

Section 7. Clinical Considerations

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This section presents information on clinical procedures performed in MTN-026. The Schedule of Study Visits and Evaluations in Appendix I of the protocol indicates when specific clinical and laboratory assessments are to take place. The Investigator of Record or designee should perform symptom-directed examinations at his/her discretion at any time during any visit if s/he determines it to be clinically necessary, particularly if there are any on-going medical or mental health conditions which may require follow-up. The participant's research record should include documentation of these procedures.

Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in Section 9. Instructions for completing data collection forms associated with clinical procedures are provided in Section 12.

7.1 Baseline Medical and Menstrual History

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

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

In order to obtain a complete, accurate, and relevant participant self-reported medical and menstrual (if female) history, it will be necessary to ask the participant about significant past medical conditions as well as any current conditions.

It is recommended that sites use the Baseline Medical History Questions form (as a source document and available on the MTN-026 web page under Study Implementation Materials) in conjunction with the Baseline Medical History Log CRF and/or chart notes to guide and document medical history taking. These documents are provided to help guide and document medical history taking. Site clinicians are encouraged to use their clinical experience and judgment to determine

the best phrasing and approach in order to elicit complete and accurate information from the participant. This is especially important regarding details about severity and frequency of baseline medical conditions.

When collecting medical information from the participant, site clinicians should ask probing questions to obtain the most complete and accurate information possible. Details of all relevant conditions identified during the baseline medical history review should be recorded on the Baseline Medical History Log.

Baseline medical conditions are a subset of a participant's medical history, and consist of all ongoing and/or relevant medical conditions, problems, signs, symptoms and abnormal findings that are observed and/or reported at enrollment or before a potential participant is enrolled (randomized). Relevant conditions include (but are not limited to): hospitalizations, surgeries, allergies, conditions requiring prescription or chronic medication (lasting for more than 2 weeks), and any condition(s) currently experienced by the participant. The clinician should record as much information as possible about the severity and frequency of any baseline medical condition in the description field on the Baseline Medical History Log CRF to best describe the condition at the time the participant enters the study. In addition to participant-reported conditions, the following should be recorded on the Baseline Medical History Log:

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

Note: Generally, it is not expected that conditions less than Grade 1 would be included on the Baseline Medical History Log, unless determined to be relevant by the site clinician.

The baseline medical history should explore in detail any medical conditions or medications that are deemed exclusionary for this study. At the enrollment visit, a participant's history should be reviewed and updated as needed. Refer to protocol section 5.2 and 5.3 for a complete listing of study inclusion and exclusion criteria.

Further guidance about select clinical eligibility criteria is as follows:

- Willingness to abstain from sexual activity for 72 hours prior to each study visit, during product use periods AND either 72 hours or 3 days after biopsy collection. This includes refraining from receptive anal intercourse (RAI), penile-vaginal intercourse, receptive oral anogenital stimulation, vaginal or rectal stimulation via fingers, and vaginal or rectal insertion of sex toys.
- Willingness to abstain from using any non-study products in the rectum or vagina 72 hours prior to each study visit and during product use periods. For example, any rectally-administered medications or product which are not supplied to participants by clinic staff are not permitted to be used.
- Anticipated use during the period of study participation of systemic immunomodulatory medications or use of these medications within the 6 months prior to Enrollment
- History of adverse reactions to any of the components of the study products: This includes dapivirine gel, Universal Placebo gel and the applicator. Participants who have a hypersensitivity/allergy to any component of these agents should not be enrolled. For example, if a potential participant states that s/he has an allergy to methylparaben or propylparaben (commonly used cosmetics, lotions etc.), s/he may have an allergy to dapivirine gel.
- PEP/PrEP use for HIV exposure or prevention within 6 months prior to Enrollment. These criteria are intended to exclude participants who may be high-risk for HIV acquisition or may have an undetectable HIV infection due to PEP or PrEP use. Potential participants that have had an investigational exposure to drugs used for PrEP/PEP may be enrolled as

long as other exclusion criteria do not apply (e.g. participation in other investigational studies within the past 45 days is prohibited per protocol). Note: Reported anticipated use of PrEP during study participation is also prohibited.

- Anticipated use during the period of study participation of CYP3A inducer(s) and/or inhibitor(s), hormone therapy or known blood-thinners. Clinical staff should review the list of prohibited CYP3A inducer(s) and/or inhibitors available in SSP section 6 with the participant as well as those outlined in the protocol such as Plavix®, Warfarin or Heparin.

Note: Selected inclusion and exclusion criteria along with all study procedures designated for females will only apply to individuals who were female at birth. Please note transgender female with a neovagina should abstain from inserting any non-study products into the neovagina for 72 hours prior to each study visit, and during the study product use periods, and be willing to be sexually abstinent for 72 hours prior to each study visit, during the study product use periods and for 72 hours after biopsy collection.

7.1.1 Baseline Medical Conditions

The Baseline Medical History CRF is completed based on all screening source documents including, but not limited to, the Baseline Medical History Questions Sheet, Physical Exam CRF, Anorectal Exam CRF, Pelvic Exam CRF, Pelvic Exam Diagrams, Hematology CRF, Local Laboratory Results CRF, and STI Results CRF.

Information documented on the Baseline Medical History Log CRF at the Screening Visit must be actively reviewed and updated at the Enrollment Visit, especially for those conditions that were ongoing at the Screening Visit. This includes a review and update of the condition's description and severity grade. Make sure the "Is the condition ongoing?" field is completed/updated for each entry prior to final eligibility confirmation.

If a baseline medical condition is resolved as of the date of enrollment/randomization, do not make any changes to the severity grade (similar to what is done when resolving adverse events). In this case, the response to the question, "Is the condition ongoing?" must be selected "no." If a baseline medical condition first identified at the Screening Visit is ongoing at the Enrollment Visit, assess the severity at the Enrollment Visit and update the severity grade (up or down) as applicable to reflect the severity at the time of enrollment/randomization.

Recurrent Chronic Conditions: Recurrent chronic conditions should be documented as 'ongoing' at enrollment, even if the participant is not currently experiencing an acute event (e.g. intermittent headaches). Chronic conditions should be selected as "yes" for the question "Is the condition ongoing?" at the Enrollment Visit, even if the participant is not currently experiencing an acute event (e.g., intermittent headaches). For severity grading, the highest severity experienced for the condition should be used. In the 'Description of medical history condition/event' item, note the typical severity for outbreaks/acute episodes of the condition, and whether the condition is currently being experienced by the participant, or historical. When assessing chronic conditions, it is important to note what, if any, medications a participant may take for reported chronic condition during study participation may result in product discontinuation. For example, if a participant suffers from chronic asthma and uses an anti-inflammatory medication or an immunomodulatory to control his/her condition, site staff are asked to use their discretion with evaluating the eligibility of this participant.

Bleeding Events (for female participants): Note that any menorrhagia, metrorrhagia, or menometrorrhagia events ongoing at the time of randomization should be selected as "not gradable" on the Baseline Medical History Log CRF. This is because the FGGT grades these bleeding events relative to each participant's baseline bleeding pattern. In the "Description of medical condition/event" field, include text similar to what is in the FGGT row to describe the severity and frequency of the condition, and whether it is attributed to a participant's current

contraceptive method. Any past resolved (not ongoing at the time of randomization) menorrhagia, metrorrhagia, or menometrorrhagia events documented on the Baseline Medical History Log CRF should be assigned a grade from 1-4 per the FGGT. Infrequent bleeding at baseline should also be captured, using the terms “missed menses”, “oligomenorrhea” or “ammenorhea” as appropriate. If infrequent bleeding is explained by contraceptive method, note this in the description field and select ‘not gradable’. If infrequent bleeding is unexplained, assign a severity grade from 1-2 per the FGGT.

Allergic Reactions: If a participant reports having a history of anaphylactic reactions (such as difficulty in breathing or severe hives after eating peanuts), even if it has happened only once before in her lifetime, it is still important for the site clinician to document these events as a pre-existing condition on the Baseline Medical History Log CRF. In this example, record the condition/event as “allergic reaction to peanuts” and note types of symptoms (e.g., “throat swelling” or “shortness of breath”) in the “Description of medical condition/event” field including severity grade. Assign the severity grade per the “acute allergic reaction” row of the DAIDS Toxicity Table within the “Toxicity (Severity) Grade” item and when this event occurred for the “Date Medical condition/event started” item. At the Enrollment Visit, select “yes” to the question, “Is the condition ongoing?” and check “no” for the question “Is condition/event gradable?”, as the participant was not experiencing an anaphylaxis event at the time of enrollment/randomization. An AE submission for an anaphylactic reaction is required if this same event occurs after enrollment or during study follow-up.

7.2 Follow-up Medical History

It is necessary to update the participant’s medical history at all follow-up clinic visits to determine whether previously reported conditions remain ongoing and whether new symptoms, illnesses, conditions, etc. have occurred since the last medical history was performed. A history should also be performed at interim visits when a participant complains of symptoms or when the purpose of the visit is to re-assess previously-identified AEs. Any symptoms reported by the participant should be further probed and evaluated. Study clinicians should follow-up on any ongoing baseline conditions as well as any previously reported adverse events that are continuing.

One purpose of the participant-reported follow-up history is to determine whether previously-documented conditions have changed in severity or frequency. A second purpose is to determine whether new symptoms, illnesses, conditions, etc., have occurred since the medical history was last assessed. The Baseline Medical History Log CRF, chart notes, or a site-specific tool, if desired, may serve as the source document. All newly-identified participant-reported symptoms and conditions will be considered AEs and documented on the AE Log CRF and other source documents.

For purposes of this study, a “newly-identified” condition is defined as one of the following:

- not present at baseline (enrollment);
- ongoing at baseline but has increased in severity or frequency during follow-up (includes ongoing baseline conditions or AEs that increase in severity or frequency during follow-up);
- ongoing at baseline, resolves during follow-up, and then re-occurs (excludes chronic condition)

Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing and approach in order to elicit complete and accurate information from the participant.

As an example, follow-up interim history taking could be approached as follows:

- General questions about current health and medications (e.g. How are you feeling today? Any current symptoms or issues since your last visit? Have you been to your doctor or hospital outside the study clinic since the last time we spoke? Changes to any medications you are currently taking?)

- Targeted questions about ongoing baseline medical conditions and previously reported AEs (e.g. At your last visit you reported X was ongoing, how are you feeling now? You reported that you occasionally experience X, have you had any recent episodes?)

If, during follow-up, a baseline medical condition resolves or increases in severity or frequency from baseline, this is not updated on the Baseline Medical History Log CRF.

- If the condition increases in severity or frequency from baseline, and meets requirements for AE reporting, complete an AE Log CRF to document the new AE (i.e., the baseline condition at an increased severity and/or frequency). The AE Log CRF should be selected “yes” for the question, “Was this AE a worsening of a baseline medical condition?”.

At each follow-up visit, site clinicians will begin the follow-up medical history by reviewing with the participant and eliciting updates (resolution, outcome date, severity grade, etc.) on those symptoms/conditions that were documented as ongoing since the participant’s last visit. Site clinicians should then probe and evaluate for any new onset conditions/symptoms since the participant’s last visit. Clinicians should use their clinical experience and judgment to elicit complete and accurate medical history information from participants.

Any symptoms reported by the participant should be further probed and evaluated. Be sure to ask about ongoing baseline symptoms as well as any symptoms listed as “recovering/resolving” on an AE Log CRF.

The Baseline Medical History Log CRF can be updated with new or corrected information during follow-up, but only in instances when new information related to the participant’s baseline medical history status is obtained after enrollment/randomization. If information is added to the Baseline Medical History Log CRF after the Enrollment Visit, a chart note explaining the update is required.

Participants will be counseled to report all occurrences of unusual genital bleeding that is different from baseline reports and not attributable to contraceptive method to study staff as soon as possible after identification of the bleeding. Per protocol section 8.3.1, changes in genital bleeding deemed to be related to the participant’s contraceptive use or menstruation postpartum will not be reported as an AE, unless deemed to be an adverse event.

7.3 Concomitant Medications

The Concomitant Medications Log CRF is used to document all concomitant medications used by a given participant during her study participation.

Protocol section 6.9 requires site staff to document all medications taken by study participants beginning at screening and continuing throughout the duration of the study. Medications include the following:

- Prescription and “over-the counter” medications and preparations
- Vaccinations
- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations
- Contraceptive medications
 - Record each contraceptive injection as a single entry
 - Record each contraceptive pill pack used as a single entry
 - For implants/IUCDs, record the removal date as the Date Stopped

Use of sexual lubricants should be recorded on the Sexual Lubricant CRF.

Note: Alcohol consumption and recreational drugs should not be reported as concomitant medications on the Concomitant Medications Log. Instead, excessive alcohol consumption (defined as binge drinking, heavy drinking, and any drinking by pregnant women or people younger than age 21 (as per the CDC: <https://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm>) and recreational drug use may be considered baseline medical conditions, per site clinician judgment, in which case they should be recorded on the Baseline Medical History Log.

It is helpful to ascertain the baseline medication information in the context of the baseline medical history. Site staff should ask open-ended questions to elicit participant report of current medications, and use the information obtained in the medical history to probe for additional medications that the participant may otherwise forget to report.

To help ensure accurate reporting of concomitant medications information, participants should be encouraged to bring a list of all medications to study visits.

At each follow-up visit, review the participant's concomitant medications history and document this review by completing the item "Is the participant taking any concomitant medications that have not been previously reported?" on the Follow-up Visit Summary CRF and/or Interim Visit Summary CRF. Ask the participant if s/he has started taking any new medications, and record on the Concomitant Medications Log CRF any new medications s/he reports having started since her last medications assessment.

In addition, review all previous entries that do not have a "Date Stopped" entered and ask the participant whether s/he is still taking the medication (and at the same dose and frequency). If the participant has stopped taking a medication, enter the last date the participant used the medication in the "Date Stopped" field. If the participant is taking the same medication but at a different dose or frequency, enter the date the participant last used the medication at the original dose or frequency in the "Date Stopped" field, and complete a new Concomitant Medications Log entry for the new dose or frequency. Ensure that concomitant medications mentioned in previous parts of the visit are documented correctly and consistently on the Concomitant Medications Log CRF, so that study records are not discrepant.

7.3.1 Prohibited Medications and Practices

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

Participants will be counseled on avoiding using the below-listed medications during study participation.

- Use of Heparin, including Lovenox®; Warfarin; Plavix®*
- Use of hormone therapy (tablet, injectable or gel form)*
- Use of Aspirin (greater than 81mg) or NSAIDS or any other drugs that increase the likelihood of bleeding;
- CYP3A inhibitors and inducers

* reported used results in permanent study product discontinuation

Use of any prohibited medications should be recorded on the Concomitant Medications Log CRF. Should a participant report the use of prohibited medications within 72 hours prior to a PK sample collection visit, collection of biopsies at that visit would be performed at the discretion of the IoR. Rapid PSRT consultation may be requested at IoR discretion to assist in determining whether biopsy collection should be delayed or proceed as scheduled. The PSRT and Management Team should be notified of any reported use of a prohibited medication.

7.4 Physical Exam

Protocol Section 7.13 outlines the required physical exam assessments. A comprehensive physical examination is required at Screening. At Screening, during a physical exam, site staff should assess for any other medical condition that would make participation in the study unsafe or interfere with interpreting the study data or achieving the study objectives.

A targeted physical examination (to include assessment of general appearance and vital signs at a minimum) will be done at Enrollment and only if indicated at all other follow-up visits and interim visits. Site clinicians may use their discretion to determine whether or not to conduct a more comprehensive physical exam in response to reported symptoms or illnesses present at the time of the exam.

Physical exam assessments should be documented on the Physical Exam and Vital Signs CRFs.

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

7.5 Female Genital and Rectal Exam Overview

The genital exam during the Screening and Enrollment visits is necessary to evaluate protocol exclusion criteria and to collect detailed information on baseline vaginal, genital and rectal conditions. These exams scheduled during follow-up visits are necessary to assess for safety and collect required laboratory specimens.

Guidance on the conduct of genital exams can be found in the remainder of this section.

Genital exam procedures must be performed in the order shown on the Genital Exam Checklist and at designated area(s) of the genitalia as noted on the checklist, if specified. The order of specimen collection is critical to ensure that the first specimens collected do not affect subsequent specimens. Collect specimens away from apparent abnormalities and exclude swabbed areas from subsequent examination.

Prior to the exam, prepare all required equipment, supplies, and paperwork; label specimen collection supplies as needed. Review documentation of prior exams and other relevant documentation from the current visit and prior visits. Explain the procedure to the participant and answer any questions s/he may have.

7.6 Detailed Procedural Instructions for Pelvic Exams

Exams during vaginal bleeding: Pelvic exams ideally should not be performed if the participant is experiencing menstrual-like bleeding as this may interfere with visualization of the vagina and cervix and complicate interpretation of lab assays. However, given the frequency of scheduled exams it is recognized that vaginal bleeding may coincide with some study visits. If a participant is experiencing mild spotting, it is reasonable to proceed with a pelvic exam and collection of samples. If she is experiencing greater than mild bleeding 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 visit window (as part of a split visit, if allowable).

See below for special circumstances in the event a participant is experiencing her menses or any vaginal bleeding at the time of an exam:

- During screening and/or enrollment, if the participant is experiencing or reports any vaginal bleeding, reschedule the exam and associated sample collection to be completed within the 45-day screening window. Per protocol section 7.3, menses should not coincide with a participant's Enrollment visit or Study Visits 2-6; this should be taken into consideration when scheduling enrollment.
- During a scheduled follow-up visit, the pelvic exam and associated sample collection, and vaginal swabs for PK, should still be completed as long as the participant is comfortable. Additionally, the washout period should be timed to coincide with female participants' menses to minimize the chance of participants being on their menses during Visits 7-12.
- If a female participant presents for an interim visit complaining of genital symptoms, perform a pelvic exam to evaluate her symptoms at that time. If she is not comfortable with completing an exam, she should be scheduled to return for a pelvic exam as soon as possible after vaginal bleeding stops.

General Technique:

- Maximize the comfort and privacy of the participant. Position the examination table away from the door or hang a curtain to ensure privacy. Explain what you are doing as you do it. Take as much time as needed to ensure participant comfort and accurate documentation of exam findings. If not standard of care, consider having an additional person (medical assistant or nurse) present during the examination to ensure participant comfort.
- Use clean hand/dirty hand technique, and/or assistants, to avoid contamination. Keep extra gloves available as two hands may be needed at different time points during the exam.
- Use a speculum of appropriate type and size to permit adequate visualization of the vagina and cervix. For most participants, a Graves speculum is preferred to enable visualization of all anatomic areas and tissues. Record the type and size of the speculum used on the Pelvic Exam Diagrams form. Prior to insertion, ensure that the speculum functions properly and has no rough edges.

Position the Participant:

- Drape the participant and establish a comfortable examination position that allows for appropriate examination of the genitalia such as dorsal lithotomy with or without use of stirrups; position should allow for the perineum and vulva to be inspected. Make all necessary adjustments to equipment and room to ensure participants comfort: i.e. adjust stirrups and back elevation as needed.

Examine the External Genitalia

- For pelvic exams, a visual exam (i.e. a naked eye examination) should be performed of the external genitalia including the perineum, and perianal area. Palpate the inguinal lymph nodes to assess for enlargement and/or tenderness. Do not insert the speculum before examining the external genitalia.

Examine the Internal Genitalia (Cervix and Vagina)

- The speculum may be lubricated with warm water only, if needed. No other lubricant may be used. Gently insert the speculum and open it once past the pelvic floor muscles, using gentle downward pressure, so as to avoid trauma while enabling visualization of the cervical face and upper vagina. If the cervix is poorly visualized, to avoid iatrogenic injury, remove the speculum and use a gloved finger (lubricated with warm water if needed) to establish the position of the cervix. Then re-insert the speculum. Perform naked eye exam of the cervix and vagina, noting any abnormal findings.
- To complete the naked eye examination of the vagina, slowly withdraw the speculum with the blades moderately open, re-focusing as needed. Alternatively, the speculum may be

rotated ninety degrees to allow visualization of the anterior and posterior vaginal walls; retract the speculum away from the cervix and close the blades to rotate.

- Removal of Visual Obstruction: After collection of vaginal and endocervical specimens, any obstruction (e.g., mucus, cellular debris) may be removed using a large saline-moistened swab (scopette) in a gentle dabbing fashion to remove the obstruction. Avoid twisting or rolling the swab over the surface of epithelium. Do not use a dry swab to remove any obstruction at any time, as this may cause trauma to the epithelium. If saline is not available, a swab moistened with water will also suffice.

Perform Bimanual Exam: A bimanual examination will be performed at the screening visit and when clinically indicated. After completing all of the above-listed tissue examinations and specimen collection and removing the speculum, perform a bimanual exam for adnexal or fundal masses and/or tenderness.

7.6.1 Pelvic Specimen Collection

Cervicovaginal Fluid Collection for PK:

Cervicovaginal fluids will be collected from the posterior fornix to capture dapivirine concentration. Site staff should weigh each swab and document the pre-collection weight on the LDMS Tracking Sheet. Following collection, site staff should place the swab back in the designated pre-weighed cryovial, obtain the post weight for each swab using an analytical balance, and document the post weight on the LDMS Tracking Sheet. Complete details can be found in section 9 of this manual.

Chlamydia trachomatis (CT)/ Neisseria gonorrhoea (GC):

Collection of the vaginal swab for NAAT for GC/CT can be done using the Gen Probe APTIMA or GeneXpert kit. The clinician/assistant will use the collection swab provided. The clinician/assistant will open the peel pouch containing the swab. Insert the swab 1 ½ inches into vagina and rotate 360° against lateral vaginal wall. After specimen collection, put the swab in the transport medium and break the shaft at the painted breakpoint. Re-cap tube securely by snapping the cap into place.

CVL for PD and PK:

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

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

Papanicolaou (Pap) Test (only if indicated)

Pap smears are performed only if clinically indicated at Screening for women ≥ 21 years old that do not have documentation of a satisfactory Pap within the past 3 years prior to Enrollment. If a Pap smear is required, ecto- and endocervical cells will be collected after all tissues have been visually inspected and all other required specimens have been collected. The testing will be done at the site's local laboratory.

During screening, Pap results are not reported on CRFs, but will be used to evaluate eligibility for enrollment. Grade 1 or 2 Pap results are not exclusionary, however, if further evaluation is required (i.e. colposcopy and/or biopsy) per site SOPs, this should be scheduled as appropriate during study follow-up.

Abnormal Pap results obtained at screening should be recorded within the Baseline Medical History Log CRF.

Abnormal Pap smear findings should be initially reported and graded based on the "Pap" row of the FGGT. AGC and AGC-favor neoplastic are not specifically mentioned in the "Pap" row, but should be assigned severity grades 1 and 2, respectively. If abnormal cytology uncovered at screening is followed by a biopsy during follow-up, sites should report an AE for the histologic diagnosis IF the biopsy result is a higher grade than the baseline pap smear. For example, consider a participant who has an LGSIL pap result (grade 1) at screening and undergoes a colposcopy with biopsy at month 6. If the biopsy result is grade 1, no AE need be reported; HOWEVER, if the biopsy result is grade 2 or higher, an AE should be submitted using the histologic diagnosis (CIN II, for example).

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., 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., 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 that takes place after receipt of the Pap test result report. Provide treatment as needed based on the results of the protocol-specified tests.

Cervical Biopsies for PK:

Cervical biopsies should be the last vaginal sample collected.

Using forceps, two cervical biopsies, each measuring approximately 3 mm by 5 mm, will be taken from two different areas of the cervix to measure tissue concentration of Dapivirine.

Usually, biopsy of the cervix does not require an anesthetic; this procedure typically feels like a sharp pinch or a cramp. Bleeding may be controlled through a combination of applied pressure, silver nitrate and/ monsel's solution. If silver nitrate and/or monsel solution is used during the collection of cervical biopsies, this should be recorded on the Concomitant Medications Log CRF.

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

All participants will be instructed to abstain from inserting anything into the vagina, including having vaginal sex for 72 hours prior to and 7 days following the collection of these samples. Participants will also be counseled to refrain from the use of NSAIDs, aspirin and/or other drugs that are associated with the increased likelihood of bleeding for 72 hours prior to biopsy collection.

Cervical biopsies for PK are required to be weighed. Site staff should weigh each and document the pre-collection weight on the LDMS Tracking Sheet. Following collection, site staff should obtain the post weight for each and document the post weight on the LDMS Tracking Sheet. Complete details can be found in section 9 of this manual.

7.6.2 Documentation of Pelvic Exam Findings

Pelvic exam findings (normal and abnormal) should be documented using the Pelvic Exam Diagrams form.

All abnormal findings during screening and enrollment will be documented on the Pelvic Exam CRF and the Baseline Medical History Conditions Log CRF.

All abnormal findings identified during follow-up will be documented on the Pelvic Exam CRF and Adverse Event Log CRF, as appropriate. Supplemental information may also be recorded in chart notes or on other designated source documents as needed.

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

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

IUCD strings may be visible upon exam and are also considered a normal finding. If documented, they should be present on the Pelvic Exam Diagrams form. Sites may determine whether they choose to consistently document the presence of IUCD strings (best practice) or not. It is recommended that if a participant has an IUCD but the strings are not visible upon exam, this should be documented and followed up on.

Per Protocol section 8.3.1, bleeding at the time of speculum insertion/removal and/or biopsy collection that is judged by the clinician to be within the range of normally anticipated will not be reportable as an AE. Bleeding of greater quantity or longer duration than typical will still be reported.

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

Epithelium

Integrity:

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

Color:

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

Blood Vessels

Integrity:

- Intact
- Disrupted

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

**Figure 7-1
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. May be sharp or diffuse.
Edema	Intact	Intact	
Petechiae	Intact	Disrupted	≤ 3 mm
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 often but not always deep.			

7.7 Detailed Procedural Instructions for Anorectal Exams

General Technique

- Maximize the comfort and privacy of the participant. Position the examination table away from the door or hang a curtain to ensure privacy. Explain what you are doing as you do it. Take as much time as needed to ensure participant comfort and accurate documentation of exam findings. If not standard of care, consider having an additional person (medical assistant or nurse) present during the examination to ensure participant comfort.
- Use clean hand/dirty hand technique, and/or assistants, to avoid contamination. Keep extra gloves available as two hands may be needed at different time points during the exam.

Position the Participant

- Position the participant in the left lateral decubitus position (fetal position) with both legs flexed allowing a full view of the anus, perianus and buttocks.

External anorectal examination

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

Swab Collection for HSV Detection

- The HSV 1/2 swab should be collected after visual examination of the perianal area and **prior** to the digital examination. The swab for detection of HSV 1/2 is only done if clinically indicated (i.e. the presence of shallow perianal ulceration or vesicle crops).

Internal anorectal examination (Digital Rectal Exam)

- This examination is performed prior to the insertion of the anoscope or flexible sigmoidoscopy. The purpose of this exam is two-fold. First, this examination is intended to relax the anal sphincter around the opening of the anus in preparation for the subsequent anoscopy/ flexible sigmoidoscopy and specimen collection. In addition, the examination enables the clinician to assess potential findings such as lumps/areas of discomfort. The clinician will lubricate a gloved finger with Good Clean Love lubricant. The clinician will then gently and slowly insert a gloved index finger (palmar surface down) into the anus. The clinician should sweep the finger circumferentially around the entire anal/distal rectal surface. Any abnormal findings or unexpected discomfort should be noted. It is not required for this exam to assess the prostate gland.
- Potential participants identified at screening with abnormalities of the rectal mucosa, or anorectal symptoms that represent a contraindication to study participation are not eligible for the study. For participants who enroll in the study, abnormal anorectal exam findings (that are not exclusionary) identified at the Screening and Enrollment Visits should be recorded as a baseline medical condition.

7.7.1 Rectal Specimen Collection

Using study provided lubricant (Good Clean Love lubricant), the clinician should sparingly lubricate the anoscope prior to insertion. The anoscope with obturator should then be inserted into the anal canal until the anoscope 'wings' touch the anal verge. The clinician should maintain pressure on flange to ensure continued placement of the anoscope and then remove the obturator. Using a lighted instrument (e.g. otoscope or torch) to illuminate the rectum after removing the obturator, the rectal lumen should be visible at the end of the anoscope. The clinician should visually assess the rectum after the anoscope is in place and prior to specimen collection. Following specimen collection, the clinician should assess the anal canal as the anoscope is withdrawn.

Chlamydia trachomatis (CT)/ Neisseria gonorrhoea (GC)

Collection of the rectal swab for NAAT for GC/CT is done using the Cepheid GeneXpert NAAT method only. The clinician/assistant will use the GeneXpert collection swab. The clinician/assistant will open the peel pouch containing the swab. After removing the obturator, advance the anoscope slightly then insert the swab into the proximal rectal lumen that is visible at the end of the anoscope. Rotate it 360 degrees and remove. After specimen collection, put the swab in the transport medium and break the shaft at the painted breakpoint. Re-cap tube securely by snapping the cap into place.

Rectal Fluid Collection for Microflora, Adherence PK, and Mucosal Safety

Site staff should plan to allot sufficient time to prepare for the rectal swabs and sponge procedure. A **flocked nylon swab** will be used to collect samples for **microflora assessment**. A **pre-weighed dacron swab** will be used to collect samples for **PK**. A **rectal sponge** will be used to collect samples for **mucosal safety**.

To collect specimens, (these should immediately follow the GC/CT swab)

- Introduce the flocced nylon swab through the anoscope into the rectum. Rotate the flocced nylon swab along the lateral wall of the rectum several times. Remove the flocced nylon swab and place it into the collection tube.
- Introduce the pre-weighed dacron swab extension held with one of the methods detailed in section 9.8.4 of the SSP, into the proximal rectal lumen (in touch with the rectal walls) and hold it against the mucosa for 2 minutes. Remove the dacron swab and place it into the appropriate collection tube.
- Introduce the sponge, attached to the pipette sponge holder extension, into the proximal rectal lumen (in touch with the rectal walls). Hold (or leave) sponge in place for 2 minutes. Remove the sponge and place it into the appropriate collection tube.

NOTE: Both the Dacron swab and sponge specimens may be collected simultaneously

Instructions for sponge/swab and extender pipette assembly (also see image below): Cut the distal end of the transfer pipette at the first gradation for swabs or second gradation for sponges. These will serve as extension/holder device for the sponge/swab. Attach the sponge or swab, via the stick, to the transfer pipette and ensure that they are secure.

Sponge



Swab



Rectal Enema Effluent for PD and PK

After swab and sponge collection but prior to each rectal biopsy procedure and sigmoidoscopy, each participant will have a rectal enema performed.

A rectal enema is a procedure, which involves instilling a sterile saline solution to wash the rectum to cleanse the lower bowel and remove any obstruction (stool). This enema should take place at the study site in order for staff to document that the enema was performed. The effluent will also be collected and analyzed for PD and PK.

In the event the enema does not provide instructions for use, the following procedures should be performed:

- Fill enema bottle with 125 mL (about 4 ounces) of sterile normal (0.9%) saline, if not pre-packaged.
- Have participant rotate onto his or her left-hand side with right knee bent.
- If enema bottle is not pre-lubricated, apply a small amount of Good Clean Love water-based lubricant. (DO NOT USE Surgilube or other chlorhexidine containing lubricants)
- Gently insert the tip of the enema bottle into the anus.
- Slowly instill the solution into the rectum.
- After holding the fluid in the rectum for about 3-5 minutes, ask the participant to expel the enema fluid into a collection 'hat' placed under the toilet seat designated for this purpose.
- In a 15ml conical tube, collect 10ml of the rectal enema effluent using a 20 mL syringe. Rectal enema effluent should be kept on wet ice or refrigerated and sent to the lab for processing within 8 hours of collection.

Preparation of the Sigmoidoscope

Check to ensure the sigmoidoscope light is switched on, suction is on, and air flow is working. With the participant in the left lateral decubitus position, a digital rectal exam is performed as above, the sigmoidoscope tip is lubricated with Good Clean Love lubricant and gently inserted to ~15 cm from the anal verge.

Rectal Tissue Collection for PK, PD and Mucosal Safety

All participants will be instructed to abstain from inserting anything into the rectum, including usage of the study gel and having receptive anal intercourse for 72 hours (3 days) after the collection of these samples. Participants will also be counseled to refrain from the use of NSAIDs, aspirin and/or other drugs that are associated with the increased likelihood of bleeding for 72 hours (3 days) prior to and following mucosal biopsy collection.

Participants should be instructed not to douche or take any laxatives to cleanse the rectum prior to biopsy collection as any required cleansing procedures will be conducted in clinic. Such practices may change the cells in the rectum, which must be left undisturbed in order to get an accurate sampling. Should a participant report the use of such drugs or engagement of such practices within 72 hours prior to a scheduled sample collection, the collection of biopsies will be performed at the discretion of the IoR. Staff may also consult the PSRT for guidance on whether/how to proceed with scheduled study visit procedures.

Note: No special preparation, including dietary, is needed before having these specimens collected. Participants may follow their regular daily routine and eat/drink as they normally would prior to arriving to the visit (with the exceptions as stated above).

The following procedures should be performed:

- Introduce endoscopic 'jumbo' forceps into the sigmoidoscope channel and commence mucosal specimen collection at ~15 cm from the anal verge. The forceps need to be washed (dipped) in water between every biopsy. Forceps measuring approximately 3.7 mm with a 3.2 mm jaw will be required in order to obtain a 15 mg biopsy.
- Each individual biopsy should be obtained before the next one is collected. See section 9 for details on how many rectal biopsies should be collected and samples should be handled.
- Following tissue collection, participant vital signs should be obtained after a period of rest (approximately 5 minutes) and documented in chart notes or on another site-specific tool and any abnormal findings should be further evaluated.

Participants should also be informed that they may experience a small amount of bleeding from the rectum (noticeable when wiping after a bowel movement) for 2 to 3 days following the procedure. Excessive bleeding is not expected. In the unlikely event that excessive bleeding occurs, it is likely to be noticed when having a bowel movement or when wiping following a bowel movement.

If the participant presents with any of the following after the flexible sigmoidoscopy procedure, the participant should be referred for assessment at the emergency department of the nearest hospital:

- Bleeding that continues after the flexible sigmoidoscopy procedure that is uncontrolled (occurring between bowel movements) and results in the passage of large blood clots
- Local or systemic features compatible with infection (fever, localized anorectal pain, anal discharge)
- Abdominal pain, swelling or fever that is consistent with perforation of a hollow viscus or any local or systemic clinical features suggestive of this condition.

In the case of any life-threatening event, participants should be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where the study clinician is based, and to request that the clinician be contacted upon their arrival. Sites should make every effort to obtain and use records from non-study medical providers to complete any safety related documentation, pending written permission from the participant.

Note: Rectal tissue biopsies (for PK) are required to be weighed. Site staff should weigh each cryovial and document the pre-collection weight on the LDMS Tracking Sheet. Following collection, site staff should obtain the post weight for each cryovial containing the biopsy and document the post weight on the LDMS Tracking

Sheet. Complete details can be found in section 9 of this manual.

7.7.2 Documentation of Rectal Exam Findings

All rectal exam, anoscopic findings and those noted during the flexible sigmoidoscopy should be documented using the Anorectal Exam CRF.

All abnormal findings must be thoroughly documented and include location and severity of the finding to ensure appropriate assessment can be provided during subsequent examinations. Supplemental information may also be recorded in chart notes or on other designated source documents as needed.

As previously mentioned, all abnormal non-exclusionary findings identified at Screening and Enrollment will be documented as baseline medical conditions on the Baseline Medical History Log CRF as well.

Any abnormal findings identified during follow-up will be documented on the Anorectal Exam and Sigmoidoscopy CRF, as appropriate and as an adverse event, if applicable, on the Adverse Event Log CRF. Any unexpected discomfort should also be noted in chart notes.

Per Protocol section 8.3.1, bleeding at the time of speculum, anoscope, or flexible sigmoidoscope insertion/removal and/or biopsy collection that is judged by the clinician to be within the range of normally anticipated will not be reportable as an AE. Bleeding of greater quantity or longer duration than typical will still be reported. Fecal urgency, bloating and flatulence associated with rectal procedures deemed to be within the range of normally expected will also not be reportable as AEs.

The results of laboratory tests performed using specimens collected during follow-up rectal exams are recorded on the STI Tests CRF.

7.8 STI/RTI/UTI Evaluation, Management and Treatment

Clinical and laboratory evaluations are performed in MTN-026 to diagnose the following STIs and RTIs:

- Chlamydia infection
- Gonorrhea infection
- Syphilis infection
- HIV 1/2
- Herpes simplex virus (HSV1/2 detection)
- Hepatitis B
- Hepatitis C

All participants diagnosed with active sexually transmitted or reproductive tract infection (STI/RTI) or UTI based on the presence of symptoms should be provided treatment and or referral for treatment per site standard of care and applicable site standard operating procedures (SOPs). STI/RTIs will be treated in accordance with current World Health Organization (WHO) guidelines which can be accessed at: <http://www.who.int/hiv/pub/sti/pub6/en/>.

Potential participants presenting with an active (symptomatic) infection requiring treatment at Screening will be excluded from study participation. Per current WHO guidelines, the following symptomatic infections require treatment and are exclusionary: symptomatic Chlamydia trachomatis (CT) infection, Neisseria gonorrhoea (GC), syphilis, active herpes simplex virus (HSV) lesions, anogenital sores or ulcers, or symptomatic genital warts.

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

Urinary tract infections (UTIs): Suspected UTIs may be clinically managed based solely on the presence of symptoms indicative of a possible UTI or other method of diagnosis (i.e., urine culture or dipstick) as per site standard of care.

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

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

Note that urine dipstick testing is only performed if clinically indicated. At the screening visit, positive dipstick results do not directly impact eligibility, but abnormal protein and glucose parameters should prompt further evaluation or consideration pending IoR review. Abnormal protein and glucose uncovered at the screening visit should be captured on the Baseline Medical History Log CRF. In follow-up, findings of abnormal protein and glucose on the dipstick should be reported on the AE log CRF as indicated. Grade the severity of the urine glucose value according to the "Proteinuria, random collection" row of the Toxicity Table. Note that findings of LE/nitrites are not gradable per the DAIDs toxicity table, and like other non-gradable labs should not be reported as Baseline Medical History conditions or AEs.

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

7.9 HIV Testing

At Screening and/or Enrollment (prior to randomization), all participants will undergo HIV serology testing. Note at Enrollment, sites will perform HIV rapid test to screen for HIV status. Participants will be ineligible for enrollment regardless of subsequent/confirmatory test results if one or both of the rapid HIV tests are positive or discordant.

If at Screening and/or Enrollment, a potential participant has signs or symptoms consistent with acute HIV infection, the participant is not eligible for enrollment. Acute HIV infection is defined as the period of rapid viral replication that immediately follows the initial establishment of infection with HIV. Symptoms of acute HIV infection may be indistinguishable from a typical viral syndrome.

These symptoms may include:

- Fever
- Fatigue
- Headache
- Myalgia
- weight loss
- pharyngitis or sore throat
- lymphadenopathy
- rash
- diarrhea

Clinicians should assess the possible causes of these symptoms, length of time the participant has been experiencing these symptoms, and severity grade. Symptoms should be managed clinically per standard of care and participant will not be eligible for study participation.

Participants who fail screening due to concern for acute HIV infection should have repeat HIV testing no earlier than two months following the prior negative HIV test. If the HIV antibody test is negative at that point, and the participant no longer has symptoms suggestive of acute viral infection, the participant may undergo a second screening attempt for the study, assuming no other interim contraindications are noted. If an alternative diagnosis for the symptoms is identified (for example, malaria or influenza) then a second screening attempt may be scheduled two-months following the initial attempt, once all symptoms have been resolved. If symptoms are not adequately resolved by the second screening attempt, and HIV testing is negative, assess for additional possible causes of symptoms and refer for further evaluation if necessary. If during the second screening attempt other contraindications for eligibility are present, the participant is not eligible for study participation.

Participants who have a reactive HIV test result during follow-up visits will be instructed to permanently discontinue study product immediately and will be further tested using confirmatory testing. In addition, if a participant has signs or symptoms consistent with acute HIV infection, or expresses a concern about recent HIV acquisition, testing will be performed immediately.

Any participant who is found to have confirmed HIV infection after enrollment, product use and study participation will be permanently discontinued. All participants with confirmed HIV infection will be counseled and referred to available resources for medical and psychosocial care and support. If the participant opts to remain in follow up, site staff must follow-up on all referrals at each subsequent follow-up visit to determine if the participant actually sought the care to which s/he was referred, the outcome of the referral, and whether additional referrals are needed. All referrals, outcomes, and follow-up plans and actions must be fully documented in participant study records.

Protocol-specified examinations and laboratory tests will provide information upon which appropriate clinical care decisions can be made. Study staff must refer participants to non-study HIV care providers. Study staff will provide and explain all study examination findings and test results to participants. They also will provide copies of laboratory test result reports to participants and their non-study providers (if the participant grants approval). Study investigators will be available to consult with non-study providers on optimal clinical care and treatment decisions for participants.

Plasma storage is required at Enrollment, Visits 7 and 16. It is required for further Laboratory Center HIV testing (CD4, HIV RNA, and HIV drug resistance) of enrolled participants in the event of a positive HIV rapid or positive HIV EIA test result, and when additional samples (e.g., Sample 2) are collected as part of algorithm testing at the site local lab to confirm a participant's HIV infection status.

7.10 Hepatitis B and C Testing

All participants will undergo screening for HBV with assessment of hepatitis B surface antigen (HBsAg) at Screening. Hepatitis B Surface Antigen (HBsAg): If this test is positive, then hepatitis B virus is present in the blood. This means that the participant has either an acute or chronic hepatitis B infection. Those with active HBV infection as evidenced by detection of HBsAg receive standardized counseling relevant to natural history and transmission risks of HBV, and are excluded from enrollment.

Hepatitis C antibody testing will be performed at Screening. Participants with a positive HCV antibody test are not eligible for study participation and will be referred to their primary provider for management.

7.11 Syphilis testing

If a reactive Rapid Plasma Reagin (RPR) or Venereal Disease Research Laboratory (VDRL) is identified during screening, a confirmatory FDA approved test (MHA-TP or TPPA, or other treponemal test) result must be received and appropriate clinical management action taken, prior to enrollment in the study. Action required prior to enrollment depends on the current health status of the participant and the availability of medical records documenting his/her prior infection, as follows:

- If the participant has clinical signs or symptoms of syphilis, s/he is not eligible for 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 titer 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 PSRT.

7.12 Coagulation Testing (INR or PT)

All participants will have their blood tested at Screening to determine how quickly their blood clots and if bleeding problems are present to ensure the biopsies are taken safely. Participants with an abnormal International Normalized Ratio (INR) greater than 1.5x site laboratory ULN, per DAIDS Toxicity Table, will be ineligible to participate in the study.

7.13 Clinical and Product Use Management

Protocol Section 9 provides detailed guidance on clinical and product use management, including general criteria for product discontinuation (Section 9.3), guidance on product discontinuation in response to observed AEs (Section 9.4), pregnancy (Section 9.5), and early study termination (Section 9.6).

All specifications of protocol Sections 6 and 9 must be followed; IoRs are encouraged to consult the PSRT with any questions related to proper interpretation of the protocol and proper management of study product use in particular. Conditions requiring permanent discontinuation are summarized in Figure 7-2 below. Please note that per protocol, no temporary product hold will be initiated for MTN-026.

The protocol specifies that permanent product discontinuation should be initiated should a participant report prohibited medication use as listed in Section 9.3 of the protocol. When possible, treatment options that are not prohibited by the protocol should be pursued; however, clinical management of the participant should be prioritized if alternative treatment is not available. If prohibited medication, other than those listed in Section 9.3 of the protocol, are used, sites should consult the PSRT.

All clinical and product use management must be fully documented in participant study records. When the PSRT is consulted in relation to clinical and product use management, completed PSRT query forms (including a response from the PSRT) must be printed and filed in participant study records. Unless otherwise specified in protocol section 9, the IoR/designee should immediately consult the PSRT for any product discontinuations. Product discontinuations must be communicated to site pharmacy staff using the Study Gel Management Slip as described in Section 6 of this manual. Product discontinuations also must be documented on the Treatment Discontinuation CRF.

Figure 7-2
Conditions Requiring Permanent Discontinuation

Condition	Permanent Discontinuation
Report of use of prohibited medications and medications (Heparin, Lovenox®, Warfarin, Plavix® (clopidogrel bisulfate) and hormone-replacement therapy in tablet, injectable or gel form.	X
Unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use, according to the judgment of the IoR/designee.	X
Anorectal STIs	X
Acquisition of HIV infection (reactive rapid test)	X
Pregnancy	X
Breastfeeding	X
Grade 3 AE related to Study Product not addressed in Section 9.5	X
Grade 4 AE not addressed in Section 9.5 (regardless of relationship)	X