Section 8. Clinical Considerations and Safety Monitoring

This section presents information on clinical procedures and safety monitoring performed in MTN-012/IPM 010. Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in Section 9. Instructions for completing data collection forms associated with clinical procedures are provided in Section 10.

8.1 Baseline Medical History

The participant's baseline medical history is initially collected and documented at the screening visit. It is then actively reviewed and updated, as necessary, at the enrollment visit. After the enrollment visit, the baseline medical history is updated only if the participant recalls information at a later visit that is thought to be relevant.

The baseline medical history should ascertain a participant's medical history and explore any medical conditions or medications that are deemed exclusionary for this study. The purpose of obtaining this information during screening and enrollment is to:

- Assess and document participant eligibility for the study
- Assess and document the participant's baseline medical conditions and symptoms for comparison with signs, symptoms and conditions that may be identified or reported during follow-up
- Monitor any potential adverse events during the course of the study

The non-DataFax Baseline Medical History form is a recommended source document for collecting baseline medical history information; however, alternative site-specific history forms may be used. That is, a site may create its own source documentation.

When obtaining the baseline medical history, it is not necessary to document the participant's lifetime medical history; rather, site staff should ask the participant to answer questions/describe conditions based on the time since he has become sexually active. Additional guidelines to collecting the baseline medical history are listed below:

- Record symptoms, illnesses, allergies, and surgeries

- Record both chronic and acute conditions, and 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 form. For ongoing recurrent conditions that are expected to be experienced during follow-up (e.g. headaches), 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 Male Genital Grading Table for Use in Microbicide Studies (MGGT). If the condition is not listed in the MGGT, refer to the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events (hereafter referred to as the "DAIDS Toxicity Table"). See Section 8.14 for further clarifications, guidelines, and tips for severity grading in MTN-012/IPM 010.

- Document medications currently taken for all ongoing conditions on the Concomitant Medications Log form as described in Section 8.4.

8.2 Pre-existing Conditions

All ongoing medical conditions, problems, signs, symptoms and abnormal findings that are observed and/or reported at the time of randomization/enrollment are considered pre-existing conditions.

For all participants enrolled in the study, all ongoing conditions recorded as pre-existing are to be thoroughly source documented and transcribed onto the Pre-existing Conditions case report form. This form is to be completed at the Enrollment Visit based on all screening and enrollment source documents including, but not limited to, the Baseline Medical History form (non-DataFax), Physical Exam form (non-DataFax), Genital Exam form, Laboratory Results form, and STI Laboratory Results form.

All pre-existing conditions noted at screening and enrollment must be graded. The purpose of grading a pre-existing condition is to determine whether abnormal conditions, symptoms, signs and findings identified during follow-up are adverse events (AEs). By definition, pre-existing conditions are present prior to enrollment/randomization and are, therefore, 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 (increases to a higher grade) or frequency during follow-up, are considered AEs. Therefore, the clinician should record as much information as possible about the severity and frequency of any pre-existing condition in source documents as well as in the comments field of the Pre-existing Conditions form to best describe the condition at study entry. This allows for greater objectiveness in noting any grade increase of the pre-existing condition.

8.3 Follow-up Medical History

It is necessary to update the participant's medical history at the Final Clinic Visit (and any interim visits) in order to determine whether previously reported conditions remain ongoing and whether new symptoms, illnesses, conditions, etc. have occurred since the last medical history was performed. The non-DataFax Follow-up Medical History Log form can be used to gather this information. At each post-enrollment visit it is only necessary to record information that has occurred or changed since the previous visit.

8.4 Concomitant Medications

The MTN-012/IPM 010 protocol requires site staff to document all medications taken by study participants beginning at screening and continuing throughout the duration of the study. This includes any preventive medications and treatments (e.g., allergy shots, flu shots, and other vaccinations), prescriptions, over-the-counter preparations, vitamins and nutritional supplements, recreational drugs and herbal and naturopathic preparations. All medications, drugs, supplements and preparations will be recorded on the Concomitant Medications Log.

It is helpful to ascertain the baseline medication information in the context of the baseline medical history. Site staff should ask open-ended questions to elicit participant report of current medications, and use the information obtained in the medical history to probe for additional medications that the participant may otherwise forget to report. For example, if the participant reports headaches as part of his medical history, but does not spontaneously list any medications taken for headaches; ask if he takes any medications for headaches. Similarly, if a participant reports taking a medication for a condition that he inadvertently did not report when providing medical history information, add the condition to the baseline medical history source document.

At the Final Clinic Visit, or during an interim visit, retrieve the participant's previously completed Concomitant Medications Log form, record any new medications provided to the participant by study staff, and actively ask the participant whether he 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. To further probe for updates, if the participant reports any illnesses, symptoms, etc. since his last medical history, ask whether he took any medications for those. 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 he inadvertently did not report when providing follow-up medical history information, add the condition to his follow-up medical history source document. To help ensure accurate reporting of concomitant medications information, participants should be encouraged to bring all medications to study visits.

8.5 Prohibited Medications and Products

For MTN-012/IPM 010 the following medications are prohibited from use during the study:

- Immunosuppressive agents, e.g. oral steroids for asthma
- Genitally-applied preparations, except use of usual cleansing products for genital hygiene, other than the study product

Usual cleansing products are any products that the participant regularly uses for genital cleansing purposes, such as soap or cleansing gels. Participants should be counseled to not initiate use of any genitally-applied preparations, including a new cleansing product, during study participation.

If a participant reports using a prohibited medication during the study, this must be recorded on the Concomitant Medications Log. Should a participant report using any of the above listed medications or products, study staff should consult the PSRT regarding product use.

8.6 Physical Exam

A physical exam is completed at the Screening, Enrollment, and Final Clinic Visits. It should also be performed at Interim Visits if it is clinically indicated. At all scheduled time points, physical exams should include the assessments listed in protocol section 7.7 and repeated below. Site clinicians may use their discretion to determine whether or not to conduct a more comprehensive physical exam in response to reported symptoms or illnesses present at the time of the exam.

Following is a list of required physical exam components:

- Height (may be omitted after the Screening visit)
- Weight
- Vital Signs
    - Temperature
    - Pulse
    - Blood pressure
- General appearance
- Ear, nose, throat
- Oral mucosa
- Abdomen
- Other components as indicated be participant symptoms

The Physical Exam (non-data fax) form is a recommended source document for recording physical exam findings. The participant's weight should be documented on the Laboratory Results form.

For participants who enroll in the study, ongoing abnormal physical exam findings (that are not exclusionary) identified at the Screening and Enrollment Visits and ongoing at the time of randomization/enrollment should be recorded on the Pre-existing Conditions form. Abnormal findings found during physical exams performed during follow-up should be documented and/or reported as described below in Section 8.12.

Physical exams may identify additional baseline medical information that participants inadvertently do not report in their baseline medical history. For example, the clinician may identify a skin condition during the physical exam and upon further inquiry learn that the participant has had this intermittent chronic condition since age 15. In such situations, the clinician should add the newly identified information to the Baseline Medical History form and the Pre-existing Conditions form as well, since the condition was present at the time of enrollment.

8.7 Genital Exams

Genital exams are required at the Screening, Enrollment, and the Final Clinic Visits. It should also be performed at Interim Visits if it is clinically indicated.

At all scheduled time points, genital exams should include the assessments listed in protocol section 7.7 and repeated below.

- General inspection via naked eye and hand-held magnifying glass of the following:
    - Entire penile surface

        - Internal and external foreskin (if present)
        - Shaft
        - Glans
        - Urethral meatus
    - Scrotum
    - Inguinal lymph nodes

Genital exam procedures are included in the sample visit checklists provided in Section 5 of this manual.

Potential participants identified at screening or enrollment with a clinically apparent Grade 1 or higher genital exam finding, observed by study staff, and/or participants who report Grade 1 or higher genital or urinary symptoms are not eligible for the study. In addition, participants with penile, scrotal piercing, or penile tattoos observed during the genital examination at screening or enrollment are not eligible for the study. For participants who enroll in the study, abnormal genital exam findings (that are not exclusionary) identified at the Screening and Enrollment Visits and ongoing at the time of randomization/enrollment should be recorded on the Pre-existing Conditions form. Abnormal findings found during genital exams performed during follow-up should be documented and/or reported as described below in Section 8.12.

8.8 STI/RTI/UTI Evaluation and Management

Clinical and laboratory evaluations are performed in MTN-012/IPM 010 to diagnose Urinary Tract Infections and the following STIs and RTIs:

- Chlamydia infection
- Gonorrhea infection
- Syphilis infection

Signs and symptoms commonly associated with the above-listed infections are presented in Figure 8-1 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.

The presence of symptoms indicative of a possible UTI as well as positive dipstick urinalysis results for either nitrites or leukocyte esterase (LE) should prompt the site to conduct a urine culture. Urinary tract infections (UTIs) will be diagnosed in MTN-012/IPM 010 based on the positive urine culture result. If a site clinician suspects that a participant may have a UTI, but the participant does not have a positive urine culture, the clinician may choose to provide treatment for the UTI. However, the site should not report an AE using the term "Urinary Tract Infection". Instead, each symptom should be reported as its own AE on a separate AE Log form. A positive urine LE or positive nitrites result on dipstick urinalysis should not be reported separately as its own AE. Rather, the positive dipstick results will be captured on the Laboratory Results CRF completed for the visit.

A dipstick urinalysis is required at the Screening and Final Clinic Visits and when clinically indicated at other visits. The following symptoms are considered indicative of a possible UTI and should prompt dipstick urinalysis for nitrites and LE:

- Frequent urge to urinate
- Passage of only a small volume of urine accompanied by sensation of incomplete evacuation
- Pain and burning during urination
- Lower abdominal pain and/or uncomfortable pressure above the pubic bone
- Milky/cloudy, reddish, or bloody urine

Any participant diagnosed with an STI, RTI, or UTI, requiring treatment, during the screening process will be ineligible for the study, per exclusion criteria #2. For enrolled participants, STI/RTI/UTIs diagnosed during follow-up are considered AEs that must be documented, reported and clinically managed.

Figure 8-1
Signs and Symptoms Commonly Associated with STIs/RTIs

STI/RTI	Common Signs and Symptoms
Chlamydia infection	Most infections are symptomatic and may be accompanied by discharge from their penis or a burning sensation when urinating. Men might also have burning and itching around the opening of the penis. Pain and swelling in the testicles can occur but are uncommon
Gonorrhea infection	Some men with gonorrhea may have no symptoms at all. However, most men have signs or symptoms that appear two to five days after infection; symptoms can take as long as 30 days to appear. Symptoms and signs include a burning sensation when urinating, or a white, yellow, or green discharge from the penis. Sometimes men with gonorrhea get painful or swollen testicles.
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 non-itchy skin rash, mucous patches. May include fever, swollen lymph glands, sore throat, patchy hair loss, headaches, weight loss, muscle aches, and fatigue
Syphilis infection — latent	Patients are without clinical signs of infection.

Adapted from CDC STD Fact Sheets: *http://www.cdc.gov/std/general/default.htm*

8.8.1 STI/RTI Treatment

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

http://www.cdc.gov/std/treatment/2010/default.htm

Figure 8-2 briefly summarizes current CDC treatment guidelines for each of the infections listed above. In day-to-day practice, the CDC guidelines should be referenced to obtain complete information on treatment regimens, contraindications, etc. To optimize cure rates, directly observed single dose treatment regimens should be provided whenever possible.

Figure 8-2
Recommended Treatment Guidelines for STIs/RTIs

STI/RTI	Recommended Treatment
Chlamydia infection	• Azithromycin 1 g orally in a single dose OR • Doxycycline 100 mg orally twice a day for 7 days
Gonorrhea infection	• Ceftriaxone 250 mg IM in a single dose OR, IF NOT AN OPTION • Cefixime 400 mg orally in a single dose OR • Single-dose injectible cephalosporin regimens PLUS • Azithromycin 1g orally in a single dose OR • Doxycycline 100 mg orally twice a day for 7 days
Syphilis infection — primary and secondary	• Benzathine penicillin G 2.4 million units IM in a single dose
Syphilis infection — latent	• Early latent infection: Benzathine penicillin G 2.4 million units IM in a single dose • Late latent infection: Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

8.9 Calculating Creatinine Clearance Rates

Each time a participant's serum creatinine level is tested, his creatinine clearance rate must be calculated, using the Cockcroft-Gault formula:

mL/min = (140 - age in years) x (weight in kg) /72 x (serum creatinine in mg/dL)

To facilitate proper calculation, all sites are encouraged to use the creatinine clearance calculation worksheets provided in the Study Implementation Materials section of the MTN-012/IPM 010 web page.

Sites should enter creatinine results into the worksheet with one decimal place. Participant weight and age should be entered into the worksheet in whole numbers (no decimal places). Once the calculation is complete, sites should print a copy of the worksheet to file in the participant binder.

8.10 Management of Laboratory Test Results

Hematology, liver function, and renal function testing will be performed in MTN-012/IPM 010. For each study participant, the IoR or designee is responsible for monitoring these test results 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.

In addition to the above, all sites must establish SOPs for reporting and managing critical laboratory values in MTN-012/IPM 010. At a minimum, all test results of severity grade 3 and higher, and all results requiring product discontinuation, 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 routinely review MTN-012/IPM 010 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.

8.11 Clinical and Product Use Management

Protocol Section 9 provides detailed guidance on clinical and product use management, including general criteria for permanent discontinuation of product (Section 9.3), guidance on discontinuation in response to observed AEs (Section 9.4), and management of specific toxicities (Sections 9.5).

Participants will be permanently discontinued from product use for any of the following reasons:

- Participant is 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
- Participant reports the use of PEP for possible HIV-1 exposure
- Grade 2 AEs judged to be related to study product
- Grade 3 or 4 AEs, regardless of relationship to study product

Due to the short period of study product exposure in MTN-012/IPM-010 participants are not anticipated to be temporarily held from study product for any reason. Therefore, guidance on temporary holds is not provided in the protocol. However, if a participant reports over the phone an AE that may warrant permanent discontinuation, they may be instructed to stop product use temporarily until the AE can be evaluated further at the clinic. In this situation, the Product Hold/Discontinuation Log (PH-1) should also be completed to document the temporary hold.

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, completed PSRT query forms (including a response from the PSRT) must be printed and filed in participant study records. Permanent discontinuations must be communicated to site pharmacy staff using the Study Product Request Slip, as described in Section 5 of this manual. Any clinician-initiated product hold or permanent discontinuation must be documented on Product Hold/Discontinuation Log form.

8.12 Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-012/IPM 010. Please also refer to Section 8 of the MTN-012/IPM 010 Protocol and the following resources relevant to AE assessment and reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004, (Clarification Dated August 2009)
- Male Genital Grading Table for Use in Microbicide Studies (Addendum 2)
- Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0, January 2010
- DAERS Reference Guide for Site Reporters and Study Physicians
- Investigators Brochure for Dapivirine gel
- Investigators Brochure for Universal Placebo

8.12.1 Adverse Events

The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (ICH-E6) defines an adverse event (AE) as any untoward medical occurrence in a clinical research participant administered an investigational product and that does not necessarily have a causal relationship with the investigational product. As such, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

The MTN-012/IPM 010 protocol specifies that any untoward medical occurrence experienced by a participant after enrollment, which begins at the time of random assignment, is considered an AE, regardless of the study group to which the participant is assigned.

In MTN-012/IPM 010, all AEs are reportable. That means that all AEs should be recorded on the Adverse Experience (AE) Log form (See Section 10) and the form should be faxed to the MTN Statistical and Data Management Center (SDMC) via DataFax. Each site's SOP for source documentation (See Section 3) should define the extent to which the AE Log form will be used as a source document. Site-specific delegation of duties documentation should designate study staff authorized by the Investigator of Record (IoR) to complete AE Log forms. Regardless of who initially completes these forms, a clinician listed on the site's FDA Form 1572 should review them to ensure the accuracy of the data reported and to help maintain consistency of reporting across clinicians.

8.12.2 Serious Adverse Events

ICH-E6 defines a serious adverse event (SAE) as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or may require intervention to prevent one of the outcomes listed in the definition above

SAEs are a subset of all AEs. For each AE identified in MTN-012/IPM 010, an authorized study clinician must determine whether the AE meets the definition of SAE, listed above. The Adverse Experience Log case report form includes an item (item 8) to record whether the AE is also an SAE.

8.12.3 Adverse Events Requiring Expedited Reporting

For MTN-012/IPM 010 all SAEs will be reported to DAIDS in an expedited fashion. This includes all SAEs occurring following randomization through the participant's final study contact, regardless of the relationship to the study agents (see Figure 8-3).

Expedited AE reports must be made to the DAIDS Regulatory Support Center (RSC) Safety Office, also known as the DAIDS Safety Office, via the online DAIDS Adverse Event Reporting System (DAERS). If a report needs to be modified or updated, or a report submitted in error needs to be withdrawn, this can also be done through DAERS. For questions about DAERS, contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov or from within the DAERS application itself. Information about DAERS is also available on the RSC website at http://rsc.tech-res.com. All SAEs will be reported via DAERS Reporting System within three (3) reporting days of site awareness (the site's recognition that the event fulfills the criteria for expedited reporting) to the DAIDS Safety Office according to the procedures specified in the DAIDS Manual for Expedited Reporting of AEs.

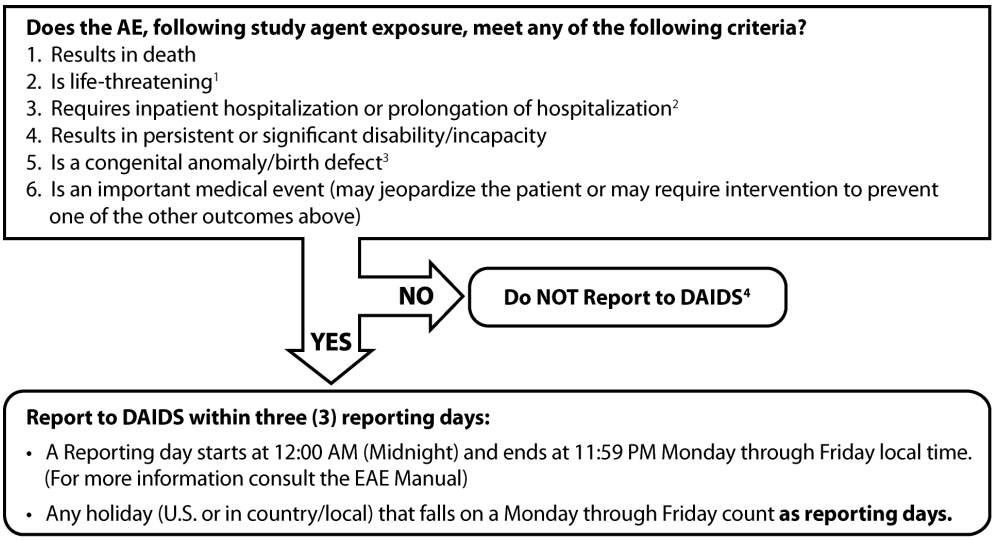
If the site cannot use DAERS to report an AE on an expedited basis, the AE must be documented on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form) and submitted as specified by the DAIDS Manual for Expedited Reporting of AEs. This form may be found on the Regulatory Support Center (RSC) website at http://rsc.tech-res.com.

For questions or other communications regarding expedited reporting of AEs, see below.

Website:	http://rsc.tech-res.com
Office Phone:	301-897-1709 or toll free in the US: 800-537-9979
Office Fax:	301-897-1710 or toll free in the US: 800-275-7619
Office Email:	DAIDSRSCSafetyOffice@tech-res.com
Office Hours:	Monday through Friday, 8:30 AM to 5:00 PM ET

The AE Log case report form includes an item (item 9) to record if the AE is also being reported as an EAE. When completing AE Log CRFs and DAERS report, study clinicians should carefully review all documentation of the event to ensure accuracy, completeness and consistency. All AE descriptions and details (e.g., onset date, severity grade, relationship to study product) must be recorded consistently across all documents. All expedited AE reports submitted to the DAIDS Safety Office will be compared with AE Log forms received at the MTN SDMC to ensure that all reports that should have been received by both DAIDS Safety Office and the SDMC have been received and that the details recorded on each form are consistent.

Figure 8-3
Expedited Adverse Event Reporting Requirements for MTN-012/IPM 010



Contact Information for the DAIDS Safety Office:
Website: http://rcc.tech-res.com • **E-mail:** RCCSafetyOffice@tech-res.com
Office Phone: 1-800-537-9979 (U.S. only) or +1-301-897-1709 • **Fax:** 1-800-275-7619 (U.S. only) or +1-301-897-1710
(Office Phone and Fax are accessible 24 hours per day)
Mailing Address: DAIDS Safety Office 6500 Rock Spring Drive, Suite 650, Bethesda, MD 20817

[1] "Life-threatening" refers to an event in which the patient was at risk of death at the time of the event. It does NOT refer to an event that hypothetically might have caused death if it were more severe.

[2] Per the ICH SAE definition, hospitalization is NOT an adverse event (AE), but is an outcome of the event. **DO NOT REPORT**: Any admission unrelated to an AE (e.g., for standard labor/delivery, cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep); protocol-specified admission (e.g., for a procedure required by protocol); admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) **and** has not increased in severity or frequency as judged by the clinical investigator. (**NOTE**: A new AIDS-defining event in a subject already known to be HIV-infected would be considered an increase in severity of a pre-existing condition [HIV infection] and **would be** reportable.)

[3] Clinically insignificant physical findings at birth, including those regarded as normal variants, do NOT meet reporting criteria. If a clinically significant anomaly is reported, all findings (including those of no individual significance) should be included in the same report. For example, do NOT report an isolated finding of polydactyly (extra fingers or toes) or Mongolian spot in an infant. But if either finding occurred with a major cardiac defect, report all findings in the SAE Report.

[4] Please ensure that any other protocol-specific reporting requirements are met.

8.13 Adverse Event Terminology

Both the Adverse Experience Log case report form and the DAERS report require site staff to assign a term or description to each AE. Whenever possible, a single diagnosis should be reported, rather than a cluster of signs and/or symptoms. When it is not possible to identify a single diagnosis to describe a cluster of signs and/or symptoms, each individual sign and symptom must be reported as an individual AE. When relevant, an anatomical location should be included in the term or description.

If an abnormal laboratory test result is reported as an AE (separate from any clinical diagnosis associated with the result) the type of test performed and the direction of the abnormality should be reported (such as elevated ALT). The severity grade of the result should not be reported as part of the AE description since the grade is captured elsewhere (item 3) on the form.

Further tips and guidelines for assigning AE terms are as follows: use medical terms whenever possible, use correct spelling for all terms, and do not use abbreviations. Additional instructions on completion of AE Log forms can be found in Section 10 (both on the back of the AE Log form and in Section 10).

8.14 Adverse Event Severity

The term severity is described as the intensity of an AE (that is, the grade or level for a specific event such as mild, moderate, severe, or potentially life-threatening). Importantly, severity is not the same as seriousness, which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning (ICH E2A).

Male Genital Grading Table for Use in Microbicide Studies (MGGT) (Addendum 2 of The DAIDS Toxicity Table) will be the primary tool for grading adverse events for this protocol. Adverse events not included in that table will be graded by the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events, Version 1.0 December 2004 (Clarification dated August 2009). In cases where an AE is covered in both tables, the MGGT will be the grading scale utilized. The grading tables are available at:

http://rsc.tech-res.com/safetyandpharmacovigilance/default.aspx

There are 5 severity grades that can be assigned to AEs, which are defined as follows:

Grade 1 = Mild
Grade 2 = Moderate
Grade 3 = Severe
Grade 4 = Potentially Life-threatening
Grade 5 = Death

Further clarifications, tips and guidelines for grading the severity of AEs are as follows:

- For the grading of clinical AEs not specified in the MGGT, the DAIDS Toxicity Table, or in the protocol, sites are to use the 'Estimating Severity Grade' on page 3 of the of the DAIDS Toxicity Table

- If the severity of an AE could fall under either one of two grades (e.g., the severity could be a grade 2 or a 3), the higher of the two grades should be assigned
- If a single AE term is used as a unifying diagnosis to report a cluster of signs and symptoms, assign the highest severity grade of each of the signs and symptoms to the AE
- Seasonal allergies should be graded according to the 'Estimating Severity Grade' row of the DAIDS Toxicity Table

8.14.1 Assigning Severity Grades for Laboratory Assays on Case Report Forms

For some lab assays, the severity grade range is calculated using a value from the DAIDS Toxicity Table and a local normal range. When grading laboratory values for which the Toxicity Table specifies the use of the upper limit of normal (ULN) or lower limit of normal (LLN), 'normal' values are defined according to local age-adjusted institutional values.

When assessing ULN and LLN values, there will be times when the calculated severity range will have more significant digits than the reported lab value. This may lead to confusion regarding which severity grade to assign. For example, Grade 1 for total bilirubin is 1.1–1.5 times the site lab upper limit of normal (ULN).

When working with calculated severity grade ranges, remember the following:

1. Rounding is permitted only when recording lab values on a CRF in order to match the level of precision allowed on the CRF.

2. When calculating a severity grade range, never round on interim steps.

3. Always compare the severity grade range to the value that was recorded on the CRF (not the lab-reported value).

4. If the calculated severity grade range has more significant digits than the lab value, do not round the calculated range values. Instead, treat all missing digits in the lab value as zeros.

Example: Total bilirubin = 1.4 mg/dL, site ULN = 1.3 mg/dL

	DAIDS Toxicity Table Grade Range	Site-specific Grade Range
Grade 1	1.1–1.5 x ULN	1.43–1.95 mg/dL
Grade 2	1.6–2.5 x ULN	2.08–3.25 mg/dL

The site-specific grade range is accurate to the hundredths place (because 1.1 x 1.3 = 1.43 and 1.5 x 1.3 = 1.95, etc.). Treating the hundredths place of the total bilirubin value as a zero gives us a value of 1.40.

The lab value (1.40) falls below the minimum calculated value for Grade 1 (1.43). Do not assign a severity grade or report as an Adverse Experience.

5. If the lab value falls between two calculated severity grade ranges, assign it the

higher grade as stated in the DAIDS Toxicity Table General Instructions (page 1).

Example: Total bilirubin = 2.0 mg/dL, site ULN = 1.3 mg/dL

As in the example above, the site-specific grade range is accurate to the hundredths place. The hundredths place of the total bilirubin value is treated as a zero, giving us a value of 2.00.

The lab value (2.00) falls between the maximum calculated value for Grade 1 (1.95) and the minimum for Grade 2 (2.08). Therefore, this value should be assigned the higher grade (Grade 2).

8.15 Adverse Event Relationship Assessment

For each AE indentified in MTN-012/IPM 010, the study clinician must assess the relationship of the AE to the study product, based on the temporal relationship of AE onset to study drug administration, the pharmacology of the study product and his/her clinical judgment. When assessing relationship, the study products in MTN-012/IPM 010 that should be considered are the three gels. The categories of relatedness that will be used to assess the relationship of all AEs to study product are:

- Related: There is a reasonable possibility that the AE may be related to the study agent(s)

- Not related: There is not a reasonable possibility that the AE is related to the study agent(s)

8.16 Follow-up Documentation of Adverse Events

All AEs identified in MTN-012/IPM 010 must be followed clinically until the AE resolves (returns to baseline). In addition to performing protocol-specified assessments, at each visit, an authorized study clinician should review all previously reported ongoing AEs to evaluate and document in the participant's chart notes the current status.

A new Adverse Experience Log CRF is NOT required when submitting follow-up information for a previously reported AE. Rather, the existing CRF is updated and resubmitted. However, if an AE increases in severity or frequency, it must be reported as a new AE on a new AE Log form. The onset date on the AE Log form will be the date that the severity or frequency increased. Note that a decrease in severity should not be reported as a new AE. For additional instructions, see Section 10.

Likewise, any ongoing SAE that increases in severity to a higher grade than previously reported must be reported again as a new report in DAERS. Ongoing events that improve, but are not resolved and subsequently increase in severity to the same or lower severity grade than previously reported do not have to be reported again to the DAIDS Safety Office.

The requirements for submission of follow-up information on AEs reported to DAIDS are specified in Section 4 of the Manual for Expedited Reporting of Adverse Events to DAIDS

(Version 2.0 dated January 2010). As specified therein, for the circumstances listed below regarding an AE reported to DAIDS, the site is required to submit an updated report to DAIDS as soon as significant additional information becomes available. Requirements include:

- An updated report documenting the stable or resolved outcome of the AE, unless the initial report included a final outcome
- Any change in the assessment of the severity grade of the AE or the relationship between the AE and the study agent
- Additional significant information on a previously reported AE (e.g., cause of death, results of re-challenge with the study agent).

Note: if information regarding an AE reported to DAIDS is updated, the corresponding AE Log case report form should also be updated and resubmitted if any data recorded on the AE Log form has been updated.

8.17 Outcome of Adverse Events, Review of AE Reports, and Clinician Assessment

The site must follow the progress of each reported adverse event and record eventual outcomes in source documentation. In many cases the final outcome of an AE will not be available when the AE Log form is first completed and faxed to SCHARP DataFax. In such cases, the AE Log form should be updated when the final outcome becomes available. If the AE is still continuing at the time of the Final Clinic Visit, item 6 ("Status/Outcome") of the AE Log form should be updated to "Continuing at end of study participation". Any AE continuing at the Final Clinic Visit should be followed clinically until resolution (return to baseline). The Investigator will determine the appropriate follow-up plan for monitoring ongoing AEs at the end of the study and may consult the PSRT for guidance as needed. Clinical management and follow-up after the participant exits the study should be documented in chart notes only (the AE Log form should not be updated once the participant has terminated from the study).

The Investigator or designee should carefully review all laboratory abnormalities relevant to the participant's health available since the last visit to identify any adverse events or health problems. Documentation of this review is required by initialing and dating each page of lab results.

The severity of all lab abnormalities will be graded and recorded in source documentation. Results of protocol-specified local laboratory results will also be reported on the Laboratory Result form and if applicable, an Adverse Experience Log form. Sites should document other results if any, in visit chart notes, or in other designated site-specific documents. If any non-protocol-specified lab abnormalities meet AE criteria, these will also need to be reported on an AE Log form. Through the participant's study involvement, lab abnormalities that meet the criteria for expedited reporting to DAIDS must also be reported to DAIDS via the DAERS Reporting System.

A study clinician listed on the FDA Form 1572 must assess each participant and record the details of all adverse events in the source documentation and complete or carefully review the information transcribed onto the AE Log CRF. He/she must also review and verify the data on the DAERS report for accuracy and completeness. This physician makes the site's final assessment of the relationship between the study product and the adverse event. He/she must electronically sign the completed DAERS report. If necessary, to meet timely reporting

requirements, sites can submit an expedited adverse event report without a completed signature page. However, the completed signature page, and necessary corrections or additions, must be submitted within the next 3 reporting days.

8.18 Reporting Recurrent Adverse Events

In the rare occurrence that a resolved adverse event that was previously reported on the AE Log form later recurs, the AE is considered a new adverse event and a new AE Log form must be completed.

Likewise, if a resolved AE that was previously reported to DAIDS later recurs at a level requiring expedited reporting, the AE must be reported as a new EAE Report to the DAIDS Safety Office.

8.19 Social Harms

In addition to medical adverse events, participants may experience social harms – any non-medical adverse consequence experienced as a result of a person's participation in a study. For example, participants could experience difficulties in their personal relationships with partners, family members, and friends. They also could experience stigma or discrimination from family members and members of their community.

In the event that any social harm occurs, study staff should fully document the issues or problems and make every effort to facilitate their resolution as described in this section. There is no CRF for the reporting of social harms. However, in addition to documenting the social harm in the source files, the Investigator of Record will report any social harm, in his/her judgment, to be serious or unexpected to the IRB on at least an annual basis. Study sites may engage their Community Advisory Boards in exploring the social context surrounding instances of social harm.

The following are suggested strategies for responding to social harms that may be adapted and tailored to best meet participant needs at each site:

- When first responding to an issue or problem, actively listen to the participant's description of the problem and ask questions to elicit as much detail as possible about the problem, including the participant's perception of the severity of the problem. Record all pertinent details in signed and dated chart notes. Also report the issue or problem to all responsible IRBs, if required per IRB guidelines.

- Ask the participant to articulate his thoughts on what can/should be done to address the problem, including what he would like study staff to do in response to the problem (if anything).

- Discuss with the participant any additional or alternative strategies that you might suggest to address the problem and collaborate with him to develop a plan to try to address the problem. Document the plan in signed and dated chart notes.

- Take all possible action to try to address the problem, per the plan agreed upon with the participant. Document all action taken, and outcomes thereof, in signed and dated chart notes.

- As with medical AEs, follow all problems to resolution or return to baseline.

- Provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem.

- Consult the MTN-012/IPM 010 Protocol Safety Review Team (PSRT) for further input and guidance as needed.

8.20 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN-012/IPM 010 protocol for a complete description of the participant safety monitoring procedures in place for MTN-012/IPM 010. Also refer to Section 13 of this manual for a description of the reports prepared by the MTN SDMC in support of MTN-012/IPM 010 safety monitoring procedures.

Participant safety is of utmost concern. Primary safety monitoring and safeguarding of individual study participants is the responsibility of study site staff, under the direction of the IoR. The IoR and designated site staff also are responsible for submitting case report forms to the MTN SDMC and expedited AE reports to the DAIDS Safety Office, such that relevant safety data are available in a timely manner for other study-specific safety monitoring procedures, as follows:

- Clinical Affairs staff at the MTN SDMC will review clinic and laboratory data received at the SDMC and apply clinical data quality control notes (clinical queries) to data requiring confirmation, clarification, or further follow-up by site staff. These queries will be issued to site staff for resolution on an ongoing basis throughout the period of study implementation.

- The DAIDS Medical Officer and IPM Medical Officer will review all DAERS reports received for MTN-012/IPM 010 and follow up on these reports with site staff, the MTN-012/IPM 010 Protocol Team, and drug regulatory authorities when indicated.

- The MTN-012/IPM 010 Protocol Safety Review Team (PSRT) will routinely review safety data reports prepared for MTN-012/IPM 010 by the MTN SDMC. The PSRT will meet via conference call to discuss the accumulating study safety data and any potential safety concerns (See Section Appendix I for more details).

Management of permanently discontinuing study product relative to the occurrence of toxicities must follow the standard toxicity management procedures. Site staff should seek the advice and counsel of the PSRT on these matters.

8.21 MTN-012/IPM 010 Protocol Safety Review Team (PSRT)

8.21.1 Roles and Responsibilities of the PSRT

Per the MTN-012/IPM 010 protocol, the roles and responsibilities of the MTN-012/IPM 010 Protocol Safety Review Team (PSRT) are to:

1. Conduct regular reviews of standardized study safety data reports. Once the SDMC begins receiving study follow-up safety data, the PSRT will convene via regularly scheduled monthly conference calls. Thereafter, the frequency of calls may be adjusted throughout the period of study implementation as agreed upon by the PSRT. Should any safety concerns be identified by the PSRT, these will be referred to the MTN Study Monitoring Committee (SMC).

2. Respond to Investigator queries regarding early termination of study participation. The site IoR should consult the PSRT when he/she decides to withdraw a participant from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures.

3. Respond to Investigator queries regarding study eligibility and general AE management and reporting (not necessarily related to product use).

8.21.2 PSRT Composition

The following individuals currently comprise the MTN-012/IPM 010 PSRT:

- Ross Cranston, Protocol Chair
- Lydia Soto-Torres, DAIDS Medical Officer
- Sepideh Habibi, IPM Medical Officer
- Katherine Bunge, MTN Safety Physician
- Devika Singh, MTN Safety Physician
- Molly Swenson, SDMC Clinical Affairs Safety Associate

Ideally all of the above-listed PSRT members will take part in routine PSRT conference calls; however a quorum of at least three members, the MTN-012/IPM 010 Protocol Chair, DAIDS Medical Officer (or designee) and the MTN Safety Physician, must take part in all calls.

If a quorum is not present, the call may be deferred until the next scheduled call time unless a quorum member requests a more immediate call.

The MTN CORE (FHI) Clinical Research Manager and Prevention Research Specialist, and the SDMC (SCHARP) Project Manager, also will participate in and facilitate PSRT calls and reviews. The DAIDS PSB Program Officer(s), MTN CORE Pharmacist, MTN Network Lab representative, and Co-Sponsors also may attend calls as observers.

8.21.3 Routine Safety Data Summary Reports: Content, Format and Frequency

The SDMC will generate and distribute standard safety data reports to the PSRT via e-mail within a week prior to each PSRT conference call. Tabulations will be generated for all study participants combined (i.e., across all study regimen groups).

Reports will include summary information regarding the number and frequency of events organized by body system (using MedDRA terms) and severity, and will include information on relatedness to study product.

During PSRT conference calls, the DAIDS Medical Officer will summarize any additional DAERS reports received at the DAIDS Safety Office after the cut-off date for inclusion in the SDMC PSRT report.

8.21.4 PSRT Communication

An email distribution list will be used to facilitate communication with the PSRT. Site queries and communications with the PSRT should be sent via email to mtn012safetymd@mtnstopshiv.org. All safety data summary reports from the SDMC will be distributed via mtn012psrt@mtnstopshiv.org.

A standard PSRT query form (Appendix I) will be used to elicit sufficient information to allow the PSRT to make an informed determination and respond to each query. To ensure a timely PSRT response, the MTN-012/IPM 010 Protocol Chair, MTN Safety Physicians and DAIDS Medical Officer have ultimate responsibility for providing a final response to the query (via email) within three business days after receipt of the query (unless a more urgent response is requested by the site). All members of the PSRT are encouraged to review the information provided by the site and to offer their advice; however final determination rests with the MTN-012/IPM 010 Protocol Chair, MTN Safety Physicians and the DAIDS Medical Officer on behalf of the PSRT.

In the event that the protocol team or PSRT has serious safety concerns, the protocol team or PSRT will request a review of the data by the MTN Study Monitoring Committee (SMC). While site staff are not typically involved in these reviews, site staff should be aware that the SMC may make recommendations to DAIDS and/or the MTN leadership that could affect the study and study sites in significant ways. These decisions are based on detailed review of the available study data and careful consideration of ongoing participant safety and study viability.

Section Appendix 8-I
MTN-012/IPM 010 Protocol Safety Review Team Query Form

Instructions: Email completed form to MTN Safety Physicians: mtn012safetymd@mtnstopshiv.org

IMPORTANT: Complete all required fields so the PSRT has all information needed to respond to your query.

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

PTID: **Participant Age** (in years):

Reason for query:
- ☐ Product use consultation:
  - ☐ Should use of study product be permanently discontinued?
- ☐ Request for consultation on AE management
- ☐ Request to withdraw participant from the study
- ☐ Other, specify:

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

Primary AE of concern:

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

Relatedness to study product:
- ☐ Related
- ☐ Not related

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

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

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

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

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

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

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

End of Form for Site Staff. Email completed form to the MTN-012/IPM 010 Protocol Safety Physicians, mtn012safetymd@mtnstopshiv.org. If an email response is not received from the PSRT within 3 business days, re-contact the Protocol Safety Physicians, copying the study management team (mtn012mgmt@mtnstopshiv.org), for assistance as soon as possible.

FOR PSRT USE ONLY — PROVIDE RESPONSE TO QUERY HERE

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

Query Outcome:
☐ Approved
☐ Not approved
☐ Not applicable

PSRT Comments: