

Section 10. Clinical Considerations

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This section presents information on the clinical procedures performed in MTN-025. The Schedule of Study Visits and Evaluations in Appendix I of the protocol indicates when specific clinical and laboratory assessments are to take place. While the protocol dictates the schedule for data capture, the Investigator of Record (IoR) or designee should perform the symptom-directed examination at his/her discretion during any visit if s/he determines it to be clinically necessary, particularly if there are any on-going medical or mental health conditions that require closer follow-up. The participant's research record should include documentation of these procedures. Throughout the SSP, the term 'clinician' will refer to a study doctor or a nurse in settings where nursing training, scope of practice, and delegation, permit nurses to perform clinician activities under doctor supervision.

Further clinical considerations related to participant safety monitoring and adverse event reporting are provided in Section 11. Information on performing laboratory procedures is described in Section 13. Instructions for completing data collection forms associated with clinical procedures are provided in Section 14 and within the CRF completion guidelines.

10.1 Medical and Menstrual History

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

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

In order to obtain a complete, accurate, and relevant participant self-reported medical and menstrual history, it will be necessary to ask the participant about significant past medical conditions as well as any current conditions. It is recommended that sites use the MTN-025 Baseline Medical History Questions sheet (available on the MTN-025 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 in order to elicit complete and accurate information from the participant. This is especially important with regard to details about severity and frequency of baseline medical history conditions. Note it is not expected nor required that a participant's reported medical history for HOPE be reconciled with ASPIRE documentation.

At the enrollment visit, a participant's medical and menstrual history should be reviewed and updated, as needed.

10.1.1 Baseline Medical Conditions

Details of all relevant conditions identified during the baseline medical and menstrual history taking at screening should be recorded within the Baseline Medical History Log. 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.

In addition to participant-reported conditions, record the following on the Baseline Medical History Log:

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

The clinician should record as much information as possible about the severity and frequency of any baseline medical condition in the description field within the Baseline Medical History Log CRF to best describe the condition at the time the participant enters the study. Severity of each baseline medical condition should be assessed per the DAIDS Female Genital Grading Table for Use in Microbicide Studies (FGGT). If the condition is not listed in the Female Genital Grading Table

for Use in Microbicide Studies, refer to the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events, Version 2.0 (hereafter referred to as the “DAIDS Toxicity Table”). See Section 11 for further clarifications, guidelines, and tips for severity grading in MTN-025.

The purpose of grading the baseline medical condition is to determine whether abnormal signs, symptoms, and/or conditions identified during follow-up are adverse events (AE). By definition, baseline medical conditions that are present prior to or at enrollment are not considered AEs. New conditions identified during follow-up that were not present at enrollment, and baseline medical conditions that increase in severity (increase to a higher grade per the DAIDS toxicity table) during follow-up, are considered AEs. 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. Examples of conditions that are not gradable but could be determined to be relevant include ‘syphilis seropositivity’ for a participant who was diagnosed and treated at screening for syphilis, asymptomatic BV, previous surgeries, or expected baseline bleeding (see below).

At Enrollment and during follow-up, each baseline medical condition entry should be reviewed, updated as needed, and the status for ‘Is the condition ongoing?’ should be reviewed. Note that recurrent chronic conditions should be marked as ‘ongoing’ at enrollment, even if the participant is not currently experiencing an acute event (e.g., intermittent headaches). During follow-up, if the medical condition resolves or increases in severity grade per the DAIDS toxicity table, the “Is the condition ongoing?” item should be updated and the date that the condition resolved or increased in severity should be provided on the log form. 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. For ongoing chronic conditions that are grade 3 or higher, it is recommended that the IoR/designee also document within the chart notes whether per their discretion it is safe for the participant to enroll in the study.

Note that any menorrhagia, metrorrhagia, or menometrorrhagia events ongoing at the time of enrollment should be graded on the Baseline Medical History Log CRF according to the FGGT. Based on this guidance, expected menorrhagia, metrorrhagia, or menometrorrhagia (e.g. explained by contraception) would be marked ‘no’ mark ‘no’ for “Is condition/event gradable?” (i.e., would be considered Normal or Grade 0), while unexpected abnormal bleeding would receive a grade from 1-4. Note that unexpected abnormal bleeding conditions should be graded based on interference with social and functional activities (minimal, moderate, severe, life threatening). In the description field of the medical history condition/event entry, 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 enrollment) menorrhagia, metrorrhagia, or menometrorrhagia events documented on the Baseline Medical History Log CRF should also be assigned a grade per the FGGT.

Infrequent bleeding at baseline should also be captured on the Baseline Medical History Log, using the terms “missed menses”, “oligomenorrhea” or “amenorrhea”,

as appropriate (see SSP section 11.3.1 for term definitions). If infrequent bleeding is explained by contraceptive method, note this in the description field and mark ‘no’ for “Is condition/event gradable?”. If infrequent bleeding is unexplained, assign a severity grade from 1-2 per the FGGT.

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

Date medical history collected	20 JUL 2016
Description of medical history condition/event	ALLERGIC REACTION TO PEANUTS - SHORTNESS OF BREATH AND THROAT SWELLING; GRADE 3 WHEN ANAPHYLACTIC REACTION OCCURRED IN 2000.
Is condition/event gradable?	No
Toxicity (Severity) Grade	
Date medical history condition/event started	UN UNK 2000
Is the condition ongoing?	Yes
Date medical history condition/event ended/resolved	

In this example, note that the condition is listed as “allergic reaction to peanuts” with a short summary of signs or symptoms that occurred (e.g., ‘shortness of breath and throat swelling’, and the severity grade). At the Enrollment Visit, check ‘yes’ for the ‘Is the condition ongoing’ item and check ‘no’ for ‘Is condition/event gradable?’ as participant was not experiencing an anaphylaxis event at the time of enrollment. An AE submission for an anaphylactic reaction is required if this same event occurs after enrollment or during the study follow-up.

10.1.2 Concomitant Medications

The MTN-025 protocol requires documentation of all medications taken by study participants beginning at the Screening Visit and continuing throughout follow-up. Medications include the following:

- Prescription and “over-the counter” medications and preparations
- Medications taken for pre-exposure (PrEP) or post-exposure prevention (PEP) of HIV
- Vaccinations
- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations
- Contraceptive medications – see guidance below
 - 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

- NOTE: actual use of individual pill packs and contraceptive injections should be captured on the concomitant medication log CRF. The Family Planning log also captures information on a participant's overall family planning method, intention to use, and contraceptive switches—please refer to the CRF Completion Guidelines for guidance on completing this form. As these two CRFs collect different types of information related to a participant's family planning method use, discrepancies between these forms may occur and do not require reconciliation unless queried by SCHARP. In addition, this information is not expected to be reconciled with data from ASPIRE or family planning cards.

Note that antiseptic medications (e.g., hydrogen peroxide, iodine, etc.) should not be recorded on the Concomitant Medications Log.

Alcohol consumption and recreational drugs should not be reported as concomitant medications on the Concomitant Medications Log. Instead, excessive alcohol consumption and recreational drug use may be considered baseline medical conditions, per site clinician judgment, in which case they should be recorded within the Baseline Medical History Log.

The Concomitant Medications Log is used to document all concomitant medications in this study. This CRF is first completed at the Screening Visit, and entries are added for each participant as needed at the Enrollment Visit and throughout study follow-up.

Use the information obtained in the medical to probe for additional medications that the participant may have forgotten to report.

It is preferable to record the trade or generic name of the medication based on exactly what the participant is taking within the CRF. A combination medication can be recorded as one entry using the generic name. If a combination medication does not have a generic name or the generic name is unknown, each active ingredient must be reported as a separate entry in order to be accurately identified at SCHARP.

If a participant is unable to provide the exact name of a medication, record the type or class of medication as the medication's name with the text "name unknown". For example, if the participant knows she takes a blood thinner, but cannot provide the exact name, use "anti-coagulant – name unknown" for the medication name field.

Medication history information documented within the Concomitant Medications Log at the Screening Visit must be actively reviewed and updated at the Enrollment Visit. Review the information within the CRF with the participant at the Enrollment Visit and update as applicable.

At follow-up visits, or during an interim visit, review the participant's previously completed Concomitant Medications Log forms, record any new medications provided to the participant by study staff, and actively ask the participant whether she is still taking all previously-recorded medications, at the same dose and frequency. Also actively ask whether the participant has taken any new medications since the last medical history was taken. Add all new information to the form in log fashion. To help ensure accurate reporting of concomitant medications information, participants should be encouraged to bring a list of all medications to study visits.

10.1.3 Pre-exposure Prophylaxis (PrEP) for HIV prevention

Per protocol, oral tenofovir-based ARV use is permitted if approved, available, and provided to participants by a health care provider as PrEP. PrEP can be used concurrently with the dapivirine vaginal ring and should be documented as a concomitant medication.

The HOPE Protocol Team is committed to the provision of highest standards of HIV prevention for all participants. HOPE study participants will be encouraged to consider any and all HIV prevention tools available to them. Participants in HOPE will receive risk reduction counselling, condoms, education about the most current data supporting efficacy of PrEP in women at substantial risk for HIV and, as appropriate, referrals to local providers for PrEP in collaboration with local regulatory partners. Should national guidelines and local standard of care support PrEP, sites are encouraged to consider making PrEP available on-site. PrEP will not be delivered as part of a comprehensive HIV prevention package. Approaches of PrEP referrals/provision should/will be in harmony with those used by other HIV prevention trials in the region.

As part of study activation, all sites are required to have in place site-specific procedures in place for training staff on current local guidelines, PrEP counseling, and as applicable, PrEP provision and referrals. The following information should be addressed within PrEP SOPs:

- Current National PrEP-specific Guidelines/Policies
- Information for participants on PrEP, such as:
 - Messages and information provided as part of risk reduction counseling
 - Information about PrEP co-use with the dapivirine vaginal ring
- Guidelines and Tools for providers, such as:
 - Indications for PrEP use
 - Eligibility for/Contraindications to PrEP
 - If applicable, procedures for on-site PrEP provision including:
 - Staff Training and certification
 - Procedures for initiation of PrEP, including required baseline evaluations and counseling
 - Ongoing safety monitoring and management, including conditions for stopping PrEP
- Procedures and resources for referral for PrEP

PrEP SOPs should be routinely reviewed and updated based on changes in local guidelines/policies and availability/accessibility of PrEP. The following are a list of resources for current information on PrEP:

- <http://www.prepwatch.org/>
- <http://www.who.int/hiv/topics/prep/en/>
- <http://www.cdc.gov/hiv/risk/prep/index.html>

10.1.4 Prohibited Medications and Devices

The use of contraceptive vaginal rings specifically prohibited in MTN-025. Should a participant report use of a contraceptive vaginal ring, the MTN-025 PSRT should be informed.

Per protocol, concomitant use of devices such as diaphragms, menstrual cups, and cervical caps are discouraged. Participants will be counseled on avoiding use of these devices during study participation. No notification is needed in the event a participant reports use of a discouraged device.

NOTE: Products and practices including the use of spermicides, vaginally applied medication, douches, lubricants, tampons, etc., are not prohibited in MTN-025. However, healthy vaginal practices should be encouraged by clinic staff. Women should be advised against the use of douches, soaps, or other detergents to clean inside the vagina, as well as herbs or other materials to dry or tighten the vagina.

Use of any medications, including prohibited medications, will be recorded within the Concomitant Medications Log CRF as specified in section 10.1.2 above. Vaginal practices and use of other devices should be recorded in the source documentation (e.g., chart notes), and within CRFs, as appropriate.

10.1.5 Follow-up Medical History

It is necessary to update the participants' medical history at all follow-up clinic visits to determine whether previously reported conditions remain ongoing and whether new symptoms, illnesses, conditions, etc. have occurred since the last medical history was performed. Any symptoms reported by the participant should be further probed and evaluated. Study clinicians should follow-up on any ongoing baseline conditions as well as any previously reported adverse events that are continuing.

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

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

Changes to any medications you are currently taking?)

Targeted gynecological questions (e.g., When was your last menstrual period? Would you say this is typical for you? Have you experienced any gynecologic problems since your last visit? For example, have you been bothered by abnormal discharge, pain, or bleeding?)

Targeted questions about ongoing 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?)

Review of the medical history must be documented; this can be done in chart notes or in a site-specific tool if desired. If no new symptoms, illnesses, conditions etc., are reported, and if ongoing conditions remain unchanged, the participant chart should reflect this.

If during follow-up a baseline medical condition resolves, this update should be documented within the Baseline Medical History Log by entering a date for the item “Date medical history condition/event ended/resolved”.

All newly-identified participant-reported symptoms and conditions, as well as baseline conditions that have increased in severity per the DAIDS toxicity table, will be documented on either the Adverse Experience Log (AE) or the Grade 1 Adverse Experience Log (GAE) CRF (see Section 11 for details regarding AE documentation).

During follow-up, if a condition is identified as being present at baseline and the participant inadvertently did not report it in her baseline medical history, the clinician should add the newly-identified information to the Baseline Medical History Log CRF. A chart note should also be documented to explain why the newly-identified information is recorded on the Baseline Medical History Log CRF retrospectively.

During the enrollment visit and follow-up visits, the dates of the participant’s last menstrual period (LMP) is recorded on the Pregnancy Test result CRF. Any menstrual-like bleeding should be documented on this form. Clinical discretion should be used to determine LMP for the completion of this CRF. Recording LMP should be based on clinical impression and does not need to be consistent with AE reporting terms used to describe the bleeding. In other words, bleeding that is captured as an AE can still be considered menstrual-like for the purposes of completing the Pregnancy Test Result CRF. Note that genital bleeding that is not considered to be menses should *not* be documented on the Pregnancy Test Result CRF. Instead, document it in other source documents as applicable (such as chart notes), as well as an AE Log CRF, if it meets AE reporting requirements. See SSP Section 11.3.1 for information on reporting bleeding AEs.

10.2 Physical Exams

10.2.1 Considerations at Screening and Enrollment

The goal of the Screening physical exam is to collect detailed information on baseline conditions, as well as to evaluate eligibility. All abnormal signs/symptoms/diagnoses identified during the screening physical exam should be recorded within the Baseline Medical History Log CRF and followed up on at the Enrollment visit.

A complete physical exam will be conducted at the screening visit and a targeted (abbreviated) physical exam for all subsequent scheduled exams. Per protocol Section 7.10, the following assessments are required at the Screening physical exam (bolded assessments are also conducted at scheduled follow up exams).

- **General appearance**
- **Weight (see Section 10.2.3 for further guidance)**
- **Vital signs:**
 - **Temperature**
 - **Pulse**
 - **Blood pressure (See section 10.2.5 for further guidance)**

- **Respiratory rate**
- **Abdomen: palpable spleen, liver**
- Height
- Lymph: palpable cervical, axillary and/or inguinal lymph nodes
- Neck
- Heart: rate, rhythm, murmurs
- Lungs: observation of character of respirations, auscultation
- Extremities
- Skin: rashes, scars, bruising, needle tracks, jaundice
- Neurological
- **Assess any other medical condition that would make participation in the study unsafe or interfere with interpreting the study data or achieving the study objectives.**

The organ system/body part evaluation as part of the physical exam assessment is documented within the Physical Exam CRF. The vital signs and weight assessments are documented within the Vital Signs CRF.

10.2.2 Physical Exams Conducted at Follow-up

Physical exams are required at the Product Use End (PUEV) visit, and when clinically indicated. Scheduled follow-up physical exams should include the bolded assessments outlined in Section 10.2.1 (and protocol Section 7.10). Additional assessments may be performed at the discretion of the examining clinician in response to signs, symptoms, or other conditions present at the time of the exam.

Physical exams performed during follow-up (including unscheduled exams that are clinically indicated) are documented using the Physical Exam CRF. Abnormal physical exam findings newly-identified during follow-up are recorded and tracked using the Adverse Experience Log (AE) CRF or Grade 1 Adverse Experience Log (GAE) CRF as applicable. If one particular vital sign (for example, weight, height, blood pressure) is measured during unscheduled time points and further physical evaluation is not performed, this vital sign(s) can be noted in the participant's chart notes, as needed.

10.2.3 Weight

Participant weight must be measured as part of each scheduled physical exam and additionally when clinically indicated. Weight should be measured in kilograms and should be rounded to the nearest whole number. Scales must be calibrated at a frequency per the manufacture's recommendations or any local regulations, whichever is more stringent. It is recommended that scales be calibrated at least annually.

At each site, consistent weighing procedures should be followed for all participants. Each site may choose to consistently weigh participants fully clothed or wearing clinic gowns. Sites with seasonal weather variations should consider using gowns and/or adopting other procedures to ensure that accurate weights are measured throughout the year.

It is suggested that baseline weight be entered into the safety lab calculator tool, available on the MTN website (<http://www.mtnstopshiv.org/node/7330>), to assist with identification and grading of AEs for weight loss during study follow-up (see also SSP section 11.3.3).

10.2.4 Height

Participant height must be measured as part of the physical exam at the Screening Visit. Height should be measured in centimeters and should be rounded to the nearest whole number. Height measurement devices affixed to weight scales are often inaccurate and are not recommended. For participants with hairstyles that could affect height measurements, a tongue depressor or other device should be held horizontally to the wall chart at the top of the participant's head (not at the top of her hairstyle) to obtain accurate measurements.

10.2.5 Blood Pressure

Blood pressure must be measured as part of each scheduled physical exam and additionally when clinically indicated. Blood pressure devices are expected to be calibrated regularly per manufacturer's directions.

For participants with hypertension, it is recommended that study sites counsel the participant and refer the participant per site SOPs. Antihypertensives, including thiazide diuretics and angiotensin converting enzyme (ACE) inhibitors, are not contraindicated in MTN-025. If treatment is provided at the research clinic, site clinicians should generally follow local standards of care for antihypertensive monitoring and treatment.

In cases where the participant is known to be hypertensive at screening/enrollment and the condition is well controlled on existing medication, the condition should be documented as non-gradable and ongoing. Relevant details of the condition should be documented in the description field on the Baseline Medical History CRF. Any medication(s) should be recorded on the Con Meds Log.

If a participant is hypertensive and is prescribed medications at screening, document the severity grade based on current blood pressure measurements (per the DAIDS Toxicity Table), mark the condition as ongoing and follow-up as needed to ensure that the hypertension is well controlled. Any improvements in severity grade or other details can be added to the description field, as needed. Any medication(s) should be recorded on the Con Meds Log.

For baseline conditions regarding pregnancy-related hypertension that resolved post-delivery, sites should determine the severity grade, mark it as not ongoing, and provide additional comments in the Description field, if the clinician deems this information clinically relevant.

The most recent blood pressure reading that is used for clinical management should be recorded on the Vital Signs CRF. For further guidance on completing blood pressure entries into Medidata, please see Vital Signs CRF Completion Guidelines.

10.3 Pelvic Exams

10.3.1 Considerations at Screening

The pelvic exam during the Screening Visit is necessary to evaluate protocol exclusion criteria and to collect detailed information on baseline genital/genitourinary conditions. Guidance on the conduct of pelvic exams can be found in SSP Section 10.3.4. Screening Visit pelvic exams are documented using the Pelvic Exam Checklist, Pelvic Exam Diagrams form and the Pelvic Exam CRF.

Any abnormal pelvic exam finding, regardless of grade, should be documented within the Baseline Medical History Log CRF. Only grade 1 or 2 findings may be ongoing at enrollment, otherwise the participant is ineligible.

SPECIAL NOTE:

The findings below could potentially warrant a product hold should the participant enroll in the study. Therefore, study staff is asked to particularly assess for the following at the screening pelvic exam (some of which may be exclusionary):

- Deep epithelial disruption
- Generalized erythema or severe edema: area of more than 50% of vulvar surface or combined vaginal and cervical surface affected by erythema
- Cervicitis (including findings on exam such as inflammation and/or friability)

Note that a pelvic exam is not required at the Enrollment Visit. However, in cases where an exclusionary abnormal exam finding (grade 3 or higher) is identified at the Screening Visit, it will be necessary to re-assess the finding prior to Enrollment to confirm the participant's eligibility. If re-assessment on or prior to Enrollment confirms the exclusionary finding(s) is Grade 2 or below, the participant may be enrolled. Document the re-assessment of abnormal screening pelvic exam findings by updating the Pelvic Exam Diagrams form and the Pelvic Exam CRF completed at the Screening Visit. Alternatively, per clinician discretion, a new Pelvic Exam Diagrams form and/or Pelvic Exam CRF may be completed to document this re-assessment or to document a new pelvic finding at Enrollment. The Toxicity (severity) grade, ongoing status, and other information (as needed) of the abnormal finding should be updated on the corresponding Baseline Medical History Log entry. Enter data from the pelvic exam completed closest to the participant's Enrollment into the Medidata Rave database at within the Screening Visit folder.

Non-exclusionary pelvic exam findings do not require reassessment before enrollment.

10.3.2 Pelvic Exams Conducted at Follow-up

Follow-up pelvic exams are required at the PUEV visit, and when clinically indicated. Pelvic exams are considered clinically indicated when new genitourinary complaints are present, i.e., new bleeding not attributable to contraceptive method, vaginal discharge, pelvic pain. The need for a pelvic exam in response to new genitourinary complaints that have resolved at the time of the visit is up to clinician discretion. All new symptoms, regardless of resolution date and whether or not a pelvic exam was conducted, should be reported as adverse events per section 11.3 of this manual. Pelvic exams must also be performed before resuming use of VR after product hold due to pregnancy.

As with any study procedure, participants may decline to have a study pelvic examination. For pelvic exams scheduled per protocol or those clinically indicated to evaluate a simple AE that has since resolved, if the participant declines, a second attempt should be made to conduct the pelvic at the next scheduled visit. If, after the second attempt, the participant still declines, the site may forego asking at that

time. Ensure there is a clear clinical note documenting the offer of the exam and that failure to conduct the exam did not pose an apparent safety risk to the participant. For a clinically indicated pelvic exam to evaluate an ongoing AE, particularly if there is a clinical concern about ongoing use of the ring, additional effort should be made to conduct the exam. The site clinician should assess carefully whether to initiate a product hold if a sufficient examination cannot be done. The site should continue to ask at each participant contact/visit to have the procedure conducted until the participant consents.

Ultimately, for any of the above scenarios, the site needs to assess the clinical safety of continued product use on a case-by-case basis. If the site clinician feels that an exam is indicated but cannot conduct the exam, the site should consider whether to continue study product use. A Protocol Deviation Log CRF should be completed for each instance in which a participant refuses a required or clinically indicated pelvic exam (as outlined above). Sites should consult the PSRT for guidance on specific situations as needed/required.

Scheduled pelvic exams should be performed according to the guidance provided in the remainder of this section. Exam procedures must be performed in the order shown on the exam checklists provided on the MTN-025 website (<http://www.mtnstopshiv.org/node/7330>). Pelvic exams performed at non-scheduled visits (e.g., interim visits or in response to symptoms) should be targeted to symptoms and staff are not required to complete all components of the complete pelvic exam.

10.3.3 Pelvic Exam Overview

General Technique: Maximize the comfort and privacy of the participant. Position the examination table away from the door or hang a curtain to ensure privacy. Explain what you are doing as you do it. Take as much time as needed to ensure participant comfort and accurate documentation of exam findings.

Use clean hand/dirty hand technique, and/or assistants, to avoid contamination. Keep extra gloves available as two hands may be needed at different time points during the exam.

Use a speculum of appropriate type and size to permit adequate visualization of the vagina and cervix. For most participants, a Graves speculum is preferred to enable visualization of all anatomic areas and tissues. Record the type and size of the speculum used on the Pelvic Exam Diagrams form for each pelvic exam conducted. Prior to insertion, ensure that the speculum functions properly and has no rough edges.

Exams During Genital Bleeding: Routine pelvic exams, i.e., those required at protocol-specified time points, should be completed regardless of genital bleeding unless there is heavy bleeding and/or the participant is uncomfortable. If the exam is not completed, perform other protocol-specified procedures at the visit and schedule the participant to return for the pelvic exam as soon as possible after bleeding stops, within the visit window (as part of a split visit). If this is not possible and the pelvic exam is missed, this procedure should be made up at her next scheduled clinic visit. If a participant is experiencing genital bleeding when she presents for an interim visit complaining of genital symptoms, every effort should be made to perform a pelvic exam to evaluate her symptoms at that time.

Exams During Pregnancy: Pelvic exams, including self-administered vaginal swab collections, are considered safe throughout the duration of the pregnancy, and for this protocol, directed exams will continue for pregnant participants up to 24 weeks of gestation. While not required, it is considered safe to continue exams *after* 24 weeks of gestation, and is encouraged by the protocol team. Participants who become pregnant will be managed as described in Section 6.6 of this manual.

Exams for Participants with Hysterectomy: Potential participants who have undergone a hysterectomy are still eligible for enrollment into MTN-025. For women who have had a supracervical hysterectomy, all study procedures will be performed. For women who have had a total hysterectomy and no longer have a cervix, two study procedures will be handled slightly differently: Pap smears and cervical ectopy assessment. In these instances, clinicians should collect a vaginal Pap smear when a Pap smear is indicated and note in the comments for the pathologist that the participant is status post hysterectomy. If a vaginal Pap smear is collected, this satisfies the requirement for a "Pap smear." If completing a Paper Pelvic Exam CRF prior to data entry into the clinical database, line through the cervical ectopy field and add a note in the white space "participant post-hysterectomy", initial and date the note. When completing the Pelvic Exam eCRF within the Rave database, leave the 'cervical ectopy' item blank, save the form, and provide a comment, "participant post-hysterectomy", in the text field of the system query.

10.3.4 Detailed Procedural Instructions

Prior to the Exam: Prepare all required equipment, supplies, and paperwork; label specimen collection supplies as needed. Verify that all equipment is in good working order. Review documentation of prior exams and other relevant documentation from the current visit and prior visits. While the participant is clothed, explain the procedure to her and answer any questions she may have. Ask the participant to remove the VR just prior to the pelvic exam, as applicable.

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

Examine the External Genitalia:

- Do not insert the speculum before examining the external genitalia.
- Relax the participant's knees as far apart as is comfortable for her.
- Palpate the inguinal lymph nodes to assess for enlargement and/or tenderness.
- Perform naked eye examination of the external genitalia including the perineum, and perianal area

Examine the Cervix and Vagina:

- The speculum may be lubricated with warm water or a water-based lubricant if needed. 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.
- Assess for cervical ectopy.

Collect Specimens: Collect specimens in the order listed on the pelvic exam checklist, which is also reflected below. The order of specimen collection is critical to ensure that first specimens collections do not affect subsequent specimens. Collect specimens away from apparent abnormalities and exclude swabbed areas from subsequent examination.

- If required per protocol (at Screening, PUEV) and/or if clinically indicated, collect a vaginal sample to test for trichomonas with the rapid test kit. Vaginal samples may be collected for this test from the lateral vaginal wall.
- If clinically indicated, collect samples for any clinically indicated evaluations (e.g. swab for vaginal saline and/or KOH wet mounts for evaluation of vaginitis (yeast, trichomonas or BV) from the lateral vaginal wall, genital herpes testing if per local standard of care, etc.).
- At Screening (if required to confirm eligibility) visit, perform Pap Smear. For Pap smear management, see Section 10.4.

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

Perform Bimanual Exam: 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.

10.3.5 Documentation of Findings

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

All abnormal findings during screening and follow-up will be documented within the Pelvic Exam CRF and the Baseline Medical History Log CRF. All abnormal findings identified during follow-up will be documented on the Pelvic Exam CRF. All newly-identified abnormal pelvic exam findings will be documented on an Adverse Experience Log (AE) CRF. The results of laboratory test results performed using specimens collected during pelvic exams are recorded within the STI Test Results CRF.

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

- anatomic variants
- gland openings
- Nabothian cysts
- mucus retention cysts
- Gartner’s duct cysts
- blood vessel changes other than disruption

- skin tags
- scars
- cervical ectopy

Cervical ectopy is a required separate assessment and considered a normal finding. The percentage of cervical ectopy within the Pelvic Exam CRF should always be completed when a pelvic exam is conducted.

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 string not visible upon exam, this be documented and followed up on.

See Section 11.3.1 for guidance on documentation, reporting, and management of pelvic exam findings involving genital bleeding.

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
- Red
- White
- Other (includes “pale”)

Blood Vessels

Integrity:

- Intact
- Disrupted

Figure 10-1 below provides further information to guide and standardize terminology used to describe abnormal pelvic exam findings.

Pelvic exam findings should be documented using terminology corresponding to the FGGT and the study-specific Pelvic Exam case report form. For findings in which the finding term marked on the pelvic exam case report form is more specific than the corresponding term on the FGGT, use the more specific term.

Figure 10-1

CONRAD/WHO Terminology for Pelvic Exam Findings

Term	Status of Epithelium	Status of Blood Vessels	Comments
Erythema	Intact	Intact	Distinguished by color (erythema being redder than
Edema	Intact	Intact	

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

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

10.4 Pap Smear Results and Management

Women with a documented normal result within the 12 months prior to enrollment need not have a Pap smear during the screening period. However, copies of this Pap result must be obtained and retained on file for purposes of eligibility assessment. If a participant requires Pap specimen collection as part of study screening procedures, and an inadequate specimen is collected, a second (repeat) Pap specimen must be collected and tested prior to Enrollment in order to assess eligibility.

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. See SSP section 11.4 regarding guidance for grading Pap Smear and cervical biopsy results and AE reporting.

PapPapPapPapPapPap

Pap smear results should be managed per local standard of care as specified in site SOPs. If local standards of care require clinical colposcopy and/or biopsy to assess lower grade abnormalities (not requiring hold per protocol), the IoR/designee should advise the participant to remove the vaginal ring (if applicable) on the day of the colposcopy. The removal prevents the ring from interfering with the evaluation, biopsy, or treatment, if needed. The duration of the ring outage will depend on the procedures completed at the time of colposcopy.

- If a biopsy or treatment (excision or cryotherapy) is not undertaken, the participant should be instructed to reinsert the same ring following the colposcopy (as done with IUCD insertion or laparoscopic tubal ligation). A pelvic exam is not required for ring reinsertion, and no Clinical Product Hold/Discontinuation Log CRF or pharmacy documentation is required to document the brief removal.
- If a biopsy or treatment is performed, a new clinical product hold should be initiated. Study clinic staff should complete a Clinical Product Hold/Discontinuation Log entry and a vaginal ring request slip marked “hold”. The product hold should continue until a clinically acceptable resolution for the biopsy and/or treatment has occurred according to the judgment of the IoR/designee. Importantly, adequate healing should be confirmed on pelvic exam before reinstating product use. Assuming no contraindications are identified on pelvic exam, product use can be resumed. If the participant does not want the ring re-inserted (even though the clinician determines it is okay to do so), the additional days off product are not considered part of the product hold. Rather, they count as participant non-adherence, and should be captured as such within the Ring Adherence CRF completed at the participant’s next visit.

All ring outages, regardless of the reason(s), should be captured within the Ring Adherence CRF completed during the participant’s next scheduled study visit.

10.5 STI/RTI/UTI

10.5.1 Considerations at Screening/Enrollment

Participants diagnosed during screening with an STI/RTI/UTI requiring treatment may be enrolled in the study after treatment is complete provided all symptoms have resolved and the screening window is still open. Test of cure for STI/RTI/UTIs after treatment is NOT required before a participant is enrolled. If STI testing is required (based on symptoms) prior to or during the enrollment visit, the STI Test Results CRF completed at the screening visit should be updated as appropriate with the results of tests conducted.

Syphilis: If a reactive RPR is identified during screening, a confirmatory test (MHA-TP or TPHA) result must be received, and appropriate clinical management action taken, prior to enrollment in the study. Action required prior to enrollment depends on the current health status of the participant and the availability of medical records documenting her prior infection, as follows:

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

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

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 medical history condition of syphilis seropositivity should be documented on the "ongoing at time of assessment" at baseline. A test or cure (i.e., four-fold decrease in titer) is not required prior to enrollment; however, repeat serology is expected 6 months after treatment for clinical management purposes.

Genital warts: Genital warts requiring treatment must be treated prior to enrollment. Genital warts requiring treatment include those that cause an undue burden of discomfort to the participant, e.g., due to bulky size, unacceptable appearance, and/or physical discomfort (equivalent to a Grade 2 or 3 finding on the DAIDS FGGT). Documentation of improved participant symptoms to Grade 1 or 0 must be present before the participant is considered eligible for participation.

Vaginal candidiasis: Participants diagnosed with symptomatic vaginal candidiasis during screening are eligible once they have completed treatment and symptoms have resolved.

10.5.2 STI/RTI/UTI Diagnosis

Clinical and laboratory evaluations are performed throughout the course of MTN-025, either as scheduled evaluations or if indicated, to diagnose the following STIs and RTIs:

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

Signs and symptoms commonly associated with the above-listed infections are presented in Figure 10-2 below. 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.

Figure 10-2

Signs and Symptoms Commonly Associated with STIs/RTIs

STI/RTI	Common Signs and Symptoms
Bacterial vaginosis	Excessive or malodorous discharge is a common finding. Other signs or symptoms include erythema, edema, and pruritis of the external genitalia.
Candidiasis	Clinical presentation includes whitish vaginal discharge and erythema, edema, and pruritis of the external genitalia.
Chlamydia infection	Most infections are asymptomatic, but infection may be accompanied by cervicitis (defined as the presence of endocervical mucopurulent discharge, easily induced cervical bleeding, and/or edematous ectopy).
Genital herpes	Single or multiple vesicles which can appear anywhere on the genitalia. Vesicles spontaneously rupture to form shallow ulcers that may be painful. Lesions spontaneously resolve with minimal scarring.
Gonorrhea infection	Commonly asymptomatic but women may have abnormal vaginal discharge, or dysuria.
Syphilis infection — primary	The classical chancre is a painless indurated ulcer, located at the site of exposure.
Syphilis infection — secondary	Patients may have a highly variable skin rash, mucous patches, condylomata lata (fleshy, moist tissue growths), lymphadenopathy, alopecia, or other signs.
Syphilis infection — latent	Patients are without clinical signs of infection.
Trichomoniasis	Excessive, frothy, diffuse, yellow-green discharge is common, although clinical presentation varies from no signs or symptoms to erythema, edema, and pruritis of the external genitalia. Dysuria and dyspareunia are also frequent. The type of symptoms or signs alone does not distinguish the microbial etiology.

Adapted from: *Contraceptive Technology* (20th Revised Edition, 2011); Chapter 21: Reproductive Tract Infections; Alphabetic Catalog of Reproductive Tract Infections; pages 571-620.

Genital HSV: No laboratory testing is required for herpes simplex virus (HSV-1 or HSV-2) during the study but may be done if indicated and per local standard of care. Per the FGGT, the term ‘genital herpes’ may only be used for adverse event reporting if laboratory testing is conducted; otherwise sites are encouraged to use the most appropriate row in the FGGT which most closely resembles the clinical findings (ulceration, for example).

Urinary tract infections (UTIs): UTIs may be diagnosed in MTN-025 based solely on the presence of symptoms indicative of a possible UTI. 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

Other methods of diagnosis (i.e., urine culture or dipstick) may be performed per site standard of care per site SOP. Results must be documented in chart notes and/or on other site-specific source documents. If culture or urinalysis are used, UTI should be graded per the UTI row of the FGGT, if criteria are fulfilled. If only symptoms are used for diagnosis, the grade should be estimated based on the Estimating Severity Grade for Parameters Not Identified in the Grading Table row of the DAIDS Toxicity Table.

Incidental findings of STI/RTI on Pap: At some study sites, Pap smear results may include notations of findings associated with certain STIs (e.g., trichomoniasis). Because Pap smear methods are neither adequately sensitive nor 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 or AEs for the study.

If protocol-specified STI testing was performed on other specimens (i.e., blood, urine, vaginal samples) collected on the same day as specimen collection for Pap smear, the results of the protocol-specified testing overrule STI-related findings noted on the Pap smear result report. Provide treatment as needed based on the results of the protocol-specified tests.

If protocol-specified testing was not performed on other specimens (i.e., blood, urine, vaginal samples) collected on the same day as specimen collection for the Pap smear, collect specimens for indicated protocol-specified STI testing at the participant's next study visit after receipt of the Pap test result report. Provide treatment as needed based on the results of the protocol-specified tests. Note that BV and candida do NOT require retesting at the participant's next visit unless she is symptomatic.

10.5.3 STI/RTI/UTI Management

Treatment: All participants diagnosed with UTI based on the presence of symptoms should be provided treatment per site standard of care and applicable site standard operating procedures (SOPs).

All STIs/RTIs should be treated per site standard of care and applicable site standard operating procedures (SOPs). Asymptomatic BV does not require treatment per current WHO guidelines. Per the MTN-025 protocol, asymptomatic vaginal candidiasis also should not be treated. During screening, these asymptomatic infections are not exclusionary and during follow-up these asymptomatic infections are not considered AEs.

Current WHO guidelines can be accessed at:

<http://www.who.int/reproductivehealth/topics/rtis/evidence/en/index.html>

Syndromic Management: Syndromic management of STIs is acceptable per site SOP and local standard of care; however, a thorough laboratory evaluation is

expected in the context of this research study so that a specific diagnosis might be uncovered.

Test of Cure: STI/RTI tests of cure are not required in MTN-025, but may be recommended for pregnant participants per local guidelines. However, clinical management of syphilis infections should include repeat serology (RPR) at semi-annual intervals following diagnosis and treatment to confirm treatment effectiveness. For enrolled participants who are treated for syphilis during the screening period, a four-fold decrease in titer (for example, a drop from 1:32 to 1:8) is expected at the 6-month follow-up check after completion of treatment. If the RPR titer does not decrease four-fold or revert to seronegative within six months, the PSRT should be consulted for further management and to determine if an Adverse Event has occurred. Of note, the syphilis row of the FGGT should be used to grade syphilis adverse events.

Follow-Up for Syphilis Identified at PUEV: Sites have an obligation to ensure treatment and counseling for participants who test positive for syphilis at PUEV. If treatment, further counseling, and reliable syphilis testing are available outside the study site, participants can be appropriately counseled and referred at PUEV/SEV. Sites should provide these services if they are not available for participants via other service providers. For further questions, please consult the PSRT.

10.6 Vaginal Discharge

Both participant complaints and clinical findings of abnormal vaginal discharge are common in microbicide studies. While the evaluation of abnormal vaginal discharge may not differ between the two, whether treatment is offered and how the abnormality is reported may differ. Abnormal vaginal discharge may be associated with cervicitis, yeast, trichomoniasis, and/or bacterial vaginosis, among other conditions. Site clinicians are encouraged to thoroughly evaluate complaints and/or findings of abnormal vaginal discharge as per their discretion. Per protocol, whether to treat the underlying cause of the abnormal vaginal discharge will depend on (1.) what the underlying diagnosis is and (2.) whether the participant is symptomatic. If the evaluation reveals an underlying sexually transmitted infection such as trichomoniasis, the participant and her partner(s) should be offered treatment regardless of symptoms. If the evaluation reveals bacterial vaginosis or yeast, the participant should be offered treatment only if she is symptomatic.

Section 11.3.1 details the reporting of vaginal discharge Adverse Events. Briefly, sites are encouraged to distinguish whether the discharge was initially reported by the participant (“vaginal discharge by participant report”) or noted only on pelvic exam by the clinician (“vaginal discharge - clinician observed”). Importantly, in instances when the evaluation of clinician observed vaginal discharge reveals asymptomatic bacterial vaginosis or asymptomatic yeast, an Adverse Event should be completed for “vaginal discharge - clinician observed.” Even though asymptomatic yeast and bacterial vaginosis are not considered Adverse Events per protocol, in these instances, the clinician observed vaginal discharge should be captured as an Adverse Event.

10.7 Self-collection of Vaginal Fluid

At the Enrollment and all scheduled follow-up visits participants will collect vaginal fluid (1 Dacron swab) from the posterior fornix for biomarker analyses at MTN LC. Swabs are collected regardless of whether the participant chooses to use the vaginal ring. This should be collected prior to the participant removing the vaginal ring, if applicable, from her previous visit. If she comes to the clinic without a ring in, the swab should be collected prior to insertion of a new ring, if applicable. It is recommended that the participant collect the specimen before or after urine collection (order does not matter), but the clinician may also collect this swab if a pelvic exam is being conducted (or as needed), as long as the previous ring is still in place when this is done. Sites should have a holder available to keep the tube upright while the participant is collecting the sample. This procedure can still be conducted if the participant is on menses or if genital blood is present; if there is extremely heavy menses, participants should contact the clinical staff for guidance.

Instruct participants on the following series of steps for conducting self-collection of vaginal fluid:

1. Wash and dry your hands and undress from the waist down.
2. Carefully unwrap the kit package and remove threaded cap from vial and set aside.
3. Partially peel open the swab envelope, exposing the stick end of the swab.
4. Being careful not to lay it down on any surface, remove the swab from the package.
5. While separating the labia with one hand, use the other hand to hold the plastic swab shaft between your thumb and forefinger and insert the soft tip of the swab into your vagina approximately 4-5 cm (about the length of your little finger). Move the swab for 10-20 seconds, attempting to touch all walls of the vagina.
6. Carefully withdraw the swab and insert the swab into the vial.
7. Break off the swab shaft, leaving the soft end of the swab and throw the top portion away.
8. Put the cap back on the vial, wash hands again, and give vial to the clinical staff.

NOTE: if the swab is dropped in this process, please ask for a new test kit and repeat the entire process above. If there is blood on the swab, reference section 10.6.1.

A visual poster outlining these steps can be found on the HOPE website (<http://www.mtnstopshiv.org/node/7330>). Sites should modify the instructions above as well as the supplemental materials as needed per their site-specific process.

10.8 Pregnancy and Breastfeeding Considerations

Despite the MTN-025 eligibility criteria related to pregnancy intentions and use of contraception, as well as provision of contraception and contraception counseling throughout the study, it is expected that some study participants will become pregnant. All such participants should be managed as described in Section 6.6 of this manual. Adverse events that may be associated with pregnancy (for example, nausea), should still be graded per the DAIDS Toxicity Table and reported as an adverse event as needed. Refer to SSP Section 11.3.4 Reporting Considerations for

Pregnant Participants and Figure 11-1 Adverse Event Reporting During Pregnancy by Gestational Age for reporting AEs for pregnant participants.

After a pregnancy hold, VR use should not be resumed earlier than 2 weeks after a 1st trimester loss, or earlier than 4 weeks after 2nd trimester (or later) pregnancy loss or delivery. Note that breastfeeding must also be completed by the time of product restart. Product restart timelines should begin when the pregnancy is lost (i.e., bleeding, elective termination, etc.). This restart timeline should only be based off a negative pregnancy test if the date of pregnancy loss is completely unknown. Per protocol, a negative pregnancy test and a pelvic exam are required before resumption of product use.

The MTN-025 eligibility criteria exclude women who are breastfeeding from the study; any amount of breastfeeding or suckling is exclusionary. For women who may become pregnant and give birth during follow-up, use of study product will be held until after complete cessation of breastfeeding.

During screening and during follow-up, all women should be counseled and encouraged to breastfeed in accordance with WHO guidelines and local and/or national guidelines applicable at the study site. Key counseling messages for participants related to breastfeeding are as follows:

- The medicine in the rings being tested in MTN-025 pass into breast milk.
- The effects of having this medicine in breast milk are not well known. It is possible that having this medicine in breast milk could cause bad effects for babies who drink the breast milk.
- To avoid any possible bad effects:
 - It is very important that these women breastfeed their babies for as long as recommended by their doctors, so their babies can be as healthy as possible.
 - Women who are currently breastfeeding and who wish to join the study may be able to join later, when they are no longer breastfeeding.
 - To protect the health of their babies, women are asked to honestly inform the study staff of whether they are breastfeeding or not. Study staff will then give information to help women understand how best to protect their health and the health of their babies.
- To date, there has only been one study of the dapivirine ring in lactating women, MTN-029/IPM 039. This study showed low level of detectable dapivirine in breastmilk and a low estimated daily level of infant dapivirine exposure. Additional studies are needed and are being planned to evaluate the safety of dapivirine ring use while breastfeeding. Until more information is available on the safety of use of dapivirine vaginal rings among breastfeeding women and their infants, MTN-025 is making every effort to avoid infant exposure to dapivirine.

10.9 Care and Support for Seroconverters

During follow-up, HIV testing will be performed as described in Section 13.7.2 of this manual and participants who become infected with HIV will have modified study procedures as described in Section 6.5 of this manual. These participants are encouraged to continue follow-up visits per their original study schedule until their originally scheduled study exit date and are offered co-enrollment in MTN-015, regardless of product use.

All participants with confirmed HIV infection will be counseled and actively referred to available sources of medical and psychosocial care and support, per site SOPs (see also Section 12). Site staff must actively follow-up on all referrals at each subsequent follow-up visit to determine if the participant actually sought the care to which she 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.

While neither MTN-025 nor MTN-015 can provide clinical care and treatment for HIV infection, protocol-specified examinations and laboratory tests will provide information upon which appropriate clinical care decisions can be made. In particular, the studies will provide information on participants' stage of HIV disease, HIV RNA PCR, and CD4+ T cell count; information on HIV drug resistance will also be available when clinically indicated.

Given the above, study staff must be well positioned to refer participants to non-study HIV care providers when they meet criteria for initiation of antiretroviral therapy (ART), may be experiencing a drug-related toxicity, or may need to consider changing ART regimens due to resistance. 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. Study investigators will be available to consult with non-study providers on optimal clinical care and treatment decisions for participants.

Routine resistance testing will be completed for every participant who has a confirmed positive HIV test after enrollment. The current version of the Stanford Drug Resistance Database HIVdb Program (<http://sierra2.stanford.edu/sierra/servlet/JSierra>) will be used to generate resistance interpretations. The database categories resistance are summarized in Figure 10-3 below.

Plasma specimens designated by SCHARP will be sent to the LC during routine shipments. Resistance testing will take place at the Virology Core (VC) lab (Pittsburgh) and results will be provided from the VC to site IoRs as they become available. This information should be filed in the participant binder and discussed with the participant, and the participant should be encouraged to share the resistance report with her HIV care provider. Direct contact by site investigators/clinicians to facilitate provision of results to local care providers is encouraged whenever possible, especially in cases where HIV drug resistance mutations are identified. Members of the LC and VC will be available to site leadership to talk through resistance results on a case-by-case basis. If there are any questions related to clinical next steps, the IoR should contact the PSRT for further guidance.

Figure 10.3: Resistance Category Definitions based on Stanford Drug Resistance Database

Resistance Category	Definition
Susceptible	No evidence of reduced susceptibility compared with wildtype
Potential low-level resistance	The virus is likely to be fully susceptible yet it contains mutations that may be indicative of previous exposure to the ARV class of the drug
Low-level resistance	Virus isolates of this type have reduced in-vitro drug-susceptibility and/or patients with viruses of this genotype may have a suboptimal virologic response to treatment compared with the treatment of a wildtype virus
Intermediate resistance	The genotype suggests a degree of drug resistance greater than low-level resistance but lower than high-level resistance
High-level resistance	The genotype is similar to that of isolates with the highest levels of in vitro drug resistance and/or patients infected with isolates having similar genotypes generally have little or no virologic response to treatment with the drug

10.10 Management of Laboratory Test Results

Hematology, liver function (AST/ALT), and creatinine testing will be performed at Screening, PUEV, and at any time if indicated in MTN-025. For each study participant, the IoR or designee is responsible for monitoring these test results over time and for ensuring appropriate clinical management of all results. It is suggested that the safety lab calculator tool, available on the MTN website (<http://www.mtnstopshiv.org/node/7330>), be complete at baseline and used to assist with identification and grading of laboratory AEs during study follow-up (see also SSP section 11.3.6). All reviews of laboratory test results should be documented on the lab results printout (provided by the lab to the clinic) and/or in chart notes.

All sites must establish SOPs for reporting and managing critical laboratory values in MTN-025. At a minimum, all test results of severity grade 3 and higher, and all results requiring product hold, should be considered critical and urgently reported to a study clinician; lower grade results also may be considered critical at the discretion of the IoR.

The IoR or designee should routinely review MTN-025 participant study records to ensure proper monitoring and clinical management of laboratory test results, and documentation thereof. All reviews performed by the IoR or designee should be documented in participant study records.

10.11 Clinical and Product Use Management

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

All specifications of protocol Sections 6 and 9 must be followed; IoRs are encouraged to consult the PSRT with any questions related to proper interpretation of the protocol and proper management of study product use in particular. Conditions requiring product hold or permanent discontinuation are summarized in Figure 10-4 below. The flow charts provided on the MTN website (<http://www.mtnstopshiv.org/node/7330>) are intended to further guide study staff in following the specifications of protocol Section 9.

Participants should be advised to remove the vaginal ring prior to a laparoscopic tubal ligation or IUCD insertion procedure. The participant may reinsert the same vaginal ring after completion of the procedure unless, as a result of the procedure, the participant experiences any complications that would prompt a product hold per protocol section 9. All ring outages due to clinical procedures conducted outside of regularly scheduled visits (i.e., at interim visits) should be captured within the Ring Adherence CRF completed during the participant's next scheduled study visit. No Clinical Product Hold/Discontinuation Log CRF or pharmacy documentation is required to document these brief removals for the procedure. However, if a new clinical hold is initiated following the procedure due to complications/AEs, the participant's ring should be returned to the study clinic and study staff should complete a Clinical Product Hold/Discontinuation Log CRF, a new AE Log form, and a vaginal ring request slip marked "hold" should be sent to the pharmacy. The IoR/designee should follow relevant guidance in protocol section 9 regarding resumption of product use. If the participant does not want the ring re-inserted (even though the clinician determines it is okay to do so), the additional days off product are not considered part of the product hold. Rather, they count as participant non-adherence, and should be captured as such within the Ring Adherence CRF completed at the participant's next visit.

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. Product holds and discontinuations must be communicated to site pharmacy staff using the Vaginal Ring Request Slip, as described in Section 9.6 of this manual. Product holds and discontinuations also must be documented within the Clinical Product Hold/Discontinuation Log.

Figure 10-4
Conditions Requiring Product Hold or Permanent Discontinuation

Condition	Temporary Hold	Permanent Discontinuation
Positive HIV Rapid Test Result	X	
Confirmed HIV infection		X
Allergic Reaction to the Vaginal Ring		X
Pregnancy	X	
Breastfeeding	X	
Use of PEP for HIV Exposure	X	
Grade 3 AE Related to Study Product Use not in Section 9	X	
Grade 4 AE (regardless of relationship to study product)	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	
Superficial epithelial disruption (abrasion/peeling) which has worsened after re-evaluation in 3-5 days	X	
Deep epithelial disruption (ulceration)	X	
Symptomatic, localized erythema or edema (area <50% of vulvar surface or combined vaginal and cervical surface) which has worsened after re-evaluation in 3-5 days	X	
Asymptomatic, localized erythema or edema (area <50% of vulvar surface or combined vaginal and cervical surface) which has worsened after re-evaluation at the next scheduled visit	X	
Generalized erythema or severe edema (area >50% of vulvar surface or combined vaginal and cervical surface)	X	
Unexpected genital bleeding due to deep epithelial disruption	X	
Cervicitis (inflammation and/or friability)	X	
Coenrollment	X	

**See Protocol Section 9 for complete guidelines on clinical management and study product holds.*