

Section 10. Adverse Event Reporting and Safety Monitoring

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10.1 Overview of Section 10

This section presents information related to Adverse Event (AE) reporting and safety monitoring in HPTN 084-01. The following resources are relevant to AE reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events, corrected version 2.1 dated July 2017
- Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0 (DAIDS EAE Manual, dated January 2010)
- Current Investigational Brochure (IB) for oral and injectable cabotegravir (CAB)
- Current Truvada® (emtricitabine/tenofovir disoproxil fumarate) Package Insert (PI)
- Sections 5.0 and 6.0 and Toxicity Management Appendix VI of the HPTN 084-01 protocol (Version 1.0, dated 14 October 2019) as well as any accompanying Clarification Memos (CMs) or Letters of Amendment (LoAs)

10.2 Safety Monitoring, Review, and Oversight

Sections 6.1 and 6.2 as well as Appendix VI of the HPTN 084-01 Protocol outline the measures to monitor and safeguard participant safety. Primary safety monitoring of study participants is primarily the responsibility of study staff, under the direction of the Investigator of Record (IoR). The IoR and designated study staff are responsible for submitting required e-forms to the HPTN Statistics and Data Management Center (SDMC) and Expedited Adverse Event (EAE) reports to DAIDS, to ensure relevant safety data are available in a timely manner.

Safety monitoring procedures for this study include the Clinical Management Committee (CMC), SDMC Clinical Safety Associates, DAIDS Safety Office and Medical officer, Study Monitoring Committee (SMC), and Data and Safety Monitoring Board (DSMB). Descriptions of these groups and their responsibilities can be found on Section 14 and 15 of the HPTN MOP: <https://www.hptn.org/resources/manual-of-operations>.

10.2 Adverse Event

AEs are defined in Section 6.1 of the HPTN 084-01 protocol. This definition applies to all participants from the time a participant is enrolled to the point in time when the participant terminates from the study.

10.3 Documenting Adverse Events

Study site staff are responsible for documenting all AEs reported or observed in study participants, regardless of presumed attribution, seriousness or severity, in the study source documentation. All AEs will be graded according to the DAIDS Table for Grading Adult and Pediatric Adverse Events, corrected version 2.1 dated July 2017 (referred to herein in this section as the “DAIDS Toxicity Table”). This table will be used throughout the entire study, and can be downloaded at: <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables>.

Laboratory results that are outside of the normal range, but are not abnormal enough to reach a Grade 1, can be identified as “NCS” (not clinically significant) in the source documentation, if determined by a study clinician.

All information obtained while conducting follow-up physical examinations, review of symptoms, and laboratory tests should be recorded in the source documentation according to site Standard Operating Procedures (SOPs). This information should be reviewed after each participant visit to determine if an AE has occurred. For events captured on the Adverse Experience Case Report Form (AE CRF), **whenever possible, the final diagnosis, rather than the individual signs and symptoms, should be documented (in both the source documentation and on the AE CRF). If a diagnosis is not possible, each individual sign and symptom should be reported separately. Each site should develop a system for collecting signs, symptoms and diagnoses and ensuring that these events are captured appropriately in the source documents.** All signs, symptoms and diagnoses reported as AEs must be assessed as to whether they are related or not related to study drug.

If an AE meets the criteria of a Serious Adverse Event (SAE) / EAE, see Section 10.8 below for guidance on documentation and reporting.

It should be noted that injection site reactions (ISRs) will be captured in the study database using the Injection Site Reaction e-CRF and not on the AE Log. It is important to distinguish between signs and symptoms from the actual injection procedure versus an ISR. See Section 9.4.7 of the SSP for further guidance. Proactive assessment of ISRs occurs at

five timepoints in the study: Weeks 6, 10, 18, 26 and 34. However, a participant may report an ISR at any time during the study. All ISRs are reported using the Injection Site Reaction eCRF, using the “Site Reactions to Injections and Infusions” category for grading as found in the DAIDS Toxicity Table.

10.4 Adverse Event Severity Grading

The severity of all AEs identified in HPTN 084-01 will be graded per the DAIDS Toxicity Table (link above). The term “severity” is used to describe the intensity of an AE. The severity of all AEs identified in HPTN 084-01 must be graded on a five-point scale:

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

Severity is not the same as seriousness, which is based on the outcome or action associated with an event.

AEs not listed in the DAIDS Toxicity Table should be graded according to the “estimating severity grade” row of the table:

GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated.	Severe symptoms causing inability to perform usual social & functional activities with intervention indicated.	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

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

If a single AE term is used as a unifying diagnosis to report a cluster of signs and symptoms, and the diagnosis is not specifically listed in the Toxicity Table, assign the AE the highest severity grade among each of the associated signs and symptoms. Record the diagnosis as the AE term and record each associated sign and symptom in the AE Log comments section.

Seasonal allergies should be graded according to the “Estimating Severity Grade for Parameters Not Identified in the Grading Table” row of the Toxicity Table (not the “acute systemic allergic reaction” row).

When grading using the “Estimating Severity Grade for Parameters Not Identified in the Grading Table” row of the Toxicity Table, note that if the condition requires treatment, it must automatically be graded at Grade 2 or higher.

10.5 AE Relationship to Study Product

When assessing an AE’s relationship to study product, the site clinician should consider the study product used:

Step 1: Oral CAB

Step 2: Injectable CAB

If an AE onset date falls in between Steps, the site clinician should assess the AE’s relationship to the study product used during the last completed Step in which the participant received study product.

One of the following relationship categories must be assigned to each reportable AE:

Related: There is a reasonable possibility that the AE may be related to the study product.

Not related: There is not a reasonable possibility that the AE is related to the study product.

Note: When an AE is assessed as “not related”, an alternative etiology, or explanation should be provided in the ‘Comments’ section of the CRF. If new information becomes available, the relationship assessment of any AE should be reviewed again and updated as required.

10.6 Reporting AEs to the HPTN SDMC

This study will collect in the study database **Grade 1 and higher AEs**, and any AE that leads to study product hold/discontinuation on the AE Log case report form. Medical conditions, problems, signs, symptoms, abnormal laboratory value, and findings identified before enrollment but not meeting protocol exclusionary criteria are documented on the Medical History eCRF (Pre-Existing Conditions). If a condition is ongoing at the time of enrollment, it is a pre-existing condition. If this condition worsens (increases in severity or frequency) after enrollment, the worsened condition is considered an AE. If a pre-existing condition resolves after enrollment, but then recurs at a later date, the recurrence is considered a new AE.

For any AE at any severity grade that contributes to a temporary or permanent hold of study product, regardless of the presumed relationship, study staff should submit an AE e-Log to the HPTN SDMC and mark either “drug interrupted” or “drug withdrawn” on the Action Taken with Study Product AE CRF e-Log.

If an AE increases in severity or frequency (worsens) after it has been reported on an AE Log e-CRF, the “old” AE should be marked “recovered/resolved” for the Outcome variable and the new AE should be submitted. When an AE improves to a lower severity or becomes less frequent, a new AE submission is not necessary.

Each AE identified in HPTN 084-01 must be followed clinically through study participation until the AE resolves (returns to baseline) or stabilizes. Please consult the CMC for guidance on when to cease or reduce follow-up on an AE, or what constitutes “stability”. AE resolution date is the date that the condition is no longer present or stabilizes. If a participant is taking a medication to manage an AE that occurs during study participation, it is not considered resolved. If an event continues at end of study participation, the status/outcome of the AE should be updated to “not recovered/resolved.” Study sites should be prepared to have a plan to manage AEs with a severity grade of Grade 3 or higher, as well as an ALT \geq 3xULN PLUS total bilirubin \geq 2xULN, and any seizure event at end of study participation for each participant. The CMC (084-01-cmc@hptn.org) is available for consultation of these events, if needed.

The following are tips and guidelines for assigning AE terms:

- Whenever possible, a diagnosis should be reported, rather than a cluster of signs and/or symptoms.
- Do not include information on relatedness to study product or timing of study product use in the AE term/description. Limit the AE text to the medical description and anatomical location, when needed.
- When it is not possible to identify a single diagnosis to describe a cluster of signs and/or symptoms, each individual sign and symptom must be reported as an individual AE. The term can be updated later when a diagnosis becomes available.
- When reporting a laboratory event, describe the direction of the abnormality, (e.g., decreased hemoglobin, elevated ALT).
- A specific medical term should be used whenever possible (e.g., “ulcers” instead of “sores”)
- Correct spelling for all terms should be used and sites should avoid using abbreviations.
- When reporting an AE that is associated with an underlying condition, include the underlying condition in the AE term or description. For example, if a participant is experiencing pain related to an underlying cancer diagnosis, include the cancer diagnosis in the AE term or description.
- If possible, try to include the anatomical location of the event, such as, pain on the right arm.
- Procedures per se should not be reported as AEs; rather the underlying condition which leads to a procedure may be considered an AE. Any associated procedures may be considered treatments for the AE. For example, while “appendectomy” would not be considered an AE, “appendicitis” would, with “appendectomy” documented as a treatment provided for the AE. In addition, any event that occurs due to a study-

related procedure should be recorded as an AE. Specify in the AE text description if the AE is related to a procedure (iatrogenic). For example, if a participant experiences dizziness from a blood draw, then “dizziness due to blood draw” should be submitted as an AE.

10.7 Additional Adverse Event Reporting Considerations

10.7.1 Reporting Injection Site Reactions (ISRs) and Post Injection Adverse Events (AEs)

- Injection Site Reactions should *only* be reported on the ISR log. If the site considers an event to be related to the injection but there is no code available on the ISR form, the event should be reported on the AE log.
- If an AE location is directly at the injection site, include the term “at injection site” in the reported Event diagnosis.
- “Local” is not a defined anatomic site.
- Recording that an AE occurred at the injection site is important, as complications at the site of study product administration are grouped separately in the coding and analysis of AEs.
- The term “post-injection” should only be used for AEs related to the injection procedure, generally occurring during or immediately after the injection procedure. “Post-injection” refers to the time after the act of delivering the study product with needle and syringe. This is distinct from an AE related to the study product. See below for examples.

<u>REPORT</u> as the AE term	<u>DO NOT</u> report as the AE term
Injection site rash	<ul style="list-style-type: none"> • Rash
Post injection dizziness	<ul style="list-style-type: none"> • Dizziness

10.7.2 Reporting procedure-related Adverse Events (AEs)

AEs that are complications of procedures belong to a separate classification (for example, complications/consequences of surgery, biopsy, or dental work). This applies to any procedure, whether or not the procedures are a part of the study. For example, infection, pain, bleeding, or lightheadedness that is a consequence of a procedure is different from these events happening spontaneously.

For an AE related to a procedure, indicate relationship to the procedure in the AE term so that the AE is classified as a procedural complication. Example:

- For a wound infection that happens directly as a result of surgery, this should be reported as “post-operative wound infection.”

10.7.3 Reporting laboratory abnormalities as AEs

If an abnormal laboratory test result is reported as an AE per protocol requirements, separate from any clinical diagnosis associated with the result, the type of test performed

and the direction of the abnormality should be reported (e.g., elevated ALT). The specific value or the severity grade of the result should not be reported as part of the AE term. Laboratory values that fall outside of a site's normal range but are below severity Grade 1 are not considered AEs. These out of range but below Grade 1 values are not documented as pre-existing conditions or AEs unless requested by the Investigator of Record (IoR) or designee. When assigning severity grades, note that some sites may have normal reference ranges that overlap with the severity grade ranges. Thus, it is possible for a participant to have a result that falls within the site's normal range, but is still gradable per the Toxicity Table. Assign the severity grade based on the Toxicity Table severity grade ranges, regardless of whether or not the lab result falls within the site's normal reference range.

Lab abnormalities that meet the criteria for expedited reporting to DAIDS will be reported separately on the AE Log CRF and reported to DAIDS via the DAERS Reporting System.

10.7.4 Reporting Recurrent Adverse Events

If an AE previously reported on an AE Log CRF resolves and then recurs at a later date, the second occurrence must be reported as a new AE on a new AE Log CRF (new log line in the study database).

Some participants may have chronic, episodic, pre-existing conditions. In these situations, if the participant experiences an episode of the condition during follow-up that has not increased in severity or frequency from the baseline condition, it is not considered an AE. For example, if a participant reports experiencing three (3) migraines a month before the study, and they continue at the same frequency and severity during the study, these migraines should not be reported as AEs.

10.7.5 Reporting Sexually Transmitted Infections (STIs) as Adverse Events (AEs)

When reporting sexually transmitted infections, sites need to report infections diagnosed as part of protocol-required testing for GC/CT and syphilis on the STI eCRF as well as the AE Log eCRF. All other STIs diagnosed as part of standard of care will be reported on the AE Log eCRF only. If sites only reported STIs in one place, is not required to report retroactively.

10.8 SAEs / EAEs

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

- Results in death,
- Is life-threatening,

NOTE: The term "life threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. A grade 4 severity grading on the Toxicity Table does not necessarily mean that an event is life-threatening. When determining whether a grade 4 event meets the ICH definition of "life threatening",

consider the event in the context of any related symptoms the participant may have experienced.

- Requires in-patient hospitalization or prolongs an existing hospitalization. The following types of hospitalizations are not considered adverse events, serious or otherwise:
 - Any admission unrelated to an AE (e.g., for cosmetic procedures or pregnancy)
 - Admission for diagnosis or therapy of a condition that existed before enrollment AND has not increased in severity or frequency since baseline.
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- 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 above.

ICH guidance (E2A) also states that medical and scientific judgment should be exercised in deciding whether other adverse events not listed above should be considered serious.

SAEs are a subset of all reportable AEs. For each AE identified, an authorized study clinician must determine whether the AE meets the ICH definition of “serious”.

When assessing whether an AE meets the definition of serious, note that seriousness is not the same as severity, which is based on the intensity of the AE.

10.9 Expedited Reporting of AEs to DAIDS

Sites are responsible for reporting EAEs per the Manual for Expedited Reporting of Adverse Events to DAIDS. The manual can be found at: <https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids>

All AEs that meet the definition of “serious” (SAEs), regardless of relationship to study product, are expedited adverse events (EAE).

In addition to SAEs, sites will report in an expedited manner the following results:

- **ALT \geq 3x ULN AND total bilirubin \geq 2x ULN (must be both at the same time in order to require expedited reporting)**
- **Any seizure event**

This reporting is required for all participants from the time they are enrolled until their participation in the study ends. After this time, sites must report to DAIDS Serious, Unexpected, clinical Suspected Adverse Reactions (SUSAR), as defined in Version 2.0 of the DAIDS EAE Manual, if the study site becomes aware of the event on a passive basis, i.e., from publicly available information.

The study agents for the purposes of EAE reporting are: Oral CAB 30 mg tablet; CAB LA

injectable suspension (600 mg/mL).

Each site will use the DAIDS internet-based reporting system, DAERS (DAIDS Adverse Experience Reporting System), to report all AEs that require expedited reporting to DAIDS (see section 10.8 above for definition or refer to <https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids>). DAERS can be accessed at <https://ncrms.niaid.nih.gov/>.

The study Chairs and LOC staff should be notified of all EAEs and SAEs when the site reports them. To do this, sites should add the following to the report Notification Recipient list within DAERS:

Sybil Hosek at sybilhosek@gmail.com
Lynda Stranix-Chibanda at lstranix@uzchs-ctrc.org
erica hamilton at ehamilton@fhi360.org

DAERS can be accessed at <https://ncrms.niaid.nih.gov/NCRMS/Main/Login.aspx>. In the event of system outages or technical difficulties, expedited adverse events may be submitted via the DAIDS EAE form (paper format). This form is available on the DAIDS RSC website at <https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting>. For questions about DAERS, contact DAIDS-ES at DAIDSRSCSafetyOffice@tech-res.com. Site queries may also be sent from within the DAERS application itself.

All EAEs must also be reported as AEs on the AE Log e-CRF and to be submitted to the HPTN SDMC within 72 hours of the site awareness date. When completing AE Log e-CRFs and EAE forms, study clinicians should carefully review all documentation of the event to ensure accuracy, completeness, and consistency. All AE descriptions and details (e.g., AE term, onset date, severity grade, relationship to study product) must be recorded consistently across all documents. All EAE forms received at the DAIDS Safety Office will be compared with the AE Log CRFs received at the HPTN SDMC to ensure that all key data elements are matched with consistent details.

Table 10-1 provides an overview of AE and EAE reporting for HPTN 084-01.

Table 10-1: Reference Guide for Reporting AEs and EAEs

The table below is an “at a glance” reference guide for reporting AEs to the study database at the HPTN SDMC, and AEs that also meet the definition for expedited reporting to DAIDS (EAEs). HPTN 084-01 will follow the SAE (Serious Adverse Event) Reporting Category for adverse events that require expedited reporting (EAEs), as defined the Manual for Expedited Reporting of Adverse Events to DAIDS, January 2010. An SAE in this study is defined as: results in death, is life threatening, requires hospitalization, results in persistent or significant disabilities or incapacity, is a congenital anomaly/birth defect; is an important medical event – see below.

AE	Report on AE Log	Report as EAE
SERIOUS ADVERSE EVENT		
Results in death	Yes	Yes, regardless of relatedness to study drug
Is life-threatening	Yes	Yes, regardless of relatedness but does not include all Grade 4 events (see Note 1 below)
Requires inpatient hospitalization or prolongation of existing hospitalization	Yes	Yes, regardless of relatedness to study drug (see Note 2 below)
Results in persistent or significant disabilities or incapacities	Yes	Yes, regardless of relatedness to study drug
Is a congenital anomaly/birth defect	Yes	Yes, regardless of relatedness (see Note 3 below)
Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the above definition	Yes	Yes, regardless of relatedness to the study drug
IS A REPORTABLE ADVERSE EVENT TO THE HPTN SDMC, BUT MAY OR MAY NOT ALSO BE A SERIOUS ADVERSE EVENT		
Grade 1 and higher AEs	Yes	Only if it meets the definition of an SAE as outlined above
OTHER ADVERSE EVENT IDENTIFIED FOR REPORTING		
ALT \geq 3x ULN AND total bilirubin \geq 2x ULN	Yes	Yes, regardless of relatedness to study drug
Any seizure event	Yes	Yes, regardless of relatedness to study drug

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

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

3: Clinically insignificant physical findings at births including those regarded as normal variants do NOT meet reporting criteria unless there is also a clinically significant anomaly being reported. Refer to the Manual for Expedited Reporting of Adverse Events to DAIDS for full details.

10.10 Social Impact Reporting

In addition to medical AEs, participants in HPTN 084-01 may experience social impacts — participant reported non-medical adverse consequences or benefits — as a result of their participation in the study. For example, participants could experience difficulties in their personal relationships with partners, family members, and friends, if they find out they are participating in the study. They also could experience stigma or discrimination from family members and members of their community. In the event that a social impact occurs, study staff should fully document the issues or problems and make every effort to facilitate their resolution as described in this section. In addition, the social impact must be recorded on the Social Impact e-Log. As with medical AEs, follow all problems to resolution (until they no longer exist), or stabilization (they exist, but at a manageable level). Provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem.

If the reported social impact is associated with an AE, report the AE on the AE e-Log. If the social impact is associated with an AE that meets criteria for expedited reporting to DAIDS, report it on the AE e-Log and as an EAE. Also report the issue or problem to all IRBs/ECs responsible for oversight of HPTN 084-01, if required per IRB guidelines.

10.11 Product Safety Information

Once a site has completed protocol registration, it will begin to receive product safety information on the study product being used in the study. The information that the sites may receive is:

- Revised Investigator Brochures
- IND Safety Reports
- Safety Memos, reports or updates
- Other safety memoranda and updates

This information will be forwarded to the sites by the HPTN Leadership and Operations Center via an email alias set up for this purpose. Each site should maintain copies of each communication in their regulatory files. This information originates from the DAIDS Regulatory Support Center (RSC). Each email will indicate how the information is to be handled. **In many cases, this information must be submitted to the site's IRB/EC.** Product safety information does not require IRB/EC approval; however, sites should maintain a copy of the IRB/EC submission cover letters indicating the date of submission and identifying the content of the submission in their regulatory files. Any acknowledgements from the IRB/EC should also be filed in the regulatory file. The Investigator of Record and the Study Coordinator are responsible for reviewing this information, disseminating this information to their staff and ensuring that it is submitted to the IRB/EC.