Section 11. Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-003. Please also refer to Section 8 of the MTN-003 protocol and the following resources relevant to AE assessment and reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events
- Female Genital Grading Table for Use in Microbicide Studies
- Manual for Expedited Reporting of Adverse Events to DAIDS
- DAERS Reference Guide for Site Reporters and Study Physicians
- Package Insert for tenofovir disoproxil fumarate (Viread)
- Package Insert for emtricitabine/tenofovir disoproxil fumarate (Truvada)
- Investigators Brochure for tenofovir gel

11.1 Definitions and General Reporting Guidance

11.1.1 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-003, the ICH-E6 definition is applied to all participants in all five study groups, beginning at the time a participant is randomized through when she terminates from the study. Study staff must document in source documents all AEs reported by or observed in MTN-003 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)

Study staff also must follow all AEs to resolution or stabilization. As a general operational guideline, "resolution" is 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 three consecutive monthly evaluations.

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 Sections 4, 7, and 10 of this manual, and reported on the Pre-Existing Conditions case report form. 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.

11.1.2 Reportable Adverse Events

Per Section 8.2 of the MTN-003 protocol, study staff will report on case report forms the following subset of AEs reported by or observed in enrolled participants:

- All genital, genitourinary, and reproductive system AEs except the following:
  - Asymptomatic bacterial vaginosis
  - Asymptomatic candidiasis
  - Genital bleeding clinically assessed to be expected (see Figure 11-1 and SSP Section 10.6 for further guidance)
  - Dipstick findings of hematuria that are not confirmed by microscopy (see Figure 11-1 for further guidance)
  - Fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths) will not be reported as AEs. However, untoward maternal conditions that either result in or result from fetal losses are reported as reproductive system AEs
- Amenorrhea that is a new onset during follow-up AND is considered by the site clinician to be unexpected (i.e. not associated with contraceptive use)
- All fractures
- All AEs of severity grade 2 or higher in the following categories: dizziness, headache, nausea, vomiting, diarrhea, abdominal pain, rash
- All AEs of severity grade 3 or higher
- All serious AEs, as defined by ICH-E6 (see also Section 11.1.3)
- All AEs that result in permanent discontinuation of study product use
- All laboratory test abnormalities specified in the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004, that are not otherwise associated with a reported clinical AE
- AEs that do not meet the above-listed criteria but do meet expedited reporting requirements per Section 8.3 below. This includes all congenital anomalies identified in the fetuses and/or infants of study participants

See Figures 11-1 and 11-2 for clarifying information related to reporting genital, genitourinary, and reproductive system AEs and reporting AEs involving abdominal pain.

Although not explicitly stated in the MTN-003 protocol, asymptomatic candidiasis is not reportable as an AE in MTN-003. This is because the *DAIDS Female Genital Grading Table for Use in Microbicide Studies* (FGGT) that is used to grade the severity of genital findings characterizes the identification of candida in the absence of symptoms as a normal finding. See Section 11.3 below for more information on severity grading.

Laboratory values that fall outside of a site's normal range, but do not meet criteria for severity grading as grade 1 or higher per Section 11.3 below, 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. Similarly, vaginal pH levels greater than 4.5 should not be reported as AEs. Similarly, 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 Safety Laboratory Results CRF completed for the visit.

The Adverse Experience Log case report form is used to report the above-listed reportable AEs to the MTN Statistical and Data Management Center (SDMC). All sites are strongly encouraged to use AE tracking tools to ensure that all AEs are source documented and that all reportable AEs are reported to the MTN SDMC on the Adverse Experience Log form; sample tracking tools are available in the Study Implementation Materials section of the MTN-003 web page.

Figure 11-1
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, sexually transmitted infections (STIs), reproductive tract infections (RTIs), and urinary tract infections (UTIs) fall in this category.

A urine dipstick for hematuria should be performed only when clinically indicated, and specimens found to be positive for heme by dipstick should be confirmed with microscopy. Hematuria confirmed by red blood cells on microscopy should be reported as "Hematuria" and graded per the "Hematuria" row in the Female Genital Grading Table. Unconfirmed dipstick findings of hematuria should not be recorded as adverse events.

If a participant reports blood in the urine during menses, the clinician should avoid performing gross or microscopic examination for hematuria and defer this evaluation once the participant's menses has ended.

If the site clinician cannot determine if the blood in the urine is related to menses or if a participant reports blood in the urine unrelated to menstruation, the clinician should evaluate the urine for blood by microscopy. If the presence of blood is confirmed by red blood cells on microscopy, an AE for "Hematuria" should be reported and graded per the "Hematuria" row in the Female Genital Grading Table. If the presence of blood is not confirmed, all AE's describing the participant's complaint should be reported as "Discolored Urine."

For pregnant participants, AEs that are related to the pregnancy, worsened by the pregnancy, or require changes in clinical management of the pregnancy are considered reproductive system AEs and will be reported as such. For example:

- Nausea and vomiting related to pregnancy (hyperemesis) are considered reproductive system AEs, but nausea and vomiting due to gastroenteritis during pregnancy are considered gastrointestinal AEs.
- New occurrences of hypertension or diabetes associated with pregnancy are considered reproductive system AEs.
- Pre-existing hypertension worsened by pregnancy is considered a reproductive system AE, as is pre-existing diabetes previously controlled by diet that requires insulin during pregnancy.

Elective abortions are not AEs.

Fetal losses are not reportable as AEs. However, maternal complications or side effects associated with fetal loss that would otherwise be reported as an AE are considered reproductive system AEs.

Bleeding and pelvic pain or contractions are common complaints in pregnancy and also often accompany a fetal loss. Depending on the circumstances pain and bleeding may be reported as an AE. In general, bleeding associated with 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. The following table displays the appropriate term to be used when filling out the Adverse Event Log CRF for bleeding or pelvic pain in a pregnant participant.

	Adverse Event Reporting 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 Bleeding row in section 8.2 of protocol)	Bleeding Prior to Onset of Labor (Grade per Bleeding row in section 8.2 of protocol)	Bleeding Prior to Onset of Labor (Grade per Bleeding row in section 8.2 of protocol)
	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 Bleeding row in section 8.2 of protocol)	**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

Figure 11-2
Reporting Abdominal Pain as an AE

When reporting abdominal pain as an AE in MTN-003, 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" or "lower abdominal pain" should be used to describe the AE. As noted above, abdominal pain of severity grade 2 and higher is reportable in MTN-003.

If abdominal pain is assessed as genitourinary or reproductive in nature, the pain should ideally be localized to a genitourinary or reproductive organ and described as such (e.g., adnexal pain, bladder pain). If the pain cannot be localized to a specific organ, it should be described using terms that identify a reproductive or genitourinary anatomical location (e.g., pelvic pain, urinary tract pain). Pain associated with menstruation is reproductive in nature and should be described using the term dysmenorrhea. As noted above, all genitourinary and reproductive pain is reportable in MTN-003, regardless of severity grade.

As noted above, source documentation for all AEs should minimally include the following: AE term/diagnosis, severity grade, onset date, outcome, outcome date, and treatment (if any). For reportable AEs, the following also must be source documented:

- Date reported to site
- Relationship to study product
- Action taken with study product as a result of the AE
- Whether the AE is serious per ICH guidance (see Section 11.1.3)
- Whether the AE meets expedited AE reporting requirements (see Section 11.1.4)
- Whether the AE is a worsening of a pre-existing condition (see Section 11.1.1)

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.

Site-specific delegation of duties documentation 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 them to ensure the accuracy of the data reported and to help maintain consistency of reporting across clinicians.

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

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

- 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 Toxicity 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 randomization AND has not increased in severity or frequency since baseline.*

- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

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. In addition, the guidance states that "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 in the definition above" should usually be considered serious.

SAEs are a subset of all AEs. For MTN-003, all SAEs are reportable AEs. For each AE identified in MTN-003, an authorized study clinician must determine whether the AE meets the ICH definition of "serious". The Adverse Experience Log case report form includes an item (item 8) to record this determination.

When assessing whether an AE meets the definition of serious, note that <u>seriousness is not the same as severity</u>, which is based on the intensity of the AE (see Section 11.3 for more information on severity grading). Further note that the *DAIDS Table for Grading Adult and Pediatric Adverse Events* and the *Female Genital Grading Table for Use in Microbicide Studies* identify AEs of severity grade 4 as <u>potentially</u> life-threatening. As such, it is not necessary or expected that all grade 4 AEs will be assessed as serious. Rather, each AE should be assessed for seriousness according to whether it is immediately life-threatening (i.e., places the participant at immediate risk of death) or otherwise meets the definition of serious as listed above. In particular, it is not expected that asymptomatic grade 4 laboratory abnormalities will be assessed as "serious".

All AEs that meet the definition of "serious" (SAEs), regardless of relationship to study product, are expedited adverse events (EAE). 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. In some cases, DAIDS may be required to report an EAE to the US Food and Drug Administration (FDA).

11.1.4 Reporting EAEs

All EAEs must be reported within three reporting days of site awareness of the EAE. The definition of a "reporting day" is that which counts toward the 3-day timeline provided for reporting of EAEs to DAIDS. The criteria are as follows:

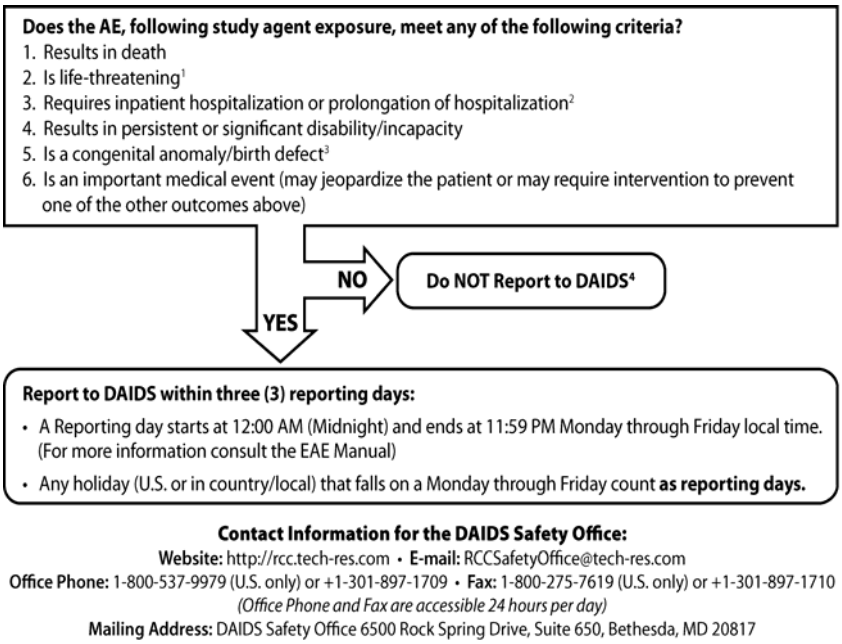
- Monday through Friday count as reporting days.
- Saturday and Sunday are not considered reporting days.
- Any holiday (U.S. or in-country/local) that occurs on a Monday through Friday counts as a reporting day.
- A reporting day starts at 12:00 AM (midnight) and ends at 11:59 PM local time (in the site's time zone).
- The day site personnel become aware that an AE has met the definition of an EAE shall count as day 1 if that day occurs on a reporting day (i.e., Monday through Friday). This is true, regardless of the time of the day site personnel become aware of the EAE. If the day site personnel become aware of the EAE is a non-reporting day (i.e., Saturday or Sunday), then the next reporting day shall count as day 1.

The Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, January 2010) defines levels of EAE reporting that may be used in DAIDS-sponsored studies. For MTN-003, the "standard" reporting level will be followed. Figure 11-3 details EAE reporting requirements. For each MTN-003 participant, the EAE reporting period begins with study randomization, and ends with the participant's termination visit. All EAEs should be reported to the DAIDS Regulatory Support Center (RSC) using the internet-based DAIDS Adverse Experience Reporting System (DAERS), per instructions provided in the DAERS Reference Guide for Site Reporters and Study Physicians. The 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. The IoR or designee is responsible for designating on the designation log at least one other physician, who is listed on the FDA form 1572, at the site who can perform the assessment and signature. This will ensure uninterrupted coverage of AE/EAE monitoring and reporting in the event that the IoR is unavailable. If an EAE report is not completed and submitted within three reporting 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.

Figure 11-3
Expedited Adverse Event Reporting Requirements for MTN-003



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

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

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

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

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

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*.

All EAEs, including congenital anomalies and birth defects identified among infants born to study participants, must also be reported on Adverse Experience Log case report forms. When completing Adverse Experience Log case report forms 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) must be recorded consistently across all documents. All EAE reports received at the DAIDS RSC will be compared with Adverse Experience Log forms 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 any EAE reports are modified after initial reporting, the AE Log form must also be modified to correspond with the EAE report.

11.2 Adverse Event Terminology

Study staff must assign a term or description to all AEs identified in MTN-003. 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, i.e., 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 severity grade of the result should not be reported as part of the AE term.

Further tips and guidelines for assigning AE terms are as follows: use specific medical terms whenever possible (e.g., “ulcers” instead of “sores”), use correct spelling for all terms, and 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.

Additional guidance for reporting certain types of AEs in MTN-003 is provided in the figures below.

Figure 11-4
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 *Female Genital Grading Table for Use in Microbicide Studies* (FGGT) and the MTN-003 Follow-Up Pelvic Exam case report form.

For AEs in which the finding term marked on the Follow-Up Pelvic Exam form is more specific than the corresponding term on the FGGT, use the more specific term to report the AE. Consider for example a pelvic exam finding identified as a vulvar laceration. The term corresponding to this finding on the FGGT is "vulvar lesion" but the term marked on the Pelvic Exam form will be "laceration." Because the term "laceration" is more specific than the term "lesion," the term "vulvar laceration" should be used for AE reporting.

Always include the specific anatomical location of pelvic exam findings (e.g., cervical, vaginal, vulvar) in the AE term.

Use the term vulvovaginitis to report combinations of vulvar and vaginal pain, itching, erythema, edema, rash, tenderness, (any two or more) unless laboratory testing confirms the presence of a sexually transmitted or reproductive tract infection (STI/RTI) that is considered the underlying cause of all signs and symptoms. In this case, report the name of the STI/RTI as the AE term on the AE Log form, and record all related signs and symptoms in the comments section of the AE Log.

Use the term cervicitis to report combinations of dyspareunia, erythema, edema, tenderness, and/or discharge (any two or more) unless laboratory testing confirms the presence of an STI/RTI that is considered the underlying cause of all signs and symptoms. In that case, report the name of the STI/RTI as the AE term on the AE Log form.

Figure 11-5
Reporting Sexually Transmitted and Other Reproductive Tract Infections as AEs

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 bacterial vaginosis and symptomatic vulvovaginal candidiasis should not be reported as AEs based on participant symptoms alone.

Bacterial vaginosis: Only report symptomatic infections that are confirmed with OSOM blue testing as AEs, using the term "symptomatic bacterial vaginosis."

Candidiasis: Only report symptomatic infections that are confirmed with KOH wet prep and microscopy as AEs, using the term "vulvovaginal candidiasis"

Chlamydia: Report all infections using the term "genitourinary chlamydia infection."

Gonorrhea: Report all infections using the term "genitourinary gonorrhea infection."

Genital herpes: Report all genital herpes outbreaks as AEs, regardless of whether infection with genital HSV-1 or HSV-2 was known to be pre-existing before enrollment/randomization. Note however that the *Female Genital Grading Table for Use in Microbicide Studies* (FGGT) requires laboratory testing (of lesion or by serology) in order to use the term "genital herpes" for AE reporting. Because such testing is not required or expected in MTN-003, genital herpes outbreaks should be reported using the term marked on the Follow-Up Pelvic Exam case report form to describe the lesion (e.g., vesicle, ulceration), together with the anatomical location of the finding (e.g., vulvar, vaginal).

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

Syphilis: Report all infections, using the term "syphilis infection" (no anatomical location is required when reporting syphilis infections).

Trichomoniasis: Report only Grade 2 infections, using the term "vaginal trichomoniasis."

Figure 11-6
Reporting Bone Fractures as AEs

Report all bone fractures as AEs.

In the AE term, first specify the fracture as either "traumatic" or "pathological." Ideally, traumatic or pathological should be the first word in the AE term. Compression fractures and other fragility fractures should be considered pathological.

In the AE term, further specify the type of fracture (e.g., stress, open, compression, fragility) and the anatomical location of the fracture.

In the comments section of the AE Log case report form, note whether the fracture diagnosis was confirmed by x-ray.

Figure 11-7
Reporting Hospitalization as AEs

Procedures should not be captured as adverse events; rather the underlying condition which leads to a procedure may be considered an adverse event. For example, while "appendectomy" would not be considered an adverse event, "appendicitis" would. Likewise, a "cesarean section" would not be considered an adverse event; 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.

- Maternal conditions (i.e. hemorrhage, preeclampsia, etc.) which result in a cesarean section should be captured as adverse events. 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 (no matter what the underlying cause- 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.

- A scheduled cesarean section performed because of a history of cesarean section, should **not** result in an adverse event as the indication for the cesarean section (uterine scar due to a previous cesarean section) would be a preexisting condition.

This guidance holds for both scheduled and unscheduled cesarean sections. Whether a cesarean section results 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 adverse events regardless of the indication for the surgery. If the complication results in a prolonged hospital stay, it will be considered serious.

11.3 Adverse Event Severity

The term severity is used to describe the intensity of an AE. The severity of all AEs identified in MTN-003 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 11.1.3.

The severity of all AEs identified in MTN-003 will be graded using the:

- *DAIDS Table for Grading Adult and Pediatric Adverse Events* (Toxicity Table), dated December 2004 and

- *Female Genital Grading Table for Use in Microbicide Studies* (FGGT), dated November 2007.

Genital bleeding during pregnancy prior to the onset of labor (regardless of trimester) will be graded as follows:

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Spotting or bleeding less than menses	Bleeding like menses or heavier, no intervention indicated	Profuse bleeding with dizziness or orthostatic hypotension, transfusion indicated	Potentially life-threatening bleeding and/or shock

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.

Both the FGGT and the Toxicity Table can be accessed on the DAIDS RSC web site (http://rsc.tech-res.com). Copies also are provided at the end of this section.

Further clarifications, guidelines, and tips for grading the severity of AEs in MTN-003 are as follows:

- 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. If the AE is reportable, 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).

- Participant weight will be monitored throughout follow-up and <u>unintentional</u> weight loss should be graded according to the "unintentional weight loss" row of the Toxicity Table. The grading guidance in this row of the Toxicity Table references loss of body weight as a percentage of the participant's baseline weight. The participant's weight at her Screening Part 2 visit should be considered her baseline weight. An example of calculating a percentage decrease in weight is as follows: if a participant weighs 50.0 kg at Screening Part 2, and then is found to weigh 45.0 kg at Month 3, the percent difference is $[(50\text{-}45) \div 50] = [5 \div 50] = .10 = 10\%$

  Note: Unintentional weight loss is considered a clinical AE, and not a laboratory abnormality, even though participant weight measurements are recorded on lab-related case report forms.

- Proteinuria should be graded per the "proteinuria" row of the Toxicity Table. Glycosuria also should be graded per the "proteinuria" row of the Toxicity Table.

- 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. The row for grading UTI on the FGGT requires urine culture results and, because cultures are not required in MTN-003, the FGGT should not be used to grade UTI. 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 gradable per the DAIDS Toxicity Table.

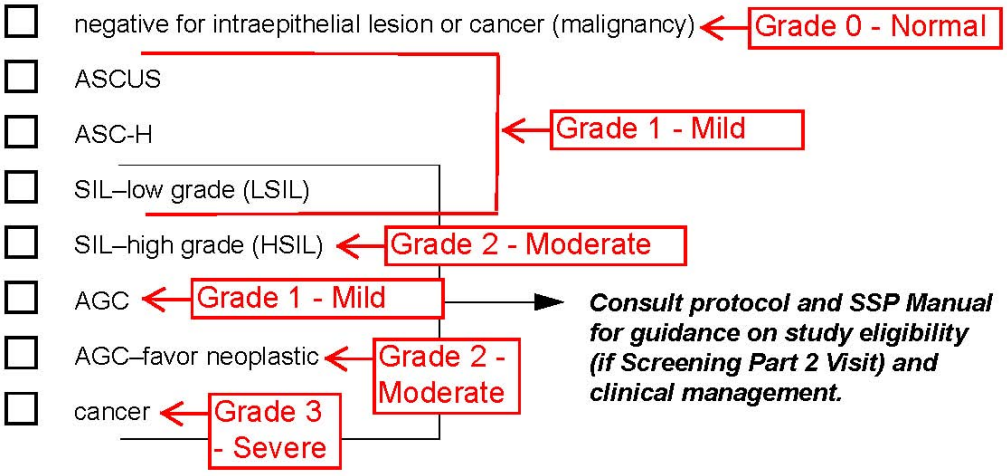
- It is preferable that abnormal Pap smear findings are reported and graded based on results of a biopsy, using the "Intraepithelial Neoplasia by biopsy" row of the FGGT (below). However, if further evaluation of the Pap smear finding is not performed, or is scheduled to be performed at a later date, then abnormal Pap smear findings that represent an increase in severity should be reported as AEs and graded according to the "Pap" row of the FGGT (see below).

  Note: AGC and AGC-favor neoplastic are not specifically mentioned in the "Pap" row, but should be assigned severity grades 1 and 2, respectively.

  If a biopsy is performed at a later date, update the AE Log CRF to indicate the results of the biopsy (item 1 - AE Diagnosis) and update the severity grade (item 3), as appropriate, per the "Intraepithelial Neoplasia by biopsy" row of the FGGT.

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 only if treatment performed without diagnostic testing, otherwise use biopsy category above)	nl PAP	ASCUS or LSIL	HSIL	Carcinoma in situ or Carcinoma	NA

- Below are the result categories on the Pap Test Results CRF; the boxes in red indicate the severity grade assigned to each result (per the "Pap" row of the FGGT).



- Bone fractures should be graded as follows:
  - Traumatic fractures should be graded according to the "estimating severity grade" row of the Toxicity Table.
  - Vertebral compression fractures and other fragility fractures should be graded according to the "bone mineral loss" row of the Toxicity Table and should fall into severity grade 3 or 4, which correspond to pathological fracture (including loss of vertebral height).

- When assigning severity grades to laboratory test results that require calculations based on the site normal reference range, the calculated severity grade range may have more significant digits than the reported test result. This can lead to uncertainty in determining what severity grade to assign to the test result. Do not round calculated grade ranges when determining the severity grade. Once the severity grade ranges are calculated, the lab value as recorded on the case report form should then be compared to the calculated grade ranges. If the lab value recorded on the case report form has fewer digits than the calculated grade range, then the missing digit(s) should be treated as zero(es), *regardless* of how the original lab result is reported by the site laboratory. Below is an example.

  For creatinine, the grade 1 range per the Toxicity Table is 1.1-1.3 times the site's upper limit of normal (ULN) and the grade 2 range is 1.4-1.8 times the ULN. If the site's ULN is 1.5 mg/dL, the calculated grade 1 range is 1.65 – 1.95 mg/dL and the calculated grade 2 range is 2.1 – 2.7 mg/dL. Do not round the calculated grade ranges, as these are interim steps. Since the Safety Laboratory Results form captures serum creatinine results to the tenths digit, a test result of 1.64 mg/dL at this site is rounded to one decimal place and recorded on the form as 1.6 mg/dL, Since the value of 1.6 mg/dL has less significant digits than the calculated grade ranges, the missing digit can be treated as a zero for purposes of assigning a severity grade. In this case, 1.6 mg/dL is treated as 1.60 mg/dL, which is less than 1.65 mg/dL and thus should not be assigned a severity grade. Even though the original lab result was reported by the site laboratory as 1.64 mg/dL, for purposes of assigning severity grades, site staff should a) use the value recorded on the CRF, and b) fill in zeroes for the missing digits, as needed, so that the lab value has the same number of significant digits as the calculated grade ranges. This is t he only way that SCHARP can check that the appropriate severity grade has been assigned to a given lab value, as SCHARP does not have access to the site's original laboratory result reports. Continuing with this same example, a test result of 1.95 mg/dL is rounded to one decimal place and recorded on the Safety Laboratory Results form as 2.0 mg/dL. Again, the value on the case report form should be used to assign a severity grade. In this case, 2.0 mg/dL is treated as 2.00 mg/dL, which is greater than the grade 1 range and less than the grade 2 range. It should be assigned severity grade 2, because a result that falls between two grade ranges should always be assigned the higher of the two grades.

Creatinine	Test result	Grade 1 range	Grade 2 range
		1.1-1.3xULN	1.4-1.8xULN
Site ULN- 1.5 mg/dL		1.65-1.95 mg/dL	2.1-2.7 mg/dL
Test result 1 without rounding	1.64		
Test result 1 with rounding	1.6 (1.60)	No grade assigned	
Test result 2 without rounding	1.95		
Test result 2 with rounding	2.0 (2.00)		Grade 2 AE

- 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 Toxicity Table. Assign the severity grade based on the Toxicity Table severity grade ranges, regardless of whether or not the lab result falls within the site's normal reference range.

- Phosphate test results should be graded according to the "Phosphate, serum, low" rows of the Toxicity Table. The grade 1 range for phosphate is 2.50 mg/dL to < LLN. If a site's lower limit of normal (LLN) is less than or equal to 2.50 mg/dL, then the grade 1 range for that site is simply the value 2.50 mg/dL.

- Hemoglobin test results should be graded according to the "hemoglobin" rows of the Toxicity Table:

  - For HIV negative persons ages 57 days and older, the grading guidance references both absolute hemoglobin values and decreases in hemoglobin values over time. Decreases should be calculated from the participant's baseline hemoglobin value only, not between sequential hemoglobin tests. Both the absolute values and decreases from baseline must be considered when grading results. If the severity of the absolute value differs from the severity of the decrease, the higher of the two grades should be assigned to the AE.

  - For participants who become HIV-infected during follow-up, the hemoglobin row for HIV positive persons ages 57 days and older should be applied beginning on the collection date of the blood sample that confirms the participant's HIV infection. For most participants who become infected with HIV, this will be the collection date of "sample 2" in the follow-up HIV testing algorithm. For those participants whose HIV infection is not confirmed until testing of "sample 3," the hemoglobin row for HIV positive persons ages 57 days and older should be applied beginning on the collection date of "sample 3."

- For HIV-uninfected participants, lymphocyte test results should be graded according to the "absolute lymphocyte counts" row for HIV negative persons greater than 13 years of age in the Toxicity Table. For participants who become HIV-infected, the severity of lymphocyte test results should not be graded.

- For participants who become HIV-infected, the severity of CD4+ cell counts and HIV viral load test results should not be graded.

11.4 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.

When an AE is assessed as "not related" to the study products, an alternative etiology, diagnosis or explanation should be provided. If new information becomes available, the relationship assessment of any AE should be reviewed again and updated as required.

When assessing relationship, the study products that should be considered are the four oral tablets (tenofovir, Truvada, tenofovir placebo, and Truvada placebo), the two vaginal gels (tenofovir gel, and placebo gel), and the applicator in which the gels are packaged. For participants assigned to gel, any AEs thought to be related to an applicator should be documented as such by choosing "related" and using descriptive text, comments, or other notations to indicate that the presumed relationship is with the applicator.

11.5 Adverse Event Outcomes and Follow-Up Information

All AEs identified in MTN-003 — regardless of whether they are reportable per Section 11.1.2 — must be followed clinically until they resolve (return to baseline) or stabilize (persist at a certain severity grade (above baseline) for three 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. For reportable AEs, outcomes must also be reported on Adverse Experience Log case report forms. In many cases, the final outcome of a reportable 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 three consecutive monthly evaluations. For laboratory test results that are reported as AEs, clinical management and follow-up of the AE should proceed per the specifications of Section 9 of the MTN-003 protocol. If, however, a laboratory AE is not addressed in Section 9 of the protocol, at a minimum, follow-up testing should be performed at scheduled monthly study visits until resolution or stabilization has been documented. An example of this approach is provided in Figure 11-8. More frequent testing may be performed at any time if required to properly monitor and/or manage participant safety, at the discretion of the IoR or designee.

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 any SAEs/EAEs that are ongoing at the termination visit, the IoR or designee must establish a clinically appropriate follow-up plan for the AE. At a minimum, the SAE/EAE 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 or designee. The same approach must be taken for any AEs that are found to have increased in severity at the termination visit. The MTN-003 Protocol Safety Review Team (PSRT) also may advise on whether any additional follow-up is indicated on a case by case basis.

For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment will be re-assessed at least once within 30-60 days after the study end date. The MTN-003 Protocol Safety Review Team (PSRT) also may advise on whether any additional follow-up is indicated on a case by case basis. 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, and may be communicated to the PSRT, if applicable; however, no updates should be made to any case report forms based on the re-assessments.

If a reportable AE increases in severity or frequency (worsens) after it has been reported on an Adverse Experience Log case report form, it must be reported as a new AE, at the increased severity or frequency, on a new Adverse Experience Log case report form. In this case, the outcome of the first AE will be documented as "severity/frequency increased." 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 or frequency increased. If an EAE/SAE increases in severity to a higher grade than previously reported, the existing EAE form must be updated using DAERS. Please note that a new EAE form does not need to be submitted for any change in the assessment of the severity grade or the relationship between the AE and the study product. However, the increase in severity must be reported as a new AE to the SDMC (as described previously).

Figure 11-8
Example of Follow-up of a Laboratory Test Result AE

Consider an HIV-uninfected participant with a baseline hemoglobin level of 11.4 g/dL, which is not gradable per the DAIDS Toxicity Table. At her Month 6 visit, this participant's hemoglobin level has decreased to 10.8 g/dL, which is a grade 1 abnormal result per the Toxicity Table. Grade 1decreased hemoglobin should be source documented and reported as an AE when the hemoglobin test result is received. Although the MTN-003 protocol does not require hematology testing again until the Month 12 visit, the IoR or designee must ensure that additional testing is performed to follow-up this AE to resolution or stabilization. As such, hemoglobin testing should be repeated at the participant's Month 7 visit (or sooner, if clinically indicated per the clinical judgment of the IoR or designee).

- If the participant's hemoglobin level has returned to baseline (i.e., not gradable per the Toxicity Table) at Month 7, the AE is considered resolved at that time, and no further testing is required.
- If the participant's hemoglobin level has not returned to baseline at Month 7, the AE is considered continuing, and additional testing will be required. Repeat the test again at the Month 8 visit (or sooner if clinically indicated).
- If the participant's hemoglobin level has returned to baseline at Month 8, the AE is considered resolved at that time, and no further testing is required.
- If the participant's hemoglobin level has not returned to baseline at Month 8, additional testing will be required. Repeat the test again at the Month 9 visit.
- If the participant's hemoglobin level has returned to baseline at Month 9, the AE is considered resolved at that time, and no further testing is required.
- If the participant's hemoglobin level has not returned to baseline at Month 9, the AE is considered ongoing but stabilized at the grade 1 level, and no further testing is required until the next testing time point specified in the study protocol, which is at Month 12.

Note that this example assumes that the participant's decreased hemoglobin level either resolved or persisted at the grade 1 level between Months 6 and 9. If her hemoglobin level had worsened over this time (i.e., had increased in severity), additional safety monitoring and AE reporting would be required.

Study staff are not required to report the outcome of EAEs to the DAIDS RSC, unless outcome information is specifically requested. However, EAE follow-up information 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
- Results of re-challenge with the study product, if performed

The last circumstance listed above relates to re-challenge with study product. In MTN-003, 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 cases such as this, site staff should provide follow-up information to the 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.

11.6 Reporting Recurrent Adverse Events

If a reportable 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 for MTN-003 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.

- For HPV, genital warts present before randomization are 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 as described in Figure 11-5.

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.

11.7 Social Harms

In addition to medical AEs, participants in MTN-003 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.

The MTN-003 Oral and Vaginal Product Adherence and Behavior Assessment forms actively ascertain, on a quarterly basis, whether participants have had "any problems with the following people [list] as a result of being in the study." 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. Participants will also be asked similar questions during administration of the Study Exit Behavior Assessment form.

Prior to study initiation, study staff teams at each site 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 if reported. 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.

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

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

- 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.

- 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 11.1) report the AE on an Adverse Experience Log form. If the social harm is associated with an AE that meets criteria for expedited reporting to the DAIDS RSC, report it as an EAE as described in Section 11.1.3. Also report the issue or problem to all IRBs/ECs responsible for oversight of MTN-003, if required per IRB/EC guidelines.

- Consult the MTN-003 PSRT for further input and guidance as needed.

As is the case for medical AEs, data collected on social harms will be monitored by the MTN-003 PSRT and the NIAID Vaccine and Prevention Data and Safety Monitoring Board (DSMB), as described below.

11.8 MTN-003 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN-003 protocol and Section 14 of the MTN Manual of Operations for a complete description of the participant safety monitoring procedures in place for MTN-003. Also refer to Section 17 of this manual for a description of the reports prepared by the MTN SDMC in support of MTN-003 safety monitoring procedures.

Participant safety is of paramount importance in MTN-003. Primary safety monitoring and safeguarding of individual study participants is the responsibility of study staff, under the direction of the IoR. The IoR and designated study staff also are responsible for submitting case report forms to the MTN SDMC 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 Affairs 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 issued to site staff for resolution 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. In these cases, the Protocol Safety Physicians will document the contact (including the date of the contact, the persons involved, the reason for the contact, and the outcome of the contact).

- The DAIDS RSC, DAIDS RAB Safety Specialist, and DAIDS PSB Medical Officers will review all EAE Forms received for MTN-003 and follow up on these reports with site staff, the MTN-003 Protocol Team, and drug regulatory authorities when indicated.

- The MTN-003 PSRT will routinely review safety data reports prepared for MTN-003 by the MTN SDMC. As described further in Section Appendix 11-1, the PSRT will meet via conference call to discuss the accumulating study safety data and any potential safety concerns. To preserve blinding, data reviewed by the PSRT will be pooled across study groups.

- The NIAID Vaccine and Prevention DSMB will routinely review safety data reports prepared by the MTN SDMC. It is expected that the DSMB will review the MTN-003 data approximately every six months. Data reports prepared for the DSMB will present safety data in a coded manner by study group with codes provided separately to allow DSMB members to unblind themselves when reviewing the data. A brief summary report from each DSMB review will be distributed to the MTN-003 Protocol Team shortly after the review takes place. IoRs must forward copies of these reports to all IRBs/ECs responsible for oversight of research at their site.

Prior to reviews by the DSMB, and independently, the MTN Study Monitoring Committee (SMC) also will periodically review MTN-003 study data with a focus on performance indicators such as participant accrual and retention, protocol adherence, intervention adherence, and data quality. While site staff are not typically involved in these reviews, site staff should be aware that both the SMC and the DSMB 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.

11.9 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 Package Inserts
- Updated Investigators Brochures
- IND Safety Reports
- DSMB review summaries
- 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.

Section Appendix 11-1
MTN-003 Protocol Safety Review Team Plan

Roles and Responsibilities of the PSRT

Per the MTN-003 protocol, the roles and responsibilities of the MTN-003 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, MTN Study Monitoring Committee (SMC) and/or DAIDS Vaccine and Prevention Data and Safety Monitoring Board (DSMB), 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 resumptions 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.

5. Respond to requests for participant unblinding. There are no circumstances under which it is expected that unblinding will be necessary for the provision of medical treatment or to otherwise protect the safety of study participants. However, if an investigator feels that specific product knowledge is necessary to protect participant safety, the investigator may notify the PSRT to consider and rule upon the request.

PSRT Composition

The following individuals comprise the MTN-003 PSRT:

- Katie Bunge, Protocol Safety Physician
- Z Mike Chirenje, Protocol Chair
- Ross Cranston, Protocol Safety Physician
- Jeanne Marrazzo, Protocol Chair
- Benoît Mâsse, Protocol Statistician
- Patrick Ndase, Regional Physician
- Jeanna Piper, DAIDS Medical Officer
- Sharon Riddler, Protocol Physician
- Barbra Richardson, Protocol Statistician
- Devika Singh, Protocol Safety Physician
- Molly Swenson, MTN SDMC Clinical Affairs Safety Associate

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 Protocol 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 CORE Clinical Research Managers, SDMC Project Managers, and SDMC Statistical Research Associates may attend PSRT calls as observers and/or discussants.

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 all study groups) and will 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 probably or definitely related to study product by body system and severity
- 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
- Tabulations of pregnancies and pregnancy outcomes
- A cumulative listing of reported social harms
- Tabulations of product holds/discontinuations and resumptions

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 (mtn003psrt@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-003 PSRT Query Form, which is available in the Study Implementation Materials section of the MTN-003 web page. Site staff will email completed query forms to the Protocol Safety Physicians (mtn003safetymd@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. 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).

An emergency safety telephone number (+001-412-641-8947) is also available to site staff. This telephone uses a US number (toll call from outside the US) and is carried by the Protocol Safety Physicians 24 hours a day, seven days a week. It is intended for use in emergency situations only, in which immediate consultation with a Protocol Safety Physician is needed. Questions that can wait for email communication should be handled using the PSRT query process described above.

To document calls made to the emergency safety telephone number, near the time of the call (either before or after) site staff will complete the site section of the MTN-003 Emergency Phone Contact form (available in the Study Implementation Materials section of the MTN-003 web page) and email the form to the Protocol Safety Physicians. Within 24 hours after

the call, the responding Protocol Safety Physician will complete the remainder of the form and email the completed version to site staff, copied to the study management team.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

This clarification of the DAIDS Table for Grading the Severity of Adult and Pediatric AE's provides additional explanation of the DAIDS AE Grading Table and clarifies some of the parameters.

I. Instructions and Clarifications

Grading Adult and Pediatric AEs

The DAIDS AE Grading Table includes parameters for grading both Adult and Pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both Adult and Pediatric populations, separate sets of parameters for Adult and/or Pediatric populations (with specified respective age ranges) are given in the Table. If there is no distinction in the Table between Adult and Pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both Adult and Pediatric events of that type.

> **Note:** In the classification of adverse events, the term "**severe**" is not the same as "**serious**." Severity is an indication of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "**serious**" relates to a participant/event outcome or action criteria, usually associated with events that pose a threat to a participant's life or functioning.

Addenda 1-3 Grading Tables for Microbicide Studies

For protocols involving topical application of products to the female genital tract, male genital area or rectum, strong consideration should be given to using Appendices I-III as the primary grading scales for these areas. The protocol would need to specifically state that one or more of the Appendices would be primary (and thus take precedence over the main Grading Table) for items that are listed in both the Appendix and the main Grading Table.

- Addendum 1 - Female Genital Grading Table for Use in Microbicide Studies - PDF
- Addendum 2 - Male Genital Grading Table for Use in Microbicide Studies - PDF
- Addendum 3 - Rectal Grading Table for Use in Microbicide Studies - PDF

Grade 5

For any AE where the outcome is death, the severity of the AE is classified as Grade 5.

Estimating Severity Grade for Parameters Not Identified in the Table

In order to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located on Page 3.

Determining Severity Grade for Parameters "Between Grades"

If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE. If a laboratory value that is graded as a multiple of the ULN or LLN falls between two grades, select the higher of the two grades for the AE. For example, Grade 1 is 2.5 x ULN and Grade 2 is 2.6 x ULN for a parameter. If the lab value is 2.53 x ULN (which is between the two grades), the severity of this AE would be Grade 2, the higher of the two grades.

Values Below Grade 1

Any laboratory value that is between either the LLN or ULN and Grade 1 should not be graded.

Determining Severity Grade when Local Laboratory Normal Values Overlap with Grade 1 Ranges

In these situations, the severity grading is based on the ranges in the DAIDS AE Grading Table, even when there is a reference to the local lab LLN.

For example: Phosphate, Serum, Low, Adult and Pediatric > 14 years (Page 20) Grade 1 range is 2.50 mg/dL - < LLN. A particular laboratory's normal range for Phosphate is 2.1 – 3.8 mg/dL. A participant's actual lab value is 2.5. In this case, the value of 2.5 exceeds the LLN for the local lab, but will be graded as Grade 1 per DAIDS AE Grading Table.

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II. Definitions of terms used in the Table:

Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. Young Children Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
NA	Not Applicable
Operative Intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual Social & Functional Activities	Adult Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. Young Children Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children > 10 cc/kg) indicated
Hypertension				
Adult > 17 years (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	**≥** 180 mmHg systolic OR **≥** 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Correction: in Grade 2 to 160 - 179 from > 160-179 (systolic) and to ≥ 100 -109 from > 100-109 (diastolic) and in Grade 3 to ≥ 180 from > 180 (systolic) and to ≥ 110 from > 110 (diastolic).				
Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval				
Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Prolonged QTc				
Adult > 16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Comment: Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.				
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea				
Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric < 1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset) **– Adult ≥ 18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 **–** 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) **– Adult ≥ 18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure **– Pediatric < 18 years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Comment: Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, ≤1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Comment: Parameter changed from "Infant, < 1 day" to "Infant, ≤1 day"				
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

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LABORATORY

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemoglobin (Hgb)				
Comment: The Hgb values in mmol/L have changed because the conversion factor used to convert g/dL to mmol/L has been changed from 0.155 to 0.6206 (the most commonly used conversion factor). For grading Hgb results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for that lab.				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *5.24 – 6.23 mmol/L*	7.5 – 8.4 g/dL *4.62–5.23 mmol/L*	6.50 – 7.4 g/dL *4.03–4.61 mmol/L*	< 6.5 g/dL *< 4.03 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *6.18 – 6.79 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *1.58 – 2.13 mmol/L*	9.0 – 9.9 g/dL *5.55 - 6.17 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *2.14 – 2.78 mmol/L*	7.0 – 8.9 g/dL *4.34 - 5.54 mmol/L* OR Any decrease ≥ 4.5 g/dL *> 2.79 mmol/L*	< 7.0 g/dL *< 4.34 mmol/L*
Comment: The decrease is a decrease from baseline				
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *5.24 – 5.86 mmol/L*	7.0 – 8.4 g/dL *4.31 – 5.23 mmol/L*	6.0 – 6.9 g/dL *3.72 – 4.30 mmol/L*	< 6.00 g/dL *< 3.72 mmol/L*
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *5.87 - 6.54 mmol/L*	8.0 – 9.4 g/dL *4.93 – 5.86 mmol/L*	7.0 – 7.9 g/dL *4.34 – 4.92 mmol/L*	< 7.00 g/dL *< 4.34 mmol/L*
Infant*†, ≤ 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *7.42 – 8.09 mmol/L*	10.0 – 11.9 g/dL *6.18 – 7.41 mmol/L*	9.0 – 9.9 g/dL *5.59- 6.17 mmol/L*	< 9.0 g/dL *< 5.59 mmol/L*
Correction: Parameter changed from "Infant < 21 days" to "Infant ≤ 21 days"				
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
CHEMISTRIES	***Standard International Units are listed in italics***			
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN[†]	2.6 – 5.0 x ULN[†]	5.1 – 10.0 x ULN[†]	> 10.0 x ULN[†]
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Comment: Some laboratories will report this value as Bicarbonate (HCO_3) and others as Total Carbon Dioxide (CO_2). These are the same tests; values should be graded according to the ranges for Bicarbonate as listed above.				
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Infant[*†], ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant[*†], ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Infant[*†], < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
Infant[*†], < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Comment: Do not adjust Calcium, serum, low or Calcium, serum, high for albumin				

[*] Values are for term infants. Preterm infants should be assessed using local normal ranges.

[†] Use age and sex appropriate values (e.g., bilirubin).

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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Infant*†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate	ULN - < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

Comment: Added ULN to Grade 1 parameter					
LDL cholesterol (fasting)					
	Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
	Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase		1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low		1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase		1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low					
	Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
	Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
	Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high		5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low		3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high		146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low		130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)		NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*
URINALYSIS	***Standard International Units are listed in italics***			
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*
Pediatric > 3 mo - < 10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m^2/24 h *> 1.000 g/d*

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

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Addendum 1
Female Genital Grading Table for Use in Microbicide Studies

INDIVIDUAL SIGNS/SYMPTOMS					
PARAMETER	**GRADE 0 NORMAL**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
GENERAL					
Odor	No complaint	Mild-moderate unpleasant odor	Severe unpleasant odor	NA	NA
PAIN AND TENDERNESS **(Specify Area: Vulvar/Perineum, Vagina, Cervix (including cervical motion tenderness), Uterus, Adnexae, Pelvic/Lower Abdominal, or Ovulatory)** ***Note – if both pain and tenderness are present, only report the one with the most severe grade**					
Pain* [1]	None	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities or the need for non-narcotic medication	Pain causing inability to perform usual social & functional activities or the need for narcotic medication	Disabling pain causing inability to perform basic self-care functions OR hospitalization (other than emergency room visit) indicated
Tenderness* [1]	None	Mild tenderness	Moderate tenderness	Severe tenderness	NA
Dyspareunia (pain with sexual activity)	None	Pain causing no or minimal interference with sexual function	Pain causing greater than minimal interference with sexual function	NA	NA
Dysmenorrhea/cramping with menses	None	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities or the need for non-narcotic medication	Pain causing inability to perform usual social or functional activities or the need for narcotic medication	NA

[1] If pain or tenderness is included in the grading of another category (e.g., PID), it should not be graded again in the pain or tenderness category.

NOTE: For protocols utilizing this Addendum, when the same parameter appears in both this Female Genital Grading Table and the main DAIDS AE Grading Table, use the grading scheme in this table.

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INDIVIDUAL SIGNS/SYMPTOMS					
PARAMETER	**GRADE 0 NORMAL**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
GENITOURINARY SIGNS/SYMPTOMS – VULVA					
Vulvar/vaginal itching	None	Itching causing no, mild, or moderate interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities; may require intervention such as antihistamine or bathing to provide relief	NA	NA
Vulvar edema	None	Mild, non-pitting edema	Moderate, 1-2+ pitting edema	3+ pitting edema, severe enough to require urinary drainage, or weeping edema ± skin breakdown	NA
Vulvar erythema	None	Erythema covering < 50% of vulvar surface	Erythema covering ≥ 50% of vulvar surface	NA	NA
Vulvar lesions (findings seen only by colposcopy should not be included here)	Normal variants including skin tags, moles, scars, etc.	Blisters, ulcerations, or pustules - no treatment indicated	Blisters, ulcerations or pustules, with treatment indicated	Severe epithelial disruption with hospitalization indicated	NA
Vulvar rash	None	Rash covering < 50% of vulvar surface	Rash covering ≥ 50% of vulvar surface	Severe epithelial disruption with hospitalization indicated	NA
Bartholin's or Skene's gland	No findings	Cyst with no inflammation	Cyst or abscess with outpatient intervention indicated	Cyst or abscess with hospitalization indicated	Necrotizing fasciitis from Bartholin's abscess
GENITOURINARY SIGNS/SYMPTOMS – VAGINA **** Note – if vaginal discharge is present both by history and on examination, only report the one with the most severe grade**					
Vaginal edema	None	Mild-moderate engorgement	Loss of ruggae and friability	NA	NA
Vaginal erythema	None	Erythema covering < 50% of vaginal surface	Erythema covering ≥ 50% of vaginal surface	NA	NA

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INDIVIDUAL SIGNS/SYMPTOMS					
PARAMETER	**GRADE 0 NORMAL**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Vaginal dryness	No complaint	Dryness causing no or minimal interference with usual sexual, social, & functional activities	Dryness causing greater than minimal interference with usual sexual, social, & functional activities	NA	NA
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	NA	NA
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	NA	NA
Vaginal abrasions or lacerations (including probable applicator injuries)	None	Superficial disruptions and disruptions extending through the mucosa with minimal impact on life	Large disruptions extending through the mucosa or large superficial disruptions, hospitalization not indicated	Large disruptions extending through the mucosa or large superficial disruptions, hospitalization indicated	Lacerations extending into the peritoneal cavity, bladder, or rectum
Vaginal lesions (findings seen only by colposcopy should not be included here)	Normal variants including skin tags, moles, scars, etc.	Blisters, ulcerations, or pustules, no treatment indicated	Blisters, ulcerations, or pustules with treatment indicated	Severe epithelial disruption requiring hospitalization	NA
Vaginal and Cervical masses (polyps, myomas, or possible malignancy)	None or normal variants such as Nabothian cyst or Gartner duct cyst	Polyp or myoma or undiagnosed mass without symptoms	Polyp, myoma, or undiagnosed mass causing mild symptoms, e.g., bleeding/pain not requiring more than mild analgesia	Polyp, myoma, or undiagnosed mass causing severe symptoms, e.g., bleeding/pain affecting bladder and bowel function	Visible cervical cancer
GENITOURINARY SIGNS/SYMPTOMS – CERVIX					
Cervical edema and friability	None	Edema without friability	Friable cervix	NA	NA

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INDIVIDUAL SIGNS/SYMPTOMS					
PARAMETER	**GRADE 0 NORMAL**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cervical erythema	None	Erythema covering < 50% of cervix	Erythema covering ≥ 50% of cervix	NA	NA
Cervical discharge	White or clear discharge	Small amount of purulent discharge at os	Purulent discharge extending onto cervix or vagina	NA	NA
Visible cervical lesions (findings seen only by colposcopy should not be included here)	Normal variants including skin tags, moles, scars, etc.	Blisters, ulcerations, or pustules, no treatment indicated	Blisters, ulcerations, or pustules with treatment indicated	NA	NA
GENITOURINARY SIGNS/SYMPTOMS – UTERUS					
Uterine masses/enlargement based on bimanual examination	Normal to 8 week size, no palpable myomas	Enlarged uterus and mild symptoms, e.g., bleeding/pain requiring mild analgesics	Enlarged uterus/myoma with moderate pain or symptoms, e.g., bleeding	Mass causing severe bleeding/pain or with impact on bowel/bladder function	Uterine mass that requires transfusion or surgery
Polyp, submucosal fibroid, or thickened endometrium detected by transvaginal ultrasound (new or increasing in size from prior exam)	None or unchanged/reduced in size from prior exam	New myomas < 6 cm diameter (single or multiple) or diameter increased < 6 cm since prior exam	New myomas ≥ 6 cm diameter (single or multiple) or diameter increased ≥ 6 cm since prior exam	Hospitalization and/or surgery indicated	NA
GENITOURINARY SIGNS/SYMPTOMS – ADNEXA					
Not pregnancy- or infection-related adnexal masses based on bimanual exam (use if no ultrasound done; if ultrasound done, use ultrasound categories below)	None, ≤ 4 cm, normal size ovary	> 4 cm with minimal or no symptoms	> 4 cm with severe symptoms, e.g., pain, but hospitalization not indicated (see footnote #1)	> 4 cm with severe symptoms, e.g., pain and hospitalization indicated (see footnote #1)	NA
Hydrosalpinx based on ultrasound	None	Asymptomatic, suspected hydrosalpinx	Hydrosalpinx with pain, but without evidence of infection or ectopic pregnancy	Signs/symptoms of infection with hospitalization and/or surgery indicated	NA
Adnexal mass based on ultrasound	None	Simple cyst, asymptomatic	Simple cyst, symptomatic	Mass suspicious for malignancy	Malignant mass

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INDIVIDUAL SIGNS/SYMPTOMS					
PARAMETER	**GRADE 0 NORMAL**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
GENITOURINARY SIGNS/SYMPTOMS – ABDOMEN					
Abdominal mass not palpable on pelvic exam of unknown diagnosis	None or known (pre-existing) mass unchanged in size	New mass or increased size of known mass requiring mild analgesia with minimal impact	New mass or increased size of known mass with moderate symptoms	Mass causing severe bleeding/ pain with impact on bladder/bowel function or with hospitalization indicated	Malignancy
GENITOURINARY SIGNS/SYMPTOMS – URINARY TRACT					
Urinary frequency	None	Up to 2 times participant's normal frequency	> 2 times participant's normal frequency	NA	NA
Dysuria	None	Superficial only	Deep ± superficial	Inability to void due to pain	NA
Hematuria	None	Microscopic, no intervention indicated (beyond evaluation for infection)	Gross blood in urine or medical intervention/ evaluation indicated (beyond evaluation for infection)	Persistent bleeding with transfusion, hospitalization or intervention indicated to obtain hemostasis (endoscopy, interventional radiology, or operative)	Profuse hemorrhage with shock or orthostatic dizziness

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COMPOSITE SIGNS/SYMPTOMS (Use instead of individual categories if 2 or more signs/symptoms are present)					
PARAMETER	**GRADE 0 NORMAL**	**GRADE 1 MILD** (Use if all signs/ symptoms would individually be Grade 0 or 1)	**GRADE 2 MODERATE** (Use if one or more signs/symptoms would individually be Grade 2 and all others Grade 0 or 1)	**GRADE 3 SEVERE** (Use if one or more signs/symptoms would individually be Grade 3)	**GRADE 4 POTENTIALLY LIFE-THREATENING**
NO ORGANISM IDENTIFIED BUT INADEQUATE TESTING PERFORMED					
Vulvovaginitis (combinations of pain, itching, erythema, edema, rash, tenderness, or discharge)	None	Mild signs/ symptoms	Moderate signs/ symptoms	Severe signs/ symptoms	NA
Cervicitis (combinations of dyspareunia, erythema, edema, tenderness, and discharge)	None	Mild signs/ symptoms	Moderate signs/ symptoms	Severe signs/ symptoms	NA
PID (if Gonorrhea or Chlamydia identified use that category)	None	NA	Cervicitis with mild uterine tenderness, ± mild cervical motion tenderness, no signs of peritoneal irritation	More diffuse tenderness, any signs of peritoneal irritation, or indications for hospitalization	Tubo-ovarian abscess or surgery required for resolution
NO ORGANISM IDENTIFIED AFTER APPROPRIATE TESTING PERFORMED					
Vulvovaginitis (combinations of pain, itching, erythema, edema, rash, tenderness, or discharge)	None	Mild signs/ symptoms	Moderate signs/ symptoms	Severe signs/ symptoms	NA
Cervicitis (combinations of dyspareunia, erythema, edema, tenderness, and discharge)	None	Mild signs/ symptoms	Moderate signs/ symptoms	Severe signs/ symptoms	NA
PID (if Gonorrhea or Chlamydia identified use that category)	None	NA	Cervicitis with mild uterine tenderness, ± mild cervical motion tenderness, no signs of peritoneal irritation	More diffuse tenderness, any signs of peritoneal irritation, or indications for hospitalization	Tubo-ovarian abscess or surgery required for resolution

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INFECTIONS AND DYSPLASIA					
PARAMETER	**GRADE 0 NORMAL**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
GENITOURINARY INFECTIONS					
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
Candida	Absence of symptoms regardless of candida test results	Positive culture, wet mount, or other laboratory test for yeast, with mild symptoms	Positive culture, wet mount, or other laboratory test for yeast, with moderate to severe symptoms	NA	NA
Trichomonas	Negative	NA	Positive wet mount, culture, PCR or other licensed test, excluding pap smear, showing T. vaginalis, regardless of symptoms	NA	NA
Bacterial Vaginosis (BV)	Negative	Asymptomatic BV diagnosed by Amsel criteria, wet mount, Gram stain, or licensed diagnostic test	Symptomatic confirmed by wet mount, Gram stain, or any licensed diagnostic test	NA	NA

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INFECTIONS AND DYSPLASIA					
PARAMETER	**GRADE 0 NORMAL**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Chlamydia	Negative	NA	Positive culture or other diagnostic test for Chlamydia, asymptomatic or with mild uterine or cervical motion tenderness (no signs of peritoneal irritation)	Positive test for Chlamydia with abdominal or uterine or adnexal tenderness on examination, with or without adnexal mass, diffuse tenderness, any signs of peritoneal irritation, or indications for hospitalization	Tubo-ovarian abscess or surgery required for resolution
Gonorrhea	Negative	NA	Positive culture or other diagnostic test for Gonorrhea, asymptomatic or with mild uterine or cervical motion tenderness (no signs of peritoneal irritation)	Positive test for Gonorrhea with abdominal or uterine or adnexal tenderness on examination, with or without adnexal mass, diffuse tenderness, any signs of peritoneal irritation, or indications for hospitalization	Tubo-ovarian abscess or surgery required for resolution or disseminated gonococcal infection
Urinary tract infection (by urinalysis and urine culture)	Negative	5-10 WBC/hpf on urinalysis with a negative culture per protocol definition (with or without symptoms)	> 10 WBC/hpf on urinalysis OR a positive culture per protocol definition (with or without symptoms)	Pyelonephritis	Sepsis (septicemia) due to urinary tract infection

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INFECTIONS AND DYSPLASIA					
PARAMETER	**GRADE 0 NORMAL**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Syphilis	Negative treponemal or non-treponemal test or both positive with known treatment and stable titers (< 4 fold increase)	NA	Syphilis diagnosed by a positive treponemal test along 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	Criteria for Grade 2 Syphilis in the presence of neurologic symptoms or a positive CSF VDRL or FTA-ABS	NA
GENITAL DYSPLASIA					
Condyloma (specify site: cervical, vaginal, vulvar, perianal)	None	Condylomata causing no or mild interference with daily function	Condylomata causing moderate interference with daily function	Condylomata causing severe interference with daily function, secondary infection, or hospitalization indicated	NA
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 only if treatment performed without diagnostic testing, otherwise use biopsy category above)	nl PAP	ASCUS or LSIL	HSIL	Carcinoma in situ or Carcinoma	NA

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UTERINE BLEEDING AND PREGNANCY COMPLICATIONS					
PARAMETER	**GRADE 0 NORMAL**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
ABNORMAL UTERINE BLEEDING UNRELATED TO PREGNANCY					
Menorrhagia [2] (prolonged and/or heavy menstrual bleeding)	Participant report of normal bleeding relative to her baseline	Increase from usual with no or minimal interference with usual social & functional activities (including sexual functioning)	Increase from usual with moderate interference with usual social & functional activities (including sexual)	Incapacitating or severe interference with usual social & functional activities (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock
Metrorrhagia [2] (intermenstrual or frequent bleeding)	None or any expected nonmenstrual bleeding	Increase from usual with no or minimal interference with usual social & functional activities (including sexual functioning)	Increase from usual with moderate interference with usual social & functional activities (including sexual)	Incapacitating or severe interference with usual social & functional activities (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock
Unexplained infrequent bleeding (excludes expected absence of menses due to hormonal contraception or pregnancy/postpartum)	Participant report of normal or expected bleeding frequency	No menses for 1-3 months (missed menses)	No menses for > 3 months (oligomenorrhea/ amenorrhea)	NA	NA
Postcoital bleeding	None	Occasional (< 25% of coital acts) OR Increase from usual with no or minimal interference with usual social functioning (including sexual functioning)	Frequent (25-75% of coital acts) OR Increase from usual with moderate interference with usual social functioning (including sexual)	Consistent (> 75% of coital acts) OR Incapacitating or severe interference with usual social functioning (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock

[2] If both Menorrhagia and Metrorrhagia are present, a single adverse event should be reported as "Menometrorrhagia" and graded per the Menorrhagia grading scale.

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UTERINE BLEEDING AND PREGNANCY COMPLICATIONS					
PARAMETER	**GRADE 0 NORMAL**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
COMPLICATIONS OF PREGNANCY					
First trimester bleeding	None	Spotting or bleeding less than menses with continuation of pregnancy	Bleeding like menses or heavier with continuation of pregnancy	Spontaneous abortion, or profuse bleeding with dizziness or orthostatic hypotension, transfusion indicated	Spontaneous abortion with profuse bleeding and/or shock
Postabortal endometritis/salpingitis	None	Low grade fever and uterine tenderness, resolved with oral antibiotics	Moderate symptoms, requiring ≤ 3 days of parenteral antibiotics	Severe symptoms requiring > 3 days of IV antibiotics or development of tubo-ovarian abscess	Ruptured TOA or diffuse peritonitis or severe uterine infection for which operative intervention indicated
Postpartum hemorrhage	EBL < 500 cc for vaginal delivery or < 1000 cc after CS or reported as normal	EBL 500-1000 for vaginal delivery or 1000-1500 for CS or reported as slightly increased	EBL > 1000 for vaginal delivery or > 1500 for CS, with or without mild dizziness, no transfusion required	Hemorrhage at a level for which transfusion of 1-2 units of packed cells, but no other blood products indicated	Hemorrhage with shock or coagulopathy, for which transfusion of > 2 units of packed cells or any amount of other blood components is indicated
Postpartum endometritis	None	Low grade fever and uterine tenderness, resolved with oral antibiotics	Moderate symptoms, treated by ≤ 3 days of parenteral antibiotics	Severe symptoms treated with > 3 days of IV antibiotics or addition of heparin	Severe infection or infection for which operative intervention is indicated
Chorioamnionitis	None	Fever (38°C – 38.4°C or 100.4°F – 100.9°F) with two or more: FHR > 160 BPM, maternal HR > 120, uterine tenderness between contractions or purulent AF or preterm labor	Same as Grade 1 plus fever 38.5°C – 40°C or 101°F – 104°F	Criteria for Grade 2 plus fetal distress or fever > 40°C or 104°F	Criteria for Grade 3 plus either fetal demise or maternal symptoms of shock

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UTERINE BLEEDING AND PREGNANCY COMPLICATIONS					
PARAMETER	**GRADE 0 NORMAL**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Episiotomy infection	None	Mild erythema, edema, and tenderness of wound	Fever > 38°C or 100.4°F with erythema, edema, and tenderness of wound	Fever with wound dehiscence or debridement required	Fever with signs of wound infection and shock or necrotizing fasciitis
Second/third trimester bleeding	None	Bleeding less than menses	Bleeding like menses or greater, but not requiring intervention	Bleeding requiring delivery or other intervention, e.g., transfusion	Bleeding with fetal demise or coagulopathy
Preterm rupture of membranes	None	NA	Preterm rupture with hospitalization but not resulting in delivery at less than 37 weeks' gestation	Delivery at 33-36 weeks' gestation or 1501-2500 grams birth weight	Delivery < 33 weeks' gestation or ≤ 1500 grams birth weight
Preterm contractions	None	Preterm contractions which resolve without medical intervention	Preterm contractions with cervical change which result in medical intervention but not resulting in preterm delivery	Delivery at 33-36 weeks' gestation or 1501-2500 grams birth weight	Delivery < 33 weeks' gestation or ≤ 1500 grams birth weight
Poor fetal growth	At or above 10th percentile	Fetal growth < 10th percentile but ≥ 3rd percentile for gestational age by ultrasound or newborn exam	NA	Fetal growth < 3rd percentile for gestational age by ultrasound or newborn exam	NA

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