Section 7. Clinical Considerations

7. Introduction

This section presents information on clinical procedures performed in MTN-033. 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 (Laboratory Considerations) of this manual. Instructions for completing data collection forms associated with clinical procedures are provided in Section 12 (Data Collection) of this manual.

7.1 Baseline Medical History

A participant's baseline medical 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 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 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 sheet (available on the MTN-033 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. Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing and approach (using probing questions as listed on the Baseline Medical History Questions sheet) 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.

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 CRF:

- Baseline medical Grade 1 and higher lab values
- Medically-relevant physical exam abnormalities
- Rectal and/or genital 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 sections 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 rectal sexual activity for 72 hours before and after each study visit. This includes refraining from receptive anal intercourse (RAI), receptive oral-anal stimulation, rectal stimulation via fingers, and rectal insertion of sex toys.
- Willingness to abstain from using any non-study products in the rectum for 72 hours prior to and following each study visit. 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 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 in cosmetics, lotions etc.), s/he may have an allergy to dapivirine gel.
- PrEP use for prevention within 1 month or PEP use for HIV exposure 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 30 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.

7.1.1 Baseline Medical Conditions

The Baseline Medical History Log CRF is completed based on all screening source documents including, but not limited to, the Physical Exam CRF, Anorectal Exam CRF, Genital Exam CRF, 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 "*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). 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 that could result in product discontinuation. For example, if a participant suffers from chronic asthma and uses an immunomodulatory to control his/her condition, site staff are asked to use their discretion with evaluating the eligibility of this participant.

Allergic Reactions: If a participant reports having a history of anaphylactic reactions (such as difficulty in breathing or severe hives with throat closure) to any food, product or drug, even if it has happened only once before in their 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. Record the condition/event as, for example, "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. 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 (using probing questions) and approach 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 your occasionally experience X, have you had any recent episodes?)

If, during follow-up, a medical condition resolves or increases in severity or frequency from baseline, this should not be documented on the Baseline Medical History Log CRF as this is meant to remain a snapshot of the participant's baseline medical history at Enrollment. Document resolution of a baseline condition in chart notes or another site-specific tracker. If the baseline condition reoccurs or increases in frequency, complete an AE Log CRF to document the change as a new AE and leave the condition's status as 'ongoing" on the Baseline Medical History Log CRF. The AE Log CRF should have the "yes" box marked 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.

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.

7.3 Concomitant Medications

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

Protocol section 6.8 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

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 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 his/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

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 7.7 outlines the required physical exam assessments. A comprehensive physical examination is required at Screening and Enrollment. 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 only if indicated at Visits 3-6 and at interim visits. Site clinicians may use their discretion to determine whether 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 Log CRF, as well as the participant's chart notes, since the condition was present at the time of enrollment.

7.4.1 Pharyngeal Swab

One swab (pharyngeal) will be collected to test for chlamydia and gonorrhea at Screening and when clinically indicated at all other visits. To collect the swab, the participant should be instructed to open his or her mouth as widely as possible, allowing the clinician to make adequate contact with key areas of the throat (posterior wall, tonsils and uvula). If needed, a tongue depressor may be used. Insert the swab and vigorously rub the tonsillar pillars and posterior pharynx (behind the uvula). When removing the swab following collection, carefully ensure that the swab does not touch any area of the mouth (including the tongue, cheeks or teeth) before placing the swab in the appropriate specimen collection tube.

7.5 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 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 rectal 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 genitalia examination:

- A visual exam (i.e. a naked eye examination) should be performed of the external genitalia including of the entire penile surface: glans, urethral meatus, internal and external foreskin (if present) and shaft; scrotum; and inguinal lymph nodes

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 swab for detection of HSV 1/2 is only done if clinically indicated (i.e. the presence of shallow perianal ulceration or vesicle crops). The HSV 1/2 swab should

be collected after visual examination of the perianal area and **prior** to the digital examination.

Internal examination (Digital Rectal Exam):

- This examination is performed prior to the insertion of the anoscope or flexible sigmiodoscopy. 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 rectal exam findings (that are not exclusionary) identified at the Screening and Enrollment Visits should be recorded as a baseline medical condition.

7.7 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) 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 gonorrhea (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 Microbiome and PK:

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 **microbiome**. A **pre-weighed dacron swab** will be used to collect samples for **PK**.

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

- Introduce the flocked nylon swab through the anoscope into the rectum. Rotate the flocked nylon swab along the lateral wall of the rectum several times. Remove the flocked 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.

To assemble the swab and extender pipette, cut the distal end of the transfer pipette at the first gradation for swabs. These will serve as extension/holder device for each swab. Attach the swab, via the stick, to the transfer pipette and ensure that it is secure.

Rectal Enema Effluent for PD and PK

After swab 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 20mL 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, Ex-Vivo/PD, Biomarkers and Mucosal Safety:

All participants will be instructed to abstain from inserting anything into the rectum, including 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 to obtain a 15mg biopsy.
- Each individual biopsy should be obtained before the next one is collected. See Section 9 (Laboratory Considerations) of this manual for details on how many rectal biopsies should be collected and how 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 unlikelihood 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, s/he 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 and Proteomics 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.

7.7.1 Documentation of Rectal Exam Findings

All rectal and genital exams, anoscopic findings and those noted during the flexible sigmoidoscopy should be documented using the Anorectal Exam and/or Genital Exam CRFs.

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 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 coital simulation device use, applicator use, anoscope, or flexible sigmoidoscope insertion/removal and/or biopsy collection that is judged by the clinician to be within the range 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 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-033 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 Centers for Disease Control and Prevention (CDC) guidelines which can be accessed at: (http://www.cdc.gov/std/treatment).

Potential participants presenting with an active infection requiring treatment at Screening or Enrollment will be excluded from study participation. Per current CDC guidelines, the following infections require treatment and are exclusionary: Chlamydia trachomatis infection, gonorrhea, 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.

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.

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 performed based on symptoms) 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 UTI, 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 Male Genital Grading Table. 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 conditions or AEs.

7.9 HIV Testing

At Screening, Enrollment (prior to randomization) and at Visit 6, all participants will undergo HIV serology testing. Note at Enrollment, the site must perform an HIV rapid test to screen for HIV status prior to randomization. Participants will be ineligible for enrollment regardless of subsequent/confirmatory test results if the HIV test is positive or discordant.

Any participant who is found to have confirmed HIV infection after enrollment, product use and study participation will be permanently discontinued. 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. All participants with confirmed HIV infection will be counseled and referred to available resources for medical and psychosocial care and support. 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. 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 testing for HBV with assessment of hepatitis B surface antigen (HBsAg) at Screening. 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 also 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 CDC 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, in consultation with the PSRT.
- 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 and the participant's current RPR titer is greater than 1.4, the participant is not eligible for enrollment.

  If syphilis is diagnosed during screening, 'syphilis seropositivity' should be recorded within the Baseline Medical History Log CRF and the screening RPR titer included ("RPR titer: 1 to X"). A baseline condition of syphilis seropositivity should be marked 'ongoing' at baseline.

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), and early study termination (Section 9.5). 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 7-1 below.

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 Request Slip as described in Section 6 (Study Product Considerations for Non-Pharmacy Staff) of this manual. Product discontinuations also must be documented on the Treatment Discontinuation CRF.

Figure 7-1
Conditions Requiring Permanent Discontinuation

Condition
Report of use of prohibited medications and medications (Heparin, Lovenox®, Warfarin, Plavix® (clopidogrel bisulfate) and hormone-replacement therapy in tablet, patch, injectable or gel form.
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.
Anorectal STIs
Acquisition of HIV infection (reactive rapid test)
Grade 3 AE **related** to Study Product not addressed in Section 9.4
Grade 4 AE not addressed in Section 9.4 (regardless of relationship)