Section 11. Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in HPTN 035. Please also refer to Section 6 of the HPTN 035 protocol and the Manual for Expedited Reporting of Adverse Events to DAIDS in Appendix VI of the protocol.

NOTE: Effective with Version 2.0 of this section, prior references to the HIV Prevention Trials Network (HPTN) have been replaced where applicable with references to the Microbicide Trials Network (MTN). Also effective with Version 2.0, this section reflects the modified adverse event reporting requirements included in protocol Version 3.0. All study sites must obtain IRB/EC approval and DAIDS protocol registration approval for protocol Version 3.0 before implementing Version 3.0 procedures. Prior to obtaining these approvals, protocol Version 2.0 (including Letters of Amendment #1 and #2) and Version 1.6 of this section must be followed.

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.

The HPTN 035 protocol specifies that any untoward medical occurrence experienced by a study participant after randomization is considered an AE, regardless of the study group to which the participant is assigned. Therefore AEs must be identified, documented, and followed to resolution for HPTN 035 participants in the three study gel groups as well as for participants in the condom only (no gel) group. Source documentation for each AE should minimally include the following information: AE term/diagnosis, severity grade, onset date, outcome, outcome date, and treatment.

Medical conditions, problems, signs, symptoms, and findings identified prior to randomization 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 (see Section 13.6). If a pre-existing condition worsens (increases in severity or frequency) after randomization, the worsened condition is considered an AE.

11.1.2 Reportable Adverse Events

Per Version 3.0 of the HPTN 035 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
- All serious AEs, as defined by ICH-E6 (see also Section 11.1.3)
- All AEs of severity grade 3 or higher (see also Section 11.3)
- All AEs that result in permanent discontinuation of study product use
- All laboratory test abnormalities not otherwise associated with a reported
- clinical AE
- AEs that do not meet the above-listed criteria but do meet expedited AE reporting requirements (see also Section 11.1.4)

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 are considered to fall in this category. All fetal losses — including spontaneous fetal deaths, still births, spontaneous abortions, and ectopic pregnancies — are considered reproductive system AEs. Elective abortions are not considered AEs; however, complications or untoward sequelae of elective abortions are considered reproductive system AEs. 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. For example, nausea and vomiting related to pregnancy (hyperemesis) are considered reproductive system AEs, but nausea and vomiting due to gastroenteritis during pregnancy are not. Chronic hypertension worsened by pregnancy would be considered a reproductive system AE, as would diabetes previously controlled by diet that requires insulin during pregnancy.

The Adverse Experience Log case report form (see Section 13.6) is used to report the above-listed reportable AEs to the MTN Statistical and Data Management Center (SDMC) via DataFax. All study sites are strongly encouraged to utilize 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 HPTN 035 web page.

As noted in Section 11.1.1, source documentation for all AEs should minimally include the following information: AE term/diagnosis, severity grade, onset date, outcome, outcome date, and treatment. For reportable AEs, the following additional data elements 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-E6 (see Section 11.1.3), and whether the AE meets expedited AE reporting requirements (see Section 11.1.4). 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 Investigator or Record (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 Event (SAE)

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

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongs an existing hospitalization,
- Results in persistent or significant disability/incapacity, 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 and 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 also usually be considered serious.

SAEs are a subset of all AEs. All SAEs are reportable AEs. For each AE identified in HPTN 035, an authorized study clinician must determine whether the AE meets the definition of SAE. The Adverse Experience Log case report form includes an item (item 8) to record this determination.

11.1.4 Expedited Adverse Event (EAE)

Expedited adverse events (EAEs) are AEs that meet criteria specified in the study protocol as requiring additional reporting for rapid review and assessment by DAIDS. In some cases, DAIDS may be required to report the EAE to the US Food and Drug Administration (FDA). All EAEs must be reported to the DAIDS Safety Office within three business days of site awareness of the EAE.

Although seriousness is a consideration in determining whether an AE meets the definition of EAE, the terms SAE and EAE are <u>not</u> synonymous. The two terms refer to two different, but overlapping, subsets of AEs. For HPTN 035, the subset of AEs that are considered EAEs includes some AEs that are serious and some that are not serious.

The Manual for Expedited Reporting of Adverse Events to DAIDS defines levels of EAE reporting that may be used in DAIDS-sponsored studies. For HPTN 035:

- the "intensive" reporting level was followed in the Phase II portion of the study

- the "standard" reporting level is followed in the Phase IIb portion of the study

With the one exception described in Section 11.1.4.2 below, EAE reporting is undertaken only for participants assigned to the three study gel groups. For each participant, EAE reporting is undertaken through completion of the participant's study exit visit. For participants enrolled in the Phase II portion of the study, intensive reporting requirements were followed through the participant's Month 3 follow-up visit; thereafter, standard reporting requirements are followed. For participants enrolled in the Phase IIb portion of the study, standard reporting requirements are followed throughout follow-up. Thereafter, for all participants, after study exit, only pregnancy outcomes that meet criteria for expedited reporting (e.g., fetal losses) occurring among participants known to be pregnant at study exit will be reported.

All EAEs must be reported on a DAIDS Expedited Adverse Event (EAE) Form. Copies of the form and form completion instructions are available at http://rcc.tech-res-intl.com and in the Study Implementation Materials section of the HPTN 035 web page.

A study physician listed on the site's FDA Form 1572 must review and verify all data recorded on the DAIDS EAE Form for accuracy and completeness. This physician also must make the final assessment of the relationship between the EAE and study product and sign the completed form. If necessary to meet required reporting timeframes, an EAE Form may be submitted to the DAIDS Safety Office without a completed signature page. However, the completed signature page, and any necessary corrections or additions, must be submitted to the DAIDS Safety office within the next three business days.

As noted above, EAE Forms must be submitted to the DAIDS Safety Office within three business days of site awareness of the EAE. The DAIDS Safety Office fax number is shown on the first page of the EAE Form. Completed forms also may be digitally scanned and submitted to the DAIDS Safety Office via email. Contact details are as follows:

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

The DAIDS Safety Office will email a confirmation of receipt for each EAE Form received. If a confirmation of receipt is not received within 24-48 hours after submission, study sites should contact the Safety Office for more information and/or re-submit the EAE Form.

With the exception of congenital anomalies and birth defects identified among infants born to study participants, all EAEs are reportable AEs that must also be reported on Adverse Experience Log case report forms. When completing Adverse Experience Log case report forms and EAE Forms, 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 Forms received at the DAIDS Safety Office 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 Safety Office and the SDMC have been received and that the details recorded on each form are consistent.

11.1.4.1 EAEs for Participants Assigned to Gel

For participants assigned to gel, EAE reporting requirements are presented in Figure 11-3.

Figure 11-3
Expedited Adverse Event Reporting Requirements for HPTN 035

Type of Adverse Event	Phase II: Intensive EAE Reporting	Phase IIb: Standard EAE Reporting
Results in death	Report as EAE regardless of relationship to study product	Report as EAE regardless of relationship to study product
Is a congenital anomaly or birth defect or fetal loss	Report as EAE regardless of relationship to study product	Report as EAE regardless of relationship to study product
Results in persistent or significant disabilities or incapacities	Report as EAE regardless of relationship to study product	Report as EAE regardless of relationship to study product
Requires or prolongs hospitalization or requires intervention to prevent significant/permanent disability or death	Report as EAE if relationship to study product is: • Definitely related • Probably related • Possibly related • Probably not related	Report as EAE if relationship to study product is: • Definitely related • Probably related • Possibly related • Probably not related
Is life-threatening (includes all Grade 4 AEs)	Report as EAE if relationship to study product is: • Definitely related • Probably related • Possibly related • Probably not related	Report as EAE if relationship to study product is: • Definitely related • Probably related • Possibly related • Probably not related
Other Grade 3 AEs	Report as EAE if relationship to study product is: • Definitely related • Probably related • Possibly related • Probably not related	Do not report as EAE
Other Grade 1 and Grade 2 AEs	Do not report as EAE	Do not report as EAE

In addition to the events listed above, for participants assigned to gel, the following also should be reported as EAEs:

- AEs that may be related to study product (i.e., definitely, probably, possibly, or probably not related) that the IoR believes are of sufficient concern to be reported on an expedited basis to DAIDS. This includes AEs that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent a serious AE.

- Serious AEs that are not related to study product but could be associated with study participation or procedures.

- Unexpected serious AEs that may be related to study product (i.e., definitely, probably, possibly, or probably not related) that occur after the participant's study exit visit.

11.1.4.2 EAEs for Participants Assigned to Condoms Only (No Gel)

For participants assigned to condoms only (no gel), only one type of AE must be reported as an EAE:

- Serious AEs that are not related to study gel but could be associated with study participation or procedures.

11.2 Adverse Event Terminology

Study staff must assign a term or description to all AEs identified in HPTN 035. Whenever possible, a diagnosis should be assigned, rather than a cluster of signs and/or symptoms. When relevant, an anatomical location should be included in the term or description. This is especially important in HPTN 035 for distinguishing pelvic exam findings that may be observed on the vulva, in the vagina, or on the cervix.

When it is not possible to identify a single diagnosis to describe a cluster of signs and/or symptoms, each individual sign and symptom must be reported as an individual AE.

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., decreased hematocrit, elevated ALT). The severity grade of the result should not be reported as part of the AE description since the grade is captured elsewhere (item 3) on the form.

11.3 Adverse Event Severity

The term severity is used to describe the intensity of an AE. The severity of all AEs identified in HPTN 035 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 <u>not</u> 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 <u>except vulvovaginitis and cervicitis</u> will be graded using the DAIDS Table for Grading Adult and Pediatric Adverse Events (also referred to as the "Toxicity Table"), dated December 2004. Vulvovaginitis and cervicitis will be graded according to Figure 11-4, which re-printed from protocol Section 6.2:

Figure 11-4
Severity Grading for Vulvovaginitis and Cervicitis
To Be Used Adopted After Obtaining IRB Approval for Letter of Amendment #1

	Vulvovaginitis	Cervicitis
Grade 1	Vulvar and/or vaginal discomfort (including itching or burning), pelvic exam findings indicative of inflammation, and/or other exam findings* (including findings involving epithelial disruption) that do not require medical therapy and that cause no or minimal interference with usual social and functional activities	Cervical inflammation or other findings on exam (including erythema, mucopurulent discharge, and/or friability) that do not require medical therapy and that cause no or minimal interference with usual social and functional activities
Grade 2	Vulvar and/or vaginal discomfort (including itching or burning), pelvic exam findings indicative of inflammation, and/or other exam findings* (including findings involving epithelial disruption) that require minimal medical therapy (such as a course of topical or oral antibiotics or antifungals) or cause greater than minimal interference with usual social and functional activities	Cervical inflammation or other findings on exam (including erythema, mucopurulent discharge, and/or friability) that require minimal medical therapy (such as a course of oral antibiotics) or that cause greater than minimal interference with usual social and functional activities
Grade 3	Vulvar and/or vaginal discomfort (including itching or burning), pelvic exam findings indicative of inflammation, and/or other exam findings* (including findings involving epithelial disruption) that result in inability to perform usual social and functional activities and/or require significant medical intervention such as a surgical procedure or hospitalization	Cervicitis or other findings on exam (including erythema, mucopurulent discharge, and/or friability) that require significant medical intervention (such as intravenous antibiotics) or that cause inability to perform usual social and functional activities
Grade 4	Life threatening — vulvovaginitis with perforation	Life threatening

* Findings include erythema, edema, grossly white finding, petechiae, ecchymosis, peeling, ulceration, abrasion, laceration.

Several clarifications of severity grading requirements have been provided in HPTN 035 Q&A items and Data Communiqués. For ease of reference, these are summarized as follows:

- If the severity of an AE falls into more than one grading category on the Toxicity Table, assign the higher of the two grades to the AE.

- Laboratory values that fall outside of a site's normal range, but do not meet criteria for grade 1 severity, should not be considered "abnormal" for purposes of reporting pre-existing conditions or AEs, unless clinical judgment determines otherwise.

- Conditions and laboratory abnormalities that are not explicitly listed on the Toxicity Table should be graded according to the "estimating severity grade" row of the Toxicity Table.

- Seasonal allergies should be graded according to the "estimating severity grade" row of the Toxicity Table (not the "acute systemic allergic reaction" row).

- Sexually transmitted infections and reproductive tract infections should be graded according to the "infections (any other than HIV infection)" row of the Toxicity Table. If systemic antimicrobial treatment is given to treat the infection, the grade must be 2 or higher.

- Spontaneous abortions should be graded according to the "estimating severity grade" row of the Toxicity Table, taking into consideration the functional status of the participant who experiences the spontaneous abortion. For example, a participant who does not experience any symptoms but is found to have a negative pregnancy test after having a prior positive pregnancy test would have grade 1 assigned to her spontaneous abortion whereas a participant who experiences severe symptoms and possibly even hemorrhage might have grade 3 or 4 assigned to her spontaneous abortion.

- Hemoglobin test results should be graded according to the "hemoglobin" rows of the Toxicity Table. The Toxicity Table includes rows infants of age 36-56 days, HIV-negative persons ages 57 days and older, and HIV-positive persons ages 57 days and older.

    - 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 the 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 during follow-up, the severity of lymphocyte test results should not be assessed.

- When assigning severity grades to laboratory test results that require calculations based on the site normal range, there will be times when the calculated severity grade range will 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. Calculated grade ranges should not be rounded when determining the severity grade. One example from Data Communiqué #11 that illustrates how to assign severity grades using grading calculations is as follows: For total bilirubin, the grade 1 range per the Toxicity Table is 1.1-1.5 times the site's site upper limit of normal (ULN). The grade 2 range is 1.6-2.5 x ULN. The site ULN is 1.3 mg/dL. The calculated grade 1 range for this site is 1.43-1.95 mg/dL and the grade 2 range is 2.08-3.25 mg/dL. A test result of 1.4 mg/dL at this site should not be assigned a severity grade, as it does not fall within the calculated grade 1 range. A test result of 2.0 mg/dL should be assigned grade 2, because when severity falls between two grades, the higher grade should be assigned.

11.4 Adverse Event Relationship to Study Product

For each reportable AE identified in HPTN 035, an authorized study clinician must assess the relationship of the AE to study product, based on the temporal relationship of the AE to administration of product, product pharmacology and other information provided in the Investigator's Brochures, and clinical judgment. One of the following relationship categories must be assigned to each reportable AE:

- Definitely Related: The AE and administration of study gel are related in time, and a direct association can be demonstrated.
- Probably Related: The AE and administration of study gel are reasonably related in time, and the AE is more likely explained by study gel than other causes.
- Possibly Related: The AE and administration of study gel are reasonably related in time, and the AE can be explained equally well by causes other than study gel.
- Probably Not Related: A potential relationship between the AE and study gel could exist (i.e., the possibility cannot be excluded), but the AE is most likely explained by causes other than study gel.
- Not Related. The AE is clearly explained by another cause not related to study gel.

Note: *The HPTN 035 study products are comprised of the gel applicators as well as the gel contained in each applicator. Any AEs thought to be related to an applicator should be documented as such by choosing one of the "related" categories and using descriptive text, comments, or other notations to indicate that the presumed relationship is to the applicator.*

In addition to the relationship categories listed above, DAIDS allows a relationship of "pending" to be temporarily assigned to AEs that result in death, if additional time and information are needed to determine the relationship of the AE to study product. However, a final relationship assessment must be submitted to DAIDS (via the EAE Form) within three business days after first reporting the death. If a final assessment is not made within three business days, the AE will be considered possibly related to study product.

11.5 Adverse Event Outcomes and Follow-Up Information

All AEs identified in HPTN 035 — regardless of whether they are reportable per Section 11.1.2 — must be followed clinically until the AE resolves (returns to baseline) or stabilizes. In addition to performing other protocol-specified procedures, 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.

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.

Site staff are not required to report the outcome of EAEs to the DAIDS Safety Office, unless outcome information is specifically requested by DAIDS. However, if an EAE increases in severity to a higher grade than previously reported, it must be reported to the DAIDS Safety Office as a new EAE on a new EAE Form.

EAE follow-up information also must be reported to the DAIDS Safety Office 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 adverse event (this is particularly important for new information addressing cause of death if the initial assignment was "pending")
- Results of re-challenge with the study product, if performed

In these circumstances, the required follow-up information should be reported on a new EAE Form as a Follow-Up Report. See also Section 5.1 of the Manual for Expedited Reporting of Adverse Events to DAIDS.

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 HPTN 035 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 occurred before randomization, the infection is considered a pre-existing condition: report on the Pre-existing Conditions form.

- For HPV, genital warts present before randomization are considered a pre-existing condition: report on the Pre-existing Conditions form.

- Any outbreaks that occur after randomization are considered AEs, regardless of whether the viral infection was pre-existing before randomization: report on an Adverse Experience Log form.

If an EAE that was previously reported to the DAIDS Safety Office resolves and then later recurs at a level requiring expedited reporting, the second occurrence must be reported to the DAIDS Safety Office as a new EAE on a new EAE Form.

11.7 Social Harms

In addition to medical AEs, participants in HPTN 035 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 HPTN 035 Follow-Up Behavior Assessment form actively ascertains, on quarterly basis, whether participants in all study treatment groups 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.

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. If the issue or problem meets criteria for expedited reporting to the DAIDS Safety Office, report it as described in Section 11.1.3 above. Also report the issue or problem to all responsible IRBs/ECs, if required per IRB/EC guidelines.

- Ask the participant to articulate 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.

- Consult the HPTN 035 Protocol Safety Review Team (PSRT) for further input and guidance as needed.

As is the case with medical AEs, data collected on social harms will be monitored by the HPTN 035 PSRT and the NIAID Vaccine and Prevention Data and Safety Monitoring Board (DSMB), as described below.

11.8 HPTN 035 Safety Monitoring, Review, and Oversight

Please refer to Section 6 of the HPTN 035 protocol and Section 14 of the HPTN 035 Manual of Operations for a complete description of the participant safety monitoring procedures in place for HPTN 035. Also refer to Section 15 of this manual for a description of the reports prepared by the MTN SDMC in support of HPTN 035 safety monitoring procedures.

Participant safety is of paramount importance in HPTN 035. Primary safety monitoring and safeguarding of individual study participants is the responsibility of study site staff, under the direction of the IoR. The IoR and designated site staff also are responsible for submitting case report forms to the MTN SDMC and EAE Forms to the DAIDS Safety Office, such that relevant safety data are available in a timely manner for other study-specific safety monitoring procedures, as follows:

- Clinical Affairs staff at the MTN SDMC will review clinic and laboratory data received at the SDMC and apply clinical data quality control notes (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 prepare a memo to file to 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 Safety Office, DAIDS RAB Safety Specialist, and DAIDS PSB Medical Officer will review all EAE Forms received for HPTN 035 and follow up on these reports with site staff, the HPTN 035 Protocol Team, and drug regulatory authorities when indicated.

- The HPTN 035 Protocol Safety Review Team (PSRT) will routinely review safety data reports prepared for HPTN 035 by the MTN SDMC. As described further in Section Appendix 11-2, 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 the four study treatment groups.

- The NIAID Vaccine and Prevention Data and Safety Monitoring Board (DSMB) will routinely review safety data reports prepared for HPTN 035 by the MTN SDMC. To date, the DSMB has completed safety data reviews in October 2005, January 2006, and October 2006; the October 2006 review included all Phase II study data. For the remainder of the study, it is expected that the DSMB will review the Phase IIb data approximately every eight months. Data reports prepared for the DSMB will present safety data in a coded manner by study treatment 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 HPTN 035 Protocol Team shortly after the review takes place. IoRs must forward copies of these reports to all Institutional Review Boards and Ethics Committees (IRBs/ECs) responsible for oversight of research at their site.

Prior to reviews by the DSMB, and independently, the HPTN Study Monitoring Committee (SMC) also will periodically review HPTN 035 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 HPTN leadership that could affect the study and study sites in significant ways. These decisions are based on detailed review of the available study data and careful consideration of ongoing participant safety and study viability.

11.9 Safety Distributions from DAIDS

As noted in Section 1 of this manual, study sites will receive product- and safety-related information throughout the period of study implementation. This information will be distributed by DAIDS, through its Regulatory Compliance Center and/or the HPTN Coordinating and Operations Center, and may include:

- Updated Investigator's 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 the study site Essential Document files for HPTN 035. 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 all study 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
DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

Quick Reference

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.

General Instructions

Estimating Severity Grade

If the need arises to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located at the top of Page 3. For AEs that are not listed in the table but will be collected systematically for a study/trial, protocol teams are highly encouraged to define study-specific severity scales within the protocol or an appendix to the protocol. (Please see "Template Wording for the Expedited Adverse Event Reporting Section of DAIDS-sponsored Protocols".) This is particularly important for laboratory values because the "Estimating Severity Grade" category only applies to clinical symptoms.

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.

Determining Severity Grade

If the severity of an 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.

Definitions

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
PUBLISH DATE: DECEMBER, 2004

Contents

Clinical	Page
Estimating Severity Grade	3
Systemic	3
Infection	4
Injection Site Reactions	4
Skin – Dermatological	5
Cardiovascular	5
Gastrointestinal	7
Neurologic	9
Respiratory	12
Musculoskeletal	12
Genitourinary	13
Ocular/Visual	14
Endocrine/Metabolic	14

Laboratory	Page
Hematology	16
Chemistries	17
Urinalysis	20

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
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.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
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
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
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
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
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)
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
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
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)]
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.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
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.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
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.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
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.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
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.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
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

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
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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
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.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
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

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
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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)
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
PUBLISH DATE: DECEMBER, 2004

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*
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*
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
Hemoglobin (Hgb)				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *1.32 – 1.55 mmol/L*	7.5 – 8.4 g/dL *1.16 – 1.31 mmol/L*	6.50 – 7.4 g/dL *1.01 – 1.15 mmol/L*	< 6.5 g/dL *< 1.01 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *1.55 – 1.69 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *0.39 – 0.53 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *0.54 – 0.68 mmol/L*	7.0 – 8.9 g/dL *1.09 – 1.39 mmol/L* OR Any decrease ≥ 4.5 g/dL *≥ 0.69 mmol/L*	< 7.0 g/dL *< 1.09 mmol/L*
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *1.32 – 1.46 mmol/L*	7.0 – 8.4 g/dL *1.09 – 1.31 mmol/L*	6.0 – 6.9 g/dL *0.93 – 1.08 mmol/L*	< 6.00 g/dL *< 0.93 mmol/L*

* Values are for term infants.

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

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *1.47 – 1.63 mmol/L*	8.0 – 9.4 g/dL *1.24 – 1.46 mmol/L*	7.0 – 7.9 g/dL *1.09 – 1.23 mmol/L*	< 7.00 g/dL *< 1.09 mmol/L*
Infant*†, 1 – 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *1.86 – 2.02 mmol/L*	10.0 – 11.9 g/dL *1.55 – 1.85 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L*	< 9.0 g/dL *< 1.40 mmol/L*
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*
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*
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

* Values are for term infants.

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

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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 (corrected for albumin)				
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 (corrected for albumin)				
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*
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†
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*

* Values are for term infants.

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

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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	< 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
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*
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*

* Values are for term infants.

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

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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.

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

Section Appendix 11-2
HPTN 035 Protocol Safety Review Team Plan

Roles and Responsibilities of the PSRT

Per the HPTN 035 protocol, the roles and responsibilities of the HPTN 035 Protocol Safety Review Team (PSRT) are to:

1. Conduct regular reviews of standardized study safety data reports (protocol Section 6.1). Once the SDMC begins receiving study 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 (for example, calls may be less frequent after the Phase II portion of the study is completed). Should any safety concerns be identified by the PSRT, these will be referred to the HPTN Study Monitoring Committee (SMC) and/or DAIDS Vaccine and Prevention Data and Safety Monitoring Board (DSMB), as appropriate.

2. Respond to Investigator queries regarding temporary or permanent discontinuation of product use (protocol Section 4.6). The protocol specifies a limited number of situations in which study participants must discontinue product use; Investigators will implement these discontinuations in the absence of consultation with the PSRT. In other situations, however, discontinuation of product must be undertaken in consultation with the PSRT. These situations involve participants who:

   (a) experience an AE that meets criteria for expedited reporting to DAIDS that is judged possibly related to product use;
   (b) have a pelvic exam finding involving deep epithelial disruption that does not resolve over the course of an additional month of continued product use;
   (c) are unable or unwilling to comply with required study procedures; or
   (d) otherwise might be put at undue risk to their safety and well-being by continuing product use.

3. Respond to Investigator queries regarding product resumption following occurrence of an AE judged probably or definitely related to study product that meets criteria for expedited reporting (protocol Section 4.6).

4. Respond to Investigator queries regarding study eligibility and general AE management and reporting (not necessarily related to product use; protocol Section 10.2).

5. Respond to Investigator requests for participant withdrawal from the study (protocol Section 3.6).

6. Respond to Investigator requests for participant unblinding (protocol Section 7.5). 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 currently comprise the HPTN 035 PSRT:

- Salim Abdool Karim, Protocol Chair, PSRT Chair
- Zvavahera Michael Chirenje, Senior Site Investigator, PSRT Alternate Chair
- Anne Coletti, HPTN CORE Clinical Research Manager
- Nancy Connolly, Protocol Safety Physician
- Bryna Harwood, Protocol Safety Physician
- Sharon Hillier, HPTN Central Laboratory Co-Investigator
- Irving Hoffman, Protocol Co-Chair
- Hsiu-Ying Huang, HPTN SDMC Clinical Affairs Safety Associate
- Lisa Maslankowski, Protocol Co-Chair
- Benoît Mâsse, HPTN SDMC Protocol Statistician
- Barbra Richardson, HPTN SDMC Protocol Statistician
- Lydia Soto-Torres, DAIDS PSB Medical Officer
- Sheryl Zwerski, DAIDS PSB Medical Officer

Ideally all of the above-listed PSRT members will take part in routine PSRT conference calls. At a minimum, the PSRT Chair or Alternate PSRT Chair and the DAIDS PSB Medical Officer or DAIDS PSB Program Officer/Nurse Consultant must take part in all calls. If both of these two members are not present, the call may be deferred until the next scheduled call time unless a PSRT member requests a more immediate call.

HPTN 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 and distribute standard safety data reports to the PSRT via e-mail one week prior to each PSRT conference call. Tabulations will be generated for all study participants combined (i.e., across all treatment 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 and 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 grade 2, grade 3, and grade 4 AEs reported to date by body system and relationship to study product
- Information on all pregnancies and pregnancy outcomes

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

PSRT Communications

An email alias (035PSRT@HPTN.org) will be used to facilitate communication with the PSRT. All safety data summary reports from the SDMC will be distributed via this alias. A standard PSRT query form (below) will be used to elicit sufficient information to allow the PSRT to respond to each query. To ensure a timely PSRT response, one of the Protocol Safety Physicians is responsible for providing a final response to the query or a request for more information from the study site (via email) within three business days after receipt of the query. All members of the PSRT are encouraged to review the information provided by the site and to offer their advice; however final determination rests with the PSRT Chair or Alternate Chair.

HPTN 035 Protocol Safety Review Team Query Form, page 1 of 2

Instructions: Email completed form to brynah@uic.edu and nconnolly@mail.magee.edu. IMPORTANT: Complete all required fields so the PSRT has all information needed to respond to your query.

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

PTID: **Participant Age** (in years):
Enrollment Date (dd-MMM-yy):

Reason for query:
- ☐ Product use consultation:
  - ☐ Should use of study gel be temporarily discontinued (held)?
  - ☐ Should use of study gel be permanently discontinued (held)?
  - ☐ Should use of study gel be resumed?
- ☐ Request for consultation on AE management
- ☐ Request to withdraw participant from the study
- ☐ Request to unblind participant's gel assignment
- ☐ Other, specify:

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

Primary AE of concern:

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

Relatedness to study gel:
☐ Definitely related
☐ Probably related
☐ Possibly related
☐ Probably not related
☐ Definitely not related

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

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

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

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

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

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

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

End of Form for Site Staff. Email completed form to the HPTN 035 Protocol Safety Physicians (brynah@uic.edu **and** nconnolly@mail.magee.edu. If an email response is not received from the PSRT within 3 business days, re-contact the Protocol Safety Physicians and/or the MTN CORE (acoletti@fhi.org or kgomez@fhi.org) for assistance.

FOR PSRT USE ONLY — PROVIDE RESPONSE TO QUERY HERE

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

Query Outcome:
☐ Approved
☐ Not approved
☐ Not applicable

PSRT Comments: