# Section 3. Document Requirements



## 3.1 Overview of Section 3

This section contains a listing of required administrative and regulatory documentation, commonly referred to as "Essential Documents," which each study site must maintain and keep current throughout the study, as well as procedures for establishing adequate and accurate study participant source documentation records.

## 3.2 Essential Documents

Refer to the Essential Documents Section of the DAIDS Score Manual.

https://www.niaid.nih.gov/research/daids-score-manual

Refer to the appendix which specifies the administrative and regulatory documents that HPTN study sites must maintain for DAIDS-sponsored studies.

https://www.niaid.nih.gov/sites/default/files/essential-documents-recordkeeping.pdf

Also refer to *ICH E6 Good Clinical Practice: Consolidated Guidance* (https://www.fda.gov/media/93884/download) specify the administrative and regulatory documents that HPTN study sites must maintain for Division of AIDS (DAIDS)-sponsored studies. Based on this DAIDS Policy, the documentation listed below must be maintained for HPTN 084. When required documents are modified or updated, the original and modified/updated versions must be maintained. Although all required documentation must be available for inspection at any time, all documents need not be stored together in one location.

- Protocol (implementation version and any subsequent amendments, Letters of Amendment [LoAs] and Clarification Memos [CMs])
- Informed Consent Forms (ICFs) (all IRB/EC-approved versions, all signed and dated forms from screened/enrolled study participants), as well as any "Dear Participant" Letters (all IRB/EC-approved versions) for all screened/enrolled participants.
- Signed and dated Food and Drug Administration (FDA) Form 1572, original and subsequent versions
- Documentation of approved protocol registration from DAIDS, protocol registration for the original study and Version 3 (OLE) and for all subsequent protocol modifications
- Documentation of study activation from HPTN Leadership and Operations Center (LOC)
- Documentation of local regulatory authority correspondence, authorization, and/or approval of the protocol
- Federal Wide Assurance (FWA) number(s) and expiration date
- Institutional Review Board (IRB)/Ethics Committee (EC) roster(s)
- All correspondence to and from the local IRB/EC, including documentation of all submissions, reviews and approvals and copies of site-specific interim and annual reports
- All IRB-approved participant informational/educational materials and advertisements for participant recruitment, as well as subsequent updates
- Screening and enrollment logs
- Participant identification code list (if applicable)
- Study staff roster, signature sheet, and delegation of duties, including Investigator of Record (IoR) responsibilities
- Signed and dated Curriculum Vitae (CV) for each study staff member, current within the last two years
- Financial disclosure forms from all key staff listed in the FDA form 1572
- Documentation of staff members' current human subjects training (within 3 years)

- Documentation of staff members' study-specific training, including training on all official revisions/amendments/regulatory actions such as version 3 (OLE) related to the protocol
- Documentation of staff members' current Good Clinical Practice (GCP) training (within 3 years)
- Documentation of appropriate laboratory staff members' current Good Clinical Laboratory Practice (GCLP) training. Refer any questions to the HPTN Laboratory Center (LC).
- Local laboratory accreditations/certifications, if applicable
- Product Safety Information/Reports/Memos (Investigational New Drug [IND] Safety Reports provided by DAIDS)
- Current cabotegravir (CAB) (oral and injectable) Investigator Brochure (IB) and subsequent updates
- Current Truvada® (TDF/FTC) Package Insert and subsequent updates
- All study product accountability records
- Local laboratory reference intervals for protocol-specified testing
- Key study-related correspondence with the HPTN LOC, HPTN Statistics and Data Management (SDMC), HPTN Laboratory Center (LC), DAIDS Pharmaceutical Affairs Branch (PAB) and DAIDS, as well as other study-related communication
- Documentation of study-related conference calls and meetings
- Applicable local public health reporting requirements pertinent to study procedures
- Final version of each local site- and study-specific Study Operating Procedures (SOPs) that will be used for HPTN 084 and all subsequent updates
- DAIDS reference materials including:
    - Division of AIDS Clinical Research Policies
        - https://www.niaid.nih.gov/research/daids-clinical-research-policies-and-other-information

- Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual
    - https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations
    - DAIDS Protocol Registration Policy and Procedures Manual:
        - https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual
- Study specific procedures (SSP) manual, original versions and all updates, bulletins, clarifications, and communiqués
- Monitoring visit log, reports, and site response to visit findings (for the monitor, HPTN LOC, SDMC, LC, PAB, and other site visits). Sites should print monitoring visit reports for their files from the DAIDS website for Clinical Research Management System (https://ncrms.niaid.nih.gov/NCRMS/Main)
- A complete, blank copy of the electronic case report forms (CRFs) (original and all revisions – these will be provided by the HPTN SDMC). Sites may choose to print the forms and file as part of their essential documents or they may choose to file electronically.
- All completed CRFs, which will include electronic initials and dates per the electronic data capture system (these will be provided by the HPTN SDMC at the end of the study)
- Site specific e-CRFs as Source Documentation Table (Table 3-1a OR 3-1b) and Source Documentation for Eligibility Criteria (Table 3-2)
- Source documents
- Signed agreements related to the study (e.g., between IoR and affiliated sites/ Materials Transfer Agreements (MTAs)/ Protocol Signature Page, etc.)

## 3.3 Investigator Responsibilities

Study sites must maintain an accurate and complete participant research record containing all information pertinent to the study for each study participant. The research record consists of the following: original subject-signed ICF(s), participant source documents, and CRFs.

Refer to Investigator Responsibilities section of the DAIDS Score Manual at https://www.niaid.nih.gov/sites/default/files/score-investigator-responsibilities.pdf.

### 3.3.1 Concept of Source Documentation

A source document is defined as the first document on which study-related information is recorded. Study sites must adhere to the standards of source documentation specified in the *DAIDS Score Manual* and the standards outlined in this manual.

For HPTN 084 including OLE, participant source documents will consist of narrative chart notes, visit checklists, medical records, laboratory reports, pharmacy records and CRFs and other items as defined by each participating site. As a condition for study activation, each site must establish an SOP for source documentation that specifies the use of these documents as source documents.

HPTN 084 will use an electronic data capture system. Electronic records are any combination of text, graphics, data, audio, pictorial, or other information in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system (21 CFR 11.3). **When data are entered directly into a computer, the electronic data in the computer becomes the source document**. A paper record (printout/hard copy/"print screen") of the electronic data is considered to be a copy. Requirements for documentation, record keeping and record retention apply to electronic records the same as they do for paper systems.

Examples of electronic records include but are not limited to:

1. Participant data, reports, and/or results
2. E-mail communications pertaining to a participant or protocol management (e.g., directives from protocol chairs, clinical management committee (CMC), Clinical Research Site (CRS) investigators to study nurses, etc.)
3. IRB/EC correspondence pertaining to a participant or the study
4. Computer-Assisted Self-Interview (CASI) questionnaires

Each electronic record needs to be associated with an originator type, otherwise known as an authorized data originator. In HPTN 084, the authorized data originator is most likely going to be a person; however, it can also be a computer system, a device, or an instrument that is authorized to enter, change, or transmit data into the electronic record. Sites must develop and maintain a list of all authorized data originators. This list must be made available for study-related monitoring, audits, IRB/EC review, and regulatory inspection by authorized individuals at each clinical research site. Examples of data originators include, but are not limited to:

1. Clinical investigator(s) and delegated clinical study staff
2. Participants or their legally authorized representatives
3. Consulting services (e.g., a radiologist reporting on a computed tomography (CT) scan)
4. Medical devices (e.g., electrocardiograph (ECG) machine and other medical instruments such as a blood pressure machine)
5. Electronic health records (EHRs)
6. Automated laboratory reporting systems (e.g., from central laboratories)
7. Other technology

### 3.3.2 Source Documentation

Participant source documentation should contain all of the following elements:

- Participant ID number (PTID) assignment.
- Documentation that the participant provided written informed consent to participate in the study prior to the conduct of any study procedures including an Informed Consent Assessment tool (see SSP Section 4 Tables 4-1 and 4-2) to verify comprehension.
- Documentation that the participant met the study's eligibility criteria.
- A record of all contacts, and attempted contacts, with the participant.
- A record of all procedures performed by study staff during the study.
- A record of the participant's exposure to the study product.
- A record of any Adverse Events (AEs) and Social Impacts reported by participants.
- Study-related information on the participant's condition before, during, and after the study, including:
    - Data obtained directly from the participant (e.g., self-report of injection reaction)
    - Data ascertained by study staff (e.g., exam and lab findings)
    - Data obtained from non-study sources (e.g., medical records)

In general, sites should apply ALCOA* to achieve data quality.

- **A**ttributable: is it obvious who wrote it?
- **L**egible: can it be read?
- **C**ontemporaneous: is the information current and in the correct time frame?
- **O**riginal: is it a copy; has it been altered?
- **A**ccurate: are conflicting data recorded elsewhere?

*Source: "The Facts About Source Documents" by Stan W. Woollen, Presented at the 1999 DIA Annual Meeting

### 3.3.3 Examples of Source Documentation

#### 3.3.3.1 Clinic Notes

Study staff must document contacts with a study participant where data and pertinent study information are collected in a signed and dated clinic note specifying the date, type, purpose, location of the contact, and the general status of the participant. Routine study visit reminders may be documented per local site SOPs and requirements (and a site may wish to include this information in the retention SOP). Clinic notes also must be used to document the following:

- The informed consent process and/or coversheets
- Procedures performed that are not recorded on other source documents
- Pertinent data about the participant that are not recorded on other source documents
- Protocol deviations that are not otherwise captured on other source documents (such as the Protocol Deviation Form).

One way that clinic notes can be structured is by using the SOAP method. The acronym SOAP stands for Subjective, Objective, Assessment, and Plan and the following information is included in each section:

**S:** Subjective information that includes what the patient tells you about how he/she is feeling or his/her symptoms. For example, how he/she is sleeping or eating or if he/she is experiencing pain or having trouble urinating or defecating.

**O:** Objective information including vital signs, pertinent physical exam findings, and the most recent laboratory test results.

**A:** The assessment describes your diagnosis of the symptoms. The assessment also includes a summary of how the patient is doing and what has changed from the previous visit.

**P:** The plan includes how each diagnosis or problem will be addressed. This section will include information about new or changes to existing medication, laboratory tests to order, and consults to obtain.

#### 3.3.3.2 Visit Checklists

The checklists provided in Section 6 of this SSP manual may be used as a convenient tool for study staff to ensure that all study procedures are performed at each visit. The checklists as designed may not be able to serve as source documentation – see Section 6.0 for further information about this. If a site modifies the checklists to serve partly or wholly as source documents, individual study staff members must initial *only* those procedures that they complete to fulfill the source documentation requirement of identifying responsibility. In addition, if procedures listed on a single checklist are completed across multiple dates or by more than one person, the date upon which each procedure is completed must be clearly noted and initialed.

Even with modification, the checklists alone may not be sufficient for documenting all procedures. For example, chart notes may be required to document procedures performed at unscheduled study visits or to explain why procedures in addition to those specified on a checklist have been performed. Chart notes may also be required to document the content of discussions with participants (*e.g.,* issues related to study product adherence and HIV counseling). Sites are encouraged to contact the HPTN LOC with any questions about which checklists to use and/or how to modify them for site specific purposes.

### 3.3.3.3 Case Report Forms

As mentioned above, the study will utilize an electronic data capture system. Each study site must document the source documentation for each electronic CRF item by completing Table 3-1 (EITHER Table 3-1a OR Table 3-1b may be used; these tables may be modified to suit site needs), submitting a copy to the HPTN LOC, and maintaining the original document in the site's administrative and regulatory files. The comments section of Table 3-1 (1a or 1b) should be modified to accurately reflect the source documentation for each CRF item at the site. Table 3-1 (1a or 1b) will be finalized and signed at each site prior to site activation. Site staff must follow the designations in Table 3-1 (1a or 1b) consistently for all study participants throughout the study.

In the event that it is not possible to record data directly onto forms designated as source documents, the following procedures should be followed:

- Record the data onto an alternative source document.
- Enter the alternative source document into the participant's study chart.
- Transcribe the data from the alternative source document onto the appropriate case report form.
- Enter a chart note stating the relevant study, or dosing visit, date and the reason why an alternative source document was used.

## Tables 3-1a and 3-1b: HPTN 084 Source Documentation TEMPLATES

***NOTE: These tables are provided as example documents. Each site must complete either Table 3-1a or 3-1b site-specific source documentation table based on individual needs and policies. The CRFs in table 3-1b below are listed in alphabetical order and not necessarily in the order in which procedures are performed.***

*Table 3-1a: For each procedure listed below, add the source documents for each study procedure/evaluation. This is an EXAMPLE. Please add to this table if necessary.*

| Evaluation /Procedure | Source Document(s) |
|---|---|
| ADMINISTRATIVE, BEHAVIORAL AND REGULATORY | |
| Obtain Informed consent(s) | *Example: Signed and Dated Informed Consent form*<br>*Informed Consent Coversheet (or chart note)* |
| Locator information | |
| Demographic information | |
| HIV prevention counseling | |
| Offer condoms | |
| Acceptability assessments | |
| Behavioral assessments | |
| CLINICAL | |
| Medical History contraceptive use, con meds, physical exam | *Example: Medical History Questionnaires, Medical History eCRF, Concomitant Medications, and/or chart notes* |
| Dispense product | |
| Adherence counseling | |
| Hep B vaccination | |
| Blood collection | |
| Urine collection | |
| Vaginal swab collection | |
| Injections | |
| ISR evaluations | |
| LABORATORY | |
| HIV testing | *Example: Lab result report (or other required site specific form)* |
| Pregnancy testing | |
| HBV and HCV testing | |
| CBC with differential | |
| Chemistry testing | |
| Liver function tests | |
| Fasting lipid profile | |
| Syphilis serologic testing | |
| GC/CT and TV testing | |

| Evaluation /Procedure | Source Document(s) |
|---|---|
| Urinalysis (protein and glucose) | |
| Plasma storage | |
| DBS storage | |
| Whole blood storage | |

## Table 3-1b Example Source Document Reference

*For each form listed below, add which elements of the form serves as the source document for study procedure/evaluation.*

| Form | Source | | | Comments |
|---|---|---|---|---|
| | Yes | No | Mixed | |
| Additional Procedures | | | | |
| Additional Procedures Y/N | | | | |
| Additional Procedures – OLE | | | | |
| Adverse Event | | | *X* | *Example: Form is source for Alternate etiology information. For all other items, source will be based on the type of AE, including chart notes, lab report/testing log, medical questionnaires.* |
| Adverse Event Y/N | | | | |
| Adverse Event - Infant | | | | |
| Adverse Event – Infant Y/N | | | | |
| Cell Pellet Storage | | | | |
| CD4/Viral Load Results | | | | |
| Chemistry Testing | | | | |
| Concomitant Medications | | | | |
| Concomitant Medications Y/N | | | | |
| Consent - Pregnancy Infant Sub-study | | | | |
| Contraception | | | | |
| Contraception -OLE | | | | |
| Counseling | | | | |
| Date of Visit- HIV | | | | |
| Date of Visit - OLE | | | | |
| Date of Visit- Pregnancy | | | | |
| Date of Visit - Pregnancy OLE | | | | |
| Date of Visit- Yearly Visit | | | | |
| Date of Visit- Open Label Truvada | | | | |
| Date of Visit – Step 1 | | | | |
| Date of Visit – Step 2 | | | | |
| Date of Visit – Step 3 | | | | |
| Demographics | | | | |
| Dried Blood Spot Storage | | | | |
| Early Unblinding | | | | |

| Form | Source | | | Comments |
|---|---|---|---|---|
| | Yes | No | Mixed | |
| Enrollment Visit | | | | |
| Fasting Lipid Test Results | | | | |
| Hematology | | | | |
| Hepatitis B Test Results | | | | |
| Hepatitis C Test Results | | | | |
| HIV Supplemental Results | | | | |
| HIV Test Results | | | | |
| HIV Test Results Y/N | | | | |
| Infant Assessment | | | | |
| Infant Breastmilk Feeding Assessment | | | | |
| Infant Dried Blood Spot Storage | | | | |
| Infant HIV test results | | | | |
| Infant Specimen Collection - Blood (Plasma) | | | | |
| Infant Specimen- Cord Blood | | | | |
| Informed Consent V4.0 | | | | |
| Injection Administration | | | | |
| Injection Site Reaction | | | | |
| Injection Site Reaction Y/N | | | | |
| Interim Visit | | | | |
| Interim Visit Summary – OLE | | | | |
| Liver Function Tests | | | | |
| Log Revisions | | | | |
| Long Term Consent Update | | | | |
| Medical History | | | | |
| Medical History Y/N | | | | |
| Missed Visit | | | | |
| Open Label Truvada Log | | | | |
| Open Label Truvada Y/N | | | | |
| Participant Receipt | | | | |
| Participant Transfer | | | | |
| Pill Count – Enrollment | | | | |
| Pill Count – Step 1 | | | | |
| Pill Dispensation- Step 2 and 3 | | | | |
| Plasma Storage | | | | |

| Form | Source | | | Comments |
|---|---|---|---|---|
| | Yes | No | Mixed | |
| Plasma Storage-Contraceptive Substudy | | | | |
| Pregnancy History | | | | |
| Pregnancy Outcome Log | | | | |
| Pregnancy Outcome Log – OLE | | | | |
| Pregnancy Report | | | | |
| Pregnancy Report- OLE | | | | |
| Pregnancy Test Results | | | | |
| Pregnancy Test Results-OLE | | | | |
| Product Choice - OLE | | | | |
| Product Hold/Discontinuation Log | | | | |
| Product Hold Y/N | | | | |
| Product Hold - OLE YN | | | | |
| Product Hold - OLE | | | | |
| Protocol Deviation Log | | | | |
| Protocol Deviation Y/N | | | | |
| Randomization | | | | |
| Screening Chemistries | | | | |
| Screening Liver Function Tests | | | | |
| Screening Outcome | | | | |
| STI Test Results | | | | |
| Social Impact Log | | | | |
| Social Impact Log Y/N | | | | |
| Specimen Collection - Breast Milk | | | | |
| Specimen Storage-Contraceptive Sub-Study | | | | |
| Study Step | | | | |
| Sub-study Infant PTID | | | | |
| Termination | | | | |
| Ultrasound Results | | | | |
| Ultrasound - OLE | | | | |
| Urinalysis | | | | |
| VOICE Risk Score - Modified | | | | |
| Whole Blood Storage | | | | |

### 3.3.4 Document Organization

Study staff must make every effort to keep all research records - both individual participant records as well as logs and documents pertaining to all participants – confidential and secure. All records should be securely stored in an area with access limited to authorized staff only.

All study-specific documents and biological specimens that are transmitted to an off-site location, including copies of electronic CRFs, SAE/EAE Report Forms and all biological specimens processed in any way by non-study staff or transferred to an off-site location must be identified only by the participant's PTID to maintain confidentiality. Sites must ensure that any document sent by email or other communication methods does NOT contain any participant identifiers. If a document has participant identifiers, the identifying information must not be visible or legible prior to sending. When communicating via email between two institutions for transfers that do NOT include anyone external to the two institutions, sites must follow their local institution's policy for transmission of confidential information (e.g., encrypted email, redacted files, etc.). Inclusion of more than one identifier on other study records that are accessible only to authorized study staff is not prohibited by DAIDS, however, such records must be stored securely with limited access. Regardless of whether the participant identifier on a particular document is the participant's name or PTID number, the original identifier may not be obliterated or altered in any way, even if another identifier is added. When necessary to maintain confidentiality, identifiers may be obliterated or altered on **copies** of original source documents. For example, if supporting documentation of study eligibility is to be submitted to the HPTN LOC, such as chart notes or lab reports, contain a participant's name, this should be obliterated on the copy transmitted off-site, but not on the original.

All local databases will be secured with password-protected access systems.

Log books, appointment books, and any other listings that link participant PTID numbers to participant names or other personal identifiers should never be left unattended or easily accessible to unauthorized individuals.

## 3.4 Protocol Deviations

Any deviation from the protocol must be documented in participant charts and in any other pertinent source documents, including a Master Protocol Deviation Log which must be maintained on site. Any deviation from the protocol, no matter how small, must be recorded on this Master Protocol Deviation Log. All protocol deviations must be reported into the electronic data capture system.

*** NOTE**: HPTN 084 is adopting a more conservative approach for protocol deviation reporting, given that this an IND study.

### 3.4.1 Protocol Deviation Categories

Protocol deviations must be classified into a category when they are reported. Explanations of each category are provided below along with some common examples.

#### 3.4.1.1 Category: Informed consent process deviation

This category of deviations includes errors directly related to the informed consent. Errors include staff failure to follow proper consenting processes with participants, not confirming comprehension of the content of the consent, not documenting consent properly and nonadherence to what the participant agreed to.

Examples of these deviations include:

- A site made a mistake on the consent form. It did not correctly account for the blood volume needed for study testing. The consent form stated that 44mLs of blood would be taken. Instead the site was routinely taking 50mLs of blood for protocol testing.
- Participants have the ability to opt out of genetic testing on the consent form. Blood for genetic testing was erroneously collected from a participant who had already declined genetic testing.
- A participant was consented using an English consent form when it is clear from the chart notes that her understanding of English was very limited. The site had an approved translated consent in the participant's native language. The site should have used the consent the participant did not have to struggle to understand.

#### 3.4.1.2 Category: Use of non-IRB/EC-approved materials

This category of deviations includes instances where sites accidently use materials with participants or the Community without local IRB/EC body (ies) approval.

Examples of these deviations include:

- Advertisements for a study were hung up to help recruit participants, however, the advertisements had not yet been IRB-approved.
- A site with multiple levels of IRB/EC reviews received protocol/consent form approval from all review bodies except one. The site did not realize that one review was still outstanding and implemented the updated protocol/consent form on site.

#### 3.4.1.3 Category: Inappropriate enrollment

In general, any situation where eligibility criteria are not met or randomization is performed before all criteria are confirmed must be categorized as an inappropriate enrollment protocol deviation.

Examples of these deviations include:

- A site accidently enrolled a woman into the study with a voice risk score of 2 instead of a score of 5 or more (protocol version 2).
- AST and ALP were erroneously requested instead of ALT and Total Bilirubin. The site did not catch omission of the enrollment criteria before it randomized the participant.
- A participant was enrolled based on screening results that were more than 45 days old.
- A participant was enrolled with a history of seizure; though this history was not revealed to the site during screening. The participant experienced a seizure during the study and only then explained she previously had an eclamptic seizure during pregnancy.
- On a source document, staff marked "Yes" but did not provide the number of sexual encounters the participant reported having in last 30 days. Consequently, a monitor was unable to verify that the participant met the eligibility criterion of having "vaginal intercourse on a minimum of two separate days in the 30 days prior to Screening."
- A site accidently enrolled a woman that had a positive HBsAg result at the screening visit. All other screening lab results were not clinically significant, and HIV ELISA was negative.

#### 3.4.1.4 Category: Failure to follow trial randomization or blinding procedures

This type of deviation is specific to problems with the randomization procedure or blinding/unblinding requests.

Examples of this type of deviations include:

- While a study clinician was handling the syringe containing injectable study product, the barrel cover shifted just enough for the participant to view the liquid. The participant later did some research and was able to determine which arm she was randomized to.
- A participant was hospitalized after experiencing significant cognitive confusion. In its haste, the site did not properly follow emergency unblinding procedures.

#### 3.4.1.5 Category: Study product management deviation

Deviations in this category are related to the storage and shipping of study products as well as any failure to follow study product handling guidelines.

Examples of this type of deviation are as follows:

- Participant was scheduled for enrollment however the pharmacy was out of stock of study product and the participant could not be enrolled.
- Study product was stored in the pharmacy at the incorrect temperature.
- The Chain of Custody document was not properly complete for a shipment of study product arriving on site.
- Expired oral study product was administered to a participant in error.

#### 3.4.1.6 Category: Study product dispensing error

Deviations in this category are directly related to study product dispensing/administration errors made by site staff.

Examples of these deviations include:

- A site accidently forgot to sign and date a study product prescription. This mistake was caught during a PPD monitoring visit.
- A participant was given an injection after the permissible window of time post product preparation. An injection was prepared at 10:50am but was not administered until 13:00pm. As per the protocol the injection should have been given within two hours of preparation. This injection was administered at two hours and ten minutes after preparation.

#### 3.4.1.7 Category: Incorrect study product given/taken

This category of Protocol Deviations is used exclusively for instances when the wrong study product is ingested by a participant. This type of error could be the result of a study staff error or could occur if a participant takes another participant's study product.

Examples of these deviations include:

- Two participants in a waiting room were sitting next to each other. They each had oral study product bottles with them. By accident, the participants ended up switching study product bottles in the waiting room. They each took the bottles home and subsequently took the wrong oral product.
- A participant came to site for her Week 2 visit. Following the pill count, study staff accidently returned the study product for another participant. Unfortunately, the participant took oral study product in front of study staff before the error was detected. However, the mistake was caught before the participant left the clinic and she was given her original oral study product.
- At Week 5, a participant took oral study product in the morning before she received her first injection on site later that day. If the participant was randomized to CAB

LA, she would have had an oral dose of CAB in the morning and an injectable CAB dose that afternoon.

#### 3.4.1.8 Category: Breach of confidentiality

This category of deviations includes events where confidential information about the participant is released to other people without participant consent. Confidential information includes medical information, HIV status or even the fact that the participation is enrolled in the study.

An example of this type of deviation is as follows:

- In an effort to locate a participant, site staff erroneously contacted two individuals who were not indicated as participant contacts on the locator form.

#### 3.4.1.9 Category: Missed procedures

This type of deviation is specifically related to a site not conducting protocol required procedures, including failure to complete physical examinations/assessments and failure to collect any lab samples (not to include laboratory-initiated errors).

Examples of these deviations include:

- Prior to injecting participants with study product, there are several mandatory processes and labs which must be completed first. A site accidently forgot to confirm a participant was actively using a long-acting contraceptive prior to injection.
- Site staff forgot to weigh a participant during a study visit.
- Sites are required to notify the CMC for participant management guidance where indicated in the protocol. A site erroneously did not contact the CMC when a participant presented with a Grade 3 weight loss AE.
- A clinician accidently did not conduct a targeted medical exam during a follow up study visit.
- Hepatitis B vaccination is scheduled for Week 2 of the study. The vaccination was accidently omitted during a Week 2 visit for a participant.
- A site accidently forgot to collect of a swab for Trichomonas vaginalis testing during a visit at Week 33.

#### 3.4.1.10 Category: Lab assessment deviation

This category of deviations includes events where protocol procedures and lab SOPs are not properly followed by lab technicians. Lab technicians must: 1) properly process, test,

store and ship samples, 2) ensure adequate inventory of test kits and reagents to conduct timely protocol-required testing.

Examples of these type deviations include:

- A lab tech accidently performs HBsAb testing during the Screening visit instead of HBsAg analysis. The correct test was ordered, the tech simply made a mistake.
- A lab tech did not order HIV rapid kits when the supply was low and subsequently ran out of test kits. Lack of test kits caused delayed participant visits since study product cannot be dispensed until a rapid test is completed.
- A lab ran out of hematology controls due to a stick out at the vendor. Study participants had to be rescheduled resulting in some out of window visits.
- Pregnancy test kits were ordered by lab staff but a significant temperature excursion during shipping to the site rendered the kits useless. Study visits were delayed until the kits could be obtained.

#### 3.4.1.11 Category: Conduct of non-protocol procedure

This category of protocol deviations includes instances where a site accidently performs a procedure that is not mandated by either the protocol or based on participant management, and that does not fall under another category of PDs (for example over-collection of blood).

Examples of these deviations include:

- Hepatitis B vaccination was given in error; the participant was already immune.
- At visit 6.0 a urine sample was erroneously shipped to the local lab for NG/CT testing. NG/CT testing is not included in Week 6 protocol procedures. The sample was processed for NG/CT and results were sent to the clinic.

#### 3.4.1.12 Physical assessment deviation

This category of deviations includes events where protocol procedures and are not properly followed leading to errors that occur with physical assessments.

Examples of these type deviations include:

- Participant had her weight incorrectly recorded and the error in weight has resulted in the incorrect BMI calculation.

#### 3.4.1.13 Other

Events that are not specific to any of the above categories will be grouped and classified as “other.”

An example of these deviations include:

- Hematology labs were not performed per study schedule. Due to COVID transport issues, reagents were not available to process the lab samples.

### 3.4.2 Protocol Deviations During the COVID-19 Pandemic

Sites must continue to report PDs into the database during the pandemic. For missed assessments within a study visit due to COVID, a protocol deviation should be added. See example under section 3.4.1.12 Other.

Once a site identifies a protocol deviation, it should be entered into the MediData Rave system.

If the site has any question as to whether an issue is a deviation, it should email the protocol deviation email alias list at 084mgmt@hptn.org for guidance. If the suspected deviation is confirmed, the site will need to complete the Protocol Deviation Log eCRF and include the deviation on the Master Protocol Deviation Log.

### 3.4.3 Protocol Deviation Log CRF

One Protocol Deviation Log CRF should be completed for each participant affected by the deviation. If the deviation occurred over a period of time, report the date the deviation first started and when it ended or if it is ongoing at the time this report is submitted, include this information as part of the description of the deviation.

Please note that there is a limit of 1,000 characters on the Protocol Deviation Log CRF; therefore, sites are asked to be concise and clear when describing the event.

When reporting a deviation trend individual eCRFs must be entered into MediData Rave for each affected PTID.

## 3.5 Record Retention Requirements

As this study is being conducted under IND, the study-related records must be maintained for two years after the marketing application is approved for the drug(s); or if an application is not approved for the drug(s), until two years after shipment and delivery of the drug(s) for investigational use is discontinued and the FDA has been notified (21 CFR 312.57). **No documents are to be destroyed without written permission from DAIDS.**

The study-related records include but are not limited to the following:

- Study management information, including the protocol, clarifications, letters of amendment, protocol amendments, the SSP manual and associated errata, addenda, study drug shipment and supply, and bulletins.

- Signed ICFs for each study participant.
- Electronic CRFs for each study participant labeled by PTID.
- Source documents such as clinic notes, pharmacy records, and laboratory result reports.

## 3.6 Ancillary Studies

Ancillary studies (also sometimes referred to as "sub-studies") are those investigations, conducted in conjunction with a primary or "main" HPTN study, that address scientific questions not identified as study objectives in the primary study protocol.

Ancillary studies may involve HPTN investigators and/or non-HPTN investigators and may be initiated by the primary study team or by individuals inside or outside of the study team. They may:

1) involve all sites participating in a primary HPTN study or a subset of sites;
2) involve the use of data, biological specimens, or other information obtained through a primary HPTN study;
3) be either prospective or retrospective in nature;
4) involve surveys or focus groups among primary study participants; and
5) contain laboratory-based investigations using specimens obtained from participants in a primary HPTN study.

The administrative and regulatory requirements for the conduct of ancillary studies can be found in the HPTN MOP Section 17 (https://hptn.org/resources/manual-of-operations).

## 3.7 Study Publications

All manuscripts, abstracts, posters or presentations based on the results or conduct of HPTN 084 must be prepared in accordance with the HPTN MOP and HPTN 084 Protocol Publications Committee.

## Appendix 3A: Sample HPTN 084 Master Protocol Deviation Log*

| PTID | Date of event/visit | Date of site awareness | Issue/Description | Category of deviation** | eCRF completed? (yes/no) | IRB required to be notified? (yes/no) | Date IRB notified, if applicable |
|---|---|---|---|---|---|---|---|
| 333333333 | 30Oct2019 enrollment | 20Nov2019 | HIV RNA not done within 14 days of enrollment | Inappropriate enrollment | Yes | Yes | 27Nov2019 |

***(*May be adapted as needed for local use)***
***(** See section 3.4.1 for categories)***