3.0 Participant Safety Monitoring, Toxicity Management, and Adverse Event Reporting

IMPORTANT NOTE: This section of the Manual of Procedures (MOP) provides operational guidance consistent with IMPAACT 1077HS protocol Version 2.0. Please refer to prior versions of this section for corresponding guidance applicable to protocol Version 1.0.

This section presents information related to participant safety monitoring, toxicity management, and adverse event reporting. Please also refer to protocol Sections 6 and 7, protocol Appendix III, and the current version of the following resources:

- DAIDS Table for Grading Adult and Pediatric Adverse Events
- Manual for Expedited Reporting of Adverse Events to DAIDS
- DAERS Reference Guide for Site Reporters and Study Physicians
- Package insert for each of the following study-supplied study drugs:
    - lopinavir/ritonavir
    - tenofovir/emtricitabine
    - tenofovir/emtricitabine/rilpivirine
    - lamivudine/zidovudine
    - lamivudine
    - tenofovir
    - zidovudine
    - didanosine
    - atazanavir
    - raltegravir
    - ritonavir

All of the above-listed resources are available on the DAIDS Regulatory Support Center (RSC) web site: http://rsc.tech-res.com/safetyandpharmacovigilance

All study sites must submit the above-listed package inserts (and any subsequent updates) to their institutional review boards and/or ethics committees (IRBs/ECs). Some IRBs/ECs may require local versions of these documents, reflective of the drug formulations and trade names available at the site; all IRB/EC requirements must be followed.

3.1. Participant Safety Monitoring

At all sites, participant safety must be closely monitored throughout follow-up. Clinical and laboratory evaluations will be performed per the relevant schedule of evaluations and associated data on clinical staging, signs, symptoms, laboratory test results, and diagnoses will be recorded when applicable on relevant case report forms (CRFs), per the forms schedule and the individual forms instructions. Event Evaluation CRFs also will be completed when applicable per the forms instructions. Data recorded on CRFs form the basis for routine Data and Safety Monitoring Board review of the study; therefore, complete and accurate data recording are critical to ongoing participant safety monitoring throughout the study.

At each site, the Investigator of Record (IoR) is responsible for ensuring that clinical and laboratory evaluations are performed per protocol as well as for ensuring that appropriate clinical management is provided in response to the outcomes of these evaluations. Appropriate clinical management includes management of HAART regimens per protocol Sections 6.3-6.10, in consultation with the Clinical Management Committee (CMC) when applicable. See Section 1 of this manual for more information on consultation with the CMC.

3.2. Toxicity Management

Toxicity management will be undertaken at all sites per protocol Appendix III and will involve grading the severity of signs, symptoms, laboratory test results, and diagnoses. Severity will be graded on the following scale according to the current version of the *DAIDS Table for Grading Adult and Pediatric Adverse Events*:

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe
- Grade 4 = Potentially Life-Threatening
- Grade 5 = Death

The *DAIDS Table for Grading Adult and Pediatric Adverse Events* is available on the DAIDS RSC web site: http://rsc.tech-res.com/safetyandpharmacovigilance

Toxicity management per protocol Appendix III will also involve assessing the relationship of signs, symptoms, laboratory test results, and diagnoses to study-supplied study drug. For purposes of toxicity management, relationship to study-supplied study drug should be assessed according to the categories shown in Figure 3-1 below.

Figure 3-1
Relationship Assessment Categories for Toxicity Management

Relationship Category	Related to Study Drug	Definition
Definitely related	Yes	The event and administration of study drug are related in time, and a direct association can be demonstrated.
Probably related	Yes	The event and administration of study drug are reasonably related in time, and the event is more likely explained by study drug than other causes.
Possibly related	Yes	The event and administration of study drug are reasonably related in time, and the event can be explained equally well by causes other than study drug.
Probably not related	Yes	A potential relationship between the event and study drug could exist (i.e., the possibility cannot be excluded), but the event is most likely explained by causes other than study drug.
Not related*	No	The event is clearly explained by another cause not related to study drug.

*When an event is assessed as not related, an alternative etiology, diagnosis, or explanation for the event should be recorded in study source documents.

In many cases, toxicity management is undertaken by the IoR or designee in the absence of consultation with the CMC. In other cases, consultation is required; see Figure 1-3 in Section 1 of this manual for a listing of clinical management issues requiring consultation with the CMC. IoRs are also encouraged to consult with the CMC as needed on any other aspects of toxicity management.

3.3. Adverse Event Reporting to DAIDS

Please refer to protocol Section 7. Provided below are definitions, requirements, and procedures for complying with protocol-specified reporting requirements.

3.3.1. Definitions

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). The above definition of AE is applied to all participants in both study groups beginning at the time of random assignment. Medical conditions, problems, signs, symptoms, and findings identified prior to random assignment are considered pre-existing conditions. If a pre-existing condition worsens (increases in severity or frequency) after a participant is randomized, the worsened condition is considered an AE. If a pre-existing condition resolves after a participant is randomized, but then recurs at a later date, the recurrence is considered an AE.
Serious AE (SAE)	An AE that results in any of the following outcomes (ICH E6): • Death • A life-threatening condition (see more below) • A congenital anomaly/birth defect (see more below) • Inpatient hospitalization or prolongation of existing hospitalization (see more below) • Persistent or significant disability/incapacity Medical and scientific judgment should be exercised in deciding whether other AEs not listed above should be considered serious. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed in the definition above should usually be considered serious (ICH E2A).

Life-threatening AE	An AE that places the participant at immediate risk of death at the time of the event. An AE that could have resulted in death if it had been more severe is NOT considered life-threatening for purposes of determining seriousness. The *DAIDS Table for Grading Adult and Pediatric Adverse Events* identifies Grade 4 AEs as potentially life-threatening. As such, it is not expected that all grade 4 AEs will be assessed as serious. Rather, each AE should be assessed for seriousness according to whether it is immediately life-threatening (i.e., placing the participant at immediate risk of death). For example, some malignancies may be assessed as Grade 4, because they are potentially life-threatening, but not assessed as serious, because they are not immediately life-threatening. As another example, it is not expected that asymptomatic grade 4 laboratory abnormalities will be assessed as life-threatening.
Congenital anomaly	A defect that is present at birth. Version 2.0 of the *DAIDS EAE Reporting Manual* indicates that clinically insignificant physical findings at birth, including those regarded as normal variants, should generally not be considered serious. For example, an isolated finding of polydactyly or a Mongolian spot in an infant with no other findings would generally not be considered serious. However, a major cardiac defect would be considered serious. More information about congenital anomalies can be found at: http://cdc.gov/ncbddd/bd/monitoring.htm
Hospitalization	In-patient admission to a hospital or other medical facility requiring an overnight stay. Admission to an out-patient clinic/department or emergency room/department is not considered hospitalization for purposes of determining seriousness. In the absence of an event meeting the above definition of AE, hospitalization itself is not an AE or SAE. For example: • Administrative or social admission for temporary placement (e.g., patient has no place to sleep) • Admission not related to an AE (e.g., for normal labor and delivery, for elective cosmetic surgery) • Admission for treatment of a pre-existing condition not related to a new AE or with a worsening of a pre-existing condition (e.g., for work-up of persistent pre-existing lab abnormality) In each of the above examples, no AE has occurred and therefore no SAE has occurred, even though the participant was admitted to a hospital.

Unexpected AE	An AE whose nature or severity is not consistent with a study drug's current package insert.
Expedited AE (EAE)	An AE that meets protocol-specified criteria for reporting in an expedited manner to the DAIDS RSC Safety Office (see more below).
Study-supplied study drug	Study medications provided to study participants from a supply obtained from the DAIDS Clinical Research Product Management Center (CRPMC).

3.3.2 AEs that Meet Protocol-Specified Criteria for Expedited Reporting to DAIDS

Adverse events that meet protocol-specified criteria for expedited reporting to the DAIDS RSC Safety Office are referred to as EAEs.

- This study follows the **SUSAR** reporting category in Version 2.0 of the *DAIDS EAE Reporting Manual*. According to this category, all serious and unexpected AEs that occur during the EAE reporting period (defined in Section 3.3.3 below) and are considered related to study-supplied study drug will be reported as EAEs.

- In addition, all fetal deaths that occur during the EAE reporting period (defined in Section 3.3.3 below) at or after 20 weeks gestation in new pregnancies will be reported as EAEs, regardless of relatedness or expectedness.

Figure 3-2 summarizes the EAE reporting requirements for this study. Further explanation of these requirements is provided in the remainder of this section. Figure 3-5 at the end of this section presents several EAE reporting examples. When reviewing these examples, please note that even when EAE reporting is not required, AEs should be recorded on relevant CRFs, per the forms instructions.

Figure 3-2
Summary of EAE Reporting Requirements

Type of Event	EAE Reporting in Relation to Relationship Assessment	EAE Reporting in Relation to Use of Study Drugs
Unexpected SAE	Report as EAE if related to study-supplied study drugs	Report as EAE if occurred after participant started taking one or more study-supplied study drugs
Fetal death occurring at or after 20 weeks of gestation	Report as EAE regardless of relationship to study-supplied study drugs	Report as EAE if occurred after participant started taking one or more study-supplied study drugs

Note: Immune reconstitution inflammatory syndrome (IRIS) is not required to be reported as an EAE for this study, even if the event otherwise meets the reporting criteria listed above. Per Version 2.0 of the *DAIDS EAE Reporting Manual*, IRIS is an intense immune reaction that may result from a response to HIV treatment and is an anticipated event for antiretroviral therapies.

3.3.3 EAE Reporting Period

For each study participant, EAE reporting is required beginning when the participant starts (is prescribed) one or more study-supplied study drugs and ending when the participant exits the study (either scheduled completion or early discontinuation of participation).

After the end of the EAE reporting period (i.e., after a participant is no longer in study follow-up), only SUSARs are required to be reported as EAEs, if site staff become aware of such events on a passive basis (i.e., from publicly available information).

3.3.4 EAE Severity

When reporting EAEs, the IoR or designee is required to assess and report the severity of the EAE. Severity should be graded as described in Section 3.2 above, according to the current version of the *DAIDS Table for Grading Adult and Pediatric Adverse Events*.

3.3.5 EAE Relationship

When reporting EAEs, the IoR or designee is required to assess and report the relationship of each EAE to study-supplied study drug. For purposes of EAE reporting, relationship should be assessed according to the categories shown in Figure 3-3.

Figure 3-3
Relationship Assessment Categories for EAE Reporting

Relationship Category	Definition
Related	There is a **reasonable possibility** that the EAE may be related to study drug. Consistent with ICH guidance, the term "reasonable possibility" is intended to convey that there are facts, evidence, or arguments to suggest a causal relationship between the EAE and study drug. Facts, evidence, and arguments that may support a reasonable possibility of a causal relationship include: • A temporal relationship between the EAE and use of study drug • A plausible biologic mechanism for study drug to cause the EAE • Previous reports of similar events associated with study drug (or drugs of the same class) • Resolution of the event after de-challenge (hold/discontinuation of study drug) • Recurrence of the event after re-challenge (resumption of study drug after a hold) Other potential causes of the EAE (e.g., past medical history, concurrent illness, concomitant medications) should also be considered when assessing whether there is a reasonable possibility that an EAE may be related to study drug.
Not related*	There is **not** a reasonable possibility that the event may be related to study drug.

*When an event is assessed as not related, an alternative etiology, diagnosis, or explanation for the event should be recorded in study source documents.

IMPORTANT NOTE: The relationship assessment categories used for EAE reporting (shown in Figure 3-3) differ from the categories used for toxicity management and completion of CRFs (shown in Figure 3-1). Figure 3-4 presents how the five relationship categories used for toxicity management and completion of CRFs should be mapped to the two relationship categories used for EAE reporting.

Figure 3-4
Mapping of Relationship Categories For Toxicity Management to Relationship Categories for EAE Reporting

Relationship Category for Toxicity Management	Maps To	Relationship Category for EAE Reporting
Definitely related	→	Related
Probably related	→	Related
Possibly related	→	Related
Probably not related	→	Not related
Not related	→	Not related

3.3.6 Procedures for Expedited Reporting to DAIDS

All EAEs should be reported to the DAIDS RSC 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 RSC Safety Office. If an EAE report is not completed and submitted within three reporting days of site awareness that an events meets EAE reporting criteria, an explanation must be entered in DAERS before the report can be submitted.

Note: See the *DAIDS EAE Reporting Manual* for a detailed definition of "reporting days."

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. Updates also should be submitted if significant additional information becomes available after an EAE report is first submitted. Significant additional information may include, for example, an updated severity grade or relationship assessment, information on participant status after resumption of study-supplied study drug, and/or newly available information on cause of death.

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 RSC Safety Office. The EAE Form and form completion instructions are available on the DAIDS RSC 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 RSC web site.

Figure 3-5
Expedited Adverse Event (EAE) Reporting Examples

When reviewing these examples, note that even when EAE reporting is not required, AEs should be recorded on relevant CRFs per the forms instructions.

Event Description		Report as EAE?	Explanation/Comments
1	Eighteen months after being randomized to Stop HAART, a participant is found to have died of peritonitis. The participant has remained in Step 1 and has not taken any study-supplied study drugs.	No	The AE is serious (resulting in death), but it has not occurred during the protocol-specified EAE reporting period (because the participant has not started any study-supplied study drugs). Therefore, EAE reporting is not required.
2	Six months after being randomized to Stop HAART, a participant is registered to Step 2 and begins taking study-supplied HAART. One year later, the participant is found to have died of peritonitis. The package inserts for the study-supplied study drugs that the participant was taking do not list severe or life-threatening peritonitis as an adverse drug reaction, but the IoR cannot rule out a reasonable possibility of a relationship to study drug.	Yes	The AE is serious (resulting in death), suspected (related), and unexpected, and it has occurred during the protocol-specified EAE reporting period. Therefore, EAE reporting is required.
3	Six months after being randomized to Stop HAART, a participant is registered to Step 2 and begins taking HAART; however, she chooses to receive her HAART medications from her (non-study) primary care provider, rather than through the study. One year later, the participant is found to have died of peritonitis.	No	The AE is serious (resulting in death) but it has not occurred during the protocol-specified EAE reporting period (because the participant has not started any study-supplied study drugs). Therefore, EAE reporting is not required.
4	Nine months after being randomized to Stop HAART, a participant with mild pre-existing depression is hospitalized for severe depression and an associated suicide attempt. She has remained in Step 1 and has not taken any study-supplied study drugs to date.	No	The AE is serious (requiring hospitalization), but it has not occurred during the protocol-specified EAE reporting period (because the participant has not started any study-supplied study drugs). Therefore, EAE reporting is not required.
5	Nine months after being randomized to Continue HAART, a participant with mild pre-existing depression is hospitalized for severe depression and an associated suicide attempt. The package inserts for the study-supplied study drugs that the participant is taking do not list any severe psychiatric adverse drug reactions, but the IoR cannot rule out a reasonable possibility of a relationship to study drug.	Yes	The AE is serious (requiring hospitalization), suspected (related), and unexpected, and it has occurred during the protocol-specified EAE reporting period. Therefore, EAE reporting is required.

Figure 3-5
Expedited Adverse Event (EAE) Reporting Examples

When reviewing these examples, note that even when EAE reporting is not required, AEs should be recorded on relevant CRFs per the forms instructions.

Event Description		Report as EAE?	Explanation/Comments
6	Twenty-four months after being randomized to Continue HAART, a participant experiences a seizure for which she is hospitalized for five days. The package inserts for the study-supplied study drugs that the participant is taking do not list seizure as an adverse drug reaction, but the IoR cannot rule out a reasonable possibility of a relationship to study drug.	Yes	The AE is serious (requiring hospitalization), suspected (related), and unexpected, and it has occurred during the protocol-specified EAE reporting period. Therefore, EAE reporting is required.
7	Three months after being randomized to Continue HAART, a participant experiences grade 4 epistaxis (nose bleed) requiring multiple whole blood transfusions. She is also treated with an adrenaline nasal pack and liquid paraffin nasal drops. All treatments are provided on an out-patient basis but the IoR determines that the event would have been life-threatening and required hospitalization if medical intervention had not been provided. The package inserts for the study-supplied study drugs that the participant is taking do not list epistaxis as an adverse drug reaction, but the IoR cannot rule out a reasonable possibility of a relationship to study drug.	Yes	The AE is serious (because the IoR has judged it to be an important medical event per ICH E2), suspected (related), and unexpected, and it has occurred during the protocol-specified EAE reporting period. Therefore, EAE reporting is required.
8	A potential participant is screened for the study at 37 weeks gestation. She delivers a full-term infant in-hospital, with an overnight stay in the maternity department. Two days after delivery, she enrolls in the study and is randomized to Continue HAART.	No	No AE has occurred. Therefore, EAE reporting is not required.
9	A potential participant is screened for the study at 37 weeks gestation. She delivers a full-term infant in-hospital, with an overnight stay in the maternity department. The infant is found to have a heart defect. Two days after delivery, the woman enrolls in the study and is randomized to Continue HAART. She then starts taking study-supplied study drugs.	No	The congenital anomaly occurred before the protocol-specified EAE reporting period (before the participant started any study-supplied study drugs). Therefore, EAE reporting is not required.
10	A participant is found to be pregnant 12 months after being randomized to Continue HAART. She experiences a spontaneous abortion at approximately 8 weeks gestation.	No	Fetal losses occurring before 20 weeks gestation are not reportable as EAEs. Therefore, EAE reporting is not required.
11	A participant is found to be pregnant 18 months after being randomized to Continue HAART. Since the time of randomization, the participant has been taking study-supplied HAART. She experiences a fetal death at approximately 24 weeks gestation.	Yes	This fetal death occurred after 20 weeks gestation and during the protocol-specified EAE reporting period. Therefore, EAE reporting is required.

Figure 3-5
Expedited Adverse Event (EAE) Reporting Examples

When reviewing these examples, note that even when EAE reporting is not required, AEs should be recorded on relevant CRFs per the forms instructions.

Event Description		Report as EAE?	Explanation/Comments
12	A participant is found to be pregnant 18 months after being randomized to Stop HAART. Prior to her pregnancy, she had remained in Step 1 and had not taken any study-supplied study drugs to date. Upon identification of her pregnancy, she is started on a study-supplied triple ARV regimen for purposes of PMTCT. She then experiences a fetal death at approximately 24 weeks gestation.	Yes	This fetal death occurred after 20 weeks gestation and during the protocol-specified EAE reporting period (even though the participant still does not require HAART for her own health, she started taking study-supplied study drug during her pregnancy). Therefore, EAE reporting is required.
13	Twenty-one months after being randomized to Stop HAART, a participant is registered to Step 2 and begins taking study-supplied study drugs. Three months later, the participant is found to be pregnant. She subsequently delivers an infant who is found to have a heart defect.	Yes	The infant's heart defect is a serious adverse event (congenital anomaly) and it has occurred during the protocol-specified EAE reporting period. Therefore, EAE reporting is required.