

Section 11. Adverse Event Reporting and Safety Monitoring

This section presents information related to mother and infant safety monitoring and adverse event (AE) reporting procedures. Additional information on completion of the mother and infant adverse experience logs is included in Section 12 of this study specific procedures manual (SSP). Please refer to the protocol Sections 6 and 7 and the current version of the following resources:

- Manual for Expedited Reporting of Adverse Events to DAIDS” (DAIDS EAE Manual)
- Manual for Expedited Reporting of Adverse Events to DAIDS
- DAERS Reference Guide for Site Reporters and Study Physicians
- Package Insert for Tenofovir (Viread)

All of the above resources are available on the DAIDS Regulatory Compliance Center (RCC) web site; <http://rcc.tech-res.com>

In HPTN 057, AEs are reported for all mothers and infants enrolled in Cohorts 1, 3 and 4 and for all infants enrolled in Cohort 2 (mothers do not receive study drug in Cohort 2). As stated in the study protocol, any conditions or health problems occurring in mothers in Cohorts 1, 3, and 4 and infants enrolled in Cohort 2 prior to receiving study drug are to be reported as pre-existing conditions. Since infants are exposed to study drug in-utero through the mother’s dose of tenofovir disoproxil fumarate (TDF) in Cohorts 1, 3 and 4 there will be no pre-existing conditions reported in those infant Cohorts. If a pre-existing condition worsens (i.e., severity grade or frequency increases) after enrollment, it should be reported as an AE.

11.1 Adverse Event Definitions

Throughout this SSP section and in the study protocol, the following terms describe the types of reportable events and reporting requirements.

Adverse event (AE): Any untoward medical occurrence in a clinical research participant administered an investigational product and which may or may not have a causal relationship with the investigational product. An AE can be an unfavorable or unintended sign (e.g., an abnormal laboratory finding), or a symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product (International Conference on Harmonization (ICH)E6).

For HPTN 057, any untoward medical occurrence that occurs in mothers or infants directly receiving study drug or in infants exposed to study drug through the dose his/her mother received is considered an AE. As stated in the study protocol and above, any conditions or health problems occurring in mothers and infants prior to exposure to study drug are to be reported as *pre-existing conditions*, including congenital anomalies. If a pre-existing condition worsens (frequency increases and/or severity grade increases), after enrollment it should be reported as an AE.

Serious adverse event (SAE): Any AE that at any dose that results in any of the following outcomes (21 CFR 312 and ICH E6):

- Death,
- A life-threatening condition,
- A congenital anomaly/birth defect,
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

- An important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject or may require intervention to prevent one of the outcomes listed above (ICH E2A).

11.2 Adverse Events that Meet the Criteria for Expedited Reporting to DAIDS (EAEs)

In addition to the standard terms defined in the section above, the protocol and this manual also refer to **adverse events that meet the criteria for expedited reporting to DAIDS**. These are referred to as Expedited Adverse Events (EAEs) and are a special subgroup of all AEs for which additional reporting and rapid review are required. While *seriousness* of an AE is a consideration in defining this subset of AEs, it is important to note that the terms ‘SAE’ and ‘EAE’ are not synonymous and instead refer to two different, but overlapping, subsets of all AEs.

The DAIDS EAE Manual specifies different “levels” of reporting. Each level of reporting includes a slightly different subset of AEs that must be reported in an expedited manner to DAIDS, with some levels being more inclusive (conservative) than others. Individual studies may also have additional protocol-specific requirements. Three factors are considered when identifying AEs that meet the criteria for expedited reporting to DAIDS: 1) seriousness, as defined above, 2) severity and 3) relatedness, the latter two of which are described below.

As specified in Version 2.0 of the protocol, HPTN 057 will follow the DAIDS EAE Manual for the duration of the study. Specifically, the ‘intensive’ level of reporting defined in the EAE Manual will be applied. The intensive level requires expedited reporting of any adverse event that:

- Results in death, regardless of relationship to study product.
- Results in persistent or significant disabilities or incapacities, regardless of relationship to study product.
- Is a congenital anomaly, birth defect or fetal loss regardless of relationship to study product.
- Requires hospitalization or prolongs existing hospitalization and is probably not related, possibly related, probably related or definitely related to the study product.
- Is life-threatening (including Grade 4 adverse events) and probably not related, possibly related, probably related or definitely related to the study product.
- Is Grade 3 adverse event and probably not related, possibly related, probably related or definitely related to the study product.
- Requires intervention to prevent significant/permanent disability or death and is probably not related, possibly related, probably related or definitely related to the study product.

Section 3.3 of the DAIDS EAE Manual specifies that sites should also report any of the following adverse events on an expedited basis to DAIDS, even if they do not otherwise meet the specified criteria for expedited reporting:

- Any AE that the Investigator believes is of sufficient concern to be reported on an expedited basis to DAIDS that may be related to the study agent (definitely, probably, possibly, or probably not related). This includes adverse events that, based on clinical judgment, may require intervention to prevent a serious adverse event.
- SAEs that are not related to a study agent, but could be associated with study participation or procedure. For example, in HPTN 057, this might include serious infections associated with blood-drawing.

- Unexpected SAEs that may be related to the study agent (definitely, probably, possibly, or probably not related) that occur after the protocol-defined expedited reporting period if the study staff becomes aware of its occurrence.

11.2.1 Procedures for Reporting EAE's to DAIDS

All EAEs should be reported to the DAIDS RCC Safety Office using the internet-based DAIDS Adverse Experience Reporting System (DAERS), per instructions provided in the DAERS Reference Guide for Site Reporters and Study Physicians. The process of EAE reporting via DAERS involves a designated "Study Reporter" creating an electronic EAE report and a designated "Study Physician" reviewing the EAE report, signing the EAE report with an electronic signature, and submitting the EAE report to the DAIDS RCC Safety Office. If an EAE report is not completed and submitted within three business days of site awareness of the EAE, an explanation must be entered in DAERS before the report can be submitted.

DAERS also may be used to withdraw an EAE report that was submitted in error and to modify or update a previously submitted EAE report. For all submitted EAE reports, updates must be submitted to report the final or stable outcome of the EAE, unless the original report provided a final or stable outcome.

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

For questions about DAERS, please email DAIDS-ESSupport@niaid.nih.gov. Questions also may be submitted from within the DAERS application itself.

In the event that DAERS cannot be accessed (e.g., due to poor internet connectivity), paper-based EAE reporting should be used, per instructions provided in the Manual for Expedited Reporting of Adverse Events to DAIDS. Completed paper EAE Forms may be faxed or digitally scanned and emailed to the DAIDS RCC Safety Office. The EAE Form and form completion instructions are available on the DAIDS RCC web site; contact details for submission of EAE Forms are provided in the Manual for Expedited Reporting of Adverse Events to DAIDS which is also available on the DAIDS RCC web site.

11.3 Adverse Event Severity Grading

The severity (intensity) of all AEs will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004 and Clarification dated August 2009, and the protocol specific grading scales for calcium and for malnutrition and fever specified in Section 4.6 of the protocol and Section 11.4 of this manual. The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events and Clarification dated August 2009 are located at the RCC web site <http://rcc.tech-res.com>.

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

As mentioned above, in addition to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, malnutrition (failure to thrive) and axillary fever will be graded according to the Supplemental Table for Grading Severity of Malnutrition and Fever as specified in the Section 4.6 of the protocol.

When grading laboratory values for which the Toxicity Table specifies the use of a multiple of the upper limit of normal (ULN), 'normal' values are defined according to local age-adjusted institutional values.

There are five severity grades that can be assigned to AEs:

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

NOTE: For grading clinical AEs not specified in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events or in the study protocol, a guide for estimating severity is included on page 3 of the DAIDS Toxicity Table.

If the severity of an AE could fall under either one of two grades (e.g. the severity could be a grade 2 or a grade 3), the higher of the two grades should be assigned.

Note: The measurement of albumin is only for determination of severity grade for calcium levels, which calls for correction for albumin. Corrected calcium levels will be monitored for safety, therefore, separate grading and reporting of AEs for albumin is not required.

11.3.1 Assigning Severity Grades on CRFs

For some lab assays, the severity grade range is calculated using a value from the DAIDS Toxicity Table and a local site lab normal range. For example, a Grade 1 AE for total bilirubin is 1.1–1.5 times the site lab upper-limit of-normal (ULN). There will be times when the calculated severity range will have more significant digits than the reported lab value, which can lead to confusion regarding which severity grade to assign.

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

1. Rounding is permitted *only* when recording lab values on a CRF in order to match the level of precision allowed on the CRF.
2. If the lab value is reported in a unit other than that which appears on the CRF, first perform the conversion, then round the converted result to match the level of precision allowed on the CRF.
3. When calculating a severity grade range, never round on interim steps.
4. Always compare the severity grade range to the value that was recorded on the CRF (not the lab-reported value).
5. If the calculated severity grade range has more significant digits than the lab value, do not round the calculated range values. Instead, treat all missing digits in the lab value as zeros.

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

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

The site-specific grade range is accurate to the hundredths place. Treating the hundredths place of the total bilirubin value as a zero gives us a value of 1.40.

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

6. If the lab value falls between two calculated severity grade ranges, assign it the higher grade as stated in the DAIDS Toxicity Table General Instructions (page 1).

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

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

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

Note: there is a one digit gap between each grade for Blood Pressure on the DAIDS Toxicity Table. We have confirmed with DAIDS that when there is a gap between values, as noted by a “greater than” (>) symbol, this should be interpreted as “greater than/or equal to” (≥).

11.4 Adverse Event Relationship Assessment

The study clinician assesses the causal relationship based on the temporal relationship of AE onset to study drug administration, the pharmacology of the study product and his/her clinical judgment using the following categories of relatedness defined by DAIDS:

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

- **Not Related.** The adverse event is clearly explained by another cause not related to the study agent.
- **Pending.** Pending may be used as a temporary relationship assessment only for death and only if data necessary to determine relationship to study agent are being collected. The site is required to submit a final assessment within 3 business days after reporting the death. If no final assessment is made within 3 business days after the date of submission, the event will be assessed as possibly related to study agent. Any additional information received at a later time, including an autopsy report, should be submitted as a Follow-up Report.

11.5 Specific Adverse Event Documentation and Reporting Requirements for HPTN 057

All AEs occurring in mothers and infants after exposure to study drug and throughout the duration of the study must be recorded in the study source documentation and on a Mother or Infant Adverse Experience Log, case report form (CRF) for entry into the study database, regardless of seriousness, severity or relatedness. This includes AEs in infants reported by the mother or care taker and AEs identified through study assessments. The severity of all clinical and laboratory AEs must be graded according to the standard DAIDS Table for grading Adult and Pediatric Adverse Events and Clarification dated August 2009 with the following exceptions:

Calcium which will be graded using the following parameters which include correction for albumin:

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

Note: The measurement of albumin is only for determination of severity grade for calcium levels, which calls for correction for albumin. Corrected calcium levels will be monitored for safety; therefore, separate reporting of AEs for albumin is not required.

In addition, grading of malnutrition (failure to thrive) will follow the scale below:

- Grade 1 - Underweight: 60-80% of the 50th percentile expected weight for age and edema absent
- Grade 2 - Marasmus: <60% of 50th percentile expected weight for age and edema absent
- Grade 3 - Kwashiorkor: 60-80% of the 50th percentile expected weight for age and edema present
- Grade 4 - Marasmic-kwashiorkor: <60% of 50th percentile expected weight for age and edema present

Axillary measured fever will be graded as follows:

- Grade 1: 37.1 - 38.0 °C
- Grade 2: 38.1 - 38.7 °C
- Grade 3: 38.8 - 39.9 °C
- Grade 4: >39.9 °C

Table 11-1 below outlines the documentation requirements and timeframes for reporting of non-serious and serious AEs for HPTN 057.

Non-serious Adverse Events

Non-serious adverse events occurring in infants and mothers after exposure to study drug for the duration of follow-up must be recorded on the Mother or Infant Adverse Experience Log CRF (DataFax Form). Protocol-specified local laboratory results will be reported on the Mother and Infant Laboratory Results CRFs for entry into the study database, and abnormalities will be graded. (All lab abnormalities should be recorded on an AE Log CRF, regardless of severity grade.)

Serious Adverse Events (SAEs) and Adverse Events that Meet the DAIDS Expedited Reporting Criteria (EAEs)

Throughout the entire 12 month follow-up period, all SAEs – regardless of relatedness – and all EAEs will be recorded on the Mother or Infant Adverse Experience Log CRF for entry into the study database.

Also, throughout the entire 12 month follow-up period, all EAEs will be reported on the DAIDS EAE Reporting Form and sent *within three (3) business days of site awareness* (the site’s recognition that the event fulfills the criteria for expedited reporting) to the DAIDS Safety Office through their Regulatory Compliance Center (RCC) according the procedures specified in the DAIDS EAE Manual. Note that the fax number for submission and other contact information is included on Page 1 of the EAE Reporting Form and in the EAE Manual. Detailed instructions for completion of the EAE Reporting Form can be found on the RCC web site at <http://rcc.tech-res.com>.

Table 11-1: HPTN 057 Adverse Event Reporting and Additional Documentation Requirements*

	ADVERSE EVENT	RELATIONSHIP TO STUDY PRODUCT	REQUIRED REPORTING DURATION	AE LOG CRF (Infant’s or Mother’s) (DataFax to SDMC)	EAE FORM (to DAIDS RCC within 3 business days of site awareness)
SERIOUS ADVERSE EVENTS	Results in Death	Regardless of relationship	Duration of study	YES	YES
	Congenital anomalies, birth defects, or fetal losses	Regardless of relationship	Duration of study	YES	YES
	Results in persistent or significant disability or incapacity	Regardless of relationship	Duration of study	YES	YES
	Requires or prolongs hospitalization	Probably not related Possibly related Probably related Definitely related	Duration of study	YES	YES

	Requires intervention to prevent significant incapacity/permanent disability or death	Probably not related Possibly related Probably related Definitely related	Duration of study	YES	YES
	Is immediately life-threatening (including Grade 4 events)	Probably not related Possibly related Probably related Definitely related	Duration of study	YES	YES
	All other SAEs	Not related to study product	Duration of study	YES	NO (unless directly related to study participation)
NON-SERIOUS ADVERSE EVENTS	All Grade 3 AEs	Probably not related Possibly related Probably related Definitely related	Duration of study	YES	YES
	All other non-serious AEs	Regardless of relationship	Duration of study	YES	NO

* All AEs must be documented in the participant's source record and either the infants or mothers AE Log CRF for the duration of the study, regardless of seriousness, severity or relatedness.

11.6 Abnormalities at Baseline (Pre-Existing Conditions)

As stated in the study protocol and above, **any conditions or health problems occurring in mothers enrolled in Cohorts 1 and 3 and infants enrolled in Cohort 2 prior to receiving study drug are to be reported as pre-existing conditions**, including congenital anomalies and abnormal lab values that are not at exclusion criteria levels. Infants enrolled in Cohorts 1 and 3 are exposed to study drug in utero through the mother's dose and therefore will not have any pre-existing conditions reported.

Pre-existing conditions are graded using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004 and Clarification, dated August 2009 with the following exceptions calcium will be graded using the following parameters which include correction for albumin and grading of malnutrition and fever will be graded using the scale in protocol Section 4.6 and copied in Section 11.5 of this manual.

11.7 Lab Abnormalities

The Investigator or designee should carefully review participants' laboratory abnormalities since the previous visit to identify any AEs or health problems. Each page of the lab results must be initialed and dated by the Investigator or designee to document the review. The lab results must be documented in the site source documents. In addition, protocol-specified local laboratory results for infants will be recorded on the Infant Laboratory Results DataFax CRF for entry into the study database. Lab results for mothers will be recorded on the Mother Laboratory Results DataFax CRF. If a lab abnormality is not associated with a specific diagnosis or condition, the lab abnormality must be reported separately as an AE on the Mother or Infant Adverse Experience Log CRF. (All lab abnormalities, regardless of severity grade, must be recorded on an AE Log CRF.)

11.8 Follow-up Information on Adverse Events

Site clinicians are responsible for closely monitoring and following all AEs until resolution and for documenting clinical progress in the participant's source records. In addition to performing protocol-specified assessments at each visit, the study clinician should evaluate the current status of all previously reported ongoing AEs. **During the dosing phase, for infants enrolled in Cohorts 2 and 3 (thru day 5 of life), it is critical that the study clinician assess the infant's eligibility for continued dosing before each dose is given. The Toxicity Criteria for permanent study drug discontinuation in infants are included in Section 4.6.1 of the study protocol and in Section 11.16 of this Study Specific Procedures Manual.**

A new Adverse Experience Log CRF is NOT required when submitting follow-up information for a previously reported AE *unless* the AE severity grade has increased. Instead, the existing Adverse Experience Log CRF should be updated and resubmitted to the SDMC via DataFax. For additional instructions, see Section 12 of this SSP Manual.

The requirements for submission of follow-up information on EAEs are specified in Section 5.0 of the DAIDS EAE Manual. For an EAE reported to DAIDS, the site is required to submit follow-up information (when it becomes available) on a new EAE Reporting Form as a Follow-up Report, for the following circumstances:

- Requests by DAIDS for additional information.
- A change in the relationship between the adverse event and study agent 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."

11.9 Outcome of Adverse Events

The site must follow the progress of each reported AE and record eventual outcomes in the source documentation. In addition, the AE Log CRF should be updated with this information and be resubmitted to the SDMC via DataFax.

Reporting the outcome of an EAE to the DAIDS Safety Office is not required unless specifically requested by DAIDS.

11.10 Reporting Recurrent Adverse Events

If an AE that was previously reported on the AE Log CRF and subsequently fully resolved later recurs, the AE is considered a new adverse event and a new AE Log CRF must be completed.

Likewise, if an EAE that was previously reported to DAIDS and subsequently fully resolved later re-occurs at a level requiring expedited reporting, the EAE must be reported as a new EAE Report to the DAIDS Safety Office. (Resolution is the normalization or return to baseline of laboratory values, clinical signs, or symptoms related to the event.)

11.11 Reporting Change in Severity of Adverse Events

If an AE increases in severity or frequency after it has been reported on the AE Log CRF, this will be noted on the original AE Log CRF and the event will be reported at the higher severity grade or frequency as a new AE. The onset date of the new AE will be the date that the severity or frequency increased. Note that a decrease in severity should not be reported as a new AE.

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

11.12 Study Physician Assessment and Signature

A study clinician listed on the FDA Form 1572 must assess each participant and record the details of all AEs in the source documentation and complete or carefully review the information transcribed onto the AE Log CRF.

A study physician listed on the FDA Form 1572 must review and verify the data on the DAIDS EAE Reporting Form for accuracy and completeness. This physician also makes the site's final assessment of the relationship between the study agent and the AE. This physician must sign the completed DAIDS EAE Reporting Form. If necessary to meet timely reporting requirements, sites can submit an EAE report without a completed signature page. However, the completed signature page, and necessary corrections or additions, must be submitted within the following 3 business days.

11.13 Review of AE Reports

Site staff should carefully review ALL documentation regarding an AE to ensure consistency and accuracy. This includes the source documentation, the AE Log CRF and the EAE Form. Site staff should be sure that the onset date, severity grade, relationship, and all other details are consistent.

Note that all EAE Reports received at the DAIDS Safety Office will be compared with the database at the SDMC (based on the AE Log CRF) to ensure that all reports that should have been received by both DAIDS and the SDMC have been submitted and that the details are consistent.

11.14 Contact Information for DAIDS Safety Office

All completed DAIDS EAE Reporting Forms are submitted to the DAIDS Safety Office; the fax number is included on Page 1 of the EAE Reporting Form, in the EAE Manual and below. For questions or other communications regarding submission of EAE Reports, see below.

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

11.15 HPTN 057 Safety Review and Oversight

A multi-layered safety review process will be employed during the conduct of HPTN 057. The first tier includes close monitoring of all trial participants by on-site study staff, rapid NIH Medical Officer review of AE reports submitted in an expedited manner (EAEs) to the DAIDS Safety Office (RCC) and the ongoing review of safety data by clinical staff at SCHARP. Another tier includes frequent routine review of safety data by a Protocol Safety Review Team (PSRT). The roles and responsibilities of the PSRT are outlined in Section 11.18. This tiered system assures that individual and aggregate safety data are reviewed and evaluated on an ongoing basis by qualified personnel in a consistent and methodical manner.

Queries and communications with the PSRT should be sent via email to: 057PSRT@HPTN.org. To ensure a timely response to the site, the DAIDS Medical Officers have ultimate responsibility for providing an answer to the site within three business days following receipt of the query (unless a more urgent response is requested by the site). All members of the PSRT are encouraged to review the information provided by the site and to offer their opinions. However, final determination rests with the Protocol Chair on behalf of the PSRT. A standard format for site queries will be used to elicit sufficient detail to allow the PSRT to make an informed determination.

11.16 Toxicity Management Procedures

At each visit, in addition to performing protocol-specified assessments, the study clinician should evaluate the mother's and infant's health, especially during the dosing phase in Cohorts 2 and 3, to confirm infant eligibility for continued dosing. This clinical review should include at least the review from all AEs from the previous visit, all on-going AEs, and all abnormal laboratory results.

The urgency and frequency of repeat evaluations will depend on the clinical significance of the specific abnormality. Study clinicians will provide appropriate clinical management of AEs according to their best medical judgment and local practice.

For grade 3 or 4 laboratory abnormalities, repeat evaluations will be performed within 3 days, if possible. If any grade 3 or 4 clinical or laboratory abnormality is thought to be potentially due to the study drug, evaluations should be repeated approximately weekly until toxicity falls below grade 2.

Because the duration of study drug regimen being used in this study is very short, study drug treatment in an individual will either be continued as specified or permanently discontinued. There will be no dose adjustment in individuals and no resumption of treatment if interrupted due to occurrence of toxicity as specified below or for any other reason. Neither mothers nor infants will be re-dosed for any reason (e.g. if they vomit shortly after dosing).

11.16.1 Toxicity Criteria for Permanent Study Drug Discontinuation in Infants

Study drug dosing will be permanently discontinued in infants with a grade 2 or higher serum creatinine level or any Grade 3 or Grade 4 clinical or laboratory adverse event, regardless of relatedness.

For Grade 1 or 2 adverse events (other than Grade 2 serum creatinine adverse event), no interruption in the study drug dosing is necessary, even if possibly related, unless otherwise directed by the PSRT, as described in Appendix A of this SSP Manual.

All mothers and infants exposed to the study will be asked to remain in the study for the full follow-up period, even if study drug dosing is discontinued early for any reason. Mothers and

infants will undergo all scheduled follow-up procedures and assessment with the exception of pk sampling which will be discontinued following the first missed dose.

Additional safety monitoring procedures are specified in Section 6.1 of the study protocol.

11.17 Safety Distributions from DAIDS

As specified in Section 1.0 of this SSP Manual, throughout the course of the study, sites will receive safety distributions from DAIDS through its RCC. These will include Safety Reports, Safety Memos, updated Investigator Brochures and Package Inserts and other documents. Each distribution will indicate in the cover note how the information is to be handled. In many cases, this information must be submitted to all responsible IRBs/ECs for their information and retained in the site regulatory files. It is important that all relevant clinical staff be provided copies of this information or be notified of their receipt and have access to them for careful review. Safety distributions do not require IRB/EC approval; however, acknowledgement of receipt is desirable. Cover letters for these (and all) IRB/EC submissions should specify the name and date of all attachments.

11.18 Roles and Responsibilities of the PSRT

The roles of the PSRT are as follows:

- 1) To conduct regular reviews of standardized study safety data reports. During the dosing phase of the study (while mothers or infants at any site are receiving study drug), the PSRT will convene via conference call every other week. The frequency of calls thereafter is to be agreed upon by the PSRT.
- 2) To consider data and respond to notifications from SCHARP Clinical Affairs regarding potential pauses in study enrollment/dosing and/or permanent discontinuation of study drug due to occurrence of toxicities and/or other clinical events. Section 6.1 of the Study Protocol, Version 2.0, specify the following circumstances in which immediate PSRT consideration is required:
 - After exposure to Tenofovir Disoproxil Fumarate (TDF), a maternal or infant death regardless of relationship to study drug. Subsequent immediate review by the PSRT is required for each additional maternal or infant death regardless of relationship to study drug.
 - After exposure to TDF, a mother or infant experiences a potentially life-threatening toxicity (including grade 4 AEs) judged to be possibly, probably or definitely related to the study drug. Subsequent immediate review by the PSRT is required for each additional maternal or infant grade 4 AE judged to be possibly, probably or definitely related to study drug.
 - When two or more mothers dosed with TDF experience the same Grade 3 AE judged to be possibly, probably or definitely related to the study drug. Subsequent immediate review by the PSRT is required when there are two or more additional mothers who experience the same grade 3 AE judged to be possibly, probably or definitely related to study drug.

- When two or more infants exposed to the study product experience the same Grade 3 AE judged to be possibly, probably or definitely related to the study drug. Subsequent immediate review by the PSRT is required when there are two or more additional infants who experience the same grade 3 AE judged to be possibly, probably or definitely related to study drug.

If any of the above situations occur, the PSRT should be notified immediately in order for the required review to occur as close to real-time as possible. Therefore, the PSRT requests that if a site identifies a potential “pauseable” event, as identified in the protocol and above, the site is requested to immediately notify the PSRT of this event using the PSRT e-mail alias. In this e-mail the site is to include:

1. Participant ID
2. Event (including any corresponding laboratory data)
3. Severity
4. Relationship
5. Confirmation that the site PI is aware of the event and has been involved in determining the relationship
6. Date of Onset
7. Narrative describing the event, treatment given, response to treatment, follow-up plan, etc.
8. If known, the enrollment/dosing projections for the week

The PSRT also requests that the site attempt to call the SCHARP Clinical Affairs Safety Phone at (206) 786-1343 to notify them of the safety event. This phone is monitored 24 hours a day, 7 days a week.

When a potential safety pause is noted at SCHARP by Clinical Affairs staff via the safety programming, the Clinical Affairs nurse will call the Protocol Chair (or designee) and notify the PSRT via e-mail as soon as possible during working hours – or, if the information was received during off hours, by the morning of the next working day.

During a safety pause PSRT review, the PSRT will consider the relevant safety data provided by SCHARP Clinical Affairs, which will include:

- a narrative of the event provided by the site
- a comprehensive safety history, including participant’s demographics, labs, physical exam data and all reported AEs to date,
- a list of concomitant medications, if applicable
- a list of participant’s Pre-Existing Conditions, if applicable/available

Depending on the event, the PSRT will convene by conference call or e-mail within one U.S. business day of receipt of safety event notification. SCHARP Clinical Affairs staff will poll for an ad-hoc conference call time, if necessary. The PSRT will determine whether further participant accrual and product administration should continue, be temporarily paused, or be permanently discontinued.

Site clinicians may also be asked to participate in these ad hoc calls to provide additional information and respond to PSRT members’ questions.

The DAIDS Medical Officer will notify the DAIDS Regulatory Affairs Branch, which will notify the FDA and invite representatives to participate in the PSRT discussions, as needed. Other members of the protocol team and representatives from the study drug manufacturer may also be involved in a decision to permanently discontinue enrollment and study drug dosing, as appropriate

If the PSRT decides an event requires that further enrollment and dosing of mothers and infants be paused or permanently discontinued, SCHARP Clinical Affairs staff will notify all participating HPTN 057 HPTUs, via e-mail and phone contact, regarding the PSRT decision to pause or discontinue the trial. It is SCHARP Clinical Affairs' policy to make phone contact with at least one staff member at each site starting with the site Clinic Coordinator, then Pharmacist, then PI.

If the PSRT decides that the event does not indicate a need to initiate a safety pause, SCHARP Clinical Affairs will send an e-mail to all HPTN 057 HPTUs summarizing the event and the PSRT's rationale for not pausing the trial. It is the sites' responsibility to keep their IRBs informed of all of these events.

- 3) To consider and rapidly respond to queries from on-site study staff regarding management and reporting of toxicities, and other clinical events, as needed. To ensure a timely response to the site, the Protocol Chair has ultimate responsibility for providing an answer to the site within two business days following receipt of a query from the site. All members of the PSRT are encouraged to review the information provided by the site and to offer their opinions; however, final determination rests with the Protocol Chair on behalf of the PSRT. A standard format for site queries will be used to elicit sufficient detail to allow the PSRT to make an informed determination (draft form attached). Ad hoc PSRT conference calls will be held as needed.
- 4) To respond to site investigator queries regarding study eligibility issues.
- 5) To review interim summary safety data from study Cohorts 1 and 2 when the last participant enrolled has reached 6 weeks of follow-up and review any available data from PACTG 394. Determine whether there are any safety concerns that may affect a decision to adjust the maternal or infant dose in Cohort 3, according to the criteria specified in the study protocol.
- 6) To respond to queries from the SCHARP Clinical Affairs staff. The Protocol Chair is designated as the point person for SCHARP staff queries, and will consult with other PSRT members as needed.
- 7) To decide whether to enroll additional mother/infant pairs for those who are not fully evaluable as specified in Sections 5.6.8 and 7.3 of the study protocol.

Throughout the study, should any safety concerns be identified by the PSRT, the HPTN Study Monitoring Committee, the US FDA, and the study manufacturer will be notified, as appropriate.

11.18.1 PSRT Composition

The following individuals will serve as members of the HPTN 057 PSRT:

- Protocol Chair (PSRT Chair)
- Protocol Co-Chairs
- NIAID Medical Officer

- NICHD Medical Officer
- SCHARP Clinical Affairs Safety Associate (CASA)
- Pharmaceutical Company Representative

Ideally, all members of the PSRT will participate in all routine and ad hoc PSRT conference calls; however, a quorum of at least three members is required. The quorum must include:

- PSRT Chair or Protocol Co-Chair
- NIAID Medical Officer
- SCHARP CASA

The HPTN CORE (FHI) Protocol Specialist, SCHARP Project Manager assigned to the protocol will also participate in and facilitate PSRT calls and reviews. The Protocol Statistician will be consulted by the PSRT as needed.

11.18.2 Routine Safety Data Summary Reports

SCHARP Clinical Affairs staff will generate and distribute standard safety data reports to the PSRT via e-mail on a weekly basis. As noted above, routinely scheduled review calls will be held every other week during the dosing phase. During the week of the of the scheduled PSRT conference call, the safety reports will be sent out two business days preceding the call. The PSRT members are required to review the weekly safety data reports and send an email response to SCHARP Clinical Affairs, noting any concerns or requesting more information, if appropriate. The review is required regardless of participation on the scheduled conference call. On weeks when there are no safety data requiring discussion, the SCHARP CASA will poll the team about canceling the call. To cancel the call, the PSRT Chair or Co -Chair, NIAID Medical Officer, and NICHD Medical Officer must all agree.

11.18.3 PSRT Communications

An email alias (057PSRT@HPTN.org) will be used to facilitate PSRT communications. Queries or safety pause rule event notification from the sites, safety data summaries from SCHARP and other correspondence are to be sent to this address unless otherwise agreed, which includes all of the individuals listed above. At the end of this section the HPTN 057 Protocol Safety Review Team AE Notification Form

11.18.4 Pausing procedures

If any Grade 5 event (death) occurs that is deemed to be definitely, probably, possibly or probably not related to drug:

- a. PSRT is notified (via the site or SCHARP Clinical Affairs) and convenes via call or email to review the event and determine next steps
- b. If the PSRT decides to stop enrollment and study drug dosing at all sites while they are collecting more information, SCHARP will notify the study sites of this decision
- c. SCHARP will notify the site of the PSRT’s final decision (to “pause” or to “continue as is”)

If any Grade 4 AE or two of the same Grade 3 AEs (in different ptids) occur that are deemed definitely, probably or possibly related to drug:

- a. Site manages participant as per protocol (Section 4.6.1)
- b. PSRT is notified (via the site or SCHARP Clinical Affairs) and convenes via call or email to review the event and determine next steps
- c. If the PSRT decides to stop enrollment and study drug dosing at all sites while they are collecting more information, SCHARP will notify the study sites of this decision
- d. SCHARP will notify the site of the PSRT's final decision (to "pause" or to "continue as is")

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Instructions: Complete all required fields so the PSRT has all information needed to consider the adverse event.

Site: _____ **Date (dd-MMM-yy):** _____

Completed by: _____ **Email address:** _____

PTID: _____ **Participant Age:** (indicate years, or months, weeks, days, as appropriate): _____

Cohort:

Study Drug Exposure Information:

Maternal Dose

Date: _____ (dd-MMM-yy) Dose: _____ mg.

Infant Dose:

Dose #1 @ Birth: Date: _____ (dd-MMM-yy) Dose: _____ mL. not dosed

Dose #2 Date: _____ (dd-MMM-yy) Dose: _____ mL. not dosed

Dose #3 Date: _____ (dd-MMM-yy) Dose: _____ mL. not dosed

Dose #4 Date: _____ (dd-MMM-yy) Dose: _____ mL. not dosed

Dose #5 Date: _____ (dd-MMM-yy) Dose: _____ mL. not dosed

Dose #6 Date: _____ (dd-MMM-yy) Dose: _____ mL. not dosed

Dose #7 Date: _____ (dd-MMM-yy) Dose: _____ mL. not dosed

Potential Pauseable Adverse Event that occurred after exposure to TDF, as specified in the protocol:

- Maternal death judged to be possibly, probably, definitely or probably not related to the study drug
- Infant death judged to be possibly, probably, definitely or probably not related to the study drug
- Maternal Grade 4 AE judged to be possibly, probably or definitely related to the study drug.
- Infant Grade 4 AE judged to be possibly, probably or definitely related to the study drug.
- Maternal Grade 3 AE judged to be possibly, probably or definitely related to the study drug.
- Infant Grade 3 AE judged to be possibly, probably or definitely related to the study drug.

Primary AE (diagnosis or symptom): _____

AE onset date (dd-MMM-yy): _____

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Relationship to study product:

- Definitely related
- Probably related
- Possibly related
- Probably not related
- Not related

Name of site PI assigning grade and relationship to study product:

Has this AE been reported on a SCHARP AE Log form?

- Yes
- No

Has this AE been reported as an EAE?

- Yes
- No

Narrative Summary: Describe the sequence of the signs and/or symptoms, relevant past medical history, diagnosis, intervention and/or treatment, relevant lab tests and results and current status of participant. Please describe the site's follow-up plan:

Please expedite submission of the AE CRF to SCHARP and the EAE Reporting Form to RCC. Email completed form to 057PSRT@HPTN.org. The PSRT/SCHARP Clinical Affairs Associate will reply to this e-mail within one business day of receipt. The reply will indicate whether or not this event meets criteria for PSRT review. If an email response is not received from the PSRT within 3 business days, re-contact the PSRT or SCHARP Clinical Affairs (sc.clin.aff@scharp.org) for assistance.