

## Section 10. Clinical Considerations

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This section presents information on MTN-008 clinical assessments and counseling sessions. Further clinical considerations related to participant safety monitoring and adverse event reporting are provided in Section 11. Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in Section 12. Instructions for completing data collection forms associated with clinical procedures are provided in Section 13.

### 10.1 Baseline Medical/Menstrual History and Ascertainment of Concomitant Medications for Maternal Participants

A focused baseline medical/menstrual history is performed at screening and then reviewed prior to enrollment. All medications used by the participant also are ascertained at this time. The purpose of obtaining this information during screening is to:

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

#### 10.1.1 Baseline Medical/ Menstrual History for Maternal Participants

The non-DataFax Mother: Participant-reported Baseline Medical/Menstrual History form is the recommended source document for collecting baseline medical and menstrual history information for both cohorts. Detailed reference to this form is made throughout the rest of this section; however, alternative site-specific history forms may be used.

When obtaining a focused baseline medical/menstrual history for MTN-008, it is not necessary to document the participant's lifetime medical history. Rather, focus on conditions that have occurred since the participant became sexually active (with the exception of the menstrual history), and probe for the most accurate information available on the participant's current health and reproductive status vis-à-vis the reported history. Additional guidelines are presented below:

- Review the maternal participant's prenatal record for the index pregnancy, ultrasound reports and, if relevant, her inpatient chart.
- A fetal condition, e.g., choroid plexus cyst, should be reported as a maternal preexisting condition.
- Review estimated date of delivery assigned by the primary obstetrician, including dating criteria used for calculation. If a major discrepancy is noted between dates calculated by the site and primary obstetrician and participant eligibility may be impacted, sites may suggest correction to the primary obstetrician. Site staff should notify the MTN-008 Management Team at [mtn008mgmt@mtnstopshiv.org](mailto:mtn008mgmt@mtnstopshiv.org) of

changes to gestational age calculations. Document gestational age calculation methods used in participant chart notes.

- Use the list of body systems and conditions on pages 1-4 of the non-DataFax Mother: Participant-reported Baseline Medical and Menstrual History form as a guide to probe for history related to each system and condition. For conditions that are not associated with the listed systems, record relevant history in the “other medical problem” section on page 4 of the Mother: Participant-reported Baseline Medical and Menstrual History form.
- Record symptoms, illnesses, allergies, and surgeries.
- Record both chronic and acute conditions, as well as both ongoing and resolved conditions.
- Document whether each condition is currently ongoing for enrolled participants. Conditions that are ongoing at the time of enrollment/randomization are transcribed onto the Pre-existing Conditions case report form. For ongoing recurrent conditions that are expected to be experienced during follow-up (e.g., headaches, dysmenorrhea), the condition need not be present on the day of enrollment to be considered ongoing at the time of enrollment.
- For all ongoing conditions, assess and record the current severity of the condition per the DAIDS Table for Grading Adult and Pediatric Adverse Events (Toxicity Table), dated December 2004 (Clarification August 2009), and the Female Genital Grading Table for Use in Microbicide Studies (FGGT), dated November 2007. Conditions listed in both the FGGT and the Toxicity Table should be graded per the FGGT. Conditions not listed in the FGGT should be graded per the Toxicity Table. Conditions not listed in the FGGT or the Toxicity Table should be graded per the “estimating severity grade” row of the Toxicity Table. Both the FGGT and the Toxicity Table can be accessed on the DAIDS RSC web site <http://rsc.tech-res-intl.com/>. See Section 11 of this manual for further clarifications, guidelines, and tips for severity grading in MTN-008.
- For hypertensive disorders of pregnancy, the following grading scale will be employed, using diagnostic criteria consistent with the ACOG Practice Bulletin on Diagnosis and Management of Preeclampsia and Eclampsia (Number 33, January 2002):

**Table 1 Grading Scale for Hypertensive Disorders of Pregnancy**

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Hypertensive disorder of Pregnancy	Pregnancy-induced hypertension	Mild preeclampsia	Severe preeclampsia	HELLP syndrome, eclampsia, or life-threatening sequelae of preeclampsia (e.g., pulmonary edema)

- For musculoskeletal history, in addition to any other relevant information, record the details of any bone fractures the participant may have experienced.

- Record information on the participant’s use of alcohol and recreational drugs, including the specific substances used and dates and frequency of use (page 3 of the non-DataFax Mother: Participant-reported Baseline Medical and Menstrual History form). If the participant reports any diagnosed conditions associated with alcohol or drug use that are not recorded elsewhere, record the conditions and relevant details, including date of diagnosis and severity grade.
- For each genital symptom reported by the participant, the clinician should determine whether the symptom was due to a diagnosed STI/RTI. If so, the clinician should document the associated STI/RTI diagnosis on the “description” line (or in additional chart notes if needed) for the given symptom on page 4 of the Woman: Participant-reported Baseline Medical and Menstrual History form. Should the woman affirm that she is currently experiencing a genital symptom, evaluate the woman for STI/RTI and evaluate eligibility. Provide treatment as indicated per current CDC guidelines [<http://www.cdc.gov/STD/treatment/default.htm>] and document per site SOPs.
- For menstrual history, complete all items on page 5 of the Woman: Participant-reported Baseline Medical and Menstrual History form. For any menstrual symptoms, non-menstrual genital bleeding, missed menses, or other menstrual problems, record severity and other relevant details.
- For contraceptive history (page 6 of the Mother: Participant-reported Baseline Medical and Menstrual History form), record all contraceptive methods ever used by the participant and approximate dates of use for each method. Document any problems experienced with use of each method and any other relevant details.

Each participant’s baseline medical/menstrual history is initially documented at the Screening Visit, and then reviewed and updated, if necessary, at the Enrollment Visit, prior to final assessment of eligibility. History documentation must be actively reviewed on the day of enrollment. If any new symptoms or conditions occur between Screening and Enrollment, or if any new contraceptives are initiated during this time, these must be added to the Woman: Baseline Medical and Menstrual History form on the day of enrollment. Similarly, if any conditions resolve between Screening and Enrollment, this must be documented on the day of enrollment. In addition to updating previous entries on the form (using good clinical practice technique) site staff should document their review of the baseline medical/menstrual history on the day of enrollment by recording a signed and dated note on the history source document.

All pertinent exam findings should be recorded on study source documents. Some of this information will be used to complete the mother’s Pre-existing Conditions form. See Section 13 for further instructions on case report form (CRF) completion.

#### **10.1.2 Initial Ascertainment of Concomitant Medications for Maternal Participants**

The MTN-008 protocol requires documentation of all medications taken by

study participants beginning at Screening and continuing throughout follow-up. For purposes of this study, medications include all of the following, regardless of route of administration:

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

***NOTE:** For oral contraceptives taken daily, one entry should be made on the log indicating initial start date, with the box “qd” marked. Record each injection (e.g., Hepatitis B vaccination, Depo-Provera injection) as its own separate entry, so that the “Date Started” and “Date Stopped” are the same date. Mark the “once” box for “Frequency” and the appropriate box for “Route” (e.g., “IM”, or “Other” for subcutaneous injections).*

Other routes of administration, including intravenous, intravaginal and rectal medications/preparations and topical medications/preparations applied to the external genitalia are of particular interest for this study, as are douches and vaginal cleansers. Be sure to record all such medications/preparations.

The Concomitant Medications Log case report form is a recommended source document for recording participants’ medications. For oral contraceptives taken daily, one entry should be made on the log indicating initial start date, with the box “qd” marked.

Study clinicians should ascertain participants’ baseline medication information in the context of the baseline medical/menstrual history. In addition to asking open-ended questions to elicit participant report of current medications, use the information obtained in the medical/menstrual history to probe for additional medications that the participant may otherwise forget to report. For example, if the participant reports headaches as part of her medical history, but does not spontaneously list any medications taken for headaches, ask if she takes any medications for headaches. Similarly, if a participant reports taking a medication for a condition that she inadvertently did not report when providing medical history information, add the condition to the baseline medical/menstrual history source document.

## **10.2 Initial Medical History and Ascertainment of Concomitant Medications for Infant Participants**

The non-DataFax Infant Medical History form is the recommended source document for collecting baseline medical history information for infants in both cohorts. Detailed reference to this form is made throughout the rest of this section; however, alternative site-specific history forms may be used.

Because maternal and infant participants have individual PTIDs (see Section 13.3.1), a separate Concomitant Medications Log form must be used for each type of participant.

### **10.2.1 Baseline Medical History Review for Infant Participants**

The non-DataFax Infant Medical History Log is used to document and track the infant participants' medical conditions at screening (Lactation Cohort) and while on study (Pregnancy and Lactation Cohorts). The form will initially be completed at screening and then reviewed at enrollment for infants enrolled into the Lactation Cohort and at birth for infants in the Pregnancy Cohort.

### **10.2.2 Initial Ascertainment of Concomitant Medications for Infant Participants**

The Concomitant Medications Log case report form is a recommended source document for recording medications. For infants in the Pregnancy Cohort, all medications administered since the time of birth will be recorded on the infant's Concomitant Medications Log form. For infants in the Lactation Cohort, all medication administered during the study including the screening period will be recorded on the infant's Concomitant Medications Log form.

### **10.3 Pre-Existing Conditions for Both Maternal and Infant Participants**

A key purpose of obtaining the baseline medical/menstrual history is to document participants' baseline medical conditions, for comparison with conditions that may be identified during follow-up. All abnormal conditions, symptoms, and signs that are ongoing at the time of enrollment/randomization are considered pre-existing conditions. All such conditions should be thoroughly source documented and transcribed onto the Pre-existing Conditions case report form.

Because maternal and infant participants have individual PTIDs (see Section 13.3.1), a separate Pre-existing Conditions form must be used for each type of participant.

As described in greater detail in Section 11, the Pre-existing Conditions form serves as the "starting point" from which study clinicians must determine whether abnormal conditions, symptoms, and signs identified during follow-up are adverse events (AEs). By definition, pre-existing conditions are present prior to enrollment/randomization and therefore are not considered AEs. However, new conditions identified during follow-up that were not present at enrollment/randomization, and pre-existing conditions that increase in severity or frequency during follow-up, are considered AEs. With this in mind, when completing the source documents and case report forms listed above, study clinicians should document as much detail as possible about the baseline (pre-randomization) severity and frequency of each pre-existing condition.

### **10.4 Interval Medical/Menstrual History and Updating of Concomitant Medications Both for Maternal and Infant Participants**

For maternal participants sites will review medical and menstrual histories, concomitant medications, and contraceptive methods (for Lactation Cohort only) at each scheduled follow-up visit.

For infant participants, sites will review medical histories and concomitant medications at each scheduled follow-up visit.

An interval medical history should also be obtained at interim visits when a participant presents complaining of symptoms or when the purpose of the visit is to reassess previously-identified AEs. The purpose of the interval history is to determine whether previously-reported conditions remain ongoing and to determine whether new symptoms, illnesses, conditions, etc., have occurred since the last medical/menstrual history was obtained.

#### **10.4.1 Interval Medical/Menstrual History for Maternal Participants**

When taking an interval history, it is not necessary to actively review/inquire about every body system; it is acceptable to actively inquire about the current status of conditions recorded as ongoing at the time of the prior visit, and then to ask the participant an open-ended question such as “Have you had any other symptoms or health problems since your last visit?” to complete the history.

The non-DataFax Woman: Participant-reported Follow-up Medical and Menstrual History Form is a recommended source document for collecting interval medical and menstrual history data.

At the participant’s first follow-up visit, retrieve her baseline medical/menstrual history source document and her Pre-existing Conditions form for reference. At each subsequent visit, retrieve the participant’s most recent follow-up medical/menstrual history source document and the Pre-existing Conditions form for reference. Be sure to follow up on any conditions marked as ongoing from a previous visit.

For all abnormal conditions identified during follow-up, the severity grade of the condition must be documented, as must onset and resolution dates when applicable.

#### **10.4.2 Interval Medical History for Infant Participants**

The non-DataFax Infant Medical History Log is the recommended source document for tracking infant participants’ medical conditions through follow-up. The form will initially be completed at screening and then reviewed at enrollment for infants enrolled into Lactation Cohort; the form is initially completed at birth for infants in the Pregnancy Cohort. At each follow-up visits sites will actively inquire about conditions marked as ongoing at the last visit. In addition, open ended questions may be used to probe for new events; for example, it is acceptable to ask “Has your child had any health problems since your last visit?”

#### **10.4.3 Updating Concomitant Medications Information Both for Maternal and Infant Participants**

At each visit in which an interval medical/menstrual history is obtained, study staff should retrieve the participant’s previously completed Concomitant Medications Log form, and actively ask the participant whether she is still taking all previously-recorded medications, at the same dose and frequency. Study staff should also actively ask whether the participant has taken any new medications since her last medical/menstrual history. To further probe for updates, if the participant reports any

intercurrent illnesses, symptoms, etc., since her last history, ask whether she took any medications for those. Study staff should add all new information to the form in log fashion, using additional form pages as needed. If a participant reports taking a new medication for a condition that she inadvertently did not report when providing interval medical/menstrual history information, add the condition to her follow-up medical/menstrual history source document. To help ensure accurate reporting of concomitant medications information, all participants should be encouraged to bring all medications, for both women and infant participants, to all study visits.

It should be noted that all vaccinations should be recorded on the Concomitant Medications Log.

## 10.5 Physical Exams

Physical exams are required for maternal participants in both Pregnancy Cohort and Lactation Cohort at Screening, Days 0 and 6 Visits, and when clinically indicated. At all scheduled time points, physical exams should include the assessments listed in 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. If additional procedures are done during any visit, documentation of rationale should be filed in the participant's chart.

Following is a list of the required targeted physical exam components. Vital signs may be transcribed from the participant's chart if they were taken in the past hour. The non-DataFax Mother: Targeted Physical Exam form is a recommended source document for recording physical exam findings.

### Vital signs:

- Oral temperature
- Blood pressure
- Pulse

### Clinical assessments of:

- General appearance
- Abdomen
- Breasts (for Lactation Cohort only)
- Other components as indicated by participant symptoms

### 10.5.1 Abdominal Exam

Visually inspect the abdomen for both maternal cohorts. For women in the Pregnancy Cohort, palpate the fundus. For women in the Lactation cohort, palpate the abdomen. Document all findings.

### 10.5.2 Breast Exam

The breast exam is to be conducted for women being screened or enrolled into the Lactation Cohort only. This exam should be conducted at Screening, Days 0 and 6 Visits, and when clinically indicated. The exam should include visual inspection and palpation to rule out mastitis.

## 10.6 Pelvic exam

Pelvic exams are required for maternal participants in both cohorts at Screening, Days 0 and 6 Visits, prior to study product administration, and when clinically indicated. Pelvic exams must also be performed before resuming use of vaginal study product after product hold.

Pelvic exams should be performed according to the remainder of this section and to the CONRAD/World Health Organization (WHO) Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004, which may be found at [http://www.conrad.org/assets/attachments/Revised\\_Manual.PDF](http://www.conrad.org/assets/attachments/Revised_Manual.PDF) .

Exam procedures must be performed in the order shown on the exam checklists provided in Section 7 of this manual. All procedures on the exam checklists should be performed as indicated during routinely scheduled visits. When additional unscheduled exams are performed, in general, only clinically indicated procedures should be performed and the rationale and full description of additional procedures and outcomes must be fully documented.

Detailed procedural and documentation instructions for exams are provided in Sections 10.6.1 -10.6.3 below. Perform specimen collection in the sequence specified on the pelvic exam checklists (see Section 7 of this manual). Refer to Section 12 of this manual for further details on collection, processing, and testing of pelvic specimens.

#### 10.6.1 Detailed Overview of Pelvic Exam

**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. Prior to insertion ensure the speculum functions properly and has no rough edges. The speculum may be lubricated with warm water if needed. No other lubricant may be used.

**Exams During Bleeding:** Exams should proceed as scheduled even during episodes of vaginal bleeding. If the bleeding is profuse enough to obscure visualization, perform other protocol specified procedures at the visit and schedule the participant to return for a pelvic exam once the bleeding has lessened.

**Specimen Collection:** Perform specimen collection in the sequence specified on the pelvic exam checklists (see Section 7 of this manual). Refer to Section 12 for further details on collection, processing and testing of pelvic specimens.

**Lavage and Removal of Visual Obstruction:** After collection of vaginal and endocervical specimens, any obstructions (mucus, cellular debris) may be removed via lavage with sterile, isotonic, non-bacteriostatic saline. During lavage, avoid contact between the pipette and the epithelium. The lateral fornices may be lavaged without manipulation by directing the stream into them. Aspirate the fluid with the tip of the pipette against the inner surface of the posterior blade of the speculum. If lavage does not

adequately remove the obstruction, or if sites do not have access to lavage, use a large saline moistened swab in a gentle dabbing fashion to remove the obstruction. Avoid twisting or rolling the swab over the surface of the epithelium. Do not use a dry swab to remove any obstructions at any time as this may cause trauma to the epithelium. If saline is not available, a swab moistened with water will also suffice.

Document all exam findings — both normal and abnormal — on the non-DataFax Pelvic Exam Diagrams form. Document abnormal findings on the Pelvic Exam case report form. The Pelvic Exam form must be completed each time a pelvic exam is performed. Supplemental information may also be recorded in chart notes or on other designated source documents as needed. For participants who enroll in the study, (non-exclusionary) abnormal exam findings identified during screening also are recorded on the Pre-existing Conditions form. See Section 10.5.3 below for detailed instructions on classifying and documenting exam findings.

### 10.6.2 Detailed Procedural Instructions

#### **Examine the External Genitalia:**

- Do not insert the speculum before examining the external genitalia.
- Perform naked eye examination of the external genitalia including the perineum, perianal area, and the epithelial lining of the introitus.

#### **Examine the Cervix and Vagina:**

- Perform naked eye exam of the cervix and vagina.
- Assess for cervical ectopy.
- Assess for abnormal vaginal and/or cervical discharge, including mucopurulent discharge and blood-tinged discharge.

Note all findings on the Pelvic Exam Diagrams form. Further document abnormal findings on the appropriate pelvic exam case report form.

#### **Collect Specimens:**

- Collect specimens in the order listed on the pelvic exam checklists, which is also reflected below. Collect specimens away from apparent abnormalities and exclude swabbed areas from subsequent examination.
- If required per protocol, at Screening and/or if clinically indicated, collect vaginal fluid to test for trichomoniasis, using the Dacron cotton swab from an OSOM rapid test kit. Vaginal fluid may be collected for this test from the lateral vaginal wall or the posterior fornix.
- At all exams (scheduled and unscheduled), collect vaginal fluid (1 swab) for pH assessment. Swab fluid onto pH strip and then determine pH by matching the resulting color of the pH strip to the color scale provided with the strips. Vaginal fluid must be collected from the posterior fornix for this test. Do not insert the pH strip into the vagina for this test.

- If clinically indicated, collect vaginal fluid (1 swab) for KOH wet mount for candidiasis. Vaginal fluid may be collected for this test from the posterior fornix.
- Collect the specimen for quantitative vaginal culture by rotating 2 Dacron swabs several times over the lateral wall of the vagina. Insert both swabs into 1 Port-A-Cul transport tube, submerging the swabs into the gel and breaking off the shafts of the swabs, and capping.
- At all scheduled exams, collect vaginal fluid (one swab) from the lateral wall for Gram stain evaluation at the MTN Network Laboratory (NL); roll swab across two labeled slides and air dry.
- At all exams (scheduled and unscheduled), collect vaginal fluid (1 dacron swab) from the posterior fornix for biomarker analyses at MTN NL.
- At all exams (scheduled and unscheduled), collect endocervical cells for biomarker analyses at MTN NL.
- When required per protocol and/or when clinically indicated, collect ecto- and endocervical cells for Pap smear.

**Pap Smear Management:** Papanicolaou (Pap) smears may be required for both Pregnancy and Lactation Cohorts at Screening or for follow-up to adequate evaluation of an abnormal pap, when clinically indicated and/or per local clinical guidelines. To be enrolled, women must have a Pap result consistent with Grade 0 according to the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004, Clarification dated August 2009) or satisfactory evaluation of a non-Grade 0 Pap result, per clinical judgment of Site Investigator or Record (IoR)/designee) in the 12 calendar months prior to enrollment.

When a pap smear is required per protocol or for clinical management of an abnormal pap smear, document specimen collection on the Pelvic Laboratory Results form and transcribe results, once they become available, to that same form. Pap smears will be reported as per the 2001 Bethesda System

Pap smear results will be reported per the 2001 Bethesda system and will be presumed normal in the absence of intra-epithelial lesion or malignancy. Results will be recorded on the Mother: Participant-reported Baseline Medical and Menstrual History form, the Enrollment Eligibility forms for both cohorts, and the Pelvic Laboratory Results form.

For study eligibility, participants must score a Pap result consistent with Grade 0 Female Genital Grading Table for Use in Microbicide Studies or have adequate evaluation of an abnormal pap and not require further treatment, according to the The severity of abnormal results should be graded per the “Pap” row of the Female Genital Grading Table (FGGT) only if a histologic diagnosis is not available.

During follow-up, Pap smears, and further evaluation if indicated, may identify AEs. Any such AEs should be documented and/or reported as described in Section 11 of this manual.

**Perform Bimanual Exam:** After completing all of the above-listed tissue examinations and specimen collection, perform bimanual exam for adnexal or fundal masses and/or tenderness.

### 10.6.3 Documentation of Pelvic Exam Findings

All exam findings – both normal variants and abnormal findings – should be source documented on the non-DataFax Pelvic Exam Diagrams form. Supplemental information may also be recorded in chart notes or on other designated source documents as needed. Source documentation for abnormal findings should include the severity grade of the finding, assessed per the FGGT.

Abnormal findings should also be recorded on the Pelvic Exam case report form. The results of laboratory test results performed using specimens collected during pelvic exams are recorded on the Pelvic Laboratory Results form.

For enrolled participants, (non-exclusionary) abnormal pelvic exam findings identified during screening are recorded on the Pre-existing Conditions form. Abnormal exam findings identified during follow-up must be documented and reported as AEs if applicable as described in Section 11 of this manual (see Figure 11-4 in particular).

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
- atrophic changes
- blood vessel changes other than disruption
- skin tags
- scars

Per the FGGT, expected non-menstrual bleeding is considered normal (refer to the grade 0 column of the row for metrorrhagia). Cervical bleeding — in the absence of any associated tissue findings — associated with speculum insertion and/or cervical specimen collection judged to be within the range of normal according to the clinical judgment of the IoR or designee is considered expected non-menstrual bleeding. Other iatrogenic findings should be considered abnormal and documented as such (with notations added to source documents and case report forms to specify the cause of the finding). See Section 10.6 below for further detailed guidance on documentation, reporting, and management of pelvic exam findings involving genital bleeding.

Pelvic exam findings should be documented using terminology corresponding to the FGGT and the study-specific pelvic exam case report forms. For findings in which the term found on the pelvic exam case report form is more specific than the corresponding term on the FGGT, use the more specific term. Consider for example a pelvic exam finding identified as a vulvar laceration. The term corresponding to this finding on the FGGT is “vulvar lesion” but the term marked on the pelvic exam case report form will be “laceration.” Because the term “laceration” is more specific than the term “lesion,” the term “vulvar laceration” should be used to document the finding. See Figure 11-4 in Section 11 of this manual for further guidance on reporting pelvic exam findings as AEs. In addition, Figure 10-1 below provides further information to guide and standardize terminology used to describe abnormal pelvic exam findings.

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

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

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

## 10.7 Genital Bleeding

Genital Bleeding will be assessed differently depending on whether the participant is in the Pregnancy or Lactation cohort.

### 10.7.1 Genital Bleeding in Pregnancy Cohort Participants

If a pregnant participant experiences genital bleeding, study staff will clinically manage the participant per local practice standards for pregnancy. In particular, study staff will refer the participant to a qualified clinician for further evaluation, care, and treatment; pelvic exams may be performed by qualified clinicians unless contraindicated. Study staff will document the bleeding event and all follow-up actions in the participant's study records.

Study staff should refer to listings for "Second/third trimester bleeding" and "Postpartum hemorrhage" in the FGTT when documenting genital bleeding in pregnancy cohort participants. Note, normal lochia following delivery is considered expected non-menstrual bleeding (under "Metrorrhagia", Grade 0) and should not be reported as an AE.

### 10.7.2 Genital Bleeding in Lactation Cohort Participants

The remainder of this section provides procedural instructions and guidance for assessment of genital bleeding among non-pregnant participants.

### 10.7.3 Participant Reports of Genital Bleeding/Genital Bleeding Assessment

As part of the MTN-008 enrollment process, study participants will be counseled to report all occurrences of unexpected genital bleeding to the study staff as soon as possible after identification of the bleeding. Study staff will provide site contact information to each participant upon enrollment. If a participant reports genital bleeding, study staff will clinically manage the participant per local practice standard. In particular, study staff may refer the participant to a qualified clinician for further evaluation, care, and treatment; pelvic exams may be performed by qualified clinicians unless contraindicated. Study staff will document the bleeding event and all follow-up actions in the participant's study records. When reporting unexpected genital bleeding as an AE, clinically appropriate terminology should be used to reflect the cause or source of the bleeding and the bleeding itself should be graded according to the Female Genital Toxicity Table as appropriate. Any questions related to genital bleeding assessment or AE reporting for participants should be submitted to the MTN 008 PSRT as described in Section 11.

Clinicians will obtain interval medical history information from participants, including active ascertainment of whether any genitourinary symptoms including genital bleeding were experienced since the last study visit. Reports of genital bleeding should be recorded on the Participant Follow-up Medical and Menstrual History form

### 10.7.4 Clinician Assessment of Genital Bleeding

Pelvic exams will be performed to evaluate any participant report of

unexpected bleeding Pelvic examinations will be performed and documented as described in Section 10.5.

Reports of genital bleeding should be assessed for whether the bleeding may be related to product use, or whether it may be more likely attributable to another cause. These factors include:

- Complications related to pregnancy
- Sexual activity/trauma
- Trauma associated with insertion of study product or other vaginal preparations
- Trauma associated with pelvic exam procedures
- Sexually transmitted or reproductive tract infections/outbreaks
- Epithelial and/or blood vessel disruption observed on pelvic exam
- Other pathology observed on pelvic exam (e.g., polyps, carcinoma)

Assessment of genital bleeding should begin by determining whether the bleeding is *expected* or *unexpected*. Expectedness will be determined based on the participant's baseline medical history (e.g., whether the reported bleeding pattern differs from baseline. Normal lochia will be considered expected bleeding. A pelvic exam must be performed to evaluate all episodes of unexpected genital bleeding. Pelvic exams are not required to evaluate expected bleeding events; however, such exams may be performed at the discretion of the IoR or designee.

#### 10.7.5 Documentation of Genital Bleeding

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

All episodes of unexpected genital bleeding — whether participant-reported or clinician-observed or both — will be considered adverse events (AEs) that must be documented on Adverse Experience Log case report forms. Detailed information on AE reporting is provided in Section 11, however when reporting genital bleeding events, reference also should be made to the points below.

- Expected genital bleeding should not be reported as an AE.
- Unexpected complications of pregnancy should be reported as an AE according to the Complications of Pregnancy section in the Female Genital Toxicity Table.
- Unexpected genital bleeding that is associated with an observed abnormal pelvic exam finding should be reported as an AE using the term associated with the exam finding, with the anatomical location noted. For example, if a laceration is observed on exam, with blood emanating from the finding, the term "laceration" should be used to describe the AE. The fact that blood or bleeding was present also will

be documented on the Pelvic Exam Diagrams form and the Pelvic Exam case report form, and may be noted in the Comments section of the Adverse Experience Log form.

## **10.8 STI/RTI Diagnosis and Treatment**

If participant reports or clinician determines through medical record review that the participant was diagnosed with an STI, including chlamydia, gonorrhea, and/or trichomoniasis in the past 8 weeks prior to enrollment (Day 0), the participant is not eligible for enrollment into MTN-008. Care or referral for care per site SOPs should be provided to the participant, with thorough documentation in the chart.

Laboratory evaluation is conducted at screening for gonorrhea, chlamydia, trichomonas, HIV, and if syphilis negative results are not documented within the previous year of enrollment, syphilis testing. These tests may be repeated at the enrollment, Days 0 and 6, or interim visits as clinically indicated. The GC/CT NAAT testing at screening should be collected via cervical swab; any follow-up GC/CT NAAT performed after exposure to study gel should be via urine test.

Signs and symptoms commonly associated with STIs are presented in Figure 10-3 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.

STIs/RTIs will be treated per current CDC guidelines, which can be accessed at:

<http://www.cdc.gov/STD/treatment/default.htm>

In day-to-day practice, the CDC guidelines — or local site treatment guidelines based on the CDC guidelines — should be referenced to obtain complete information on treatment regimens, contraindications, etc. To optimize adherence rates, directly observed single dose treatment regimens should be provided whenever possible, except for BV.

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

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

## **10.9 Pre- and Post-test HIV Counseling**

HIV testing is required during screening. Perform and document the rapid HIV test. Before disclosing results to participant, obtain independent review, verification, and sign-off of result. Only HIV negative women are eligible for study participation. If the woman’s test results return positive,

follow site SOPs for providing referrals for treatment and emotional support for both the woman and her partner.

Test results should be transcribed onto the STI Laboratory Results form.

#### 10.10 Adverse Event Reporting Considerations

Per the MTN-008 eligibility criteria, no participant may enter the study with an STI/RTI requiring treatment per CDC guidelines. For participants diagnosed during screening with an STI/RTI requiring treatment, the STI/RTI is considered “resolved” as soon as treatment has been completed and all symptoms of the STI/RTI are no longer present. Since both of these conditions must be met prior to enrollment in the study, no STI/RTI requiring treatment should be recorded as a pre-existing condition for an enrolled participant. Therefore, any STI/RTI requiring treatment that is identified during follow-up is considered an AE that must be documented and reported if applicable as described in Section 11 of this manual (see Figures 11-4 and 11-5 in particular).

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

- If infection with HSV-2 or HPV is known to have occurred before enrollment, the infection is considered a pre-existing condition: record on the Pre-existing Conditions case report form.
- For HPV, genital warts present before enrollment are considered a pre-existing condition: record on the Pre-existing Conditions case report form.
- Any outbreaks that occur after enrollment are considered AEs, regardless of whether the viral infection was pre-existing before enrollment. Document and report as an AE as described in Section 11 of this manual. For genital herpes outbreaks in particular, see Figures 11-4 and 11-5, which further explain why such outbreaks should be reported using the term marked on the Follow-Up Pelvic Exam case report form to describe the outbreak (e.g., vesicle, ulceration) rather than terms such as “genital herpes outbreak.”

#### 10.11 Urinary Tract Infections

Urinary tract infections (UTIs) will be diagnosed in MTN-008 based on the presence of symptoms indicative of a possible UTI and positive leukocyte esterase and/or nitrite. If necessary in the opinion of the clinician, a urine culture should be performed. 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

See Section 12 of this manual for details on urine specimen collection and laboratory testing procedures. Additional UTI work-up beyond dipstick urinalysis for nitrites and LE (e.g., urine culture) may be performed if required per site standard of care and documented in chart notes and/or on other site-specific source documents.

For enrolled participants, UTIs diagnosed during follow-up are considered AEs that must be documented and reported if applicable as described in Section 11 of this manual. As explained further in Section 11, the severity of all UTIs should be graded per the “infection (other than HIV infection)” row of the Toxicity Table (not the UTI row of the FGGT).

### **10.12 Contraception Considerations**

To be eligible for MTN-008 in the Lactation Cohort, potential participants must report use of an effective method of contraception at enrollment and intent to use an effective method throughout the study follow-up period. Effective methods include abstinence, male condoms, hormonal methods, IUCDs, and sterilization of the participant or her partner or partners. For those participants who report sterilization, all sites are strongly encouraged to document credible effort to obtain medical records as part of their verification procedures.

Participants enrolled in MTN-008 for Lactation mother cohort will be offered condoms at the screening and enrollment visits.

Contraceptive methods used by study participants during screening will be recorded on baseline medical/menstrual history source documents. During follow-up, contraceptive methods will be recorded on follow-up medical/menstrual history source documents.

Some participants may experience side effects associated with use of contraception. Any side effects reported as ongoing at the time of enrollment/randomization should be recorded on baseline medical/menstrual history source documents and on the Pre-existing Conditions case report form. Side effects reported during follow-up should be recorded on follow-up medical/menstrual history source documents and documented and reported if applicable as AEs.

### **10.13 Pregnancy Considerations**

In the Lactation Cohort, it is possible that some study participants could become pregnant. All such participants should be managed as described in Section 6.8 of this manual.

Should a participant in the Lactation Cohort become pregnant, product will be discontinued permanently. Any AEs or other conditions should be followed through the full follow-up period. The participant should be offered inclusion into the MTN-016 study and will remain in the study according to their original study follow-up schedule for modified visits, for safety evaluation.

#### **10.14 Infant Procedures**

The Infant Medical History Log (non-Datafax) should be completed by mother's report and, if indicated, certified copies of medical records. For the Pregnancy Cohort, fetal health is confirmed through maternal pregnancy history, and at birth, medical history is documented on the Infant Medical History Log.

For the Lactation Cohort, infant medical history begins at birth.

Infant heel stick is to be done at the Day 6 Visit for blood PK assessment at one timepoint only. Refer to the Day 6 Visit Checklist in Section 7 of this manual for details regarding the time of collection and Section 12 for lab sample collection instruction.

#### **10.15 Management of Laboratory Test Results**

Hematology, liver function, and renal function testing will be performed on Days 0 and 6 Visits for MTN-008, and additionally if indicated. 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. All reviews of laboratory test results should be documented on the flow sheets and/or in chart notes, including a date, time, and signature, as well as an indication of clinical significance if laboratory values are out of normal range.

In addition to the above, all sites must establish SOPs for reporting and managing critical laboratory values in MTN-008. 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 should review MTN-008 participant study records to ensure proper monitoring and clinical management of laboratory test results, and documentation thereof. All reviews performed by the IoR should be documented in participant study records.

#### **10.16 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 9.3-9.5), toxicity management (Section 9.1), guidance on product hold and discontinuation in response to observed AEs (Section 9.6), and management of specific toxicities (Sections 9.7), allergic response (Section 9.8), and pregnancy (Section 9.9).

All specifications of protocol Section 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.

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 Study Product Request Slip, as described in Section 6.7.2 of this manual. Product holds and discontinuations also must be documented on Product Hold/Discontinuation Log case report forms.

Situations in which product will be held:

- regular contractions, other than Braxton Hicks contractions, consistent with possible labor,
- participant is admitted to the delivery suite for labor,
- participant's water has broken, whether or not active labor has begun,
- participant reports successful administration of  $\leq 1$  dose of study product administration at home during the week before the Day 6 visit,
- positive pregnancy test for participants in the Lactation Cohort at the Day 6 Visit,
- diagnosis of STI/RTI at the Day 6 Visit,
- Concern for participant and/or pregnancy safety at IoR's discretion, and in consultation with the PSRT, per protocol.

If deemed clinically appropriate by the IoR/designee, product exposure may be minimized to the extent possible via cervicovaginal lavage, as stated in section 9.8 of the MTN-008 protocol. In the event that the IoR/designee decides that the exposure should be minimized, the following will happen:

- The study gel will be removed by a physician investigator.
- A speculum will be placed into the vagina.
- Any evident gel will be removed with a moistened Scopette.
- Sterile saline will be lavaged into the vagina using a syringe to attempt to wash out or dilute any remaining study gel.
- The speculum will be removed.
- The subject will be observed closely for any further reactions.
- The reaction will be documented in the participant's study record, which will include a narrative note and completion of applicable adverse event forms.
- The DAIDS Medical Officer will be notified of the event.

Suspected complications of pregnancy or lactation during study participation will be referred to the appropriate clinical management team, regardless of relatedness to study participation as outlined in Section 9.9 of the study protocol.