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

The DAIDS Policy for *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* (*https://www.niaid.nih.gov/sites/default/files/daids-essentialdocpolicy.pdf* and its appendix: *https://www.niaid.nih.gov/sites/default/files/essentialdocappndx.pdf*) and *ICH E6 Good Clinical Practice: Consolidated Guidance can be found online at* https://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR and http://www.ich.org/home.html) specify the administrative and regulatory documents that HPTN study sites must maintain for DAIDS-sponsored studies. Based on this DAIDS Policy, the documentation listed below must be maintained for HPTN 084-01. 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. Electronic documents may be permitted, when appropriate.

- Protocol (implementation version and any subsequent amendments, letters of amendment and clarification memos)
- Informed Consent Forms (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 FDA Form 1572, original and subsequent versions
- Documentation of approved protocol registration from DAIDS, original protocol registration and for all subsequent protocol modifications
- Documentation of study activation from HPTN LOC
- Documentation of local regulatory authority correspondence, authorization, and/or approval of the protocol
- Federal Wide Assurance (FWA) number(s) and expiration date
- IRB/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 responsibilities
- Signed and dated 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 related to the protocol
- Documentation of staff members' current GCP training (within 3 years)
- Documentation of staff members' current GCLP training
- Local laboratory accreditations/certifications
- Product Safety Information/Reports/Memos (IND Safety Reports provided by DAIDS)
- Current CAB (oral and injectable) Investigator Brochure and subsequent updates
- Current Truvada® (TDF/FTC) Package Insert and subsequent updates

- All study product accountability records
- Local laboratory normal values/reference ranges for protocol-specified testing
- Key study-related correspondence with the HPTN LOC, HPTN SDMC, HPTN Laboratory Center (LC), DAIDS PAB or DAIDS, NICHD and/or Westat, 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, approved version of each local site- and study-specific SOPs that will be used for HPTN 084-01 and all subsequent updates
- DAIDS reference materials including:
    - DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (DWD-POL-CL-04.00 (https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf and its appendix: https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf) and subsequent updates,
    - DAIDS Policy for Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials (DWD-POL-RA-03.00 (https://www.niaid.nih.gov/sites/default/files/daids-essentialdocpolicy.pdf and its appendix: https://www.niaid.nih.gov/sites/default/files/essentialdocappndx.pdf) and subsequent updates,
    - DAIDS Protocol Registration Policy and Procedures Manual: (https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual),
    - DAIDS Policy for Enrolling Children (including Adolescents) in Clinical Research: Protocol Document Requirements (https://www.niaid.nih.gov/sites/default/files/enrollingchildrenprotocol.pdf); and
    - DAIDS Policy for Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements (https://www.niaid.nih.gov/sites/default/files/enrollingchildrenrequirements.pdf).
- Study specific procedures (SSP) manual, original versions and all updates, bulletins, clarifications, and communiqués
- Monitoring visit log, reports, and site response to visit findings (PPDHPTN LOC, SDMC, LC, PAB, and other site visits). Sites should print PPDvisit reports for their files from the DAIDS website for Clinical Research Management System (http://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)
- Record of stored specimens and shipping logs
- Site specific 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 Investigator and affiliated sites)

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. As defined by the *DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (DWD-POL-CL-04.00)*, the research record consists of the following: original subject-signed informed consent form(s), participant source documents, and case report forms (CRFs).

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 Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (DWD-POL-CL-04.00)* and the standards outlined in this manual.

For HPTN 084-01, 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 084-01 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), 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 084-01, 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 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 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). Note that the *DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* (DWD-POL-CL-04.00) requires that all protocol deviations be recorded in participants' study records, along with reasons for the deviations and/or attempts to prevent or correct the deviations if applicable.

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.

Below is an example of clinic notes using the SOAP method:

Sample Clinic Note for a Screening Visit:

26 October 2016: Participant presented for HPTN 084-01 screening at Botswana Clinic. Obtained written informed consent for screening/enrollment before initiating any procedures; HIPAA consent reviewed and signed. Copies of signed documents provided to participant. All of the participant's questions were answered. Screening procedures were completed per the visit checklist and site SOPs.

S: Participant reported no current health problems and shows no signs of acute infection. Participant was born female and met all behavioral risk criteria (see checklist). The participant has never participated in an HIV prevention or vaccine trial. No history of bleeding disorders/easy bruisability, cardiac or liver problems.

O: BP 126/54. Exam entirely WNL. HCV negative as of 3 months prior; HBV immune.

A: Healthy participant that may be eligible for HPTN 084-01.

P: Schedule follow-up with participant to review lab results and confirm eligibility.

{staff signature/date}

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 (which may be modified to suit a site's 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 should be modified to accurately reflect the source documentation for each CRF item at the site. Site staff must follow the designations in Table 3-1 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 084-01 Source Documentation TEMPLATES

NOTE: These tables are provided as <u>example</u> documents. Each site must complete a site-specific source documentation table based on their 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.

Evaluation /Procedure	Source Document(s)
ADMINISTRATIVE, BEHAVIORAL AND REGULATORY	
Obtain Informed consent(s)	*Example: Signed and Dated Informed Consent form, Informed Consent Coversheet (or chart note)*
Locator information	
Demographic information	
HIV counseling	
Offer condoms and lubricant	
Behavioral/Acceptability Assessment (CASI)	
Patient Health Questionnaire-9 (PHQ-9) **At enrollment only*	
CLINICAL	
History (including bleeding history at Screening), con meds, physical exam	*Example: Medical History Questionnaires, and/or chart notes*
Contraception counselling and provision or verification of use	
Observe participant take oral study product **At enrollment (Weeks 2 and 4 optional)*	
Adherence counseling/pill count **Pill count Weeks 2 and 4 only*	
Urine collection for urinalysis	
Urine collection for GC/CT testing	
Urine or Vaginal swab for GC/CT testing	
Oral/pharyngeal swabs for GC/CT testing	
Dispense Pills (enough for 5 weeks)	
Injections **Only in Step 2*	
ISR evaluation **Only in Step 2*	
Provision of TDF/FTC **Only at Week 34 (Step 2) and in Step 3*	
LABORATORY	
HIV testing	*Example: Lab result report (or other required site specific form)*
HBV and HCV testing	
Pregnancy testing	
CBC with differential	

Evaluation /Procedure	Source Document(s)
Chemistry testing	
Liver function tests	
Fasting lipid profile	
Syphilis testing	
Urine GC/CT testing	
Urine or vaginal swab GC/CT	
Urinalysis (protein and glucose)	
Plasma storage	
DBS storage **Only in Step 3*	
QUALITATIVE	
Interview audiofiles	

Table 3-1b: For each CRF listed below, add which elements of the form serves as the source document for study procedure/evaluation.

CRF Name	Source			Comments
	Yes	No	Mixed	
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.*
Additional Procedures				
Date of Visit				
CD4/Viral Load Results				
Chemistry Panel				
Concomitant Medications				
Counseling				
Demographics				
Discontinuation of Study Product				
Enrollment				
Fasting Lipid Test Results				
Hematology				
Hepatitis Test Results				
HIV Test Results				
Inclusion Exclusion Criteria				
Informed Consent Form				
Injection Administration				
Injection Site Reaction				
Interim Visit				

Behavioral Assessment				
CASI Tracking				
Medical History				
Missed Visit				
Participant Identifier				
Participant Receipt				
Participant Transfer				
Patient Health Questionnaire (PHQ)				
Physical Exam				
Pill Count - Enrollment				
Pill Count – Step 1				
Pregnancy Test Results				
Pregnancy Report				
Pregnancy History				
Pregnancy Outcome Log				
Product Hold Log				
Protocol Deviations Log				
STI Tests				
Social Impact Log				
Specimen Collection and Storage				
Study Termination				
Supplemental HIV Results				
Urinalysis				
Vital Signs				

3.3.3.4 Eligibility Criteria

It is essential that source documentation be provided to demonstrate that each inclusion and exclusion criterion contained in the protocol has been met before enrolling a participant. **Failure to document that each of the criteria has been met may result in an enrollment violation.** Sites are encouraged, but not required, to use Table 3-2 to show how they will document that all eligibility criteria have been met for each enrolled participant. As with Table 3-1, Table 3-2 should be modified to accurately reflect the source documentation being used at the site. Sites may choose to develop their own site-specific documentation to specify the source for each eligibility criterion. Please note, this table is required prior to study start.

If a site chooses to use Table 3-2, it should be signed and dated by the Investigator of Record, included in the regulatory files, and followed consistently for all participants throughout the study. This example table is reflective of the inclusion/exclusion criteria in Version 1.0 of the protocol.

Sites are required to use either the local modified version of the *Participant Eligibility Verification Checklist* Template found in Section 6 of the HPTN 084-01 SSP manual (which includes instructions for who is responsible for sign-off), Section 6, or a local-modified version that includes all the required elements found in the provided template, to verify the eligibility of each participant prior to enrollment in HPTN 084-01. Use of this checklist ensures that the Investigator of Record at the site (or designee) has reviewed the eligibility of that participant and confirmed that the criteria have been met. Sites should modify the checklist to be site-specific before using them. Whichever approach the site uses, the investigator signature component must be retained on the checklist. Sites are encouraged to contact the HPTN LOC for help with the task of modifying the checklist. See Section 4.5 of this manual for additional information on requirements for completing this checklist.

For each participant, sites are required to use the Participant Eligibility Verification Checklist to verify each enrollment criterion for the appropriate group checking “yes” or “no” to indicate whether the requirement was met. The staff member verifying eligibility will sign and date the form where indicated. If more than one staff member is involved in completing verification of the participant’s eligibility, then each eligibility criterion must be individually initialed and dated by the staff member performing the confirmation. It is important that each item on the checklist is completed. No item should be left blank. For example, if there are no applicable comments to include in the comment section, please write “N/A” to indicate that that section was not omitted by accident. If an item on the checklist is left blank, it will be considered incomplete. For this study, the eligibility checklist will be the first place that eligibility confirmation will be captured for the majority of criteria. This will make the eligibility checklist the source documentation for that item. In these cases, the checklist is listed as source on the Source Documentation for Eligibility Criteria Tables (Table 3-2).

Risk-related behavior criteria as outlined in Section 3.1, Inclusion Criteria, of the protocol (e.g., assigned female at birth) needs to be documented at screening and should be re-verified prior to enrollment. This is particularly important for participants who take the full 30 days to complete their screening process.

Table 3-2: HPTN 084-01: Source Documentation for Eligibility Criteria (EXAMPLE)
(NOTE: This table is an <u>example</u> document. If a site chooses not to use this document, they must complete a site-specific table based on their individual needs and local SOPs prior to site activation.)

Eligibility Requirements	Source Document
Inclusion Criteria	
Assigned female at birth	Chart Notes/Eligibility Checklist
At enrollment, aged below 18 years	Chart Notes/Eligibility Checklist
At enrollment, body weight ≥ 35 kg (77 lbs.)	Chart Notes/Eligibility Checklist
Willing to provide written informed assent/consent for the study and/or able to obtain written parental/guardian informed consent	Informed Consent Form
Self-reported sexual activity with a male (oral, anal or vaginal) in the past 12 months	Chart Notes/Eligibility Checklist
Willing to undergo all required study procedures	Chart Notes/Eligibility Checklist
Non-reactive/negative HIV test results: ❒ FDA-cleared HIV rapid test ❒ 4th or 5th generation HIV immunoassay ❒ HIV RNA performed within 14 days of Enrollment. NOTE: 14-day window starts on the day the sample for HIV RNA is collected, which is considered Day 0.	Lab Results
Hemoglobin ≥ 11g/dL	Lab Results
Absolute neutrophil count > 799cells/mm^3	Lab Results
Platelet count ≥ 100,000/mm^3	Lab Results
Calculated creatinine clearance ≥ 60 mL/minute using modified Schwartz equation (< grade 2)	Lab Results
ALT < 2 times ULN	Lab Results
Total bilirubin ≤ 2.5 times ULN	Lab Results
Hepatitis B surface antigen (HBsAg) negative	Lab Results
Hepatitis C Ab negative	Lab Results
No Grade 3 or higher laboratory abnormalities on any laboratory tests obtained at screening, including tests obtained as part of a panel of tests ordered to obtain the protocol-required laboratory test results.	Lab Results
No medical condition that, in the opinion of the study investigator, would interfere with the conduct of the study (e.g., provided by self-report, or found upon medical history and examination or in available medical records).	Chart Notes/Eligibility Checklist
Negative pregnancy test	Lab Results
Must agree to use a reliable form of long acting contraception, during the trial and for 48 weeks after stopping the long acting injectable, or 30 days after stopping oral study product that meets <1% failure rate when used consistently and correctly as stated in the product label • IUD, IUS, or hormone-based (implants/injectables only, excludes combined oral contraception)	Chart Notes/Eligibility Checklist

Eligibility Requirements	Source Document
If currently on PrEP from a non-study source, willing to stop said PrEP prior to enrollment and agree to switch to oral CAB for the lead-in period and CAB LA injections.	Chart Notes/Eligibility Checklist
Exclusion Criteria	
One or more reactive or positive HIV test results ❒ FDA-cleared HIV rapid test ❒ 4th or 5th generation HIV immunoassay ❒ HIV RNA performed within 14 days of Enrollment. NOTE: 14-day window starts on the day the sample for HIV RNA is collected, which is considered Day 0.	Lab Results
Co-enrollment in any other HIV interventional research study or other concurrent study which may interfere with this study.	Chart Notes/Eligibility Checklist
Past or current participation in an HIV vaccine trial. An exception may be made for participants that can provide documentation of receipt of placebo (not active arm).	Chart Notes/Eligibility Checklist
In the last 6 months (at the time of screening): • active or planned use of any substance use which would, in the opinion of the site investigator, would hinder study participation (including herbal remedies) o *as described in the IB or listed in the SSP, and/ or Protocol Section 4.4,* • self-report of greater than 5 different sexual partners (anal or vaginal), regardless of use of protection or knowledge of HIV status;	Chart Notes/Eligibility Checklist
Exclusively had sex with biological females in lifetime.	
Clinically significant cardiovascular disease, as defined by history/evidence of symptomatic arrhythmia, angina/ischemia, coronary artery bypass grafting (CABG) surgery or percutaneous transluminal coronary angioplasty (PTCA) or any clinically significant cardiac disease.	Chart Notes
Inflammatory skin conditions that compromise the safety of intramuscular (IM) injections, per the discretion of the Investigator of Record (IoR). Mild skin conditions may not be exclusionary at the discretion of the IoR or designee in consultation with the CMC.	Chart Notes/Eligibility Checklist
Has a tattoo or other dermatological condition overlying the buttock region, which in the opinion of the IoR or designee, in consultation with the CMC, may interfere with interpretation of injection site reactions.	Chart Notes/Eligibility Checklist
Current or chronic history of liver disease (e.g., non-alcoholic or alcoholic steatohepatitis) or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome, asymptomatic gallstones, or cholecystectomy).	Chart Notes/Eligibility Checklist
Known history of clinically significant bleeding.	Chart Notes/Eligibility Checklist

Eligibility Requirements	Source Document
Active or planned use of prohibited medications as described in the Investigator Brochure, protocol, or in the SSP Manual (provided by self-report, or obtained from medical history or medical records.) In particular, future use of TDF/FTC at any point during the study from a non-study source. The only TDF/FTC use allowed is provided by the study and only in Step 3.	Chart Notes/Eligibility Checklist
Any alcohol or substance use that, in the opinion of the study investigator, would jeopardize the safety of the participant on study (e.g., provided by self-report, or found upon medical history and examination or in available medical records).	Chart Notes/Eligibility Checklist
History of seizure disorder, by self-report (NOTE: Any episode of seizure, independent of frequency (e.g. including just one episode) or timeframe (e.g. at any time during participant's life) is exclusionary).	Chart Notes/Eligibility Checklist
Medical, social, or other condition that, in the opinion of the site investigator, would interfere with the conduct of the study or the safety of the participant (e.g., provided by self-report, or found upon medical history and examination or in available medical records).	
Plans to move out of the geographic area within the next 18 months or otherwise unable to participate in study visits, according to the site investigator.	
Pregnant or currently breastfeeding at the time of screening or intends to become pregnant and/or breastfeed while on study.	Lab Results/Chart Notes/Eligibility Checklist

_____ _____

Signature of Investigator of Record Date

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, 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 study identification number (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 Reportable Protocol Deviations

All deviations must be documented in the participant charts and any other pertinent source documents. A subset of deviations may also be considered reportable per the HPTN. The HPTN has established a process for staff at HPTN study sites, the LOC, the LC and the SDMC to document the occurrence of protocol deviations that are considered reportable and to report them to the sponsor (DAIDS), particularly those that might otherwise not be evident in the study data or reported otherwise.

As outlined in the HPTN Manual of Operations, reportable protocol deviations are defined by the HPTN as individual incidents, trends or omissions that result in:

- Significant added risk to the participant
- Non-adherence to significant protocol requirements

- Significant non-adherence to GCP

Examples of reportable protocol deviations are:

- Enrollment of an ineligible participant or prior to confirming eligibility. This also includes situations when ineligibility is found after the fact (e.g., participant did not report at baseline a history of seizures)
- Informed consent not obtained prior to performing protocol-specified procedures
- Administration of study product prior to availability and confirmation of negative/non-reactive HIV test results

  NOTE: To ensure participant's safety, if product is administered prior to availability and confirmation of HIV test results, and results are positive/reactive, please include information as part of the deviation narrative to ensure proper participant oversight.
- Any situation when any of the HPTN 084-01 HIV testing algorithms were not followed as per protocol and Section 11 of the SSP. This is applicable even if the error or omission was made by a commercial or external laboratory.
- A trend showing that protocol-specified procedures are not followed by site staff. For example, if a site forgets to provide or document collection/review of locator information for multiple participants and/or multiple visits, this would be considered a reportable protocol deviation.
- Breach of participant confidentiality
- A protocol-specified laboratory assay consistently not being performed (a single missed assay during one participant visit would not be considered a reportable protocol deviation)
- A site-specific laboratory assay is deliberately added to protocol requirements by the investigator to be conducted for all participants
- Use of prohibited medications as specified in Section 9.4.8.1 of the SSP, even when medication is administered by an outside source (e.g., primary care physician, hospital).

  Participant non-compliance with the study protocol, including treatment specifications (e.g. not taking daily oral products or refusing further injections), is not considered to be a reportable protocol deviation, but should be discussed by the protocol team.
- Participant overdose of study product.

Full documentation of all protocol deviations – including reportable deviations as defined above - should be maintained at the site and reported as required to the local IRB/EC.

The Clinical Site Monitor identifies protocol non-adherence events and violations in their monitoring reports, and some of these may also be reportable protocol deviations; however, there is not a one-to-one correlation between events reported by the Clinical Site Monitor and those to be reported through the HPTN protocol deviation reporting system. The Clinical Site Monitor may report protocol non-adherence events and

violations that encompass every infraction of the protocol. For example, if a blood specimen is drawn for ALT, but is not processed by the laboratory, it is a non-adherence event according to the Clinical Site Monitor. This would be considered a deviation, but not one that meets the HPTN definition of a reportable protocol deviation. If, however, an ALT is to be drawn at each participant visit and is not being done at all, this would be a reportable protocol deviation as defined by the HPTN, because a trend of this error has been identified.

If a site believes a deviation has occurred that would be considered reportable, the following steps should be followed:

1. Contact Erica Hamilton (ehamilton@fhi360.org) as soon as possible (within 24 hours) but no more than 3 business days once a site becomes aware of a deviation to determine whether a deviation meets the above criteria or are otherwise deemed by the protocol team to be reportable deviations before they are reported in to the electronic data capture system.

   Note: Clinical-related deviations may also be identified by the CMC. The CMC or Erica will respond with directions regarding reporting of these deviations, which will follow the same steps as below

2. If it is determined the deviation **does** meet the definition of a reportable deviation, sites must complete the following steps:

   a. Complete the Protocol Deviation eCRF (please note there is a limit of 600 characters each for Description, Plans to Address, and Plans to Prevent areas of the eCRF; therefore, sites are asked to be concise and clear when describing the event).

      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; if it is ongoing at the time the report is submitted, include this information as part of the description of the deviation.

      If 5 or more participants are involved in the same protocol deviation, report the deviation for each individual PTID in a separate eCRF, and include in the description of the deviation the number of PTIDs impacted by the deviation. Please note, when reporting trends (meaning a deviation that impacted 5 or more PTIDs), the information on eCRFs must be identical for all impacted PTIDs (with the exception of participant-specific information such as PTID and applicable dates).

   b. Download the Protocol Deviation e-CRF from the MediData system, and email it (or multiple CRFs if there is more than one) to the HPTN 084-01 Protocol Deviation email alias at 084-01PD@hptn.org indicating that a deviation has occurred and the date it was submitted to the MediData database system. If the deviation is the same for multiple PTIDs, only

append one Protocol Deviation e-CRF to the email and indicate in the body of the email how many participants are impacted by the same deviation.

The HPTN 084-01 protocol deviation email alias includes the following individuals:

- Protocol Chair and Co-Chair
- LOC, LC, and SDMC protocol representatives
- DAIDS Protocol Medical Officer
- NICHD Protocol Medical Officer
- DAIDS Protocol Pharmacist
- DAIDS HPTN Office of Clinical Site Oversight (OCSO) Program Officer Liaisons

When sending emails to the 084-01 Protocol Deviation email alias letting them know that a reportable deviation has occurred, please note:

- Site should also cc: the IoR, Study Coordinator, and Site Regulatory Coordinator.

- When reporting a deviation trend, please include one Protocol Deviation Log eCRF as part of the email sent to the 084-01 Protocol Deviation email alias and specify in the body of the email that a trend is being reported, and a list of affected PTIDs and applicable dates for each. Individual eCRFs must be entered into MediData Rave for each affected PTID.

Please use the following format when sending an email to the 084-01 Protocol Deviation email alias:

Subject line: Include "084-01 PD: [Insert PTID] – [One-line summary of reportable deviation – for example – "Dispensing error."

Body of the email: Include the following information:

1. Site name and number
2. Name of person submitting the reportable protocol deviation
3. Participant Identification number (PTID) and Week on Study (Use "Screen" if pre-enrollment)
4. Short summary of the reportable deviation

Email example:

Subject line of email: 084-01 PD: Participant 103-000012 – Randomization Error
Body of email:

- Site name and number: Site 103 – University Prevention Clinic
- Person submitting query: Hedda Lettuce, Study Coordinator

- PTID and Week on Study: 103-000012, Enrollment/Week 0
- Short Summary: Participant enrolled on December 1, 2019. During QC process, it was noticed the calculated creatinine clearance was miscalculated and participant is below the inclusion value.

It also should be noted that DAIDS has a Critical Event policy that may overlap with events that are deemed as protocol deviations by the HPTN. Sites should confirm with their DAIDS OCSO Program Officer whether a reportable deviation is also a critical event. Refer to the policy at this link: https://www.niaid.nih.gov/research/daids-clinical-research-event-reporting-safety-monitoring. The HPTN has a template available for sites to use to respond to the requirements of a critical event – it can be found at this link: https://hptn.org/resources/manual-of-operations (listed under "Other").

3.5 Record Retention Requirements

Regarding record retention requirements, the most stringent retention period is always followed (state, country-specific, and local laws, and sponsor or institutional policies). As this study is being conducted under IND, European Medicines Authority (EMA) requirements, which will apply to the parent protocol (HPTN 084), were the most demanding identified by DAIDS at the study-wide level. Based upon EMA requirements, sites should therefore plan to retain files (and any other study documentation) for more than 15 years from the end of data collection, or longer if required by local regulations.

Completion of a clinical research study occurs when the following activities have been completed:

- All research-related interventions or interactions with human subjects (e.g. when all subjects are off study);
- All protocol-required data collection of identifiable private information described in the IRB/EC-approved research plan;
- All analysis of identifiable private information described in the IRB/EC-approved research plan;
- Primary analysis of either identifiable private or de-identified information.

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 informed consent forms for each study participant.
- Electronic CRFs for each study participant labeled by PTID.
- Source documents such as clinic notes, pharmacy records, laboratory result reports, and qualitative interview audiofiles.

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 Manual of Operations (MOP) Section 17 (https://www.hptn.org/resources/manual-of-operations).

3.7 Study Publications

All manuscripts, abstracts, posters or presentations based on the results or conduct of HPTN 084-01 must be prepared in accordance with the HPTN MOP and follow HPTN 084-01 Protocol Publications Committee guidelines.