Section 10. Clinical Considerations

This section presents information on the clinical procedures performed in HPTN 035. 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.

NOTE: Effective with Version 2.0 of this section, prior references to the HIV Prevention Trials Network (HPTN) have been replaced where applicable with references to the Microbicide Trials Network (MTN).

10.1 Baseline Medical/Menstrual History and Ascertainment of Concomitant Medications

A focused baseline medical/menstrual history is obtained from potential study participants at Screening Part 2. Medications used by the participant also are ascertained and documented at this time. The purpose for obtaining this information during screening is two-fold:

- To assess and document participant eligibility for the study
- To assess and document the participants' baseline medical conditions, for comparison with signs, symptoms, and conditions that may be identified or reported during follow-up

10.1.1 Focused Baseline Medical/Menstrual History

The non-DataFax Baseline Medical History form is a recommended source document for collecting pertinent medical/menstrual history data. Alternative site-specific history forms also may be used. For enrolled participants, all ongoing baseline conditions identified prior to randomization also are documented on the (DataFax) Pre-existing Conditions form. Recurring and/or chronic conditions are considered ongoing whether or not they are present/active at baseline.

When obtaining a focused baseline medical/menstrual history for HPTN 035, it is not necessary to document the participant's lifetime medical history. Rather, focus on conditions that have occurred since the participant became sexually active, and 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 listing of body systems on the Baseline Medical History form to probe for history related to each system.
- Record symptoms, illnesses, allergies, and surgeries.
- 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. 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.

- For all genitourinary subcategories listed on the Baseline Medical History form, probe for and record as much detail as possible. Detailed baseline information in these categories is critical, since changes from baseline will be considered adverse events (AEs; see Section 11). As part of the "other" genitourinary subcategory, explore whether the participant experiences bleeding during or after vaginal intercourse and whether she has experienced (or continues to experience) any type of sexual trauma.

- For reproductive history, record the number, date, and outcome of each of the participant's pregnancies, as well as any gynecologic and obstetrical procedures/surgeries.

- Record the participant's history of contraceptive use. If applicable, enter details of the participant's current contraceptive method on the Concomitant Medications Log form. Per Section 3.4 of the study protocol, spermicides, diaphragms, and contraceptive vaginal rings should not be used during participation in HPTN 035. Participants who report current use of these contraceptive products and devices during screening must be counseled regarding the use of alternative methods and should be referred to family planning services if needed 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 judgement — together with any advice available from Community Advisory Board members or others — to determine the best phrasing in local languages to elicit complete and accurate history information from study participants.

10.1.2 Initial Ascertainment of Concomitant Medications

The HPTN 035 protocol requires documentation of all medications taken by study participants beginning at Screening Part 2 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

Intravaginal medications/preparations and topical medications/preparations applied to the external genitalia are of particular interest for this study, as are douches and vaginal cleansers. Be sure to record all such medications/preparations.

The Concomitant Medications Log form is the recommended source document for collecting information on participants' use of medications. When recording the route of medications/preparations that are applied intravaginally, mark the "other, specify" box and enter "vag" on the line provided.

It is recommended that study clinicians ascertain participants' baseline medication information in the context of conducting 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.

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/colposcopic exam described below — is to document participants' baseline medical conditions, for comparison with signs, symptoms, and conditions that may be identified or reported during follow-up. For HPTN 035, all ongoing medical conditions, problems, signs, symptoms, and (abnormal) findings existing prior to randomization 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 pre-existing conditions also 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 History form, Physical Exam form, Screening Pelvic Exam form, all screening laboratory results, chart notes, and any other site-specific source documents.

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 prior to randomization/enrollment in the study and therefore are not considered AEs. However, new conditions identified during follow-up that were not present prior to randomization, and any pre-existing conditions that increase in severity or frequency during follow-up, are 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 baseline (pre-randomization) 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" box for each condition.

10.2 Interval Medical/Menstrual History and Updating of Concomitant Medications

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

10.2.1 Interval Medical/Menstrual History

The non-DataFax Follow-up Medical History Form is a recommended source document for collecting interval medical/menstrual history data.

At the first follow-up visit, retrieve the participant's Baseline Medical History and Pre-existing Conditions forms for reference. At each subsequent visit, retrieve the participant's Follow-up Medical History form from the prior visit for reference. When completing each interval history, it is not necessary to actively review/inquire about every body system listed on the Follow-up Medical History Form. Rather, for all systems except genitourinary, it is acceptable to actively inquire about the current status of ongoing conditions recorded at the prior visit, and then to ask an participant open-ended question such as "Have you had any other symptoms or health problems since your last visit?" to complete the history. For the genitourinary categories, actively inquire as to whether the participant experienced each of the symptoms listed on the form since her last visit.

See Section 10.5 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 local languages to elicit complete and accurate follow-up information from study participants.

At quarterly follow-up visits, participants will complete a Follow-Up Behavior Assessment (FBA) interview prior to the clinical portion of the visit. The FBA collects standardized participant reports of use of various contraceptive methods and vaginal products in the last three months. Clinicians are advised to cross-reference the FBA form at quarterly visits and to use FBA responses as a basis for probing for updates to record in applicable sections of the Follow-Up Medical History form. Per Section 3.4 of the study protocol, spermicides, diaphragms, and contraceptive vaginal rings should not be used during participation in HPTN 035. Participants who report use of these contraceptive products and devices during follow-up must be counseled regarding the use of alternative methods and should be referred to family planning services if needed for provision of alternative methods. If an enrolled participant reports an unwillingness to discontinue use of a contraindicated contraceptive product or device during follow-up, contact the HPTN 035 Protocol Safety Review Team (PSRT) for guidance on appropriate action to be taken.

Note: *It is recognized that in some circumstances it may not be possible for study clinicians to review participants' FBA responses prior to conducting interval medical/menstrual histories. It also is acknowledged that detailed clinical probing of FBA responses may identify discrepancies between the FBA data and the history information recorded by the clinician. For example, a participant might report insertion of an intrauterine device (in error) in her FBA, but then identify that no such procedure took place after more in-depth discussion with the study clinician. In the event that such discrepancies occur, information recorded by the clinician will be considered primary for purposes of monitoring participants' clinical condition and documenting clinical study endpoints. In order to preserve the standardization of behavioral data collection, however, FBA responses should not be amended to correspond with the information recorded by the clinician. Clinicians will explain such discrepancies in notes entered in participant study records whenever possible.*

10.2.2 Updating of Concomitant Medications Information

At each visit in which an interval medical/menstrual history is obtained, retrieve the participant's previously completed Concomitant Medications Log, record any new medications provided to the participant by study staff, 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. 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 form.

As noted above, at quarterly follow-up visits participants will complete a Follow-Up Behavior Assessment (FBA) interview prior to the clinical portion of the visit. The FBA collects standardized participant reports of use of various contraceptive methods and vaginal products in the last three months. Clinicians are advised to cross-reference the FBA at quarterly visits and to use FBA responses as a basis for probing for updates to record on the Concomitant Medications Log form. The italicized note at the end of Section 10.2.1 applies here as well.

10.3 Physical Exams

A complete physical exam is required at Screening Part 2. This exam should include the assessments listed below:

Vital signs:
- Weight
- Height
- Oral temperature
- Blood pressure
- Pulse
- Respirations

Clinical assessments of:
- Head and eyes (HE)
- Ears, nose, and throat (ENT)
- Neck
- Lymph nodes
- Heart
- Lungs
- Abdomen
- Extremities
- Neurological
- Skin
- Breasts

Additional assessments may be performed at the discretion of the examining clinician in response to symptoms or illnesses present at the time of the exam.

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 Screening Part 2 also are recorded on the (DataFax) 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.

10.4 Pelvic/Colposcopic Exams

Pelvic exams are performed in HPTN 035 for purposes of determining eligibility and identifying primary study safety outcomes. As such, they are critical to meeting the study objectives and to ensuring the ongoing safety of study participants. Pelvic exams are performed at Screening Part 2 and routinely during follow-up, per the schedule in protocol Section 5.4. Exams also are performed when clinically indicated to evaluate genital symptoms.

Colposopy was included as a required component of pelvic exams among a subset of participants in the Phase II portion of the study. Colposcopy was performed among:

- All Phase II participants at the Philadelphia study site (n=100)
- All Phase II participants at the Harare-Chitungwiza study site (n=51)
- The first 150 Phase II participants across non-US study sites performing colposcopy (n=84 in Durban and n=66 in Lilongwe)

The MTN CORE and SDMC utilized data provided by all study sites to closely track the number of participants enrolled in the Phase II portion of the study and informed non-US sites when the targeted number of colposcopy participants was reached.

Pelvic/colposcopic 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:

At Screening Part 2:

- Pelvic Exam Diagrams
- Screening Pelvic Exam
- Repeat Screening Pelvic Exam (if applicable)
- Screening Part 2 Laboratory Results

During Follow-Up:

- Pelvic Exam Diagrams
- Pelvic Exam
- Pelvic Laboratory Results

For participants who enroll in the study, abnormal exam findings identified at Screening Part 2 (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.

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 after each participant's first 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 exam, 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 and gram stain.

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.

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

Use of Magnification: For each area examined, i.e., the external genitalia, cervix, and vagina, first perform naked eye exam. Then proceed to colposcopic exam — during Phase II, for colposcopy participants only — using low power (x4-10 magnification) and no filter to more closely examine the tissues. Colposcopic examination of the external genitalia must precede insertion of the speculum.

Documentation of Findings: Document all exam findings — both normal and abnormal — on the Pelvic Exam Diagrams form. Document abnormal findings only on the Screening Pelvic Exam and Pelvic Exam case report forms. The Screening Pelvic Exam form and 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. For participants who enroll in the study, abnormal exam findings identified at Screening Part 2 (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.

Imaging: Digital imaging was used to document abnormal colposcopic exam findings. After obtaining IRB/EC approval of protocol Letter of Amendment #1, and associated informed consent forms, study sites were permitted to use digital imaging to also document normal findings/conditions at baseline (i.e., at Screening Part 2).

- Save at least one image of each abnormal finding. Save images before probing or swabbing any findings, and take as many images as needed to capture all abnormal findings. Use appropriate magnification to ensure that all margins are captured in the image. Note the magnification used.

- Adjust the light intensity to produce the best image possible.

- Instruct the participant to hold her breath during imaging.

- Save all images electronically; back up all media routinely. Label and store printed images in participant study charts. SCHARP-provided PTID labels may be used for this purpose; the date of the image and the anatomic location of the finding may be written on the label or on the back of the image.

10.4.2 Detailed Procedural Instructions

Note: *Routine pelvic exams, i.e., those required at protocol-specified timepoints, 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. If a participant is menstruating when she presents for a visit in which a routine pelvic exam is required, perform other protocol-specified procedures at the visit and schedule the participant to return for the pelvic exam as soon as possible after menses, within the allowable visit window. 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 an exam as soon as possible after menses.*

Note: *See Section 6.8 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 and that the colposcope, computer, software, and printer are warmed up and ready for use (for exams involving colposcopy). 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.
- For exams involving colposcopy, proceed to colposcopic examination of the same areas, using appropriate magnification.
- Note all findings on the Pelvic Exam Diagrams form. Further document abnormal findings on the Screening Pelvic Exam form (at screening) or Pelvic Exam form (during follow-up). Save digital images of abnormal colposcopic findings per Section 10.4.1. After obtaining IRB/EC approval of protocol Letter of Amendment #1, and associated informed consent forms, study sites also may save images of normal findings/conditions at baseline (i.e., at Screening Part 2).

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.

- During exams not involving colposcopy, assess cervical ectopy at this time. During exams involving colposcopy, assess cervical ectopy during the colposcopic exam.

- Assess for homogenous discharge. Record outcome on the Screening Part 2 Laboratory Results form (at screening) or the Pelvic Laboratory Results form (at follow-up). If homogenous discharge is present, document the discharge on the Pelvic Exam Diagrams and in item 1 on the Screening Pelvic Exam form (at screening) or the Pelvic Exam form (during follow-up). If any other abnormal vaginal or cervical discharge and/or blood-tinged discharge is present, also document that discharge in item 1 on the Screening Pelvic Exam form (at screening) or the Pelvic Exam form (during follow-up).

- Place pH indicator strip against lateral vaginal wall, just until the paper is moistened. Avoid contact with cervical mucus, which has a high pH. Alternatively, vaginal fluids may be collected via swab and then swabbed onto the pH strip (instead of inserting the pH strip into the vagina). 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 Screening Part 2 Laboratory Results form (at screening) or the Pelvic Laboratory Results form (at follow-up).

- Collect vaginal fluids via (dry) swab for wet prep and gram stain. Collect fluids from the lateral vaginal wall, away from any apparent abnormalities. Exclude swabbed areas from subsequent examination. Document specimen collection for gram stain on the Screening Pelvic Exam form (at screening) or the Pelvic Exam form (at follow-up). See Section 12.6 of this manual for detailed wet prep and gram stain slide preparation and assessment procedures. If wet prep slides are read in-clinic by clinical staff, record results directly onto the Screening Part 2 Laboratory Results form (at screening) or the Pelvic Laboratory Results form (at follow-up). If slides are read by lab staff (either in the local laboratory or in a designated in-clinic lab area), record results onto laboratory log sheets or other laboratory source documents and then transcribe the results onto the appropriate case report form.

- At non-US sites, after all required IRB/EC approvals of Letter of Amendment #1 of protocol Version 3.0 are obtained, among consenting participants, swab vaginal fluids from the posterior fornix for specimen archive; see Section 12.6.5 of this manual for further instructions for proper swab handling and storage prior to shipment to the MTN Network Laboratory (NL). Document specimen collection on the Vaginal Swab Collection form and LDMS Specimen Tracking Sheet.

- If needed, lavage the cervix and vagina as described in Section 10.4.1 and complete naked eye exam.

- For exams involving colposcopy, proceed with colposcopic examination of the cervix, fornices (anterior, right lateral, left lateral, and posterior), and adjacent cervical trunk using appropriate magnification (usually 4-10X). If excessive glare occurs, reposition to alter the illumination angle. If necessary, manipulate the speculum slightly so the fornices may be adequately visualized. The lateral fornices are best exposed by placing a saline-moistened large swab (scopette) into the contralateral fornix and pressing toward the participant's head and laterally. For example, to view the right lateral fornix, place the moistened swab into the left lateral fornix and press gently toward the participant's head and left side. Do not use dry swabs for this purpose.

- Note all findings (variants of normal and abnormal) on the Pelvic Exam Diagrams form. Further document abnormal findings on the Screening Pelvic Exam form (at screening) or Pelvic Exam form (during follow-up). Save images of abnormal colposcopic findings per Section 10.4.1.

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 Screening Pelvic Exam form (at screening) or Pelvic Exam form (during follow-up). Save images of abnormal colposcopic findings per Section 10.4.1. After obtaining IRB/EC approval of protocol Letter of Amendment #1, and associated informed consent forms, study sites also may save images of normal findings/conditions at baseline (i.e., at Screening Part 2).

Collect Genital Ulcer Swabs: If any genital ulcers are observed during follow-up, swab the base of the ulcer using a dry plastic shaft Dacron swab. If a cluster of ulcers is observed, sample each ulcer in the cluster with the same swab. Otherwise use a different swab for each ulcer. Document specimen collection on the Pelvic Exam form and LDMS Specimen Tracking Sheet. See Section 12.6.4 of this manual for further instructions for proper swab handling and storage prior to testing at the HPTN NL.

Collect Pap Smear: At visits when a Pap smear is required (per protocol Section 5) collect ecto- and endocervical cytobrush specimens after completing all naked eye and colposcopic tissue examinations. Document specimen collection on the Screening Pelvic Exam form (at screening) or Pelvic Exam form (during follow-up) and transcribe results, when available, onto the Pap Test Result form. For enrolled participants, abnormal results identified at Screening Part 2 also should be transcribed onto the Pre-existing Conditions form. In the event that specimens collected for Pap smear at protocol-required timepoints are not evaluable, additional specimens should be collected at the first study visit occurring at least six weeks after collection of the inadequate specimens. For example, for inadequate Pap smear specimens collected at Screening Part 2, additional specimens generally should be collected at the participant's Month 2 visit; for inadequate specimens collected at Month 12 and Month 24, additional specimens generally should be collected at the participant's Month 14 and Month 26 visits, respectively.

Perform Bimanual Exam: 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.

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

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

Epithelium

Integrity:

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

Color:

- Normal
- Slightly red
- Red
- White
- Other (includes "pale")

Blood Vessels

Integrity:

- Intact
- Disrupted

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, 2002) for further examples of terminology applied to pelvic exam findings in microbicide studies.

The Screening Pelvic Exam form and 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 HPTN 035 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.

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" 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. Any questions related to genital bleeding assessment or AE reporting for pregnant participants should be submitted to the HPTN 035 PSRT.

10.5.2 Participant Reports of Genital Bleeding

As part of the HPTN 035 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 scheduled follow-up visit, study 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.

10.5.3 Clinician Assessment of Genital Bleeding

Study participants will undergo pelvic exams monthly during the first three months of the Phase II portion of the study and quarterly thereafter during the Phase IIb portion of the study. 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. 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 13.6) 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.

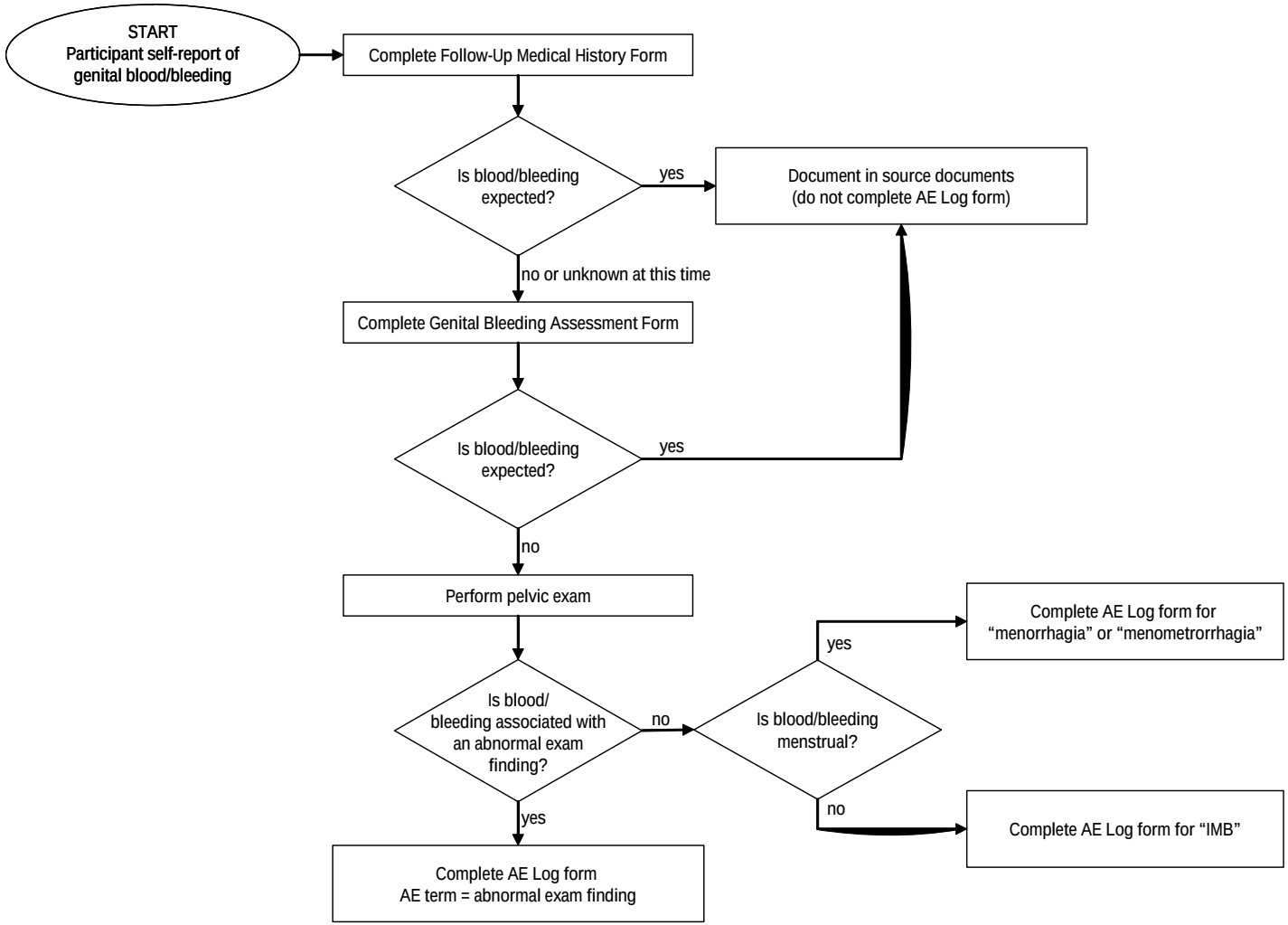
The Genital Bleeding Assessment form must be completed for participants who:

- 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:

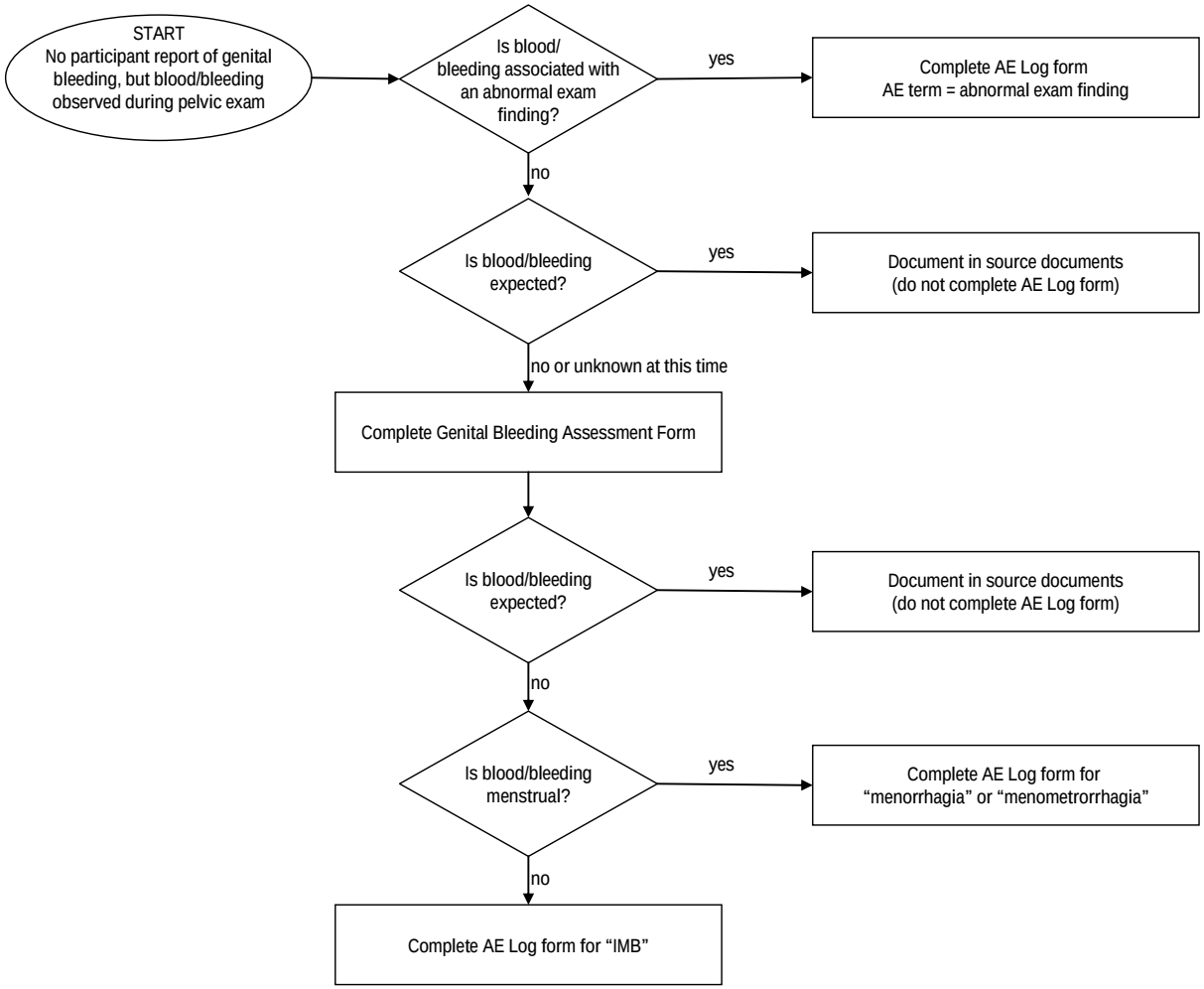
- Self-report genital bleeding that is determined to be expected prior to completion of the form
- Do not self-report genital bleeding but have genital blood/bleeding observed on pelvic exam that is associated with an abnormal exam finding.
- Do not self-report genital bleeding but have genital blood/bleeding 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 HPTN 035 — Beginning with Participant Report of Bleeding



Note: This algorithm is followed for non-pregnant participants only (see Section 10.5.1) 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 HPTN 035 — Beginning with Clinical Observation of Blood/Bleeding



Note: This algorithm is followed for non-pregnant participants only (see Section 10.5.1) 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 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 Follow-up Medical History form and the Monthly or Quarterly Visit (MQV) form. All clinically observed genital blood/bleeding will be documented on the Pelvic Exam Diagrams form and the Pelvic Exam form. 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 six 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 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 one of 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 guide for estimating severity grade on page 3 of the DAIDS Toxicity Table.

- Expected non-menstrual bleeding should not be reported as an AE.

- 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 "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 intermenstrual bleeding (IMB). 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 metrorrhagia, 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 listing for IMB on page 13 of the DAIDS Toxicity Table.

- Genital hemorrhage should be reported as an AE using the term "hemorrhage" together with terminology indicating the anatomical location of the hemorrhage (i.e., vaginal, cervical, or uterine). Alternatively, if the location is not known, the term "genital hemorrhage" should be used. Grade these AEs per the listing for hemorrhage on page 6 of the DAIDS Toxicity Table.

10.6 STD/RTI Management

Clinical and laboratory evaluations are performed throughout the course of HPTN 035 to diagnose the following sexually transmitted diseases and other reproductive tract infections (STDs/RTIs):

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

In addition, blood testing for herpes simplex virus 2 (HSV-2) will be performed in batch toward the end of study implementation.

Signs and symptoms commonly associated with the above-listed infections are presented in Figure 10-4. 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 10-4
Signs and Symptoms Commonly Associated with STDs/RTIs

STD/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.
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, condylomata lata (fleshy, moist tissue growths), lymphadenopathy, alopecia, or other signs.
Syphilis infection — latent	Patients are without clinical signs of infection.
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.

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 STD/RTI Treatment

STDs/RTIs will be treated in accordance with current WHO Guidelines for the Management of Sexually Transmitted Infections except that asymptomatic candidiasis will not routinely be treated. Current WHO guidelines are available at the following web site:

http://www.who.int/reproductive-health/publications/rhr_01_10_mngt_stis/index.html

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

Asymptomatic BV and asymptomatic candidiasis should not be treated. Please refer to the HPTN 035 Questions and Answers (Q&A) for further guidance on this topic. The HPTN 035 Q&A also provides guidance related to provision of laboratory-based versus syndromic treatment in HPTN 035. The Q&A can be found at the following web site:

http://www.hptn.org/research_studies/HPTN035QuestionsAndAnswers.htm

Figure 10-5 summarizes the 2003 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. The HPTN 035 Questions and Answers provide further guidance on the preferred use of oral versus intravaginal treatment options for symptomatic candidiasis in HPTN 035.

Figure 10-5
WHO Treatment Guidelines for STD/RTI Diagnosed in HPTN 035

STD/RTI	WHO Treatment Guideline
Bacterial vaginosis	For symptomatic patients only. Recommended: • Metronidazole, 400 or 500 mg orally twice daily for 7 days Alternative: • Metronidazole, 2 g orally, as a single dose • Clindamycin vaginal cream 2%, 5 g intravaginally, at bedtime for 7 days • Metronidazole gel 0.75%, 5 g intravaginally, twice daily for 5 days • Clindamycin, 300 mg orally, twice daily for 7 days
Candidiasis	For symptomatic patients only (per HPTN 035 protocol). Recommended: • 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 Alternative: • Nystatin, 100 000 IU intravaginally, daily for 14 days
Chlamydia infection (uncomplicated anogenital infection)	Recommended: • Azithromycin, 1 g orally, as a single dose • Doxycycline, 100 mg orally, twice daily for 7 days (contraindicated in pregnancy and lactation) Alternative: • Amoxycillin, 500 mg orally, three times daily for 7 days • Erythromycin, 500 mg orally, four times daily for 7 days • Ofloxacin, 300 mg orally, twice daily for 7 days • Tetracycline, 500 mg orally, four times daily for 7 days
Genital herpes (first clinical episode)	Recommended: • Acyclovir, 200 mg orally, five times daily for 7 days • Acyclovir, 400 mg orally, three times daily for 7 days • Valaciclovir, 1000 mg orally, twice daily for 7 days • Famciclovir, 250 mg orally, three times daily for 7 days

Figure 10-5
WHO Treatment Guidelines for STD/RTI Diagnosed in HPTN 035

STD/RTI	WHO Treatment Guideline
Genital herpes (recurrent episodes of genital lesions)	Recommended: • Acyclovir, 200 mg orally, five times daily for 5 days • Acyclovir, 400 mg orally, three 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
Gonorrhea infection (uncomplicated anogenital infection)	Recommended: • Ciprofloxacin, 500 mg orally, as a single dose (contraindicated in pregnancy, not recommended for children or adolescents) • Ceftriaxone, 125 mg IM injection, as a single dose • Cefixime, 400 mg orally, as a single dose • Spectinomycin, 2 g IM injection, as a single dose
Syphilis infection (early infection)	Recommended: • Benzathine benzylpenicillin, 2.4 million IU, IM injection, at a single session (usually two injections at separate sites) Alternative: • Procaine benzylpenicillin, 1.2 million IU, IM injection, daily for 10 consecutive days Alternative for penicillin-allergic non-pregnant patients: • Doxycycline, 100 mg orally, twice daily for 14 days • Tetracycline, 500 mg orally, four times daily for 14 days Alternative for penicillin-allergic pregnant patients: • Erythromycin, 500 mg orally, four times daily for 14 days
Trichomoniasis	Recommended: • Metronidazole, 2 g orally, as a single dose • Tinidazole, 2 g orally, as a single dose Alternative: • Metronidazole, 400 or 500 mg orally, twice daily for 7 days • Tinidazole, 500 mg orally, twice daily for 5 days • Other 5-nitroimidazoles also are effective

STD/RTI tests of cure are not required in HPTN 035; however clinical management of syphilis infections should include repeat serology (RPR) at quarterly intervals following diagnosis of a new infection to confirm treatment effectiveness. If syphilis is diagnosed during screening, a four-fold decrease in titre is not required prior to enrollment. Assuming the participant is otherwise eligible for the study, enrollment may proceed following treatment and resolution of symptoms, if any (see also Section 10.6.2 and Section Appendix 4-1). For enrolled participants, if syphilis is diagnosed during follow-up, and the RPR titre does not decrease four-fold or revert to seronegative within three months of treatment, treatment should be repeated. Please contact the HPTN NL with any questions related to quarterly testing to confirm treatment effectiveness and/or interpretation of unusual syphilis test results.

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

- Do not consider STD-related notations on Pap smear result reports when assessing participant eligibility for the study. Use only the results of protocol-specified STD tests for purposes of eligibility determination.

- If protocol-specified STD 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 STD-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 STD 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.

10.6.2 Screening and Enrollment Considerations

Potential study participants diagnosed during screening with an STD/RTI requiring treatment per WHO guidelines — other than asymptomatic candidiasis — and/or who have a screening pelvic exam finding involving deep epithelial disruption, may be enrolled in the study after completing treatment (if applicable) and all symptoms have resolved, provided that all required treatment is completed and all exclusionary conditions are resolved within 30 days of beginning the screening process (see also Section 4 of this manual). Flow charts depicting the required sequence of events prior to enrollment are presented in Figures 10-7 and 10-8. Summary information also is provided in Figure 10-8. Further detailed guidance is provided on the visit checklists provided in Section 7 of this manual. The screening and enrollment scenarios in Section Appendix 4-1 also provide examples of STD/RTI treatment and management vis-à-vis enrollment in the study.

With regard to syphilis in particular, if a reactive RPR is identified during screening, a confirmatory test (MHA-TP or TPHA) result must be received, and appropriate clinical management action taken, prior to enrollment in the study.

If a participant's test results and medical history are indicative of a current syphilis infection (requiring treatment per WHO guidelines), but the participant is otherwise eligible for the study, enrollment may proceed immediately following completion of treatment and resolution of symptoms, if any.

If a participant's test results and medical history are indicative of a prior syphilis infection, action required prior to enrollment depends on the current health status of the participant and the availability of medical records documenting her prior infection, as follows:

- If the participant has clinical signs or symptoms of syphilis, she must be treated prior to enrollment. If the participant is otherwise eligible for the study, enrollment may proceed immediately following completion of treatment and resolution of symptoms, if any.

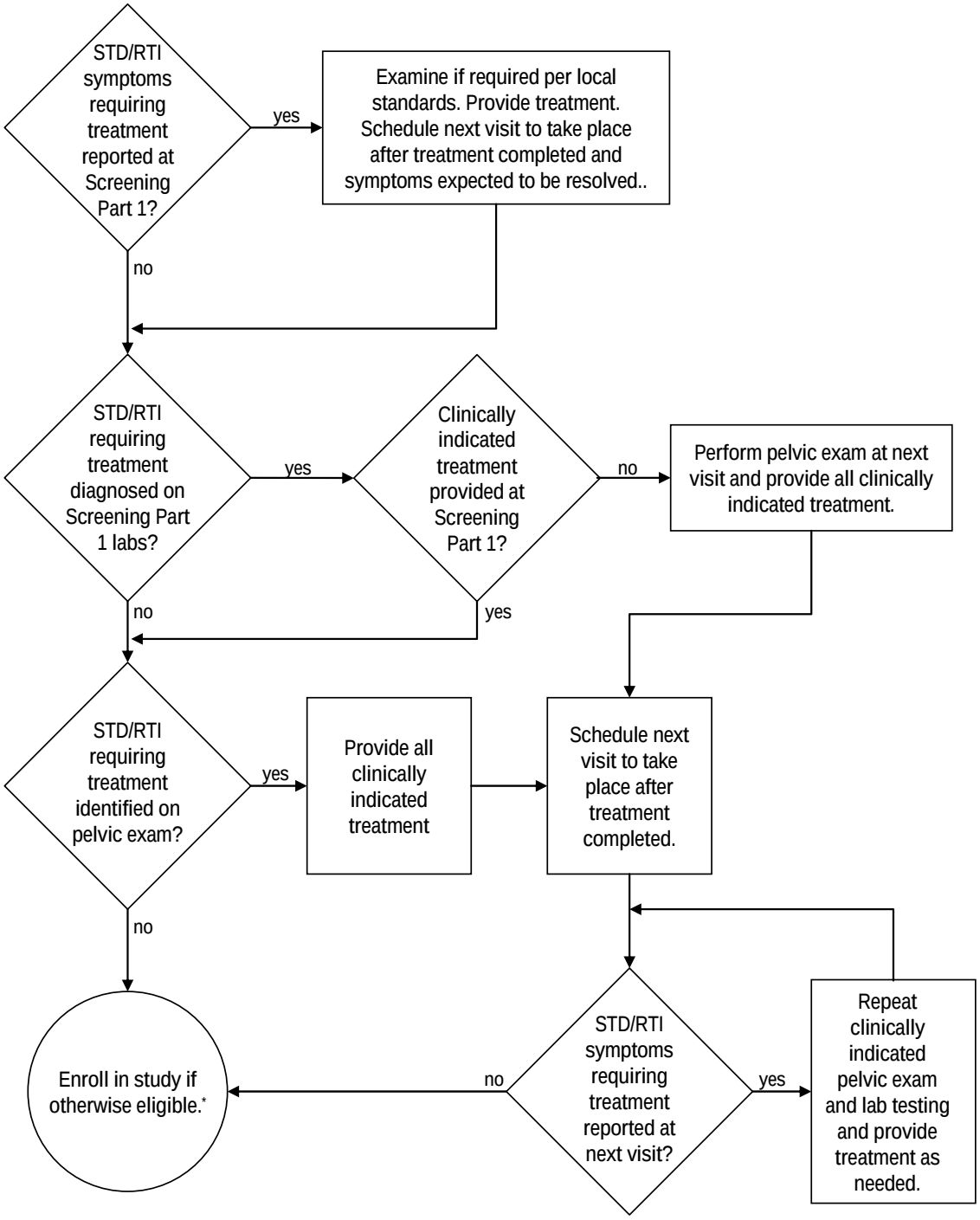
- If the participant has no clinical signs or symptoms of syphilis, but credible medical records are not available to document adequate treatment of a prior syphilis infection (per WHO guidelines), the participant must be treated prior to enrollment. If the participant is otherwise eligible for the study, enrollment may proceed immediately following completion of treatment. Should the Investigator of Record (IoR) or designee judge for any reason that treatment is not required, approval to enroll the participant without providing treatment must be obtained from the HPTN 035 PSRT prior to enrollment.

- If the participant has no clinical signs or symptoms of syphilis, and credible medical records are available to document adequate treatment of a prior syphilis infection (per WHO guidelines), but the participant's current RPR titre is greater than 1:4, consult the HPTN 035 PSRT for guidance on whether treatment is required prior to enrollment. Should the Investigator of Record (IoR) or designee judge for any reason that treatment is not required, approval to enroll the participant without providing treatment must be obtained from the HPTN 035 PSRT prior to enrollment.

- If the participant has no clinical signs or symptoms of syphilis, and credible medical records are available to document adequate treatment of a prior syphilis infection (per WHO guidelines), and the participant's current RPR titre is 1:4 or lower, the participant may be enrolled in the study without providing treatment at the discretion of the IoR or designee, without consulting the HPTN 035 PSRT.

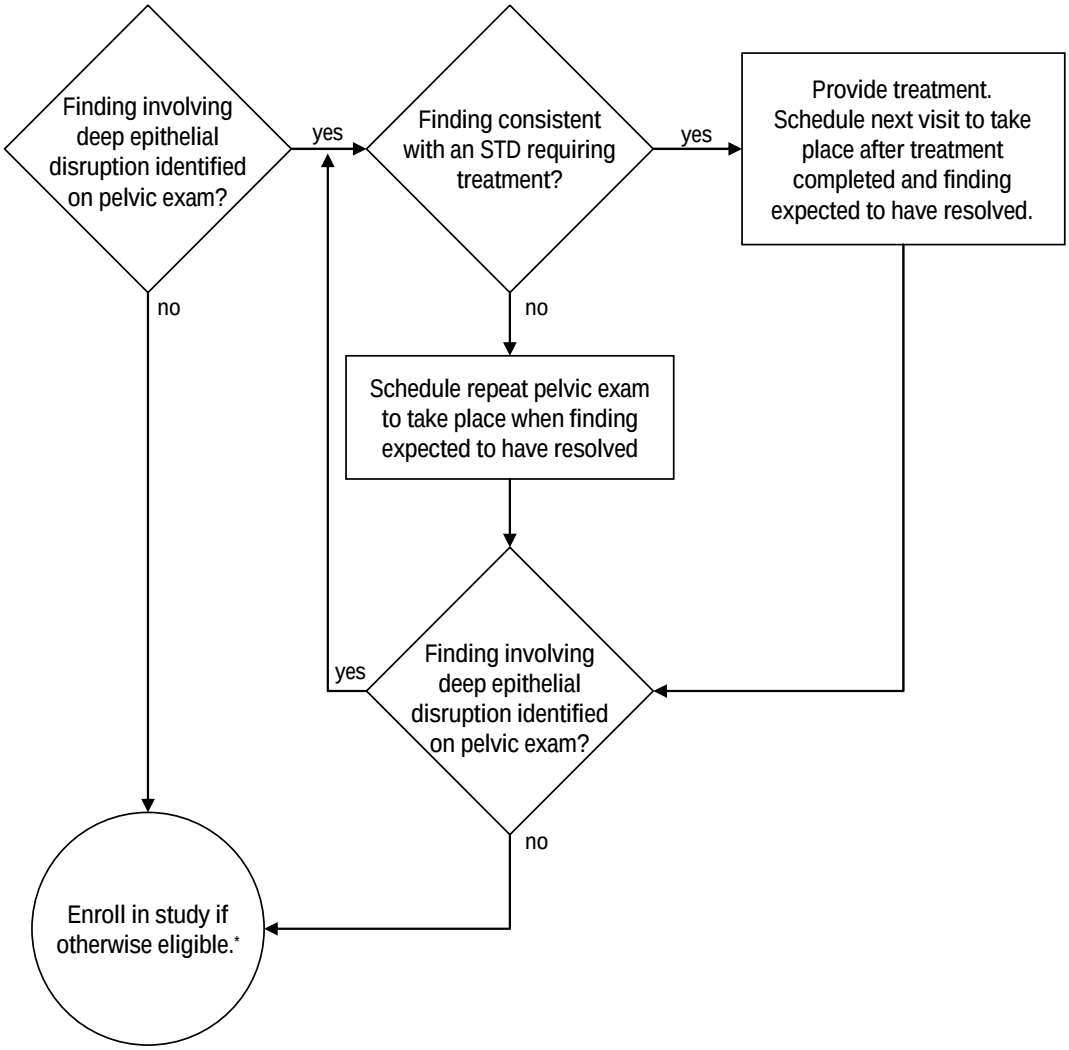
To consult the HPTN 035 PSRT, submit a query to the PSRT using the HPTN 035 PSRT query form (see end of this section) and the PSRT email group alias: 035PSRT@hptn.org. Include "Request for HPTN 035 PSRT Consultation – PTID XXX-YYYYY-Z in the subject line of the email message. The PSRT will consider the query and provide a written response (or request more information) via email within three business days.

Figure 10-6
STD/RTI Diagnosis and Treatment Algorithm for Screening and Enrollment in HPTN 035



*Enrollment must take place within 30 days of providing informed consent for screening. Otherwise all screening procedures must be repeated.

Figure 10-7
Pelvic Exam finding Management Algorithm for Screening and Enrollment in HPTN 035



*Enrollment must take place within 30 days of providing informed consent for screening. Otherwise all screening procedures must be repeated.

Figure 10-8
STD/RTI Management Summary for Screening and Enrollment in HPTN 035

STD/RTI symptoms reported at Screening Part 1	Evaluate clinically if required per local standard of care. Treat per WHO guidelines if applicable (ideally single dose). Schedule next visit (Screening Part 2) to occur after treatment is expected to be completed, symptoms are expected to be resolved, and Screening Part 1 lab test results are expected to be available.
STD/RTI symptoms reported at Screening Part 2	Evaluate clinically during protocol-specified pelvic exam, taking into account Screening Part 1 STD test results and Screening Part 2 wet prep results. Treat per WHO guidelines (ideally single dose) based on all available test results and exam findings. Schedule next visit (Enrollment) to occur after treatment is expected to be completed, symptoms are expected to be resolved, and Screening Part 2 lab test results (if any) are expected to be available.
Lab-based STD/RTI diagnosis at Screening Part 1 or Screening Part 2, no symptoms reported	Treat per WHO guidelines (ideally single dose). If single dose treatment is provided at Screening Part 2, and participant is otherwise eligible for the study, proceed with enrollment. If single dose treatment is not provided, schedule next visit (Enrollment) to occur after treatment is expected to be completed.
Pelvic exam finding involving deep epithelial disruption observed at Screening Part 2	Provide treatment per WHO guidelines if clinically indicated (ideally single dose). Schedule next visit (Enrollment) with repeat pelvic exam to take place as soon as possible after treatment (if any) is expected to be completed and finding is expected to be resolved.

10.6.3 Adverse Event Reporting Considerations

Per the HPTN 035 eligibility criteria, no participant may enter the study with an STD/RTI requiring treatment per WHO guidelines, or with any STD/RTI symptoms. For participants diagnosed during screening with an STD/RTI requiring treatment, the STD/RTI is considered "resolved" as soon as treatment has been completed and all symptoms of the STD/RTI are no longer present. Since both of these conditions must be met prior to enrollment in the study, no treatable STD or RTI should be recorded as a pre-existing condition for an enrolled participant. Therefore, any curable STD/RTI identified during follow-up in HPTN 035 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 STD/RTI AEs, the severity of the event should be graded according to the guidance for "Infections" on page 4 of the DAIDS Toxicity Table (dated December 2004).

Genital herpes and genital warts are considered non-curable STDs and are handled differently from the curable STDs. 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 for leukocytes and nitrites will be performed when clinically indicated to diagnose urinary tract infection (UTI), both during screening and during follow-up. See Section 12.4.3 for details on the required laboratory procedures. Record results on applicable testing log sheets and then transcribe results onto the appropriate laboratory results case report 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

For participants who test positive for leukocytes or nitrites, additional UTI work-up (e.g., urine culture) may be performed if required per site standards of care, and documented in participant chart notes and/or on other site-specific source documents. Once a diagnosis has been made, treatment will be provided per site standards of care and applicable site standard operating procedures (SOPs).

10.8 Product Use Management

See also protocol Section 4.6. For this study, product use management may involve temporarily holding or permanently discontinuing gel use for individual study participants, to protect their safety and well-being while in the study. Product use management in this study will not involve modification of the dose (one applicatorful) or route (intravaginal) of product administration by any participant. 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, in consultation with the HPTN 035 PSRT. Further specification of these two types of decisions and actions is provided below.

10.8.1 Circumstances In Which Product Use Must Be Discontinued

NOTE: This section now reflects the specifications of protocol Version 3.0. All study sites must obtain IRB/EC approval and DAIDS protocol registration approval for protocol Version 3.0 before implementing Version 3.0 procedures. Prior to obtaining these approvals, protocol Version 2.0 (including Letters of Amendment #1 and #2) and Version 1.6 of this section must be followed.

Per protocol, participants at all study sites must be discontinued from product use if they:

- Become pregnant. Participants who become pregnant may resume product use after giving birth or other termination of the pregnancy, as evidenced by a negative pregnancy test performed by study staff.

- Experience a Grade 4 adverse event (AE) that is judged by the IoR or designee to be probably not, possibly, probably, or definitely related to product use. Participants who experience such an AE will not resume product use at any time.

  Experience any other AE that meets criteria for expedited reporting to DAIDS (see Section 11 of this manual) that is judged by the IoR or designee to be probably or definitely related to product use. With written approval from the PSRT, participants who experience such an AE may resume product use after the AE resolves (returns to baseline) or stabilizes at a non-reportable severity grade. To obtain approval for resumption of product use from the PSRT, the IoR or designee should submit a query to the PSRT, via the HPTN 035 Protocol Safety Physicians, using the HPTN 035 PSRT query form (see end of this section). Include "Request for HPTN 035 PSRT Consultation – PTID XXX-YYYYY-Z in the subject line of the email message. The PSRT will consider the query and provide a written response (or request more information) via email within three business days.

Participants who become infected with HIV will be offered the option to continue product use unless continued use is not permitted by site regulatory authorities or IRBs/ECs. At sites where continued product use is not permitted, product use will be permanently discontinued after HIV infection is confirmed per the algorithm in Appendix V.

Participants at selected sites performing Pap smears will be temporarily discontinued from product use if they are found to have a high-grade squamous intraepithelial lesion (H-SIL) or more severe abnormality; product use may also be held in response to lower grade abnormalities, if local standards of care require clinical colposcopy and/or biopsy to assess lower grade abnormalities. In all cases, the period of product hold will begin on the day of the clinical evaluation, biopsy, and/or treatment of the abnormality. Alternatively, the hold may be initiated one to two days prior to the day of clinical evaluation, biopsy, and/or treatment if per local standards of care the participant is advised to avoid sexual intercourse on these days. The period of product hold will continue for a minimum of two weeks after biopsy and/or treatment of the abnormality. Study staff will obtain medical records documenting the evaluation, biopsy, and/or treatment of the abnormality and, assuming adequate treatment is confirmed, will perform a pelvic exam at least two weeks after the evaluation/biopsy/treatment date to confirm healing of the cervix. Thereafter, assuming no contraindications are identified on pelvic exam, product use will be resumed.

10.8.2 Circumstances In Which Product Use May Be Discontinued

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

- The participants experiences an AE that meets criteria for expedited reporting to DAIDS that is judged possibly related to product use
- The participants has a pelvic exam finding involving deep epithelial disruption that does not resolve over the course of an additional month of continued product use
- The participant is unable or unwilling to comply with required study procedures
- The participant might otherwise might be put at undue risk to her safety and well-being by continuing product use

To obtain PSRT approval for such discontinuations, the IoR or designee should submit a query to the PSRT, via the HPTN 035 Protocol Safety Physicians, using the HPTN 035 PSRT query form (see end of this section). Include "Request for HPTN 035 PSRT Consultation – PTID XXX-YYYYY-Z in the subject line of the email message. The PSRT will consider the query and provide a written response (or request more information) via email within three business days. While waiting for a response from the PSRT, the IoR may instruct the participant to discontinue product use, or not, based on his/her clinical judgement and prioritizing the safety and well-being of the participant. When the IoR chooses to discontinue product use while waiting for the PSRT response, arrangements should be made to re-contact the participant as soon as possible after the PSRT response is received, if necessary, to communicate any modified product use instructions received from the PSRT.

10.8.3 Documentation of Product Use Management

All product use management decisions must be thoroughly documented in participant's 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 HPTN 035 Study Product Request Slip, as described in Section 6.6.2, and a Product Hold/Discontinuation case report form should be completed and faxed to the MTN SDMC, as described in Section 13.6.

10.8.4 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).

10.8.5 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 remaining in her possession should be collected from her as soon as possible and returned to the pharmacy on the day of collection. Similarly, at sites where gel use is not permitted among HIV-infected participants, any unused applicators remaining in an infected participant's possession should be collected as soon as possible after infection is confirmed per the algorithm in protocol Appendix V and returned to the pharmacy on the day of collection.

It is not necessary to collect remaining applicators from participants for whom gel use is temporarily held for an expected short period of time. However, applicators may be collected from such participants, to protect their safety, if it is suspected that the participant may not comply with clinic staff instructions to refrain from gel use for the duration of the temporary hold.

For all product holds requiring collection of unused applicators, if the applicators are not collected within five working days of initiating the product hold, the HPTN 035 PSRT must be informed, using the PSRT Query Form. When informing the PSRT, please describe the reason for the product hold, actions taken to try to collect the unused applicators, and plans and timelines for further action to collect the applicators.

10.9 Pregnancy Management

Please refer to the Section 6.8 of this manual for procedural instructions for management of participant pregnancies that may occur during follow-up.

HPTN 035 Protocol Safety Review Team Query Form, page 1 of 2

Instructions: Email completed form to brynah@uic.edu and nancycsc@gmail.com.
IMPORTANT: Complete all required fields so the PSRT has all information needed to respond to your query.

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

PTID: **Participant Age** (in years):
Enrollment Date (dd-MMM-yy):

Reason for query:
- ☐ Product use consultation:
  - ☐ Should use of study gel be temporarily discontinued (held)?
  - ☐ Should use of study gel be permanently discontinued (held)?
  - ☐ Should use of study gel be resumed?
- ☐ Request for consultation on AE management
- ☐ Request to withdraw participant from the study
- ☐ Request to unblind participant's gel assignment
- ☐ Other, specify:

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

Primary AE of concern:

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

Relatedness to study gel:
☐ Definitely related
☐ Probably related
☐ Possibly related
☐ Probably not related
☐ Definitely not related

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

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

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

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

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

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

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

End of Form for Site Staff. Email completed form to the HPTN 035 Protocol Safety Physicians (brynah@uic.edu **and** nancycsc@gmail.com. If an email response is not received from the PSRT within 3 business days, re-contact the Protocol Safety Physicians and/or the MTN CORE (acoletti@fhi.org or kgomez@fhi.org) for assistance.

FOR PSRT USE ONLY — PROVIDE RESPONSE TO QUERY HERE

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

Query Outcome:
☐ Approved
☐ Not approved
☐ Not applicable

PSRT Comments: