

Section 8. Adverse Event Reporting and Safety Monitoring

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8. Introduction

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-034. Please also refer to Protocol Section 8 and the following resources relevant to AE assessment and reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.1 dated July 2017, including:
 - Addendum 1: Female Genital Grading Table for Use in Microbicide Studies (FGGT), November 2007
- Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, Jan 2010)
- DAIDS Adverse Experience Reporting System (DAERS) Reference Guide for Site Reporters and Study Physicians
- Investigator’s Brochure for Dapivirine Vaginal Ring
- Package Insert for Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF), Truvada® Tablet

8.1 Definitions

8.1.1 Adverse Event (AE)

The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (ICH-E6) 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-034, the ICH-E6 definition is applied to all participants, beginning at the time a participant is enrolled through when she terminates from the study. Study staff must document within the Adverse Experience (AE) Log CRF all reportable AEs reported by or observed in study participants, regardless of severity and presumed relationship to study product.

The AE CRF may be used as source documentation for the following AE information:

- Date reported to site
- AE term/diagnosis
- Onset date
- Severity grade
- Relationship to study product (related or not related)
- Relatedness to study product relatedness (vaginal ring or Truvada)
- Relatedness to study device or drug (vaginal ring only)
- Study product administration as related to the AE
- Outcome status
- Outcome date (or ongoing at time of termination)
- AE treatment
- Whether the AE is serious per ICH guidance (see Section 8.1.2) and onset date, as applicable
- Whether the AE meets expedited AE reporting requirements (see Section 8.1.2)
- Whether the AE is a worsening of a baseline medical condition
- Additional comments/details related to the AE

Relevant medical conditions, problems, signs, symptoms, and findings identified prior to enrollment are documented within the Baseline Medical History Log (whether they are ongoing at enrollment or not). If this condition worsens (increases in severity or frequency per the DAIDS grading table) after enrollment, the worsened condition is considered an AE. If a baseline medical condition resolves after enrollment, but then recurs at a later date, the recurrence is considered an AE.

8.1.2 Serious Adverse Events (SAEs) / Expedited Adverse Events (EAEs)

ICH-E6 defines a serious adverse event (SAE) as an AE following any exposure to study product which:

- Results in death,
- Is life-threatening,
- **NOTE:** *The term “life threatening” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. A Grade 4 severity grading on the DAIDS Grading Table does not necessarily mean that an event is life-threatening. When determining whether a Grade 4 event meets the ICH definition of “life threatening”, consider the event in the context of any related symptoms the participant may have experienced.*
- Requires in-patient hospitalization or prolongs an existing hospitalization,
- *The following types of hospitalizations are not considered Adverse Events, serious or otherwise:*
 - Any admission unrelated to an AE (e.g., for labor/delivery)
 - Admission for diagnosis or therapy of a condition that existed before enrollment AND has not increased in severity per the DAIDS Grading Table since baseline.
- Results in persistent or significant disability/incapacity, or

- Is a congenital anomaly/birth defect
- Important medical events 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 above

ICH guidance (E2A) also states that medical and scientific judgment should be exercised in deciding whether other adverse events not listed above should be considered serious.

SAEs are a subset of all reportable AEs. For each AE identified in MTN-034, an authorized study clinician must determine whether the AE meets the ICH definition of “serious”. The AE Log CRF includes a specific question to record this determination.

When assessing whether an AE meets the definition of serious, note that seriousness is not the same as severity, which is based on the intensity of the AE (see Section 8.4 for more information on severity grading).

In MTN-034, all AEs that meet the definition of “serious” (SAE), regardless of relationship to study product, are considered expedited adverse events (EAEs). Seriousness is the only consideration in determining whether an AE meets the definition of an EAE. EAEs require additional reporting for rapid review and assessment by DAIDS (see section 8.2). In some cases, DAIDS may be required to report an EAE to the US FDA.

8.2 Reporting EAEs

EAEs should be reported per the *Manual for Expedited Reporting of Adverse Events to DAIDS, version 2.0; January 2010*. Reporting guidelines outlined in SSP Section 2.1 and Appendix A should be followed.

For MTN-034 the “SAE (Serious Adverse Event) Reporting Category” will be used to report EAEs.

If 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*.

All EAEs, including congenital anomalies and birth defects identified among infants born to study participants, must also be reported within the AE Log CRFs, with the EAE specified.

When completing AE Log CRFs and EAE reports, 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, SAE criteria) should be recorded consistently across all documents when possible. In cases where one EAE involves several AEs (a motor vehicle accident, for example), ensure consistency between the EAE and associated AE Log CRFs as much as possible.

All EAE reports received at the DAIDS RSC will be compared with AE Log CRFs received at the MTN SDMC to ensure that all reports that should have been received by both the DAIDS RSC and the SDMC have been received and that the details recorded on each form are consistent.

If an EAE that was previously reported to the DAIDS RSC resolves and then later recurs at a level requiring expedited reporting, the second occurrence must be reported as a new EAE report (and a new AE Log CRF, if not already completed).

8.2.1 Updating EAE Reports

For each EAE reported to DAIDS, sites are required to submit an updated report to DAIDS as soon as significant additional information becomes available. Note that updates made to EAE reports should also be made to the corresponding AE Log CRF, as applicable. Similarly, any updates made to an AE Log CRF should also be made to the corresponding EAE report, as applicable. Follow-up information on the EAE should be reported to the DAIDS RSC, using the update function in DAERS, under the following circumstances:

- Requests from DAIDS for additional information
- A change in the relationship between the AE and study product by the study physician
- Additional significant information that becomes available for a previously reported AE (this is particularly important for new information addressing cause of death if the initial assignment was “pending”)
- Any change in the assessment of the severity grade of the AE
- An update including the final or stable outcome, unless the initial SAE submitted had a final or stable outcome noted already
- Results of re-challenge with the study product, if performed

Note that although assessment of a change in the severity grade or the relationship between the AE and the study product does not require a new EAE form it must be reported as a new AE Log CRF to the SDMC (as described previously).

In MTN-034, re-challenge with study product may occur in the context of study product use having been held in response to an EAE, but then resumed after resolution or stabilization of the EAE. In such a case, site staff should provide follow-up information to the DAIDS RSC describing the participant’s condition after resuming product use. Follow-up reports should be submitted approximately one month after resuming product use, unless safety concerns are identified before one month has elapsed. In that case, the follow-up report should be submitted as soon as possible after the safety concern is identified.

8.3 Reportable Adverse Events and Terminology

The AE Log CRF is used to report all AEs, reported by or observed in enrolled study participants, to the MTN SDMC. A site-specific tracker may be used for documentation and tracking purposes.

Study staff must assign a term or description to all AEs identified in MTN-034 (“Adverse Event (AE)” term item on the AE log CRFs). The guidance below should be followed when assigning AE terms/descriptions:

- Whenever possible, use a diagnosis as the AE term. Document associated signs and/or symptoms related to a diagnosis in the comments section of the AE Log CRF.
- When it is not possible to identify a single diagnosis to describe a cluster of signs and/or symptoms, report each individual sign and symptom as an AE.
- Include anatomical location when applicable, and use a specific location term (e.g., “vaginal” instead of “genital”)
- Use medical terms (e.g., “ulcers” instead of “sores”)
- Use correct spelling
- Do not use abbreviations. Abbreviations for the following laboratory findings are acceptable:
 - WBC
 - MCV
 - Hgb
 - Hct

Any new lab value that is severity Grade 1 or higher according to the DAIDS Grading Table, excluding baseline conditions, regardless of where the testing took place, should be reported as an AE and documented within the AE Log CRF. Lab results from outside sources should be filed in participant charts as source documentation, if they are available. Even when source documentation from an outside lab is not immediately available, self-reported lab-based AEs (for example, a participant was told by an outside health care provider that she tested positive for gonorrhea) should be captured within the AE Log CRF (and confirmed by on-site testing as soon as possible). In contrast, CRFs that capture local laboratory results should only be used to document lab results from protocol-specified tests run at site-approved labs.

Procedures per se should not be reported as AE; rather the underlying condition, which leads to a procedure, may be considered an AE. Any associated procedures may be considered treatments for the AE. For example, while “appendectomy” would not be considered an AE, “appendicitis” would, with “appendectomy” documented as a treatment provided for the AE. In addition, any event that occurs because of a study related procedure should be recorded as an AE. Specify in the AE text description if the AE is related to a procedure (iatrogenic). For example, if a participant experiences dizziness from a blood draw, then “dizziness due to blood draw” should be submitted as an AE.

When completing the AE text description, do not include information on relatedness to study product or timing of study product use in the AE term/description. Limit the AE text to the medical description and anatomical location, when needed. Including such text affects the way the AE is MedDRA-coded, and thus, how it will appear in safety reports.

However, when reporting AEs which are **due to the act of ring removal or insertion**, specifically, please follow the guidance below:

- If the AE is **due to the act** of study ring insertion or removal, include this information in the AE text. For example, use AE text of “pelvic pain due to ring removal” or “vulvar laceration due to ring insertion” rather than just “pelvic pain” or “vulvar laceration.”

It is important to clearly identify AEs that are due to the act of study ring insertion or removal because these AEs are assigned unique coding terms within the standardized MedDRA coding system.

If the AE is **not** due to the act of study ring insertion or removal, do not include mention of the ring in the AE text.

- If text is present in the “Comments” field that the AE is due to the act of ring insertion or removal, this same text needs to be in AE term item. If not, this may result in a Safety Query asking that this information be added to the AE term item in order to accurately and completely describe this AE.

Sites must include text in the “Comments” field to provide the rationale or alternative etiology for why each AE has been judged “related” or “not related” Within the “Relationship to Study Product” item.

Source documentation requirements for AEs are listed in SSP Section 8.1.1.

Sites should check local IRB/EC and drug regulatory bodies' requirements regarding the reporting of AEs and ensure that expectedness is also captured for these AEs if required by local regulatory entities.

Site-specific delegation of duties documentation should designate study staff authorized by the IoR to complete AE Log CRFs. 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.

Additional guidance for reporting certain types of AEs in MTN-034 is provided below. Further guidance on severity grading for each of these is provided in SSP Section 8.4.

8.3.1 Reporting Genital, Genitourinary, and Reproductive System AEs

The category of genital, genitourinary, and reproductive system AEs includes AEs involving the vulva, vagina, cervix, uterus, fallopian tubes, ovaries, breasts, anus, rectum, kidneys, ureters, urethra, and bladder. All AEs associated with abnormal pelvic exam findings, STIs, UTIs, and RTIs fall in this category. See the Female Genital Grading Table (FGGT) on the MTN-034 *Study Implementation Materials* section of the MTN-034 website (<https://mtnstopshiv.org/research/studies/mtn-034/mtn-034-study-implementation-materials>) for AE Text Guidance related to these conditions.

Vaginal Discharge: Vaginal discharge by participant report and abnormal vaginal discharge as observed by the clinician should be graded per the appropriate rows in the FGGT (see below). The verbatim term from the FGGT should be used to distinguish if vaginal discharge was clinician observed versus participant reported.

** Note – if vaginal discharge is present both by participant report and on examination, only report the one with the most severe grade. (Grade 3 and 4 vaginal discharge is listed as “NA” in the FGGT and is not pictured here.) If they are the same grade, report ‘vaginal discharge by participant report’ as the AE term.

Table 8-1: FGGT for Vaginal Discharge

PARAMETER	Grade 0 NORMAL	Grade 1 MILD	Grade 2 MODERATE
Vaginal discharge by participant report **	Participant's usual amount of discharge, regardless of color or quantity	Mild-moderate increase in amount above participant baseline - no sanitary protection required	Profuse increase in discharge requiring pad use or other hygienic intervention
Vaginal discharge as observed by clinician ** (red or brown discharge should be reported under bleeding, not discharge)	Slight amount of discharge, any color	Mild-moderate increase in amount	Significant increase in amount with pooling in vagina on examination

Vaginal bleeding: For MTN-034, genital bleeding that is different from baseline (per participant assessment) and not attributable to typical bleeding expected with contraceptive use or expected irregular bleeding judged to be related to the adolescent menstrual cycle (per clinician assessment) should be captured as an AE.

If the newly-identified bleeding episode is determined to be different from her baseline (i.e., longer, heavier, more/less frequent) and not related to her current contraceptive method or menstrual cycle, record the episode within the AE Log CRF. Grade and term the episode per the applicable Toxicity Table category, “Abnormal Uterine Bleeding Unrelated to Pregnancy.”

Of note, *unexpected abnormal bleeding* related to contraception or the adolescent menstrual cycle that meets the criteria for a grade 3 or higher AE and/or an SAE should be reported. Sites should consult the PSRT if there are any questions about reporting of abnormal bleeding events that may be due to contraception or the adolescent menstrual cycle.

In addition, new events of infrequent bleeding during follow-up for unknown reasons or delay of menses for more than one month should be documented within the AE Log CRF using the appropriate term below:

- For missed menses events of 1-3 months in duration, use the term “missed menses”.
- For missed menses events of 4-5 months in duration, use the term “oligomenorrhea”.
- For missed menses events of 6 months or longer, use the term “amenorrhea”.

In the event a baseline bleeding condition resolves during follow-up (e.g. a participant with amenorrhea at baseline resumes her menstrual cycle after stopping her contraceptive method), the condition should be documented as resolved in chart notes but the Baseline Medical History Log CRF should not be updated. If the change in bleeding is determined to be related to a participant’s contraceptive method, then per protocol this is not reportable as an AE.

Note that study product use can continue in the presence of unexplained genital bleeding per the clinician's discretion, but ongoing events should be further investigated by a pelvic exam. If evaluation determines bleeding is due to deep epithelial disruption, the VR should be held per Protocol Section 9.5.

Recurrent bleeding AEs in follow-up: Once a bleeding AE has been reported, each subsequent bleeding episode should be assessed to determine whether the episode is consistent with previously reported bleeding AEs, or if it is the first of its kind. Clinician discretion should be used to determine if a new AE needs to be documented or if a previously reported AE is ongoing.

- As needed, update the AE Log CRF to be 'continuing.' The dates of each irregular bleeding episode do not need to be recorded on the AE Log CRF but should be captured in source documentation.
- When reviewing files in retrospect within Medidata Rave, mark for 'inactivate' any AE Log CRFs completed for bleeding episodes that can be subsumed under the initial AE reported for the bleeding event. When/if any AEs are inactivated, clearly document the rationale in the relevant source documents.
- If applicable, review and update the Concomitant Medications CRF "Taken for a reported AE?" to ensure that no deleted/inactivated AEs are indicated on the form.

If a participant has an ongoing (recurrent) bleeding AE, a pelvic exam is not required each time the participant reports the same ongoing bleeding, provided that the clinician assesses the bleeding to be consistent with the bleeding captured by the ongoing AE. If the AE increases in severity per the DAIDS Grading Table, a new AE Log CRF should be completed to document this change in severity.

When reporting genital bleeding events, reference should be made to the points below, which standardize the terminology that should be used when reporting AEs involving genital bleeding.

- Bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal according to the clinical judgment of the IoR or designee is not considered to be an AE. If the bleeding exceeds the amount considered normal by the clinician, it should be considered an AE and should be documented and reported if applicable using the term cervical friability. The severity of cervical friability should be graded per the cervical edema and friability row of the DAIDS FGGT. If both Menorrhagia and Metrorrhagia are present, a single AE should be reported as "Menometrorrhagia" and graded per the Menorrhagia row of the FGGT.
- Bleeding that is associated with an observed abnormal pelvic exam finding should be considered an AE and should be documented and reported if applicable using the term associated with the exam finding, with the anatomical location noted. For example, if a vaginal laceration is observed on exam, with blood emanating from the finding, the term vaginal laceration should be used to document the AE. The fact that blood or bleeding was present should be documented on the Pelvic Exam Diagrams form and the Pelvic Exam CRF, and may also be noted in the comments section within the AE Log CRF, but the term metrorrhagia should not be used to document the AE.
- The term metrorrhagia should be used to refer to any bleeding that is not menses-related and is not associated with an observed pelvic exam abnormal finding. For example, the term could be used to report bleeding of variable amounts occurring between regular menstrual periods. This term should also be used to report blood-tinged discharge and blood observed in the vagina with no identified source. Note that typical bleeding determined to be related to a participant's contraceptive method is not reportable as an AE and should not be documented on the Pelvic Exam CRF. However, unexpected or abnormal bleeding that is related to contraception and requires a blood transfusion, or results in grade 3 or higher anemia, should be reported using the term *anemia due to menorrhagia* or *anemia due to menometrorrhagia*.
- If a participant reports genital bleeding after sexual intercourse, this event should be recorded as "postcoital bleeding" and graded per the "Postcoital Bleeding" row of the DAIDS FGGT.

Vaginal odor: Per the FGGT, odor is listed as a symptom and should be documented as an AE if different from baseline and not due to a larger diagnosis. This is based on participant report of the symptom only and grading based on the participant's perception of severity.

STIs/RTIs

The following terminology should be used only if STI diagnosis is based on clinical evaluation and confirmed, when appropriate/possible, by laboratory result(s). For example, symptomatic BV and symptomatic vulvovaginal candidiasis should not be reported as AEs based on participant symptoms alone.

Bacterial Vaginosis (BV): Only report symptomatic infections that are confirmed with saline wet mount testing and that fulfill Amsels criteria as AEs, using the term “symptomatic bacterial vaginosis.” “Asymptomatic bacterial vaginosis” should not be recorded as an AE. If a clinician notes abnormal vaginal discharge and ultimately diagnoses the participant with asymptomatic bacterial vaginosis, this clinical event should be captured as “vaginal discharge- clinician observed”.

Candidiasis: Only report symptomatic infections that are confirmed with KOH wet prep and/or culture as AEs, using the term “vulvovaginal candidiasis.”

Chlamydia: Report all infections using the term “genitourinary chlamydia infection.” No need to report symptomatic or asymptomatic.

Gonorrhea: Report all infections using the term “genitourinary gonorrhea infection.” No need to report symptomatic or asymptomatic.

Suspected genital herpes outbreaks: Because herpes testing is not required or expected in MTN-034, each suspected genital herpes outbreak should be reported using the term marked on the Pelvic Exam CRF describing the lesion together with the anatomical location (e.g., vulvar ulceration, vaginal blister).

Genital herpes: The criterion for diagnosing genital herpes per the *Female Genital Grading Table for Use in Microbicide Studies* (FGGT) is below. Note that laboratory testing is required in order to use the term “genital herpes” for AE reporting. Such testing is not required per protocol and should only be done if it is the local standard of care. Any new lesion/ulcer observed during the study should be reported as an AE even if it thought to be due to prior herpes diagnosis/infection.

Table 8-2: FGGT for Genital Herpes

PARAMETER	Grade 0 NORMAL	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	Grade 4 POTENTIALLY LIFE- THREATENING
Genital herpes	No lesions	Characteristic ulcerative or vesicular lesions confirmed by culture, PCR, Tzanck prep or other diagnostic test of lesion or previous type-specific serology, covering < 25% of vulva, vagina, or cervix	Same criteria as mild but covering 25-50% of vulvar, vaginal, or cervical surface	Same criteria as mild but covering > 50% of vulvar, vaginal, or cervical surface	Symptoms of significant systemic involvement, e.g., encephalitis, hepatitis

Genital warts: Report all outbreaks of genital warts as AEs, regardless of whether infection with HPV was known to be pre-existing before enrollment. Report the AE using the term “condyloma” and include the anatomical location of the warts (e.g., cervical, vaginal, vulvar, perianal). Grade according to the “Condyloma” row of the FGGT.

Syphilis: Per the FGGT, a Grade 2 Syphilis AE is defined as a positive treponemal test together with a positive non-treponemal test and no previous treatment OR a four- fold rise in titer on the non-treponemal test after previous treatment regardless of symptoms or non-oral lesions positive by darkfield exam for treponemes. Report all syphilis AEs as “syphilis infection” (no anatomical location is required when reporting syphilis infections).

Trichomoniasis: Report only Grade 2 infections per FGGT, using the term “vaginal trichomoniasis.” Trichomoniasis may be diagnosed by positive wet mount, culture, PCR, rapid Trichomoniasis or other licensed test (excluding pap smear), showing *T. vaginalis*, regardless of symptoms.

In the absence of a laboratory-confirmed STI or RTI diagnosis, use the term “vulvovaginitis” when two or more of the genital/vaginal signs or symptoms listed below are present. Comment on the individual signs/symptoms in the “Comments” field of the AE Log CRF.

- pain
- itching
- erythema
- edema
- rash
- tenderness
- discharge

Similarly, use the term “cervicitis” when 2 or more of the genital/vaginal signs or symptoms listed below are present in the absence of a laboratory-confirmed STI/RTI. Comment on the individual signs/symptoms in the “Comments” field of the AE Log CRF.

- dyspareunia
- erythema
- edema
- tenderness
- discharge

Urinary Tract Infection: Report “urinary tract infection” for all instances of lower urinary tract infections diagnosed by symptoms. Do not report “bacterial urinary tract infection” or “cystitis”. The term “urinary tract infection” is sufficient.

Sexually Transmitted Infection treated outside the clinic: At times a participant may report that she was treated for a sexually transmitted infection by an outside clinic and she is unclear about the precise infection. If further information cannot be obtained from the treating facility, report “sexually transmitted infection” and note in the comments that she was treated at an outside facility and no further information is available.

8.3.2 Reporting Abdominal Pain as an AE

When reporting abdominal pain as an AE, pain that is gastrointestinal in nature must be differentiated from pain that is genitourinary or reproductive in nature.

If abdominal pain is assessed as gastrointestinal in nature and no other overarching or unifying diagnosis is available, the term “abdominal pain” should be used to describe the AE within the AE Log CRF. Do not report “upper abdominal pain” or “lower abdominal pain”. The term “abdominal pain” is sufficient.

If the pain is assessed as genitourinary and a specific anatomic location is known, the term reported within the AE Log CRF should be described as such (i.e., “bladder pain”).

If the pain is assessed as reproductive in nature and a specific anatomic location is known, the term reported within the AE Log CRF should be described as such (e.g., “adnexal pain”, “uterine pain”). Pain associated with menstruation is reproductive in nature and the term reported within the AE Log CRF should be described using the term “dysmenorrhea”.

If the pain cannot be localized to a specific organ, it should be described within the AE CRF using terms that identify a reproductive or genitourinary anatomical location (e.g., “pelvic pain”, “urinary tract pain”).

8.3.3 Reporting Weight Loss as an AE

Follow these guidelines for reporting weight loss as an AE:

- Weight loss is reportable as an AE only if it is considered unintentional and potentially deleterious to the participant’s health by either the participant or the site clinician.
- Weight loss, whether intentional or unintentional, is not considered reportable as an AE if it is not considered deleterious to the participant’s health by either the clinician or the participant (e.g., related to increased physical activity: new job with heavy physical labor, increased walking in an urban environment, participant’s body mass index (BMI) remains normal or above normal, etc.)
- For any weight loss reported as an AE, to facilitate safety monitoring:
 - Use the term ‘weight loss abnormal,’ and
 - Add to comments section of the AE Log CRF that the AE is considered deleterious to the participant’s health.

Use the following parameters from the DAIDS Grading Table for grading weight loss.

**Table 8-3: DAIDS Toxicity Table for Weight Loss
(excludes postpartum weight loss)**

Grade 1	Grade 2	Grade 3	Grade 4
MILD	MODERATE	SEVERE	POTENTIALLY LIFE-THREATENING
N/A	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Weight loss is reportable as an AE only if the weight loss is considered potentially deleterious to the participant’s health by either the participant or the site clinician. Use the AE term ‘weight loss abnormal’			

8.3.4 Reporting Terminology Considerations for Additional Adverse Events

When the below AEs are identified, please use the following guidance on the reporting terminology:

Respiratory Tract Infection: Please use the terms “upper respiratory tract infection” or “lower respiratory tract infection” only. Do *not* use “upper respiratory-bacterial” or “upper respiratory-viral”. Note: If a participant is suspected or confirmed to have COVID-19, “COVID-19” should be reported as the AE term. If deemed not to be related to COVID-19, this should be indicated this in the comments along with the rationale (for example, the participant has a negative COVID-19 test result).

Viral Illness: Please use the terms “viral illness” rather than “flu-like illness” to refer to a generalized illness presumed to be due to a virus. Note that this does not apply to acute seroconversion illness, which should be reported as “seroconversion illness” – see section 8.3.9 below on “Reporting HIV Infection Illness”. Note: If a participant is suspected or confirmed to have COVID-19, “COVID-19” should be reported as the AE term. If deemed not to be related to COVID-19, this should be indicated in the comments along with the rationale (for example, the participant has a negative COVID-19 test result).

Anemia: If treatment, including diet recommendations, are offered, use the term “anemia”. If no instruction is provided to the participant, report “decreased hemoglobin”. It is anticipated that most participants will be informed of low hemoglobin and encouraged to increase iron-rich foods. Therefore, “anemia” will be more commonly reported.

Diarrhea: Please use the terms “diarrhea” rather than “diarrhea infectious etiology,” “infectious diarrhea” or “diarrhea related to bacterial infection.” It is not necessary to specify the cause of the diarrhea in the AE term.

Gastroenteritis: Please use the term “gastroenteritis” for clinical conditions of nausea and diarrhea. No need to specify “viral” or “bacterial” gastroenteritis.

8.3.5 Reporting Considerations for Pregnant Participants

For pregnant participants, AEs that are related to the pregnancy, worsened by the pregnancy, or require changes in clinical management of the pregnancy are all considered reproductive system AEs and should be reported, as clinically indicated, using the appropriate pregnancy related terms or indicating the AE is during pregnancy by adding ‘during pregnancy’, ‘in pregnancy’ or ‘antepartum’ when describing the AE within the AE Log CRF. If the AE is not related to the participant’s pregnancy, do not relate the event to the pregnancy when describing the AE or in the comments section. Please refer to the listed example for reporting terms when documenting the AE (after clinical judgment):

Anemia in Pregnancy

- anemia during pregnancy

Nausea and/or vomiting related to pregnancy

- nausea during pregnancy
- vomiting during pregnancy
- hyperemesis gravidarum

However, nausea and vomiting due to gastroenteritis during pregnancy are considered gastrointestinal AEs and should be reported as either nausea or vomiting, or gastroenteritis (if that is the diagnosis).

New occurrences of hypertension or diabetes associated with pregnancy

- gestational diabetes
- gestational hypertension

Fetal losses (of any kind) are not reportable AEs. However, **maternal complications or side effects associated with fetal loss** that would otherwise be reported as an AE are considered reproductive system AEs and should be reported. For example:

- vaginal bleeding associated with miscarriage
- pelvic cramping associated with spontaneous abortion

Bleeding and pelvic pain or contractions are common complaints in pregnancy and may accompany a fetal loss. Depending on the circumstances, pain and bleeding may be reported as AEs. In general, bleeding associated with delivery and the postpartum state (the 6 weeks following delivery) is not considered an AE, provided the bleeding does not exceed the expected amount. Likewise, contractions at term are considered normal and should not be reported as an AE. Pain, with the exception of term contractions, should be captured as an AE. Bleeding prior to the onset of labor should also be captured as an AE.

See Figure 8-1 for more guidance on reporting AEs during pregnancy. Events classified as “NOT AE” in the table below are not recorded on either AE Log CRFs but should be documented on alternative source documents (e.g. in the chart notes).

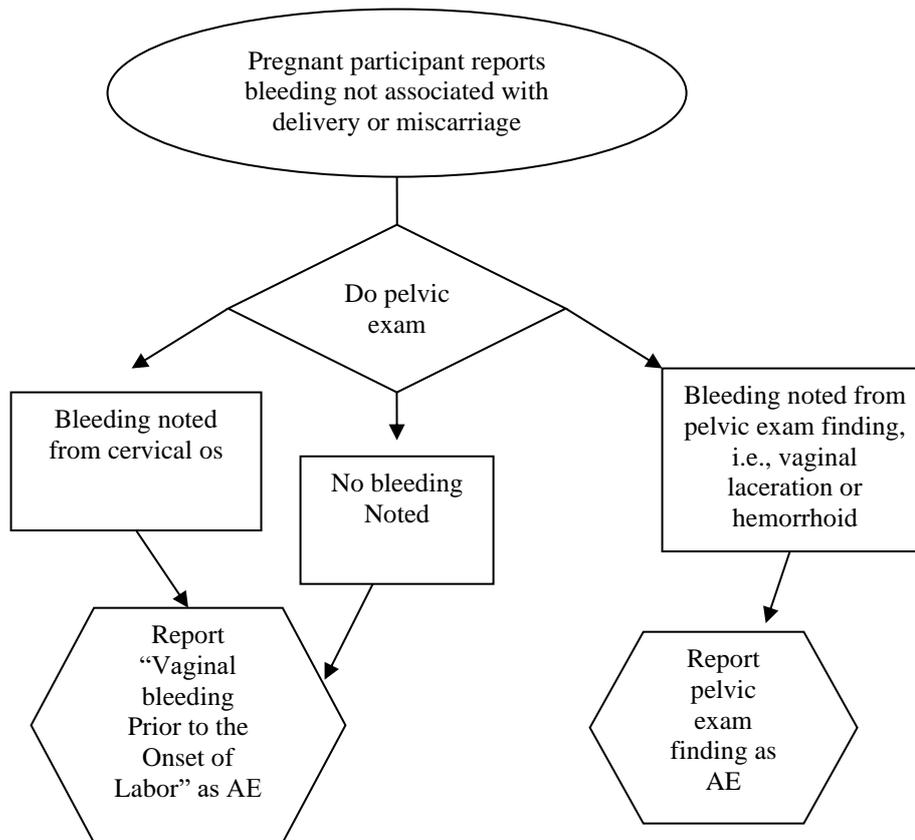
Figure 8-1 Adverse Event Reporting During Pregnancy by Gestational Age

		Figure 8-1 Adverse Event Reporting During Pregnancy by Gestational Age		
		0-20 weeks	20-37 weeks	Term ≥37 weeks
Not Associated with Pregnancy Loss or Delivery	Painful Cramping/ Uterine Contractions	Pelvic Pain in Pregnancy (Grade per Pain row of FGGT)	Preterm Contractions (Grade per Preterm Contraction row in FGGT)	NOT AE

	Vaginal Bleeding	Bleeding Prior to Onset of Labor (Grade per First Trimester Bleeding Row in FGGT)	Bleeding Prior to Onset of Labor (Grade per Second/Third Trimester Bleeding Row in FGGT)	Bleeding Prior to Onset of Labor (Grade per Second/Third Trimester Bleeding Row in FGGT)
	Fetal Loss (Fetus in Utero)	NOT AE	NOT AE	NOT AE
Associated with Pregnancy Loss or Delivery	Painful Cramping/ Uterine Contractions	Pelvic Pain in Pregnancy (grade per Pain row in FGGT)	Preterm Contractions (grade per Preterm Contraction row in FGGT)	NOT AE
	Vaginal Bleeding	Vaginal Bleeding Associated with Miscarriage (Grade per First Trimester Bleeding Row in FGGT)	NOT AE unless EBL is greater than WNL at any point in delivery If EBL >WNL, record Post Partum Hemorrhage and grade per Post Partum Hemorrhage row in FGGT	NOT AE unless EBL is greater than WNL at any point in delivery If EBL >WNL, record Post Partum Hemorrhage and grade per Post Partum Hemorrhage row in FGGT
	Fetal Loss	NOT AE	NOT AE	NOT AE
		Miscarriage	Delivery	
EBL= estimated blood loss; WNL=within normal limits				

If a pregnant participant reports bleeding (not associated with delivery) study staff should investigate the source of the bleeding. If a pelvic exam finding such as a vaginal laceration, a cervical polyp, or hemorrhoids, is identified as the source of the bleeding, the finding should be recorded as the AE and an explanation provided in the comments section of the AE Log CRF that the finding was associated with bleeding. The following algorithm is intended to clarify this point:

Figure 8-2 Overview of Assessment and Reporting Procedures for Genital Bleeding in a Pregnant Participant; Beginning with Participant Report of Blood/Bleeding



8.3.6 Reporting Pelvic Examination Findings as AEs

In general, and unless otherwise specified in this manual, report pelvic exam findings using terminology corresponding to the DAIDS FGGT and provided within the 'Abnormal Findings' section of the Pelvic Exam CRF.

All AEs should be documented per the term marked on the Pelvic Exam form. Always include the specific anatomical location of pelvic exam findings (e.g., cervical, vaginal, vulvar) in the AE term.

8.3.7 Reporting Laboratory Abnormalities as AEs

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., reduced CrCl). The severity grade of the result should not be reported as part of the AE term.

Laboratory values that fall outside of a site's normal range but are below severity Grade 1 are not considered AEs. These out of normal range, but below Grade 1 values are not documented as baseline medical history conditions or adverse events on the Baseline Medical History Log or AE Log unless requested by the IoR or designee.

When assigning severity grades, note that some sites may have normal reference ranges that overlap with the severity grade ranges. Thus, it is possible for a participant to have a result that falls within the site's normal range but is still gradable per the DAIDS Grading Table. Assign the severity grade based on the DAIDS Grading Table severity grade ranges, regardless of whether the lab result falls within the site's normal reference range.

The IoR or designee should carefully review all laboratory abnormalities relevant to the participant's health 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 the source documentation. Results of protocol-specified local laboratory results will also be submitted via the Laboratory Results CRF. Sites should document other results if any, in visit chart notes, or in other designated site-specific documents. Through the participant's study involvement, lab abnormalities that meet the criteria for expedited reporting to DAIDS will be reported separately on the AE Log CRF and reported to DAIDS via the DAERS Reporting System.

8.3.8 AEs Involving Hospitalizations/ Surgical Procedures

Procedures should not be captured as AEs; rather the underlying condition which leads to a procedure may be considered an adverse event. A "cesarean section" would not be considered an AE; however, the indication for the cesarean section may, depending on whether it reflects a maternal or fetal condition. For example, fetal conditions (i.e., breech, fetal distress, meconium staining, non-reassuring fetal heart tones), which result in a cesarean section, should not be captured as adverse events. Even though a cesarean section for a fetal condition may prolong the mother's hospitalization, because the underlying problem is not maternal, it should not be captured as an adverse event. Conditions falling in this category should be documented on alternative source documents (e.g., in the chart notes).

Maternal conditions (i.e., hemorrhage, preeclampsia, etc.) which result in a cesarean section should be captured as AE. If the condition is considered immediately life-threatening or the condition and its resultant surgery result in a prolonged hospitalization, the adverse event should be considered a serious adverse event.

If the cesarean was performed for failure to progress in labor (including conditions such as cervical dystocia, contracted maternal pelvis, large fetus, poor contraction pattern) the event should be captured as an adverse event, but the preferred term should be "cephalo-pelvic disproportion." This AE will be serious if the cesarean results in a prolonged hospitalization.

This guidance holds for both scheduled and unscheduled cesarean sections or induction of labor. Whether these events result in a reported adverse event or not completely depends on the indication.

Maternal complications following cesarean section (hemorrhage, infection, scar disruption, etc.) will be considered AEs regardless of the indication for the surgery. If the complication results in re-hospitalization or a prolonged hospital stay, it will be considered serious.

8.3.9 Reporting HIV Infection Illness

HIV acquisition (seroconversion) is one of the study endpoints, thus is not considered an AE for data collection or reporting purposes. "HIV infection" should not be reported as an AE or written anywhere on an AE Log CRF. Final determination of HIV status will instead be captured on the HIV Confirmatory Results CRF.

However, primary HIV infection is often symptomatic, and a constellation of symptoms may best be summarized as primary HIV infection illness. In this case, as in other cases when symptoms are best expressed as a unifying diagnosis, it is important to use that summary diagnosis. Thus, if a participant seroconverts and develops one or more signs or symptoms of acute HIV- infection, it is appropriate to report these sign(s)/symptom(s) as a single AE using ONLY the term "seroconversion illness" for the AE Term on the AE Log CRF. Use the comments section of the AE Log CRF to describe each HIV-related sign/symptom (e.g., fatigue, pharyngitis) and to note the alternative etiology as due to "acute HIV". To avoid generating a clinical query, please ensure that the term "acute" is included when describing the required alternative etiology in the Comments section.

Complete the other items on the AE Log CRF per the general form instructions. The onset date should be completed using the date on which the participant first reported experiencing the first sign/symptom of acute HIV-infection. If there is more than one HIV-related sign/symptom, record the highest severity grade. A seroconversion illness AE is considered 'resolved' when all of the associated signs/symptoms have resolved or returned to baseline per participant report, and medications for the symptoms are no longer indicated. Mark any medications indicated and taken for the associated symptoms, if applicable.

If one or more signs/symptoms, reported on separate AE Log entries, are later attributed to acute HIV-infection, update the AE term for the earliest reported sign/symptom AE to the "seroconversion illness" diagnosis and list any other signs or symptoms in the comments section of this AE Log CRF. Inactivate the applicable AE Log line within Medidata Rave.

8.3.10 Reporting Sexual Assault

Any physical and/or psychological sequelae that result from a sexual assault reported during the study and that meet AE reporting criteria should be reported on an AE Log CRF(s). Each physical and/or psychological sequela should be reported as its own AE with the description of the physical and/or psychological sequela as the AE text (i.e., do not mention sexual assault event) and with sexual assault survivor (and additional details, if applicable), referenced in the Comments section of the AE log form. In this instance, do not complete a separate AE log form for 'sexual assault survivor' as the AE term. In the event that a participant reports a sexual assault which did not result in physical and/or psychological sequelae, sites should report the event as a "Sexual Assault Survivor" as the AE text. Sites should specify "survivor" when reporting a sexual assault event (e.g. "sexual assault survivor"), to clarify survivor of the assault and not perpetrator of the assault. Note that site staff should accept participant report of sexual assault rather than probing regarding this issue for the purposes of AE reporting. Sites should consult the PSRT if there are any questions about classification or documentation of a sexual assault event.

Women who disclose any form of violence by an intimate partner (or other individual) or sexual assault by any perpetrator should be offered immediate support, care, and referrals according to site-specific SOPs and as advised by site social harms response mechanisms. The World Health Organization (WHO) publication, *Responding to intimate partner violence and sexual violence against women* (available at <https://www.who.int/reproductivehealth/publications/violence/9789241548595/en/>) is a useful resource that may help inform site-specific policies for responding to reports of sexual assault or other violence. Generally, response to reports of sexual assault should include first line support—listening and offering comfort, help, and information/referrals to connect her to services and social support—as well as offering the participant an opportunity to provide a complete history of events, and receive relevant physical evaluations, and treatment and/or referral for any injuries. Emergency contraceptive and STI prophylaxis/treatment should be offered. Depending on the time between the assault and presentation to the clinic (i.e. if within 72 hours), the use of PEP should also be considered. If PEP is used, refer to the MTN-034 Protocol for instructions on product hold. Plans for continued follow-up and care should be outlined to check in on the participant's well-being and uptake of referrals, as appropriate.

Sexual Assault, or SA, is any type of sexual contact or behavior that occurs without the explicit consent of the recipient. Sexual assault can be perpetrated by someone who is a stranger to the survivor, and it can also occur within intimate partnerships, or friendships or familial relationships. Sexual assault includes a range of behavior from unwanted touching and indecent exposure to forced intercourse. Examples of "force" used to commit sexual assault include but are not limited to, threats or intimidation, physical violence, abuse of power – including power related to an age differential in the case of minors – or using drugs or alcohol to incapacitate someone.

8.4 Adverse Event Severity Grading

The term severity is used to describe the intensity of an AE. The severity of all AEs identified in MTN-034 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

Severity is not the same as seriousness, which is based on the outcome or action associated with an event, as described in Section 8.1.2.

The severity of all AEs identified in MTN-034 will be graded using the:

- *DAIDS Table for Grading Adult and Pediatric Adverse Events* (hereafter referred to as the Toxicity Table), Version 2.1 dated July 2017.
- *Female Genital Grading Table for Use in Microbicide Studies* (FGGT), dated November 2007 (with the exception of asymptomatic candidiasis and asymptomatic BV, which will not be considered adverse events for MTN-034).

AEs listed in both the FGGT and the Toxicity Table should be graded according to the FGGT. AEs not listed in the FGGT should be graded according to the Toxicity Table. AEs not listed in the FGGT or the Toxicity Table should be graded according to the “estimating severity grade” row of the Toxicity Table

Table 8-4: DAIDS Estimated Severity Grades

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event NOT identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Both the FGGT and the 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-034 are as follows:

- Genital petechia/e and genital ecchymosis should be considered Grade 1 as neither requires treatment.
- If the severity of an AE falls into more than one grading category on the FGGT or 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 FGGT or 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 CRF 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).
- Urinary tract infection (UTI), which is expected to be diagnosed on the basis of symptoms should be graded according to the estimating severity row of the Toxicity Table. If culture and/or microscopy are done per site standard of care, Grade 1 and Grade 2 UTI can be graded per the UTI row of the FGGT.

- When grading adverse events per the “estimating severity grade” row (i.e. for AEs not listed specifically in the FGGT or DAIDS Toxicity table), ‘intervention’ should be defined as outlined in the “Glossary and Acronyms” section of the Toxicity Table 2.1: “medical, surgical or other procedures provided by a healthcare professional for the treatment of an adverse event.” If a participant reports treatment, the clinician must obtain further information as to whether it was self-initiated (Grade 1) vs. provider-recommended (Grade 2). Importantly, clinicians should note that grading is dependent on participant-reported impact of symptoms on her life, and whether intervention (defined as above) is *indicated*, regardless of whether the treatment was actually provided or taken by the participant. It is at the discretion of clinician to determine whether intervention was indicated for the reported AE. In the event that a (provider-recommended) intervention was indicated but not taken, the treatment should be marked as “other” rather than ‘medications’ and additional details should be included in the line provided. The AE severity grade, per the toxicity table, would be assigned Grade 2.
- Abnormal Pap smear findings should be initially reported and graded based on the “Pap” row of the FGGT (see below). AGC and AGC-favor neoplastic are not specifically mentioned in the “Pap” row, but should be assigned severity grades 1 and 2, respectively. If abnormal cytology uncovered at screening is followed by a biopsy during follow-up, sites should report an AE for the histologic diagnosis IF the biopsy result is a higher grade than the baseline pap smear. For example, consider a participant who has an LGSIL pap result (grade 1) at screening and undergoes a colposcopy with biopsy at month 6. If the biopsy result is grade 1, no AE need be reported; **HOWEVER**, if the biopsy result is grade 2 or higher, an AE should be submitted using the histologic diagnosis (CIN II, for example).
- For confirmed or suspected COVID-19 infections, grade based on the “estimating severity grade” row of the toxicity table. It is not necessary to include details on whether suspected or confirmed in the comments.

Table 8-5 FGGT for Pap

PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Intraepithelial Neoplasia by biopsy (VIN, CIN, VAIN)	None	Intraepithelial Neoplasia 1 (IN1)	Intraepithelial Neoplasia 2 (IN2)	Carcinoma in situ (CIS)	Invasive carcinoma
Pap (use this category <u>only</u> if treatment performed without diagnostic testing, otherwise use biopsy category above)	nl PAP	ASCUS or LSIL	HSIL	Carcinoma in situ or Carcinoma	NA

8.5 Adverse Event Relationship to Study Product

One of the following relationship categories must be assigned to each reportable 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.

For both 'related' and 'not related' assignments, a rationale (such as alternative etiology or explanation) is required to be provided within the Comments Section at the bottom of each AE CRF. Recording "no other cause identified" is not adequate. Although an AE's relationship status defers to clinician discretion, some clinical explanation is helpful to understand the nature of the adverse event and to present a more complete safety profile of the study product. To support assessment, the site IoR/designee may note any evaluations that were performed, alternative etiologies if present, and continuation or cessation of symptoms in relation to product use, including the onset date of the AE and which study product the participant was exposed to at the time of the AE.

In the event the site IoR/designee notes the AE is a "known side effect" as the rationale, the side effect must be listed in the current version of the Truvada package insert and/or the dapivirine ring investigator's brochure (IB). Of note, the section of the dapivirine ring IB entitled "Adverse Drug Reactions" (section 6.11.2) is likely the most useful section to reference in decisions of relatedness. Adverse Drug Reactions (ADRs) were identified based on pooled safety analyses across multiple trials. Site clinicians should use their clinical judgement per usual, but if the rationale for related indicates "known side effect," the PSRT may ask for more information, especially if that AE is not included in this list.

The relationship status of an AE may be changed if new information becomes available at a later date, after the AE is first reported, that would change the assessment. If the relationship status is changed at a later date update the "Relationship to Study Product" item. Then, review the entire form for completeness and add additional rationale in the Comments.

Example: Participant-reported "vaginal discharge" is reported as an AE and deemed 'related' in the "Relationship to Study Product" item with the rationale that the discharge presented after the participant started using the ring. The site evaluation was unremarkable; yet the participant continued to report the discharge. The AE remained open during the participant's vaginal ring use. When the participant changed study product administration to the oral Truvada, she noted that the discharge continued. At this point the site might conclude that the discharge is not related to the ring as it continued despite the ring being removed. The "Relationship to Study Product" item of the AE Log entry should be updated from "related" to "not related". Additional notes should be added the Comments Section to clarify the rationale.

8.6 Adverse Event Outcomes and Follow-Up Information: During the Study

All AEs identified in MTN-034 must be followed clinically until they resolve (return to baseline) or stabilize (persist at a certain severity grade above baseline for three months).

- At each follow-up visit, an authorized study clinician should review all previously identified ongoing AEs (all AE Log CRF entries with an "ongoing" status in the 'status/outcome' field) and evaluate and document their current status.
- For all AEs, outcomes must be reported within the AE Log CRF, or chart notes or other site-specific tracking log
- In many cases, the final outcome of a reportable AE will not be available when the AE Log CRF is first completed. In such cases, the AE CRF should be updated when the final outcome becomes available.
- Prior to initiating a new product (in the 2nd or 3rd product use periods, or when switching products in the 3rd product use period), study clinicians should review any AE that has resulted in a study product hold. Product holds should be managed per Section 9 of the protocol, and if requirements are not met for product use resumption, the site must consult the PSRT for guidance

Clinical management and follow-up of AEs detailed in Section 9 of the MTN-034 protocol should proceed per those specifications. If an AE is not addressed in Section 9 of the protocol, follow-up evaluations should be performed at an appropriate schedule as determined by the clinician until resolution or stabilization (the same grade for three months) has been documented. In general, evaluations of an AE may be performed at any time if required to properly monitor and/or manage participant safety, at the discretion of the IoR or designee. It is acceptable for AE follow-up/evaluation to be conducted over the phone, as clinically appropriate.

If an AE increases in severity per the DAIDS toxicity table after it has been reported initially within the AE Log, it must be reported as a new AE within a new Adverse Event Log (AE) entry at the increased severity per the DAIDS toxicity table. In this case, the outcome of the first AE will be documented as “Recovered/resolved” on the initial AE Log CRF. The outcome date of the first AE and the onset date of the new (worsened) AE will both be the date upon which the severity per the DAIDS toxicity table increased (see instructions for these items within the CRF Completion Guidelines for additional guidance).

Resolution dates for AEs of any AE requiring treatment should be based on the date when all associated symptoms resolve or when treatment is completed (whichever occurs later). For asymptomatic STIs, the resolution date is the date the participant completes treatment.

8.7 Adverse Event Outcomes and Follow-Up Information: After Study Termination

A subset of AEs must be followed after a participant's termination visit.

- SAEs/EAEs that are ongoing at the termination visit
- AEs that are found to have increased in severity at the termination visit. **NOTE:** this includes AEs that are newly occurring/identified at the termination visit.
- Any newly reported Grade 3 AEs

For any AEs that fall under the above listed categories, a clinically appropriate follow-up plan must be established. At a minimum, the AE must be re-assessed by study staff 30 days after the termination visit; additional evaluations also may take place at the discretion of the IoR/designee.

For any AE that requires re-assessment per the above guidelines, if not resolved or stabilized at the time of re-assessment, additional assessments should occur at the following frequency:

- If the study is ongoing, continue to reassess at least once per month while the study is ongoing until resolution/stabilization.
- If the AE has not resolved by study end (i.e., once all participants are exited), these AEs should be re-assessed at least once within 30-60 days after the study end date. The site is to send an informational query regarding the case to the PSRT at the time of reassessment. The MTN-034 PSRT also may advise on whether any additional follow-up is indicated on a case by case basis.

For AEs that are continuing at the termination visit but do not meet the criteria above (i.e., not an SAE/EAE, not an AE that has increased in severity at the termination visit and not a newly diagnosed Grade 3 AE), it is left to the discretion of the IoR or designee as to whether the AE needs to be followed. Should the IoR or designee determine the AE needs follow-up, the plan and frequency for clinical management will be as determined by the IoR/designee. The PSRT can be consulted as needed.

Documentation: For AEs that are re-assessed after a participant's termination visit, information on the status of the AE at the time of re-assessment will be recorded in chart notes, and may be communicated to the PSRT, if applicable; however, no updates should be made to any AE Log CRF. All AEs that are ongoing at the time of final clinic visit should have a status/outcome marked as “continuing at the end of study participation.” Regardless of whether a participant has an ongoing AE requiring reassessment per protocol or clinical discretion, the termination date should be documented as the date of her final visit. However, if a test result is still pending after the final clinic visit, it is up to the site's discretion as to when a participant is considered no longer part of the study (i.e. termination date). For example, if lab results from samples collected during the participants final visit are pending, it is up to the site's discretion to determine if the participant's termination date is the date of her final visit or the date that her test results were received.

8.8 Reporting Recurrent Adverse Events

If an AE previously reported within an AE Log CRF resolves and then recurs at a later date, the second occurrence may be reported as a new AE on a new AE Log CRF as applicable, or previous occurrences of this AE may be reopened and documented as ongoing, depending on participant well-being and site preference.

Regular occurrences of the same adverse event that are expected in follow-up are not typically considered separate adverse events. For example, a participant is in a car accident and develops a Grade 3 headache not related to study product. The first event is captured as an AE with an onset and outcome date. At the next visit, the participant notes that Grade 3 headaches are now a recurring issue after the car accident. Rather than open separate AEs for each headache, the site can update the first AE for headache and note in the comments section that this is a recurring event. The status should be changed to ongoing.

8.9 Social Harms (Social Impacts)

In addition to medical AEs, participants in MTN-034 may experience social harms — non-medical adverse consequences — as a result of their participation in the study, including as a result of their use of the tablets or ring. 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.

MTN-034 participants will be asked if “At any time during the past 3 months, have you experienced a negative change, event, or experience in your life related to your study participation?” on the Social Benefits and Impacts CRF. In addition to responding to this standardized question each quarter, participants also may spontaneously report study-related issues and problems to study staff at any study visit. If a social harm is reported at any time, an entry on the Social Impact Log CRF should be completed. Ongoing social harms should be followed up on until they have resolved, it has been determined that they will not be resolved, or the participant’s study participation has ended.

Prior to study initiation, study staff teams at each site should develop plans to review and recommend action on reported or identified social harms that occur during the study. Requirements for plans to respond to social harms, including the creation of a social harms committee – or modification of existing mechanism where applicable – are further detailed in the MTN-034 Social Harms Planning Rationale, provided to clinical research sites for use with committee members.

In addition to specific social harms planning, site teams should discuss as a group, and with community representatives, what issues and problems are most likely to be encountered by participants at their site, and should agree upon how these issues and problems should be handled logistically. Roles and responsibilities should be defined for all staff members, such that each staff member is aware of what actions he/she can appropriately take, and what actions should be referred to other members of the team. During study implementation, staff teams at each site should continue to discuss actual participant experiences, successful and unsuccessful response strategies, and other lessons learned among themselves and with community representatives. Based on these discussions and lessons learned, procedures for responding to issues and problems should be reassessed and updated as needed throughout the study.

While sites should utilize strategies recommended via planned social harms response mechanisms, the following are suggested general 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.

Ask the participant for her thoughts on what can/should be done to address the problem, including what she 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 her 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 stabilization, up through study termination.

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

If the reported social harm is associated with an AE (per the definition in Section 8.3.1) report the AE within an AE Log CRF. If the social harm is associated with an AE that meets criteria for expedited reporting to the DAIDS RSC, report it as an AE as described in Section 8.4. Also report the issue or problem to all IRBs/ECs responsible for oversight of MTN-034, if required per IRB/EC guidelines.

Consult the MTN-034 PSRT for further input and guidance as needed.

8.9.1 Reports of Intimate Partner Violence (IPV)

According to the World Health Organization, Intimate Partner Violence, or IPV, refers to any behavior within an intimate relationship that causes physical, psychological or sexual harm to those in that relationship. It includes acts of physical aggression (slapping, hitting, kicking, or beating, for example), psychological abuse (intimidation, humiliation, and threats, for example), forced sexual intercourse or any other controlling behavior (including isolating a person from family or friends, monitoring their movements or restricting access to information or assistance, for example). Intimate partner violence also includes violence committed by former partners and individuals in dating relationships.

In addition to social harms which are, by definition, related to study participation, participants will be asked about any experiences of IPV via ACASI. Intimate partner violence may also be reported directly to site staff and if it is related to study participation, it will be reported on the Social Harms Log as indicated above. IPV not related to study participation should be recorded in source documentation.

Irrespective of whether IPV is related to study participation, participants should be provided the appropriate support, counseling, and referrals per site SOPs and social harm response plans to help manage any reported IPV, and steps should be taken as needed to improve participant safety. See also SSP section 8.3.10 above on reporting sexual assault and also the WHO guidance document, [Responding to intimate partner violence and sexual violence against women](#), which can be used as a resource for developing site-specific policies for responding to reports of IPV.

In the event IPV is reported by a participant and is not directly related to study participation, sites may also refer participants to the social harms committee for appropriate support and further guidance.

If the reported IPV is associated with an AE (per the definition in Section 8.1) report the AE within an AE Log CRF. If the IPV is associated with an AE that meets criteria for expedited reporting to the DAIDS RSC, report it as an EAE as described in Section 8.4.

8.10 MTN-034 Safety Monitoring, Review, and Oversight

Refer to Section 8 of the MTN-034 protocol for a complete description of the participant safety monitoring procedures in place for MTN-034. Also refer to Section 14 of this manual for a description of the reports prepared by the MTN SDMC in support of MTN-034 safety monitoring procedures.

Participant safety is of paramount importance in MTN-034. Primary safety monitoring and safeguarding of individual study participants is the responsibility of study staff, under the direction of the IoR. Any study staff member who is regularly involved in the source documentation of safety data for this trial (including documentation of participant symptoms, physical exam findings, pelvic exam findings etc.) should be listed as a sub-investigator on the FDA Form 1572. If allowable per country standards and guidelines, nurses may perform these tasks, but study doctors must be able to demonstrate that appropriate oversight was conducted. Decisions regarding severity determination for an AE, relationship to study product, and study product management must be done by a study doctor. Documentation of this clinical oversight for AEs must be present in the participant file, particularly if nursing staff is responsible for completing the AE Log CRF.

The IoR and designated study staff are also responsible for completing CRFs within the clinical database and EAE reports to the DAIDS RSC, such that relevant safety data are available in a timely manner for other study-specific safety monitoring procedures, as follows:

- Clinical staff at the MTN SDMC will review clinic and laboratory data received at the SDMC and apply clinical data quality control notes (queries) to data requiring confirmation, clarification, or further follow-up by site staff. These queries will be placed in the clinical database for site staff to review and resolve on an ongoing basis throughout the period of study implementation. In addition, Protocol Safety Physicians may contact site staff directly, if needed, for additional clarification of safety data.
- The DAIDS RSC, DAIDS RAB Safety Specialist, and DAIDS PSP Medical Officers will review all EAE Forms received for MTN-034 and follow up on these reports with site staff, the MTN-034 Protocol Team, and drug regulatory authorities when indicated.
- The MTN-034 PSRT will routinely review safety data reports prepared for MTN-034 by the MTN SDMC. As described further in Section Appendix 8-1, the PSRT will meet via conference call to discuss the accumulating study safety data and any potential safety concerns.

The MTN Study Monitoring Committee (SMC) also will periodically review MTN-034 study progress, including rates of participant accrual, participant retention, protocol and intervention adherence, data quality, laboratory quality and completion of primary and secondary endpoint assessments. Since MTN-034 is not subject to DSMB review, the SMC also will review participant safety data. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. The SMC may consider recommending termination of this study if recruitment is lower than targeted, or if study data quality is poor. If at any time, a decision is made to discontinue participants, DAIDS after consultation with the protocol team, will inform the US Food and Drug Administration (FDA). The Site PIs will notify the responsible IRBs/ECs expeditiously. 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.

8.11 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 LOC, and may include:

- Updated Investigators Brochures and Package Inserts
- 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.

Appendix 8-1 MTN-034 Protocol Safety Review Team Plan

Roles and Responsibilities of the PSRT

Per the MTN-034 protocol, the roles and responsibilities of the MTN-034 Protocol Safety Review Team (PSRT) are to:

1. Conduct regular reviews of standardized study safety data reports. Once the SDMC begins receiving follow-up safety data, the PSRT will convene via regularly scheduled monthly conference calls. 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 Protocol Team, or MTN Study Monitoring Committee (SMC) as appropriate.
2. Respond to queries regarding product use management. The protocol specifies a number of situations in which study product use should be temporarily held, permanently discontinued and/or resumed; designated site staff will implement these holds, discontinuations, and/or resummptions in the absence of consultation with the PSRT. In other situations, however, product use management must be undertaken in consultation with the PSRT.
3. Respond to queries regarding study eligibility and adverse event (AE) assessment, reporting, and management.
4. Respond to notifications of participant withdrawal from the study.

PSRT Composition

The following individuals comprise the MTN-034 PSRT:

- REACH Protocol Chairs
- MTN Safety Physicians
- DAIDS Medical Officer
- IPM Representative
- Gilead Representative

Ideally all PSRT members will take part in routine PSRT conference calls. At a minimum, a Protocol Chair, the DAIDS Medical Officer (or designee, if the DAIDS Medical Officer is not available), and a MTN Safety Physician must take part in all calls. If these three members are not present, the call may be deferred until the next scheduled call time unless a PSRT member requests a more immediate call. MTN LOC Clinical Research Managers, SDMC Clinical Data Managers, and SDMC Statistical Research Associates may attend PSRT calls as observers and/or discussants.

The SDMC Clinical Safety Associate (CSA) serves as the primary liaison between the PSRT and the SDMC. The CSA will participate in the PSRT calls, and, based on PSRT discussion and request, will place clinical queries in the study database and communicate with sites as needed. The CSA will also bring to the calls for discussion any data trends or issues observed in the context of routine study clinical data reviews.

PSRT Communications

A group email address (mtn034psrt@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-034 PSRT Query Form, which is available on the MTN-034 web page (<http://www.mtnstopshiv.org/node/6826>). Site staff will email completed query forms to the Protocol Safety Physicians (mtn034safetymd@mtnstopshiv.org) who will work with the PSRT to prepare a consensus response to the query, and then email the final response to the site. This process is expected to occur within three business days. When necessary, site requests for responses within one business day can usually be accommodated provided the need for an expedient response is indicated in the text of the email. All members of the PSRT are encouraged to review the information provided by the site in the query form and to contribute to the response; however, final determination rests with the Protocol Chair(s).