

## Section 7: Adverse Event Reporting and Safety Monitoring

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### 7.1 Overview of Section 7

This section presents information related to adverse event (AE) reporting and safety monitoring in HPTN 091. The following resources are relevant to AE reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.1 corrected, dated July 2017.
- Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0 (DAIDS EAE Manual, dated January 2010)
- Current Truvada<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate) Package Insert
- Current Descovy<sup>®</sup> (emtricitabine/tenofovir alafenamide) Package Insert (US sites only)
- Current Package Insert for the Gender Affirming Hormonal Therapy (GAHT) available at the site
- Current Section 5.7 and Toxicity Management Appendix II of the HPTN 091 protocol (Version 1.0, dated April 13, 2020)

## 7.2 Adverse Event

AEs are defined in Section 7.1 of the HPTN 091 protocol. This definition applies to all participants from the time a participant is randomized through when they terminate from the study.

## 7.3 Documenting Adverse Events

Study site staff will document in source documents all AEs independently of grading or relationship to study products (e.g., PrEP or hormonal therapy). AEs that will be reported on an eCRF are:

- Grade 3 or higher AEs regardless of relatedness to study products
- Any AE that leads to a study product hold (temporary or permanent) or change in regimen regardless of severity and presumed relationship to study products.
- All Serious Adverse Event (SAE)/ Expedited Adverse Event (EAE)

All AEs will be graded according to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.1 corrected, 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: <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-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 SOPs. This information should be reviewed after each participant visit to determine if an AE has occurred. For events captured on the Adverse Experience Log (AE Log), **whenever possible, the final diagnosis, rather than the individual signs and symptoms and lab abnormalities, should be documented (in both the source documentation and on the AE Log). If a diagnosis is not possible, each individual sign and symptom and lab abnormality 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 Serious Adverse Events (SAEs) / Expedited Adverse Events (EAEs), see Section 10.5 below for guidance on documentation and reporting.

## 7.4 Adverse Event Severity Grading

The severity of all AEs identified in HPTN 091 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 091 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 for Parameters Not Identified in the Grading Table” row of the table:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event <b>NOT</b> identified elsewhere in the grading table	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 or hospitalization 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 and record the unifying diagnosis as the AE.

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.

## 7.5 Adverse Event Relationship to Study Product

Relatedness is an assessment made by a study clinician of whether or not the event is related to the study product. The relationship of all AEs to the study product will be assessed per the clinical judgment of the investigator based on the package insert and investigator’s brochure, and as defined in Version 2.0, January 2010 (or most current version) of the DAIDS EAE Reporting Manual, which is available on the DAIDS

Regulatory Support Center (RSC) website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

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 alternate etiology section of the CRF. If new information becomes available, the relationship assessment of any AE should be reviewed again and updated as required.

## 7.6 Reporting Adverse Events to the HPTN SDMC

As noted in Section 7.3, only the following AEs will be documented on a CRF and uploaded to the study database:

- Grade 3 or higher AEs regardless of relatedness to study products
- Any AE that leads to a study product hold (temporary or permanent) or change in regimen regardless of severity and presumed relationship to study products.
- All Serious Adverse Event (SAE)/ Expedited Adverse Event (EAE)

Medical conditions, problems, signs, symptoms, abnormal laboratory value, and findings identified before randomization but not meeting protocol exclusionary criteria are documented on the Pre-Existing Conditions e-form. If a condition is ongoing at the time of randomization, it is a pre-existing condition. If this condition worsens (increases in severity or frequency) after randomization, the worsened condition is considered an AE. If a pre-existing condition resolves after randomization, 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 CRF to the HPTN SDMC and mark either “held” or “permanently discontinued” on the Study Regimen Administration section of the AE CRF Log.

If an AE increases in severity or frequency (worsens) after it has been reported on an AE Log e-CRF, the event must be reported on a new AE Log e-CRF to the HPTN SDMC. In this case, the status and outcome of the first AE will be recorded as “recovered/resolved” on the first AE Log e-CRF and the outcome date of the first AE should match the onset date of the new AE. When an AE improves to a lower severity or becomes less frequent, a new AE submission is not necessary.

Each AE identified in HPTN 091, even if does not meet the criteria for reporting into the study database, must be followed clinically through study participation until the AE resolves (returns to baseline) or stabilizes. In some cases, a Site Investigator may determine that an AE has “stabilized” i.e., it has not increased in intensity for a period of time. 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 $\geq$ 2.5xULN PLUS total bilirubin $\geq$ 2xULN. The CMC 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.
- 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. 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 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 avoid using abbreviations unless it is a commonly used laboratory abbreviations such as ALT, AST or CPK.
- 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.

## **7.7 Additional Adverse Event Reporting Considerations**

### **7.7.1 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.”

### **7.7.2 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 AND the AE Log eCRF. Additionally, if the diagnosis is confirmed, report the diagnosis as the AE term and not the test result. For example, if gonorrhea is confirmed then the AE term should be “gonorrhea” and not “gonorrhea test positive”. All other STIs diagnosed as part of standard of care will be reported on the AE Log eCRF only.

### **7.7.3 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. Laboratory values from any non-HPTN Laboratory Center approved venue should not be included in the AE database (i.e., not reportable as an AE) and should be documented in the participant chart and followed to resolution. For any value that meets the criteria of reportable AE, sites should confirm these results and document accordingly. 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.

### **7.7.4 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.

## **7.8 Serious Adverse Events (SAEs) / Expedited Adverse Events (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)
  - Admission for diagnosis or therapy of a condition that existed before randomization 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.

## 7.9 Expedited Reporting of Adverse Events 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 <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual>. All AEs that meet the definition of “serious” (SAEs), regardless of relationship to study product, are expedited adverse events (EAE).

This reporting is required for all participants from the time they are randomized until their participation in the study ends. After this time, sites must report to DAIDS serious, unexpected, clinical suspected adverse drug reactions, 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 expedited adverse event (EAE) reporting are: Oral FTC/TDF PrEP, oral FTC/TAF PrEP, and gender-affirming hormone therapy.

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. DAERS can be accessed at <https://ncrms.niaid.nih.gov/>. 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, please contact [CRMSSupport@niaid.nih.gov](mailto:CRMSSupport@niaid.nih.gov). Site queries may also be sent from within the DAERS application itself. For questions about EAE reporting, please contact the RSC at [DAIDSRSCSafetyOffice@tech-res.com](mailto:DAIDSRSCSafetyOffice@tech-res.com).

All EAEs must also be reported as AEs on the AE Log e-CRF and to be submitted to the HPTN SDMC within 3 days 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.

An asymptomatic, abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited timeframe unless it meets protocol-specific reporting requirements.

Table 10-1 provides an overview of AE and EAE reporting for HPTN 091.

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 091 will follow the SAE (Serious Adverse Event) Reporting Category for adverse events that require expedited reporting (EAEs), as defined in 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
<b>SERIOUS ADVERSE EVENT</b>		
Results in death	Yes	Yes, regardless of relatedness to study drug
Is life-threatening	Yes	Yes, regardless of relatedness but does <b>not</b> 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)



AE	Report on AE Log	Report as EAE
<b>SERIOUS ADVERSE EVENT</b>		
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
<b>IS A REPORTABLE ADVERSE EVENT TO THE HPTN SDMC, BUT MAY OR MAY NOT ALSO BE A SERIOUS ADVERSE EVENT</b>		
Grade 3 and higher clinical AEs	Yes	Only if it meets the definition of an SAE as outlined above

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.

3: Clinically insignificant physical findings at birth 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.

## 7.10 Social Impact Reporting

It is possible that participants' involvement in the study could become known to others, and that a social impact may result (i.e., because participants could be perceived as being HIV-infected or at risk or "high risk" for HIV infection). For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities. A social impact that is reported by the participant and judged by the IoR/designee to be serious or unexpected will be reported to the responsible site's IRBs at least annually, or according to their individual requirements.

In the event that a participant reports a social impact, every effort will be made by study staff to provide appropriate care and counseling to the participant as necessary, and/or referral to appropriate resources for the safety of the participant. Each site will provide such care and counseling in accordance with standardized guidance in the SSP Manual. Social impacts will be collected and reported on applicable eCRF(s) during regular visits.

In addition, the social impact must be recorded on the Social Impact e-Log CRF. 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 CRF. If the social impact is associated with an AE that meets criteria for expedited reporting to DAIDS, report it on the AE e-Log CRF and as an EAE.

While maintaining participant confidentiality, study sites may engage their CAB in exploring the social context surrounding instances of social impacts, to minimize the potential occurrence of such an impact.

## 7.11 HIV Reporting

HIV acquisition (seroconversion) is a secondary study endpoint and is thus not considered an AE for data collection or reporting purposes. "HIV infection" should not be reported as an AE or written anywhere on an AE Log CRF.

However, primary HIV infection is often symptomatic, and a constellation of symptoms may best be summarized as primary HIV infection illness. In this case, as in other cases when symptoms are best expressed as a unifying diagnosis, it is important to use that summary diagnosis. Thus, if a participant seroconverts and develops one or more signs or symptoms of acute HIV-infection, it is appropriate to report these sign(s)/symptom(s) as a single AE using ONLY the term "seroconversion illness" for Item 1 within the AE Log CRF. Use the alternative etiology section of the AE Log CRF to describe each HIV-related sign/symptom (e.g., fatigue, pharyngitis, etc.).

Complete the other items on the AE Log CRF per the general form instructions. The onset date should be completed using the date on which the participant first reported experiencing the first sign/symptom of acute HIV-infection. If there is more than one HIV-related sign/symptom, record the highest severity grade. A seroconversion illness AE is considered 'resolved' when all of the associated signs/symptoms have resolved or returned to baseline per participant report, and medications for the symptoms are no

