, in a single dose <p>Alternative:</p> <ul style="list-style-type: none"> • Amoxicillin, 500 mg orally, 3 times a day for 7 days • Erythromycin, 500 mg orally, 4 times a day for 7 days • Ofloxacin, 300 mg orally, twice a day for 7 days • Tetracycline, 500 mg orally, 4 times a day for 7 days
Genital herpes (first clinical episode)	<p>Recommended:</p> <ul style="list-style-type: none"> • Acyclovir, 200 mg orally, 5 times daily for 7 days • Acyclovir, 400 mg orally, 3 times daily for 7 days • Valaciclovir, 1 g orally, twice daily for 7 days • Famciclovir, 250 mg orally, 3 times daily for 7 days <p><i>NOTE: Famciclovir should be used preferentially for genital herpes in the absence of contraindications</i></p>

Figure 10-4
(2003) WHO Guidelines for the Management of Sexually Transmitted Infections
for STI/RTI Diagnosed in MTN 001

STI/RTI	WHO Sexually Transmitted Infections Treatment Guidelines
Genital herpes (recurrent episodes of genital lesions)	<p>Recommended:</p> <ul style="list-style-type: none"> • Acyclovir, 200 mg orally, 5 times daily for 5 days • Acyclovir, 400 mg orally, 3 times daily for 5 days • Acyclovir, 800 mg orally, twice daily for 5 days • Valaciclovir, 500 mg orally, twice daily for 5 days • Valaciclovir, 1000 mg orally, once daily for 5 days • Famciclovir, 125 mg orally, twice daily for 5 days <p><i>NOTE: Famciclovir should be used preferentially for genital herpes in the absence of contraindications</i></p>
Gonorrhea infection (uncomplicated anogenital infection)	<p>Recommended:</p> <ul style="list-style-type: none"> • Ciprofloxacin, 500 mg orally, as a single dose • Ceftriaxone, 125 mg by intramuscular injection, as a single dose • Cefixime, 400 mg orally, as a single dose • Spectinomycin, 2 g by intramuscular injection, as a single dose
Syphilis infection (early infection)	<p>Recommended:</p> <ul style="list-style-type: none"> • Benzathine benzylpenicillin, 2.4 million IU, IM injection, at a single session (usually two injections at separate sites) <p>Alternative:</p> <ul style="list-style-type: none"> • Procaine benzylpenicillin, 1.2 million IU, IM injection, daily for 10 consecutive days <p>Alternative for penicillin-allergic non-pregnant patients:</p> <ul style="list-style-type: none"> • Doxycycline, 100 mg orally, twice daily for 14 days • Tetracycline, 500 mg orally, four times daily for 14 days
Trichomoniasis	<p>Recommended:</p> <ul style="list-style-type: none"> • Metronidazole, 2 g orally, as a single dose • Tinidazole, 2 g orally, as a single dose <p>Alternative:</p> <ul style="list-style-type: none"> • Metronidazole, 400 mg or 500 mg orally, twice daily for 7 days • Tinidazole, 500 mg orally, twice daily for 5 days

STI/RTI tests of cure are not required in MTN 001; however clinical management of syphilis infections should include repeat serology (RPR) following diagnosis of a new infection to confirm treatment effectiveness. If syphilis is diagnosed during screening, the participant will be eligible for enrollment when treatment is complete and the participant is asymptomatic. In some cases this may occur on the same day that the screening results are available. Please contact the MTN NL with any questions related to quarterly testing to confirm treatment effectiveness and/or interpretation of unusual syphilis test results.

10.6.2 Screening and Enrollment Considerations

Potential study participants diagnosed during screening with an STI/RTI per WHO guidelines via laboratory tests will be excluded from enrollment. The only exceptions to this are women with clinical evidence or laboratory evidence of BV or vulvovaginal candidiasis but who are asymptomatic. If the participant is otherwise eligible, she may be enrolled after completing treatment and all symptoms have resolved within 30 days after screening. If symptoms resolve after 30 days, she may be re-screened.

At some study sites, Pap smear results may include notations of findings associated with certain STIs (e.g., trichomoniasis). Because Pap smear methods are not adequately sensitive and specific for STIs, Pap smear findings associated with STIs should not be considered diagnostic of any infections. Rather, such findings should be handled as follows:

- Do not consider STI-related notations on Pap smear result reports when assessing participant eligibility for the study. Use only the results of protocol-specified STI tests for purposes of eligibility determination.
- If protocol-specified STI testing was performed on other specimens (i.e., blood, urine, vaginal fluids) collected on the same day as specimen collection for Pap smear, the results of the protocol-specified testing overrule STI-related findings noted on the Pap smear result report. Provide treatment as needed based on the results of the protocol-specified tests.
- If protocol-specified testing was not performed on other specimens (i.e., blood, urine, vaginal fluids) collected on the same day as specimen collection for the Pap smear, collect specimens for indicated protocol-specified STI testing at the participant's next study visit after receipt of the Pap test result report. Provide treatment as needed based on the results of the protocol-specified tests.

10.6.3 Adverse Event Reporting Considerations

Per the MTN 001 eligibility criteria, no participant may enter the study with an active STI/RTI diagnosed per WHO guidelines via laboratory tests. Since no treatable STI or RTI should be recorded as a pre-existing condition for an enrolled participant, any curable STI/RTI identified during follow-up in MTN 001 is considered an AE that must be documented on an Adverse Experience Log case report form. Detailed information on AE reporting is provided in Section 11. When reporting STI/RTI AEs, the severity of the event should be graded according to the "Genitourinary Infections" section of the Female Genital Toxicity Table (with the exception of asymptomatic bacterial vaginosis and vulvovaginal candidiasis).

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

- If infection with HSV-2 or HPV is known to have occurred before randomization, the infection is considered a pre-existing condition: report on the Pre-existing Conditions form.
- For HPV, genital warts present before randomization are considered a pre-existing condition: report on the Pre-existing Conditions form.
- Any outbreaks that occur after randomization are considered AEs, regardless of whether the viral infection was pre-existing before randomization: report on an Adverse Experience Log form.

10.7 Urinary Tract Infections

Dipstick urinalyses will be performed at Screening, and when clinically indicated during follow up, to diagnose urinary tract infections (UTI). See Section 12 for details on the required laboratory procedures. Record results on applicable testing log sheets and then transcribe results onto the STI Laboratory Results form.

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

When clinically indicated, a urine culture and sensitivity should be performed, and the culture should be documented on the STI Laboratory Results form. The sensitivity test results should be documented in the participant's chart notes only. Once a diagnosis has been made, treatment will be provided per site standards of care and applicable site standard operating procedures (SOPs).

10.8 Management of Laboratory Abnormalities

Clinical management strategies for specific toxicities are detailed in Protocol Section 9.5.

10.8.1 ALT/AST Elevation

Oral Product

Participants with Grade 1 or Grade 2 AST/ALT elevation identified on a single blood draw should have confirmatory laboratory testing as soon as possible (at most within 1 week). Study product may be continued during this time, at the discretion of the investigator, provided the participant is asymptomatic.

Participants that have a Grade 3 AST/ALT elevation should have a repeated laboratory testing as soon as possible (at most within 1 week), and product should be held. Participants should be followed weekly until levels are Grade ≤ 1 at which point study medication may be restarted with close follow-up and in consultation with the PSRT. If lab documentation is not available that levels have returned to Grade ≤ 1 within three weeks, study products must be permanently discontinued. For participants who are restarted on study product, any return to a level of Grade 3 or above should result in permanent discontinuation of study product.

For participants that have a Grade 4 AST/ALT elevation, product should be permanently discontinued. Participants should be followed weekly until levels are Grade ≤ 1 .

Vaginal Product

For participants with Grade 1 or 2 AST/ALT elevation, product may be continued at the discretion of the investigator.

Participants that have a Grade 3 AST/ALT elevation assessed to be possible, probably, or definitely related to study product should be held product in consultation with the PSRT. Participants should be re-evaluated at least weekly up to 2 weeks. If documentation is not available within 2 weeks to show an AST/ALT reduction to ≤ 2 , the product must be permanently discontinued. For participants who are restarted on study product, any return to a level of Grade 3 or above should result in permanent discontinuation of study product.

For participants that have a Grade 4 AST/ALT elevation, product should be held. If the investigator determines that elevation is definitely not related to the study product, the investigator will consult the PSRT for consultation about restarting study product. Participants should be re-evaluated at least weekly up to 2 weeks. If documentation is not available within 2 weeks to show an AST/ALT reduction to ≤ 2 , the product must be permanently discontinued. For participants who are restarted on study product, any return to a level of Grade 3 or above should result in permanent discontinuation of study product.

10.8.2 Hypophosphatemia

Participants with an initial laboratory abnormality of Grade 1 or 2 hypophosphatemia should have the phosphate level repeated as soon as possible (at most within 2 weeks). Participants can be encouraged to consume phosphate rich foods during this time. Participants with confirmed Grade 1 and 2 hypophosphatemia, should be encouraged to increase consumption of phosphate rich foods; in addition, supplemental phosphate in the form of neutral phosphate solution can be prescribed to the participant at the discretion of the investigator.

For participants with a Grade 3 hypophosphatemia assessed to be possible, probably, or definitely related to study product should be held product in consultation with the PSRT and the phosphate level repeated as soon as possible (at most within 1 week). During this time, supplemental phosphate with phosphate rich foods should be encouraged, neutral phosphate solution can be prescribed to the participants at the investigator's discretion, and other causes of low phosphate should be investigated.

Product should be held for participants with a Grade 4 hypophosphatemia, regardless of the relationship to study product. During this time, supplemental phosphate with phosphate rich foods should be encouraged, neutral phosphate solution can be prescribed to the participants at the investigator's discretion, and other causes of low phosphate should be investigated.

Oral Product

For Grade 1 and 2, participants may continue product use per the discretion of the investigator.

Participant with Grade 3 and 4 hypophosphatemia should be evaluated within a week to show response to supplementation. If documentation is not available within one week to show resolution to \leq Grade 2, oral study product must be permanently discontinued.

Vaginal Product

For Grade 1 and 2, participants may continue product use per the discretion of the investigator.

Participants that have a Grade 3 hypophosphatemia assessed to be possible, probably, or definitely related to study product should be held product in consultation with the PSRT. Participants should be re-evaluated at least weekly up to 2 weeks. If documentation is not available within 2 weeks to show hypophosphatemia resolution to ≤ 2 , product must be permanently discontinued. For participants who are restarted on study product, any return to a level of Grade 3 or above should result in permanent discontinuation of study product.

For participants that have a Grade 4 hypophosphatemia elevation, product should be held. If the investigator determines that elevation is definitely not related to the study product, the investigator will consult the PSRT for consultation about restarting study product. Participants should be re-evaluated at least weekly up to 2 weeks. If documentation is not available within 2 weeks to show a hypophosphatemia reduction to ≤ 2 , product must be permanently discontinued. For participants who are restarted on study product, any return to a level of Grade 3 or above should result in permanent discontinuation of study product.

10.8.3 Creatinine Clearance

For participants with a creatinine clearance laboratory value of <50 mL/min, laboratory testing should be repeated within 1 week of the receipt of the results in consultation with the PSRT. If the creatinine clearance is confirmed to be <50 mL/min, the oral study product must be permanently discontinued. For participants who fail to have a confirmatory test, the oral study product will be permanently discontinued. Vaginal study product may be continued at the discretion of the investigator.

10.9 Pharmacokinetic Procedures

During the “Mid-Study” and “End of Study Visits” at all three periods (oral, vaginal, and dual use), samples will be collected for PK measures. All PK results will be documented on the Pharmacokinetics – Non-intensive form (Non-US sites) or the Pharmacokinetics – Intensive form (US sites). Participants will be asked to record the three doses (hour: minute) of tenofovir taken prior to the study visit. To ensure that time will be recorded correctly, at enrollment, all participants will be provided a watch device. When providing the watch device to participants, site staff need to counsel participants on how to use the watch, how and where to record the time, and remind participants of the importance of bringing these records to these visits. Sites are encouraged to develop strategies to ensure participants are reminded to record the timing of their last three doses prior to their visits as well as bring this record to the clinic. These strategies may include phone calls, letters, and appointment calendars.

NOTE: If participants forget to bring documentation of the time of the last three doses, site staff should make every effort to work with the participant to obtain the best estimates of timing of previous product use. When completing the appropriate CRF, sites need to write a note in the white space next to the times that these are estimates.

10.9.1 Mid-Study Period

At 3-Week, 10-Week, and 17-Week study visits (Mid-Study-Period Visits) all participants will provide blood samples to be tested for tenofovir levels. At these visits, participants will not take an observed dose of product.

10.9.2 End of Study Period

At 6-Week, 13-Week, and 20-Week study visits (End of Study Period Visits) all participants will provide a blood sample within 15-30 minutes prior to taking an observed dose of product(s). Participants will be asked to bring one dose of product(s) to these visits and take this dose in the presence of study staff. For the observation of the vaginal product, each site will determine the most culturally appropriate method for observing the dose. For example, a site may choose to directly observe the product insertion or they may choose to allow the participant to insert the product behind a privacy curtain. Regardless of the method chosen, site staff need to ensure that the product has been inserted. Following insertion of the vaginal dose, it is recommended that participants ambulate between 10-15 minutes to increase the gel distribution.

PK procedures may not be split over multiple days, meaning that all PK procedures must be completed on the same day (see Section 6.3.3). In addition, every effort should be made to schedule these visits when the participant is not experiencing her menses. However, if the participant is on her menses at the time of the visit, all PK procedures will be conducted, including collection of CVL, cervical cytology brush, and vaginal biopsies if applicable.

Prior to the End of the Study Period visit, study participants will be asked to abstain from sex, if possible, at least 24 hours prior to their study visit. If participants are not able to abstain from sex, participants should be reminded to negotiate male condom use.

Sites participating in the Non-intensive PK procedures (Non-US sites), will follow the guidelines described in Section 10.9.2.1. Sites participating in the Intensive PK procedures (US sites) will follow the procedures described in Section 10.9.2.1.

10.9.2.1 Non-Intensive PK

At the Non-US sites, participants will be assigned to a sampling window based on their sequence randomization assignment:

- 1-3 hours, Sequence E and F
- 3-5 hours, Sequence A and B
- 5-7 hours, Sequence C and D

These participants will have one blood sampling time pre-dose, and only one sampling time post-dose that will include blood sample and CVL sample (see Figure 10-5).

**Figure 10-5
Non-Intensive PK Procedures**

	PRE-DOSE	POST-DOSE TIMING		
		1-3 HOURS	3-5 HOURS	5-7 HOURS
Blood: <ul style="list-style-type: none"> Flow cytometry (at sites with capacity) 	Study Regimen Sequences A, B, C, D, E, and F			
Blood: <ul style="list-style-type: none"> PBMC cell lysate (intracellular tenofovir diphosphate) (at sites with capacity) Tenofovir 	Study Regimen Sequences A, B, C, D, E, and F	Study Regimen Sequences E and F	Study Regimen Sequences A and B	Study Regimen Sequences C and D
CVL <ul style="list-style-type: none"> Tenofovir Proteomics and markers of inflammation 		Study Regimen Sequences E and F	Study Regimen Sequences A and B	Study Regimen Sequences C and D

Post-dose samples must be collected within 15-30 minutes of each other and either sample may be taken first. Site staff need to record the time that each sample is collected with hour:minute accuracy in the Pharmacokinetics – Non-Intensive form.

During the pelvic exam, procedures will be done in the following order:

- Vaginal pH
- Wet mount
- CVL
- Bi-manual examination

Cervicovaginal Lavage (CVL)

CVL samples will be taken after pelvic exam procedures such as examination of the external genitalia, vagina, and cervix, assessment of pH and collection of swabs for wet prep. Lavage will be performed by rinsing the cervix with 10 ml of sterile saline with a syringe and then collecting the pooled fluid in the vaginal fornix with the same device.

10.9.2.2 Intensive PK

The US sites will participate in the Intensive PK measures. These participants will provide cervical cells and vaginal tissue which will be used for measurement of tenofovir levels. All 72 participants will be randomized into groups (see Figure 10-6) to provide collection of pelvic exam specimens pre-dose, 2, 4, or 6 hours after dosing.

During the pelvic exam, procedures will be done in the following order:

- Vaginal pH
- Wet mount
- CVL
- Cervical brush
- Vaginal biopsy
- Bi-manual examination (if clinically indicated)

All participants in this group will have blood collected pre-dose, and 1, 2, 4, 6, and 8 hours following dosing.

**Figure 10-6
Intensive PK Procedures**

SPECIMEN	PRE-DOSE	1 HOUR	2 HOURS	4 HOURS	6 HOURS	8 HOURS
Blood draw <ul style="list-style-type: none"> • PBMC cell lysate (intracellular tenofovir diphosphate) (at sites with capacity) • Tenofovir 	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)
Blood draw <ul style="list-style-type: none"> • Flow cytometry 	Groups M, N, O, and P)					
Cervical cytology brush <ul style="list-style-type: none"> • Cell lysates (intracellular tenofovir diphosphate) • Tenofovir 	12 ppts (Group M)		12 ppts (Group N)	12 ppts (Group O)	12 ppts (Group P)	
CVL <ul style="list-style-type: none"> • Tenofovir • Proteomics and markers of inflammation 	Group M		Group N	Group O	Group P	
Vaginal biopsies <ul style="list-style-type: none"> • Cell lysates (intracellular tenofovir diphosphate) • Tenofovir 	Group M		Group N	Group O	Group P	
Rectal Fluid (Bronx-Lebanon Hospital Center CRS only)	Group M		Group N	Group O	Group P	

Cervicovaginal Lavage (CVL)

CVL samples will be taken after the following pelvic exam procedures; examination of the external genitalia, vagina, and cervix, assessment of pH and collection of swabs for wet prep, and before the cytology collection, vaginal biopsy and, if clinically indicated, bimanual examination. Lavage will be performed by rinsing the cervix with 10 ml of sterile saline with a syringe and then collecting the pooled fluid in the vaginal fornix with the same device.

Cervical Cytology Brush

The cervix must be visualized with the speculum in-situ under adequate lighting. A lubricant should not be used for insertion of the speculum. If bimanual examination is indicated, it should be carried out only after sampling to prevent lubricant contamination, trauma or dislodgment of diagnostic cells.

The cytobrush should be applied to with some degree of firmness to ensure maximal contact. Place the cytobrush in the cervical os and rotated around the full circumference (360° turns) at least two times. The cytobrush should be vigorously stirred in the solution for collection (see Section 12.7.3) so that an adequate sample is deposited into the solution. Slight bleeding at the cervix may occur and a small amount of blood in the sample will not interfere with interpretation. Similarly, a small amount of mucus in the sample does not affect interpretation.

Vaginal Biopsy

The vaginal biopsy will always be the last sample collected. After the cytobrush sample has been obtained, the vagina should be cleansed with a bacteriostatic solution. 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. Taking a nonsteroidal anti-inflammatory drug (NSAID), such as ibuprofen, 20 minutes before the procedure may help relieve any discomfort during the procedure.

Rectal Fluid

Participants at the Bronx-Lebanon Hospital Center CRS who opt to have rectal fluid samples taken, will have these samples taken after (within 15 minutes) the vaginal specimens are taken. A short (approximately 3 ½ inch length) and narrow (approximately 1 ½ inch diameter) hollow plastic tube called an anoscope will be used to help collect the rectal fluid samples. The anoscope will be placed gently into the participants' rectum, and two special swabs used to collect fluid will be placed in the anoscope. The swabs and anoscope will remain in the rectum for about 5 minutes.

10.10 Product Use Management

For this study, product use management may involve temporarily holding or permanently discontinuing either gel or pill use for individual study participants, to protect their safety and well-being while in the study. A participant may be temporarily or permanently discontinued from one study product and be eligible to use the other product; however, if a participant is temporarily or permanently discontinued from either study product, she cannot use any product during the dual period. Product use management in this study will not involve modification of the dose (one applicator or one pill) or route (intravaginal or oral) of product administration by any participant.

If a participant is permanently or temporary discontinued from oral study product, and if the Tenofovir 1% Gel Period has not yet begun for this participant, the investigator in consultation with the PSRT may decide that she may participate per protocol in the Tenofovir 1% Gel Period as scheduled according to her sequence randomization. If a participant is permanently or temporary discontinued from gel study product, and if the TDF 300 mg Oral Tablet Period has not yet begun for this participant, the investigator in consultation with the PSRT may decide that she may participate per protocol in the TDF 300 mg Oral Tablet Period as scheduled according to her sequence randomization. However, a participant who has been permanently or temporary discontinued from either type of study product will not take any study product during the Dual Formulation Period (if this study period has not yet begun for an individual participant), but will be followed according to regularly scheduled evaluations of safety, according to Protocol section 7.4.5.

It is the responsibility and obligation of the IoR and other authorized study clinicians to assess participants' eligibility for continued product use throughout their participation in the study.

Certain product use management decisions and actions must be undertaken, per protocol, under the direction of the study site IoR. Other product use management decisions and actions are undertaken, under the direction of the IoR/PI, in consultation with the MTN 001 PSRT as described in Section 11.

10.10.1 Circumstances In Which Product Use Must Be Either Temporarily Held or Permanently Discontinued

Product use must be temporarily held in the following circumstances:

- Evidence of vaginal biopsy may be apparent in follow-up examinations. Vaginal product use should not be held if the biopsy sites are healing normally with intact epithelium or healthy granulation tissue. Vaginal product use should be temporarily held if the investigator deems the biopsy site to be inappropriately healing with evidence of infection or other epithelial disruption. In these instances, the site must consult the PSRT.

With respect to documentation of vaginal biopsy sites, any biopsy site which is visible to the naked eye should be documented on the Follow-Up Pelvic Exam Form. While the majority of vaginal biopsy sites will be completely healed within four weeks after biopsy, it is not unusual to see evidence of a vaginal biopsy for up to 6 weeks. Evidence of a normally healing biopsy site within 6 weeks of biopsy is considered expected and therefore does not meet the requirement for adverse event reporting. Normally healing biopsy sites should show evidence of re-epithelialization. Abnormally healing biopsy sites, which should prompt adverse event reporting, include biopsy sites with evidence of infection at any time, evidence of bleeding after one week, or any other characteristics which the IoR deems to be abnormal and reason for concern.

- Vaginal product may be held if the participant has signs or symptoms of Grade 2 STI(s)/RTI(s) requiring treatment according to the discretion of the investigator and in consultation with the PSRT. Once treatment is complete and any symptoms have resolved, vaginal product use can be resumed. In cases in which the participant is in the dual study product period, if treatment is completed in a single dose and that participant is asymptomatic, study gel need not be held. If at the discretion of the IoR a participant is temporarily or permanently held from one study product, she will be eligible to use the other product; however, if a participant is discontinued from either study product, she cannot use any product during the dual period.

- The participant experiences a Grade 3 AE that is judged by the IoR or designee to be possibly, probably, or definitely related to product use. In general, and unless otherwise decided in consultation with the PSRT, the investigator should re-evaluate the participant at least weekly up to 2 weeks. If documentation is not available within two weeks to show that the adverse event is \leq Grade 2, the current study product must be permanently discontinued. To obtain approval for resumption of product use from the PSRT, the IoR or designee should submit a query to the PSRT, via the MTN 001 Protocol Safety Physicians, using the MTN 001 PSRT query form as described in Section Appendix 11-3. The PSRT will consider the query and provide a written response (or request more information) via email within three business days.

If the same Grade 3 adverse event recurs after reintroduction of study product, the current study product must be permanently discontinued if the investigator considers the adverse event possibly, probably, or definitely related to study product. However if the investigator determines that the toxicity is definitely not related to study product, participants may continue the study product and the PSRT must be notified.

- The participant experiences a Grade 4 adverse event, regardless of relationship to study product. If the investigator determines that the toxicity is definitely not related to study product(s), the IoR or designee will consult the PSRT to consider restarting study product(s), and product cannot be restarted until approval from the PSRT is obtained. The participant should be re-evaluated at least weekly up to 2 weeks. If documentation is not available within two week to show that the adverse even is \leq Grade 2, the current study product must be permanently discontinued.
 - *NOTE: The above product management guidelines are applicable to any adverse event experienced by the participant in addition to any genital conditions such as deep epithelial disruption, intermenstrual bleeding, and pelvic exam finding of generalized erythema or severe edema.*
- If a participant experiences Grade \geq 3 nausea and/or vomiting, oral study product must be held until the toxicity grade returns to Grade \leq 2 and be treated symptomatically.
- If a participant experiences new onset Grade \geq 3 diarrhea that is unresponsive to antimotility agents and for which an alternative etiology (e.g., infectious diarrhea) is not established, oral study product must be held until the toxicity grade returns to Grade \leq 2 or to baseline and be treated symptomatically.
 - *NOTE: Unless other product hold guidelines apply, vaginal study product need not be held for diarrhea or vomiting unless the investigator has compelling evidence that the toxicity is possibly, probably, or definitely related to vaginal study product.*
- If a participant experiences AST or ALT elevations \geq 3 ULN, oral study product must be held up to 2 weeks until the toxicity returns to Grade \leq 1 (with repeat measures done according to the clinical judgment of the investigator).

Product use must be permanently discontinued in the following circumstances:

- Study product-related toxicity requiring permanent discontinuation of study product(s) per Section 9 of the protocol
- Completion of regimen as defined in the protocol
- Request by participant to terminate study product(s)
- Clinical reasons determined by the physician
- HIV infection

NOTE: Study product should be held immediately after the first reactive rapid test or ELISA pending confirmatory WB testing. If participant is confirmed to be HIV uninfected per WB testing, product may resume. If HIV infection is confirmed, product must be permanently discontinued.

- Hepatitis B infection
- Pregnancy or breastfeeding
- Use of the following medications: acyclovir, valacyclovir, and tenofovir disoproxil fumarate/emtricitabine
- If documentation is not available within 2 weeks to show that a Grade 3 AE is \leq Grade 2, the current study product must be permanently discontinued.
- If documentation is not available within 2 weeks to show that a Grade 4 AE is \leq Grade 2, the study product(s) must be permanently discontinued. If the same Grade 4 adverse event recurs at either grade 3 or 4 level within 4 weeks of reintroduction of study product(s), study product(s) must be permanently discontinued.
- If Grade 4 elevation in AST or ALT, oral study product must be permanently discontinued. ALT/AST must be followed weekly until levels have returned to a Grade ≤ 1 .
- If documentation is not available within 3 weeks to show that a Grade 3 elevation in AST or ALT has not returned to Grade ≤ 1 , oral study product must be permanently discontinued.
- If documentation is not available within 1 week to show response to supplementation (resolution to ≤ 2) for a Grade 3 or 4 hypophosphatemia, the oral product must be permanently discontinued.
- If creatinine clearance is confirmed to be $<50\text{mL}/\text{min}$, the oral study product must be permanently discontinued.

10.10.2 Circumstances In Which Product Use May Be Either Temporarily Held or Permanently Discontinued

Product use may be either temporarily held or permanently discontinued, at the discretion of the IoR, under the following circumstances and in consultation with the PSRT:

- The participant is unable or unwilling to comply with required study procedures
- The participant might otherwise be put at undue risk to her safety and well-being by continuing product use

10.10.3 Documentation of Product Use Management

All product use management decisions must be thoroughly documented in participants' study charts. It is expected that signed and dated chart notes, together with correspondence to and from the PSRT, when applicable, will serve as the primary source documentation for these decisions; however other site-specific source documents also may be used. In addition to this documentation, product holds should be communicated to study pharmacy staff using the MTN 001 Study Product Hold/Resume/pK Supply/Re-supply Slip, as described in Section 6 and a Product Hold/Discontinuation case report form should be completed and faxed to the MTN SDMC, as described in Section 13.

10.10.4 Participant Follow-Up During Periods of Product Use Discontinuation

Participants who either temporarily or permanently discontinue product use will not routinely be withdrawn from the study. Rather, every effort will be made to complete all protocol-specified follow-up visits and procedures with these participants (with the exception of product-related procedures that are not applicable during the period of product use discontinuation).

10.10.5 Collection of Product Supplies During Periods of Product Use Discontinuation

If a participant becomes pregnant or experiences an adverse event that requires permanent discontinuation of product use, any unused applicators and/or pills remaining in her possession should be collected from her as soon as possible per the guidance provided in Figure 10-7 and returned to the pharmacy on the day of collection.

Figure 10-7: Retrieval of Study Product after discontinuation

Permanent discontinuation due to HIV seroconversion	Retrieve within 24 hours
Permanent discontinuation due to severe (Grade 3 or higher) renal or hepatic toxicity	Retrieve within 24 hours
Permanent discontinuation for any other reason	Retrieve within 5 working days
Temporary hold for any reason if there are safety concerns	Retrieve within 5 working days

For all product holds requiring collection of unused applicators and/or pills, if the applicators and/or pills are not collected within the timeframe specified in Figure 10-7, the MTN 001 PSRT must be informed, using the PSRT Query Form as described in Section Appendix 11-3. When informing the PSRT, please describe the reason for the product hold, actions taken to try to collect the unused applicators and/or pills, and plans and timelines for further action to collect the study product.

10.11 Pregnancy Management

Please refer to the Section 6 of this manual for procedural instructions for management of participant pregnancies that may occur during follow-up.

Section Appendix 10-1
Scenarios for AE Grading using Female Genital Toxicity Table

10-1.1 During the Screening/Enrollment Visit, Ms. X reports that her menses usually occur every four weeks and lasts for five to seven days. She gives no previous history of intermenstrual or prolonged/heavy bleeding. When she returns for her 6-Week Clinic Visit, she reports that her menses started that day, approximately one week earlier than expected. What procedures should be followed?

- Depends on the clinician’s judgment. If the clinician considers this event to be early onset menses, this event should not be reported as an AE. However, if the clinician considers this event to be unexpected bleeding, then report this genital bleeding as an AE using the term metrorrhagia and grade according to the Female Genital Toxicity Table under “Abnormal Uterine Bleeding Unrelated to Pregnancy”. The Clinician should perform a pelvic exam for further evaluation.

Why? This event is considered metrorrhagia if it is unexpected (i.e. her baseline history does not have any previous history of intermenstrual bleeding).

10-1.2 Continuing from the scenario above, suppose the clinician judged the genital bleeding to be unexpected and decided to conduct a safety visit to follow up on the AE of metrorrhagia. At the Follow up Clinic Visit, seven days later the participant is still bleeding. What would you do?

- Update item 1 of the metrorrhagia AE log form to “menometrorrhagia”, and grade according to menorrhagia row in the Female Genital Toxicity Table under “Abnormal Uterine Bleeding Unrelated to Pregnancy”. The clinician should perform a pelvic exam for further evaluation. The clinician should attempt to follow this AE until resolution.

Why? The prolonged menses is part of the same bleeding event reported on the previous visit; therefore the term used to describe this event needs to be updated to reflect the participant’s current bleeding symptoms. Grade this event per the Female Genital Toxicity table.

10-1.3 Ms. Y reports at her 10-Week Clinic Visit that she had menstrual cramps during her last period that were so painful that she stayed home from work, in bed, for two days. Generally this participant has very mild menstrual symptoms, if any. What would you do?

- Report this event as an AE using the term dysmenorrhea and grade according to the Female Genital Toxicity Table under “General”. The Clinician should perform a pelvic exam for further evaluation.

Why? The reported menstrual cramps are a change from this participant’s baseline menstrual symptoms. It is important that the clinician evaluates if there is an anatomical reason why the participant is having pain.

Section Appendix 10-1
Scenarios for AE Grading using Female Genital Toxicity Table

10-1.4 Suppose instead, Ms. Y reports to the Clinic at her 10-Week Clinic Visit and reports that two days ago, she experienced some vaginal spotting after having sex with her partner. What would you do?

- Report this event as an AE of Postcoital Bleeding, and grade according to the Postcoital Bleeding Row in the Female Genital Toxicity Table. Clinician should perform a pelvic exam for further evaluation (e.g. anatomical location of bleed).
- If the clinician identifies the anatomical source of bleeding, the adverse event should be reported using the anatomical site (e.g., cervical friability)

Why? Postcoital bleeding is considered unexpected non-menstrual bleeding, and should be considered an AE. The term “metrorrhagia” (intermenstrual bleeding) *should not* be used to describe this AE.

10-1.5 Ms. Z reported at baseline that her usual menstrual cycle is about 29 days and that she usually has 8 menstrual bleeding days per cycle. At her last weekly visit, Ms. Z reported that her last menses lasted 9 days. Should this be reported as an AE?

- If the reported length of bleeding is greater than baseline, you must grade according to the “Menorrhagia” row under “Abnormal Uterine Bleeding Unrelated to Pregnancy” in the Female Genital Toxicity Table and determine whether an increase in severity has occurred. If there is an increase in severity you would need to report the occurrence of menorrhagia at the higher severity grade as an AE.

Why? Ms. Z should be considered to have menorrhagia as a pre-existing condition (menses lasting longer than 7 days). At baseline you will need to grade the pre-existing menorrhagia based on the guidance provided in the Female Genital Toxicity Table under “Abnormal Uterine Bleeding Unrelated to Pregnancy” and record the grade on the Baseline Medical History form and Pre-Existing Conditions form. By having this information recorded on the Baseline Medical History form and Pre-Existing Conditions form, you will be able to assess whether or not an AE has occurred and the grade of the AE.

Section Appendix 10-1
Scenarios for AE Grading using Female Genital Toxicity Table

10-1.6 At her 10-Week Clinic Visit, Ms. P has a positive pregnancy test. She discontinues study product use per protocol, but she agrees to stay in the study for follow up. At her 13-Week Clinic Visit, she reports genital bleeding. What should you do?

- Take a detailed history and determine whether the bleeding, and possible abortion, was induced or spontaneous.
- Report this AE using clinically appropriate terminology reflecting the cause or source of the bleeding. If this is a spontaneous abortion, use the correct terminology including the term spontaneous. Grade this AE according to the *Complications of Pregnancy* row of the Female Genital Toxicity Table. The participant should be referred to a qualified clinician for further evaluation, care and treatment.
- If this is an elective abortion (e.g. the patient took an herbal inducement) this would not be an adverse event and should only be reported if the bleeding is unexpected.

Why? The term “metrorrhagia” (intermenstrual bleeding) should not be used in this case because the participant is pregnant, and the bleeding may be associated with complication in pregnancy.

10-1.7 Suppose Ms. W reports at her 3-Week Clinic Visit she had vaginal itching, rash, and vaginal discharge two days before the clinic visit. On the day of the visit, the clinician performs a pelvic exam and notices an area with erythema and another area with an edema. What do you do?

- Determine if all these signs and symptoms could be grouped together as one condition. Since all these symptoms/signs are related, report this event as an AE and grade according to the Female Genital Toxicity Table under “Composite Signs/Symptom.”

Why? Whenever possible and particularly if two or more signs/symptoms are present, you will use a diagnosis for reporting instead of individual categories.

10-1.8 At her 3-Week Clinic visit, Ms. T reports vaginal discharge. During the pelvic exam, a wet prep is collected for Wet Mount testing. When the wet prep slide is read, yeast is observed. What do you do?

- Complete an AE log for vaginal candida or yeast vaginitis and grade according to the Genitourinary Infection section of the Female Genital Toxicity Table. Treat this participant in accordance with current WHO Sexually Transmitted Infections Treatment Guidelines. Product may be temporarily discontinued for this participant, based on the judgment of the investigator.

Why? Product may be temporarily held for this participant at the judgment of the investigator, per the MTN 001 protocol, Section 9.5.6.