

Section 11. Adverse Event Reporting and Safety Monitoring

This section presents information related to infant safety monitoring and adverse event reporting procedures. Additional information on completion of the infant adverse experience log is included in Section 12 of this SSP, and details on the reporting of adverse events that meet the criteria for expedited reporting to DAIDS are included in the ‘Manual for Expedited Reporting of Adverse Events to DAIDS’, dated 6 May 2004, which is included as Appendix I (along with the Expedited Adverse Event (EAE) reporting form and form instructions) of this SSP Manual and available at the following websites: <http://www.hptn.org> and <http://rcc.tech-res.com>. For sites who are submitting EAEs electronically and have questions about the DAERS system, email queries to DAIDS-ESSupport@niaid.nih.gov.

In HPTN 046, adverse events are reported only for infants (not for mothers) as mothers do not receive the open-label nevirapine (NVP) or the study drug. As stated in the protocol, any conditions or health problems occurring in infants prior to enrollment are to be reported as pre-existing conditions, including congenital anomalies. If a pre-existing condition worsens (e.g., to a higher grade level) post-enrollment, it should be reported as an adverse event.

11.1 Adverse Event Definitions

Throughout this section and the protocol, the following terms are used and are associated with different 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. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product (ICH E6).

For HPTN 046, any medical occurrence that occurs in an infant *after enrollment* is considered an adverse event (AE). As stated in the protocol and above, any conditions or health problems occurring in infants prior to enrollment are to be reported as *pre-existing conditions*, including congenital anomalies. If a pre-existing condition worsens post-enrollment (frequency increases and/or severity grade increases), it should be reported as an adverse event.

- Serious adverse event (SAE): Any adverse event occurring 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 (*considered a pre-existing condition in HPTN 046*),
 - 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 and 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 SSP Manual also refer throughout to **adverse events that meet the criteria for expedited reporting to DAIDS**. These are referred to as “EAEs” and are a special subgroup of all adverse events 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 Manual for Expedited Reporting of Adverse Events to DAIDS 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. A combination of three factors contribute to defining the subset of 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. For HPTN 046, the subgroup of AEs that meet the criteria for expedited reporting to DAIDS (i.e., are considered EAEs) includes some serious adverse events and some non-serious adverse events.

As specified in Version 3.0 of the protocol, HPTN 046 will follow the Manual for Expedited Reporting of Adverse Events to DAIDS for the duration of the study. Specifically, the ‘standard’ level of reporting defined in the EAE Manual will be applied. The standard level requires expedited reporting of any adverse event that:

- Results in death, regardless of relationship to open-label NVP or study drug.
- Results in persistent or significant disabilities or incapacities, regardless of relationship to open-label NVP or study drug.
- Is a congenital anomaly/birth defect (*not applicable in HPTN 046 as this is considered a pre-existing condition*).
- Requires hospitalization or prolongs existing hospitalization and is probably not related, possibly related, probably related or definitely related to open-label NVP or study drug.
- Is life-threatening (including Grade 4 events if immediately life-threatening/serious) and probably not related, possibly related, probably related or definitely related to open-label NVP or study drug.
- Requires intervention to prevent significant/permanent disability or death and is probably not related, possibly related, probably related or definitely related to open-label NVP or study drug.

The DAIDS EAE Manual (Section 3.3) also 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 open-label NVP or study drug (definitely, probably, possibly, or probably not related), including adverse events that, based on clinical judgment, may require intervention to prevent a serious adverse event.
- SAEs that are not related to open-label NVP or a study drug, but could be associated with study participation or procedure. For example, in HPTN 046, this might include serious infections associated with blood-drawing.
- Unexpected SAEs that may be related to open-label NVP or the study drug that occur after the protocol-defined expedited reporting period.

In addition, as specified in Version 3.0 of the HPTN 046 protocol, there is also a protocol-specific requirement for expedited reporting of the following events (i.e., they are considered EAEs in HPTN 046):

- grade 3 and 4 skin rashes, regardless of relatedness
- grade 3 and 4 ALT levels, regardless of relatedness

All AEs that meet the requirements for expedited reporting to DAIDS (EAEs) must be reported on an Expedited Adverse Event (EAE) Form according to the instructions provided in the DAIDS Manual *within 3 business days of site awareness* (the site's recognition that the event fulfills the criteria for expedited reporting). The DAIDS EAE Manual, the EAE Report Form and detailed instructions for completing the EAE form are included in Appendix I of this SSP Manual and are available at the following websites: http://www.hptn.org/research_studies/HPTN046StudyDocuments.htm and <http://rcc.tech-res.com>. The fax number and contact number are included on Page 1 of the EAE Form and in the Manual.

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, dated December 2004. The Grading Table is located in Appendix E of this SSP Manual and at: <http://www.hptn.org> and <http://rcc.tech-res.com>.

The term severity is described 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 specified in the protocol, the following **exceptions** to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events will apply for the duration of the study:

Cutaneous/skin rash, dermatitis, malnutrition and ancillary-measured fever will be graded according to the Supplemental Table for Grading Severity of Cutaneous/Skin Rash/Dermatitis, Malnutrition and Fever (Appendix III of the protocol and Appendix F of this SSP Manual).

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 for infants and children.

There are five severity grades that can be assigned to AEs, which are defined as follows:

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe
- Grade 4 = Potentially life-threatening
- Grade 5 = Death
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NOTE: For the grading of clinical AEs not specified in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events or in the protocol, a guide for estimating severity is included on page 3 of the DAIDS grading 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.

11.3.1 Assigning Severity Grades on Case Report Forms

For some lab assays, the severity grade range is calculated using a value from the DAIDS Toxicity Table and a local normal range. For example, Grade 1 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. When calculating a severity grade range, never round on interim steps.
3. Always compare the severity grade range to the value that was recorded on the CRF (not the lab-reported value).
4. 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.

5. 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 = 1.3 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).

11.4 Adverse Event Relationship Assessment

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

- **Definitely Related.** The adverse event and administration of open-label NVP or study drug are related in time, and a direct association can be demonstrated.
- **Probably Related.** The adverse event and administration of open-label NVP or study drug are reasonably related in time, and the adverse event is more likely explained by open-label NVP or study drug than other causes.
- **Possibly Related.** The adverse event and administration of open-label NVP or study drug are reasonably related in time, and the adverse event can be explained equally well by causes other than open-label NVP or study drug.
- **Probably Not Related.** A potential relationship between open-label NVP or study drug 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 open-label NVP or study drug.
- **Not Related.** The adverse event is clearly explained by another cause not related to the open-label NVP or study drug.
- **Pending.** Pending may be used as a temporary relationship assessment only for death and only if data necessary to determine relationship to open-label NVP or study drug 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 open-label NVP or study drug. 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 046

All AEs occurring in infants after enrollment and throughout the duration of the study must be recorded in the study source documentation, regardless of seriousness, severity or relatedness. This includes AEs in infants reported by the mother or caretaker and AEs identified through study assessments. The severity of all clinical and laboratory AEs must be graded according to the standard DAIDS Toxicity Table.

As stated in the study protocol, **the following typical childhood illnesses** (defined in Section 9.7.1 of this SSP Manual) will be recorded in study source records and captured in the study database as interim medical history or physical examination findings, but **will not be reported separately in the Infant's Adverse Experience Log CRF**:

- diaper rash
- otitis media
- afebrile upper and lower respiratory tract infections including bronchiolitis.

However, if one of these conditions results in death, it will be reported as an SAE/EAE.

Additionally, normal variations in typical neonatal conditions that are not regarded as unfavorable are not considered adverse events as defined in section 11.1; examples include clinical conditions such as milia, miliaria and newborn peeling and laboratory findings, which are not gradable events per the DAIDS Toxicity Table, such as slightly elevated or low monocyte, basophil or MCH counts, or elevated platelet, neutrophil or lymphocyte counts.

All mothers' reports of conditions that were apparently transient, absent on physical exam, not objectively measured or not otherwise substantiated are not to be reported as adverse events. Examples of this are if at a visit a mother reports that the child "felt hot", but she was not able to give a quantified measurement, or if she reports that the infant "had a cough", but there was no cough while at the clinic. These symptoms are to be charted in the infant's file as being part of the mother's concern, but noted that these symptoms were not substantiated.

Appendix V of the study protocol (included as Table 11-1 below and Appendix J of this SSP manual) outlines the documentation requirements and timeframes for reporting of non-serious and serious AEs for HPTN 046.

Non-serious Adverse Events

Non-serious adverse events occurring in an infant between randomization and 8 months of life must be recorded on the Infant's Adverse Experience Log CRF (DataFax Form). Protocol-specified local laboratory results will be reported on the Infant's Laboratory Results CRF for entry into the study database, and abnormalities will be graded. In addition, lab abnormalities that are asymptomatic or not attributable to a clinical diagnosis will also be reported on the Infant's Adverse Experience Log CRF, if the severity grade is ≥ 3 .

After 8 months of life, information on all AEs will continue to be recorded in the participant source records, but only SAEs (regardless of relatedness) and EAEs (including grade 3 and 4 skin rashes and grade 3 and 4 ALT levels, regardless of relatedness) will be reported on the Infant's Adverse Experience Log CRF for entry into the study database. In other words, non-serious AEs occurring in an infant after 8 months of life that do not meet the criteria for expedited reporting to DAIDS will not be recorded on Infant's Adverse Experience Log CRF – only in the participant's source documentation.

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

Throughout the entire 18 month follow-up period, all SAEs – regardless of relatedness – and all EAEs will be recorded on the Infant's Adverse Experience Log CRF.

Also throughout the entire 18 month follow-up period, all EAEs will be also reported on the DAIDS Expedited Adverse Event (EAE) 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 manual. Note that the fax number for submission and other contact information is included on Page 1 of the EAE Form and in the EAE Manual and detailed instructions for completion of the EAE Form are also included in Appendix I of this SSP Manual and on the websites specified above.

TABLE 11-1 HPTN 046 Adverse Event Reporting and Additional Documentation Requirements*

	ADVERSE EVENT	RELATIONSHIP TO OPEN-LABEL NEVIRAPINE OR STUDY DRUG	REQUIRED REPORTING DURATION	AE LOG CRF (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
	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	Probably not related Possibly related Probably related Definitely related	Duration of study	YES	YES
	All other SAEs	Not related	Duration of study	YES	NO (unless directly related to study participation)
NON-SERIOUS ADVERSE EVENTS	Grade 3 or 4 skin rash**	Regardless of relationship	Duration of study	YES	YES
	Grade 3 or 4 ALT**	Regardless of relationship	Duration of study	YES	YES
	All other non-serious AEs	Regardless of relationship	Through 8 months of life	YES	NO

* All AEs must be documented in the participant’s source record for the duration of the study, regardless of seriousness, severity or relatedness.

**These events could be serious; refer to definition of SAE. Regardless, they are considered EAEs in HPTN 046.

NOTE: The following typical childhood illnesses will be recorded in study source records and captured in the study database as interim medical history or physical examination findings, but will not be reported separately as an adverse event unless resulting in death: diaper rash, otitis media and afebrile upper and lower respiratory tract infections including bronchiolitis.

Note: A grade 4 asymptomatic laboratory adverse event is considered a serious adverse event (SAE) only if it is immediately life-threatening or otherwise meets the criteria for an SAE as defined in this protocol (Section 7.0) and the Manual for Expedited Adverse Event Reporting to DAIDS.

11.6 Abnormalities at Baseline (Pre-Existing conditions)

As stated in the study protocol and above, **any conditions or health problems occurring in infants prior to enrollment are to be reported as pre-existing conditions**, including congenital anomalies. Pre-existing conditions are also graded using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, dated December 2004 and the Supplemental Table for Grading Severity of Cutaneous/Skin Rash/Dermatitis, Malnutrition and Fever, so the clinician can evaluate and document if the condition worsens after study enrollment (increases in frequency or severity), in which case it would be reported as an AE.

11.7 Lab Abnormalities

The Investigator or designee should carefully review all laboratory abnormalities relevant to the infant's health available since the last visit to identify any adverse events or health problems. Documentation of this review is required by initialing and dating each page of lab results.

The severity of all lab abnormalities will be graded and recorded in the source documentation. Results of protocol-specified local laboratory results will also be reported on the Infant's Lab Result DataFax CRF for entry into the study database. Through 8 months of age, lab abnormalities that are asymptomatic or not attributable to a clinic diagnosis will also be reported separately as an AE on the Infant's Adverse Experience Log CRF *if the severity grade is ≥ 3* . After 8 months of age, only lab abnormalities that otherwise meet the criteria for expedited reporting to DAIDS will be reported separately on the Infant's Adverse Experience Log CRF and reported to DAIDS on the EAE Reporting Form.

Note: For reporting purposes, a grade 4 asymptomatic laboratory adverse event is considered a serious adverse event (SAE) only if the event is immediately life-threatening or otherwise meets the criteria for an SAE as defined in the protocol (Section 7.0) and the Manual for Expedited Adverse Event Reporting to DAIDS.

11.8 Follow-up Information on Adverse Events

Site clinicians are responsible for closely monitoring and following all AEs until resolution and documenting this in the participant's source records. In addition to performing protocol-specified assessments, at each visit, the study clinician should review all previously reported ongoing AEs to evaluate the current status. **During the open-label NVP and study drug dosing phase of an infant's participation (the first 6 months), it is critical that the study clinician assess the infant's eligibility for continued dosing at each follow-up visit. The Toxicity Management Table included in Appendix IV of the study protocol and in Appendix H of this SSP Manual should be closely followed. In addition, infants are to be taken off open-label NVP or study drug immediately if the child is found to be HIV-infected.**

A new Infant's Adverse Experience Log CRF is NOT required when submitting follow-up information, for a previously reported AE (unless the AE increases in severity grade). The existing CRF should be updated and resubmitted. For additional instructions, see Section 12.

The requirements for submission of follow-up information on EAEs are specified in Section 5.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS. As specified therein, for the circumstances listed below regarding an EAE reported to DAIDS, the site is required to submit follow-up information when it becomes available on a new Expedited Adverse Event Form as a Follow-up Report:

- Requests by DAIDS for additional information.

- A change in the relationship between the adverse event and open-label NVP or study drug 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 open-label NVP or the study drug, if performed.

11.9 Outcome of Adverse Events

The site must follow the progress of each reported adverse event and record eventual outcomes in the source documentation. In addition, the Infant’s 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 adverse event that was previously reported on the Infant’s 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 recurs 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 Infant’s AE Log CRF, this will be noted on original AE Log CRF and the event will be reported at the higher severity grade or frequency as a new AE. The onset date 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 DAIDS Expedited Adverse Event Reporting Form. Ongoing events that improve, but are not resolved and subsequently increase in severity to the same or lower severity grade than previously reported 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 adverse events 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 Expedited Adverse Event Reporting Form for accuracy and completeness. This physician also makes the site's final assessment of the relationship between the study product (open-label NVP or study drug) and the adverse event. This physician must sign the completed DAIDS Expedited Adverse Event Reporting Form. If necessary to meet timely reporting requirements, sites can submit an expedited adverse event 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 adverse event to ensure consistency and accuracy. This includes the source documentation, the AE Log CRF and the EAE Form. Site staff should be sure that onset dates, severity grades 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 Expedited Adverse Event Forms are submitted to the DAIDS Safety Office; the fax number is included on Page 1 of the EAE 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 046 Safety Review and Oversight

A three-tiered safety review process will be employed during the conduct of HPTN 046.

The first tier includes close monitoring of all trial participants by on-site study staff, expedited NIH Medical Officer review of EAE Reports submitted to the DAIDS Safety Office from the sites, and the ongoing review of clinical and laboratory safety data by clinical staff of the HPTN Statistical and Data Management Center (SDMC).

The second 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 Appendix G of this SSP Manual.

The third tier of the safety review process is the periodic review by the NIAID Data and Safety Monitoring Board (DSMB). Through this three-tiered system, both individual and aggregate safety data are reviewed and evaluated on an ongoing basis by qualified personnel through a consistent and methodical process.

Prior to each DSMB review and independently, the HPTN Study Monitoring Committee will also periodically review trial data with a focus on performance indicators such as accrual, retention and intervention adherence compared with targets. While site staff are not typically directly involved with these reviews, it is important to be aware that these groups may make decisions or recommendations to the sponsor (DAIDS) or the HPTN leadership that affect the study and the sites in a significant way. These decisions are based on careful review of the study data and consideration of participant safety and study viability.

11.16 Toxicity Management Procedures

In addition to performing protocol-specified assessments, at each visit, the study clinician should review all AEs ongoing at the previous visit and all abnormal laboratory results available since the last visit to evaluate the infant's health and, during the dosing phase, to confirm eligibility for continued dosing.

Participant safety is of utmost concern. Management of adverse events should be according to the best clinical practice available and the judgment of the site Investigator or designated clinician. Management of open-label NVP or study drug dosing (temporarily holding or permanently discontinuing either open-label NVP or study drug dosing) relative to the occurrence of toxicities must follow the Toxicity Management Table in Appendix IV of the study protocol (a copy of which is also in Appendix H of this SSP Manual). Site staff should seek the advice and counsel of the PSRT on these matters.

One of the key roles of the PSRT is to consider and rapidly respond to queries from on-site study staff regarding open-label NVP or study drug dosing resumption or discontinuation following occurrence of toxicities as outlined in Appendix IV of the study protocol. **Queries and communications with the PSRT should be sent via email to: 046PSRT@HPTN.org.** To ensure a timely response to the site, the DAIDS Medical Officer has 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 DAIDS Medical Officers 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 (see Appendix G).

11.17 Safety Distributions from DAIDS

Sites will receive safety distributions from DAIDS through its Regulatory Compliance Center. 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 for all relevant clinical staff to 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 (though not required). Cover letters for these (and all) IRB/EC submissions should specify the name and date of all attachments.