

Section 11. Adverse Event Reporting and Safety Monitoring

11.1 Overview of Section 11

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN 005. Please also refer to Section 8 of the MTN 005 protocol and the following resources relevant to AE assessment and reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events (Toxicity Table), dated December 2004 (Clarification August 2009)
- DAIDS Female Genital Grading Table (FGGT), (Addendum 1 to the Toxicity Table)
- Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2 (DAIDS EAE Manual), dated January 2010
- DAERS Reference Guide for Site Reporters and Study Physicians
- Investigator Brochure for Non-Medicated Intravaginal Ring

11.2 Definitions and General Reporting Guidance

11.2.1 Adverse Event (AE)

The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (ICH-E2A) defines an 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.

For MTN 005, the ICH-E2A definition is applied to all participants in both study groups, beginning at the time of random assignment. Study staff must document in source documents all AEs reported by or observed in MTN 005 participants, beginning at the time of random assignment, regardless of severity and presumed relationship to study product. Source documentation for all AEs should minimally include the following:

- AE term/diagnosis
- Severity grade
- Onset date
- Outcome
- Outcome date
- Treatment (if any)
- Action taken with the study product

Medical conditions, problems, signs, symptoms, and findings identified prior to random assignment are considered pre-existing conditions. Such conditions should be documented per the screening and enrollment visit guidance provided in Section 4 of this manual, and reported on the Pre-Existing Conditions case report form (including severity grade). If a pre-existing condition worsens (increases in severity or frequency) after randomization, the worsened condition is considered an AE. If a pre-existing condition resolves after randomization, but then recurs at a later date, the recurrence is considered an AE.

Procedures per se should not be reported as adverse events; rather the underlying condition which leads to a procedure may be considered an adverse event. Any associated procedures may be considered treatments for the adverse event. For example, while “appendectomy” would not be considered an adverse event, “appendicitis” would, with “appendectomy” documented as a treatment provided for the adverse event. In addition, any event that occurs as a result of a study-related procedure should be recorded as an AE. For example, if a participant experiences vaginal pain as a result of the pelvic exam, the vaginal pain should be submitted as an AE.

11.2.2 Reporting Adverse Events

Per Section 8.3 of the MTN 005 protocol, study staff will report on case report forms (AE log form), all AEs in enrolled study participants either reported by participants or observed by site staff regardless of severity and presumed relationship to study product. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dates August 2009) and the DAIDS Female Genital Grading Table (FGGT), (Addendum 1 to the Toxicity Table). The FGGT should serve as the primary source for grading AEs. If the affected body system is not listed in the FGGT, the Toxicity Table should be used.

Due to some of the clinical procedures, study participants may experience some expected AEs. These may include bruising from a blood draw, for example. Expected AEs should also be captured on the AE CRF.

The Adverse Experience Log case report form is used to report AEs to the MTN Statistical and Data Management Center (SDMC). All sites are strongly encouraged to use an AE tracking tool to ensure that all AEs are source documented. The Follow-up Medical History non-DataFax case report form may be used for this purpose.

Laboratory values that fall outside of a site's normal laboratory reference ranges, but do not meet criteria for severity grading as grade 1 or higher, should not be considered "abnormal" for purposes of AE reporting, unless the Investigator of Record (IoR) or designee determines otherwise based on his/her clinical judgment. In addition, a laboratory result that is not listed in the DAIDS toxicity table will not be reported as an AE. For example, a positive urine LE or positive nitrites result on dipstick urinalysis should not be reported separately as its own AE on its own AE Log form. Rather, the positive dipstick results will be captured on the Local Laboratory Results CRF completed for the visit.

Each site's SOP for source documentation should define the extent to which the Adverse Experience Log form will be used as the source document for these data elements.

Documentation of site-specific delegation of duties should designate study staff authorized by the IoR to complete Adverse Experience Log forms. Regardless of who initially completes these forms, a clinician listed on the site's FDA Form 1572 should review each AE Log form to ensure the accuracy of the data reported and to help maintain consistency of reporting across clinicians.

If, at any time, site staff has questions about participant safety or reporting clinical events, they should send an email to the MTN 005 Safety Physicians: mtn005safetymd@mtnstopshiv.org

11.2.3 Serious Adverse Events (SAEs)

Serious Adverse Events (SAEs) are defined by the ICH E2A definition, as described in Section 2.1 of the *Manual for Expedited Reporting of Adverse Events to DAIDS version 2 (DAIDS EAE Manual)*, dated January 2010. Note that the criteria below apply to all study participants (IVR and no IVR groups). An SAE is any untoward medical occurrence that at any dose:

1. Results in death,
2. Is life-threatening,
3. Requires inpatient hospitalization or prolongation of existing hospitalization,
4. Results in persistent or significant disability/incapacity,
5. Is a congenital anomaly/birth defect, or
6. Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

process of EAE reporting via DAERS involves a designated “Study Reporter” creating an electronic EAE report and a designated “Study Physician” reviewing the EAE report, signing the EAE report with an electronic signature, and submitting the EAE report to the DAIDS RSC. If an EAE report is not completed and submitted within three business days of site awareness of the EAE, an explanation must be entered in DAERS before the report can be submitted.

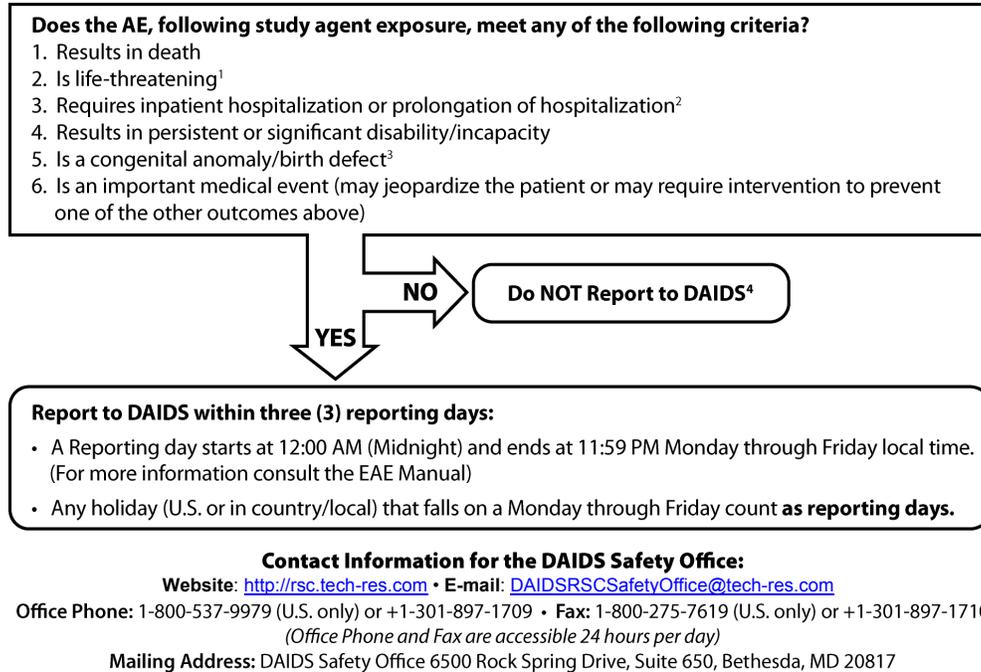
DAERS also may be used to modify or update an EAE report or to withdraw an EAE report that was submitted in error.

DAERS incorporates a report printing function that should be used to print all EAE reports—including modifications and updates—for filing in participant study notebooks. Automated email messages confirming submission of EAE reports also should be printed and filed with the print-out of the associated EAE report.

In the event that DAERS cannot be accessed (e.g., due to poor internet connectivity), paper-based EAE reporting should be used, per instructions provided in the *Manual for Expedited Reporting of Adverse Events to DAIDS*. Completed paper EAE Forms may be faxed or digitally scanned and emailed to the DAIDS RSC via email. The EAE Form and form completion instructions are available on the DAIDS RSC web site (<http://rsc.tech-res.com>). Contact details for submission of EAE Forms to the RSC are provided in the *Manual for Expedited Reporting of Adverse Events to DAIDS*.

IMPORTANT: At the time of EAE reporting, sites are asked to submit the AE Log CRF corresponding to the EAE to SCHARP. All data collected on the two documents must be the same. For example, the onset/outcome dates, severity, relationship to study product must all be consistent between the two documents.

Figure 11-1
Expedited Adverse Event Reporting Requirements for MTN 005
IVR Participants Only (Do not report EAEs for no-IVR Group Participants)



¹ “Life-threatening” refers to an event in which the patient was at immediate 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.

11.3 Adverse Event Terminology

Study staff must assign a term or description to all AEs identified in MTN 005. Whenever possible, a diagnosis should be assigned. 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 identified and documented as an individual AE. When relevant, for AEs that may occur in more than one anatomical location, record the anatomical location in the AE term or description. Whenever possible, use specific terms to indicate the anatomical location of the AE (e.g., “vaginal” instead of “genital”).

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 (e.g. elevated ALT). The specific value or the severity grade of the result should not be reported as part of the AE term.

Further tips and guidelines for AE descriptive text are as follows:

1. Use a diagnosis whenever possible.
2. Use specific medical terms whenever possible (e.g. “ulcers” instead of “sores”);
3. Use correct spelling for all terms; and,
4. Do not use abbreviations.

When reporting an AE that is associated with an underlying condition, include the underlying condition in the AE term or description. For example, if a participant is experiencing pain related to an underlying cancer diagnosis, include the cancer diagnosis in the AE term or description.

11.4 Adverse Event Severity

The term severity is used to describe the intensity of an AE. The severity of all AEs identified in MTN 005 must be graded on a five-point scale:

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

The severity of all AEs identified in MTN 005 will be graded using the *DAIDS Female Genital Grading Table* (FGGT) and if not identified there, the *DAIDS Table for Grading Adult and Pediatric Adverse Events* (Toxicity Table), dated December 2004 (Clarification August 2009). The DAIDS Toxicity Table can be accessed on the DAIDS RSC web site (<http://rsc.tech-res.com/safetyandpharmacovigilance/>).

Further clarifications, guidelines, and tips for grading the severity of AEs in MTN 005 are as follows:

- If the severity of an AE falls into more than one grading category on the Toxicity Table, assign the higher of the two grades to the AE.
- If a single AE term is used as a unifying diagnosis to report a cluster of signs and symptoms, and the diagnosis is not specifically listed in the Toxicity Table, assign the AE the highest severity grade among each of the associated signs and symptoms. Record the diagnosis as the AE term and record each associated sign and symptom in the AE Log comments section.
- Seasonal allergies should be graded according to the “estimating severity grade” row of the Toxicity Table (not the “acute systemic allergic reaction” row).
- If a participant reports an adverse event that is not identified in the DAIDS AE grading table, use the category “Estimating Severity Grade” located on Page 3 of the Toxicity Table. This category should only be used for reporting clinical events. Do not use this category for reporting laboratory results.
- Urinary tract infection (UTI), which is expected to be diagnosed on the basis of symptoms and positive findings for nitrites and leukocyte esterase on dipstick urinalysis, should be graded according to the “infection (other than HIV infection)” row of the Toxicity Table. A suspected UTI in the absence of both a positive urine LE and nitrites on dipstick urinalysis may be treated (with antibiotics) as a UTI; however, the AE should not be reported using the term “Urinary Tract Infection”. Instead, each related 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 as its own stand-alone AE as it is a laboratory result that is not gradeable per the DAIDS Toxicity Table.

11.5 Adverse Event Relationship to Study Product

One of the following relationship categories must be assigned to each AE:

- Related: There is a reasonable possibility that the AE may be related to the study product.
- Not related: There is not a reasonable possibility that the AE is related to the study product.

When an AE is assessed as “not related” to the study products, an alternative etiology, diagnosis or explanation should be provided in the “Comments” line of the AE Log CRF. If new information becomes available, the relationship assessment of any AE should be reviewed again and updated as required. When recording an AE that is the result of a study-related procedure, mark the “Relationship to study product” as “Not Related” and provide an explanation in the “Comments” line that the event is a result of a study-related procedure.

11.6 Adverse Event Outcomes and Follow-Up Information

All AEs identified in MTN 005 must be followed clinically until they resolve (return to baseline) or stabilize (persist at a certain severity grade (above baseline) for two consecutive monthly evaluations).

At each follow-up visit, an authorized study clinician should review all previously identified ongoing AEs and evaluate and document their current status. Outcomes must also be reported on Adverse Experience Log case report forms. In many cases, the final outcome of an AE will not be available when the Adverse Experience Log form is first completed and faxed to DataFax. In such cases, the form should be updated when the final outcome becomes available and re-faxed to DataFax at that time.

As noted above, “resolution” of an AE is generally defined as returning to the condition or severity grade that was present at baseline (i.e. at the time of randomization) and “stabilize” is defined as persistence at a certain severity grade (above baseline) for two consecutive monthly evaluations. For clinical events that are AEs, clinical management and follow-up of the AE should proceed per the specifications of Section 9.2 of the MTN 005 protocol. If, however, a clinical AE is not addressed in Section 9.2 of the protocol, at a minimum, follow-up evaluations should be performed at scheduled study visits until resolution or stabilization has been documented.

For AEs that are ongoing at the termination visit, the status/outcome of the AE should be updated to “continuing at end of study participation” and the AE Log form should be re-faxed to DataFax. For these AEs, the IoR or designee must establish a clinically appropriate follow-up plan. At a minimum, the AE must be re-assessed by study staff within 30 days after the termination visit; additional evaluations also may take place at the discretion of the IoR or designee. The same approach must be taken for any AEs that are found to have increased in severity at

the termination visit. Sites should notify the Protocol Safety Review Team (PSRT; mtn005psrt@mtnstopshiv.org) team for guidance in such situations.

For AEs that are re-assessed after the termination visit, information on the status of the AE at the time of re-assessment will be recorded in source documents; however, no updates should be made to any case report forms based on the re-assessments.

11.7 Reporting Recurrent Adverse Events

If an AE that was previously reported on an Adverse Experience Log case report form resolves and then recurs at a later date, the second occurrence must be reported as a new AE on a new Adverse Experience Log case report form.

An important clarification of this guidance relates to genital herpes and genital warts. Genital herpes and genital warts are associated with chronic viral infections — HSV-2 and HPV — and periodic symptomatic outbreaks — genital ulcers and genital warts.

- If infection with HSV-2 or HPV is known to have occurred before randomization, the infection is considered a pre-existing condition: report the infection as ongoing on the Pre-existing Conditions form.
- Any outbreaks that occur after randomization are considered AEs, regardless of whether the viral infection was known to be pre-existing before randomization: report the outbreak on an Adverse Experience Log form.

If an AE that was previously reported to the DAIDS RSC in an expedited manner resolves and then later recurs at a level requiring expedited reporting, the second occurrence must be reported as a new EAE report.

11.8 Social Harms

In addition to medical AEs, participants in MTN 005 may experience social harms — non-medical adverse consequences — as a result of their participation in the 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 harms occur, study staff should fully document the issues or problems and make every effort to facilitate their resolution as described in this section. In addition, the social harm must be recorded on the Social Harm Log case report form and faxed to SCHARP DataFax.

- The MTN Study Monitoring Committee (SMC) also will periodically review MTN 005 study data with a focus on performance indicators such as participant accrual and retention, protocol adherence, and data quality. 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 sites in significant ways. These decisions are based on a detailed review of the available study data and careful consideration of ongoing participant safety and study viability.

11.10 Safety Distributions from DAIDS

Study sites will receive product- and safety-related information throughout the period of study implementation. This information will be distributed by DAIDS, through its RSC and/or the MTN Coordinating and Operations Center, and may include:

- Updated Investigators Brochures
- IND Safety Reports
- Other safety memoranda and updates

Each distribution will include a cover memo providing instructions on how the document is to be handled. In all cases, a copy of the distribution must be filed in on-site essential document files. Also in all cases, study staff responsible for clinical oversight of study participants should be made aware of any newly available safety information. In many cases, the distribution will need to be submitted to site IRBs/ECs. Safety distributions do not require IRB/EC approval; however acknowledgement of receipt is desirable. Submission letters/memos for IRB/EC submissions should specify the name and date of all documents submitted.

Routine Safety Data Summary Reports: Content, Format and Frequency

The SDMC will generate standard safety data reports to the PSRT one week prior to each PSRT conference call. Tabulations will be generated for all study participants combined (i.e. across both study groups) and may include:

- Listings of new AEs by body system (using MedDRA terms), severity, and relationship to study product
- A cumulative listing of all SAEs/EAEs reported to date
- A cumulative listing of all AEs reported to date as related to study product by body system and severity
- A cumulative listing of all grade 2, grade 3, grade 4, and grade 5 AEs reported to date by body system and relationship to study product
- A cumulative listing of reported social harms

During PSRT conference calls, the DAIDS Medical Officer will summarize any additional EAE reports received at the DAIDS RSC after the cut-off date for the SDMC data summary.

PSRT Communications

A group email address (mtn005safetymd@mtnstopshiv.org) will be used to facilitate communication with the PSRT. All PSRT communications will be sent to this email address.

Site consultation with the PSRT will be facilitated using the MTN 005 PSRT Query Form, which is available in the Study Implementation Materials section of the MTN 005 web page (see Section Appendix 11-2).

Comments: Provide additional details relevant to this query.

End of Form for Site Staff. Email completed form to the MTN 005 PSRT: mtn005safetymd@mtnstopshiv.org and copy the MTN 005 management team: 066mgmt@mtnstopshiv.org. If an email response is not received from the PSRT within 3 business days, re-contact the PSRT, copying the study management team, for assistance as soon as possible.

FOR PSRT USE ONLY — PROVIDE RESPONSE TO QUERY HERE

PSRT Responding Member:

PSRT Response Date (dd-MMM-yy):

PSRT Response: