5. Study Procedures Overview

5.1 Overview of Section 5

This section provides a brief overview of requirements and procedures during follow-up (e.g. once a participant is enrolled in the study). Additional procedure-specific details can be found in the HPTN 084-01 protocol and relevant SSP manual sections (e.g. clinical, laboratory, data management procedures).

5.2 Study Overview

All participants enrolled in the study will follow three steps:

- Step 1: All study participants will receive daily oral CAB tablets for 5 weeks.

  Note: Participants in Step 1 of the study who do not transition to Step 2 of the study for any reason other than HIV infection will no longer be followed in the study (See Protocol Section 5.4.1)

- Step 2: All participants will receive an injection administration at two time points four weeks apart [Week 5 (first injection) and Week 9 (second injection)], and then Weeks 17, 25 and 33.

  NOTE: Participants in Step 2 of the study who prematurely stop receiving injections before their study participation ends for any reason other than HIV infection will transition to Step 3 of the study, starting approximately 8 weeks after their last injection.

- Step 3: All participants (except those who become HIV-infected or otherwise contraindicated), including those who permanently discontinue receiving injections before their Step 2 participation in the study ends, will be offered study-provided open-label TDF/FTC 300mg/200mg fixed dose combination daily oral tablets, one tablet daily for up to 48 weeks starting any time following the last study injection and before Step 3 entry. Participants also have the option to join an open-label (OLE) CAB study for Step 3, if available in their area.

- Step 3 will start approximately 8 weeks after the last injection.

All participants will be transitioned to locally-available HIV prevention services, including services for PrEP, if available, when their participation in the study ends.

5.3 Study Visits

Protocol-required visits: Step 1, Step 2, and Step 3 are described in Section 5 and Appendices I, II and III of the Protocol, as well as described in Section 13 of the SSP manual (Data Management).

For each required study visit, there is target visit window described in Section 13.5 of the SSP. Visits conducted outside of the target visit windows are allowable without restriction. Efforts should be made to conduct study visits within the target visit window and may be conducted over multiple days within the target visit window if necessary (see below regarding Split visits); however, if it is not possible to complete the required visit within the target visit window, the visit may be completed within the allowable visit window.

Interim visits: Interim contacts and visits may take place between regularly-scheduled visits. These contacts/visits may be done at participant request (e.g., to receive further counseling or clarify any questions) or as deemed necessary by the investigator or designee at any time during the study (e.g., to follow-up on an adverse event). Procedures to be performed during these contacts/visits will be based on the reason for it.

Split visits: A Split visit is defined as visits conducted over multiple days. Ideally, all procedures specified by the protocol to be performed at a visit will be completed at a single visit on a single day. In the event that all required procedures cannot be completed on a single day (e.g., because the participant must leave the study site before all required procedures are performed), the remaining procedures may be completed on subsequent day(s) within the **allowable target visit window**. When this occurs, the visit is considered a split visit. All case report forms completed for a split visit are assigned the same visit code (even though the dates recorded on the case report forms may be different).

Considerations for Split Visits:

- HIV testing is required on the second day of a split visit only if it was not already performed on the first day of that split visit OR if study product will be dispensed/administered on that day – even if the required HIV testing was performed at the first part of the split visit. Please remember, the required HIV testing must be performed and resulted prior to the administration of study product (please see additional information regarding 4th generation EIA in Example 2 below). Below are two examples describing this requirement:

Example 1:

Split visit where study product is dispensed/administered on the first part of the split visit (Day 1):

- Day 1: All procedures have been performed, including all required HIV testing and sample storage, except for administration of a CASI interview.
- Day 2: Only the administration of the CASI interview is required. HIV testing does not have to be repeated.
  Note the following for this case: If a visit at which a CASI interview is required is conducted as a split visit, the entire CASI interview must be completed on one day. If a CASI interview is begun, but not completed, on Day 1 of a split visit, the entire CASI questionnaire must be administered (starting from the beginning) on Day 2 of the split visit. If this occurs, the SDMC does not need to be notified.

Example 2:

Split visit where study product IS NOT dispensed/administered on the first part of the split visit (Day 1):

- Day 1: All procedures have been performed, including all required HIV testing and sample storage, except study product was not dispensed/administered.
- Day 2: A rapid HIV test (including pre- and post-HIV counseling) must be performed and a plasma sample must be stored (even if Day 2 is the next day). This is also true if the second part of the split visit occurs within 6 days of Day 1. For example, if Day 1 is on a Wednesday and the participant comes in the following Tuesday, a rapid HIV test and plasma storage is required. If the second part of the split visit is on Day 7 or beyond, a rapid HIV test AND a 4th generation EIA test is required, as well as plasma storage. The result of the 4th generation EIA is not required prior to study product dispensation/administration. For example, if Day 1 is on a Wednesday and the participant comes in the following Wednesday, a rapid HIV test, a 4th generation EIA test and plasma storage are required.

- Plasma storage collection is required whenever HIV testing is done, even when HIV testing is performed multiple times during a split visit.

- For Week 4, given the implications for transition to Step 2, every effort should be made to remind participants to return study product at this visit. If a participant does not bring study product at this visit for in-person pill counting, a split visit can be done, taking into consideration the following requirements:

  - If the Week 4 visit occurs within the target window, then study product must be provided for in-person pill counting within the same target

window; meaning, both parts of the split visit must be done within the target window.

- For example, a participant presents to the clinic on Day 26 (target window is Day 25 to Day 31) for Week 4 visit but does not bring the study product for pill counting. Participant returns on Day 30 and brings study product. Since the second part of the visit took place within the target window, adherence calculated at this visit can be taken into consideration for transition to Step 2.

- If the Week 4 visit occurs outside the target window, then study product must be provided for in-person pill counting within 72 hours of the first part of the split visit; meaning, if a participant comes for Week 4 visit outside the target window, the participant should be asked to return to the clinic and bring study product for in-person pill counting within 72 hours (3 days) from first part of the split visit.

  - For example, a participant presents to the clinic on Day 32 (target window is Day 25 to Day 31) for Week 4 visit but does not bring the study product. In this case, the participant must bring study product to the clinic by Day 35 (72 hours after the first part of the split visit) for adherence to be taken into consideration for transition to Step 2.

Missed or Late:

Even though study visits are "allowed" anytime during the study, for data management purposes, if a visit is not conducted within the allowable window, per Section 13 of the SSP, a Missed Visit e-CRF should be completed to document the missed visit at the end of the allowable window period.

In general, when a visit is missed altogether and a participant reports to the site for the next scheduled visit, the procedures from the missed visit that are not also required for the current visit should be performed. Important considerations for a missed visit or late visit:

- Missed visit during Step 1 and Step 3 of the study: the CMC does not need to be consulted in advance regarding additional clinical considerations for the timing of the visit.
  - During Step 1, participants should keep to the schedule and not prolong Step 1 duration.
- Missed visit during Step 2 of the study: action taken will depend on which type of visit is missed:
  - It is not required to contact the CMC for out of target window safety visits no matter when they occur; however, an injection visit may never be completed without a preceding safety visit being completed. All laboratory results from this visit must be available and reviewed, and

deemed within the protocol approved range, to be able to receive the next injection.

- In general, participants should keep to the schedule and not stretch out Step 2 duration.

Merged Study Visits: In unforeseen circumstances, and at sites with the capacity of rapidly (same day) receiving laboratory tests results, including all required HIV test results (FDA-cleared HIV rapid test, and 4th or 5th generation HIV immunoassay), missed safety visit procedures can be merged with an injection study visit. In this case, all laboratory test results must be received and reviewed prior to administration of study product - without repeating laboratory testing. Although safety visit procedures are conducted, sites should use the visit code for the injection visit for all laboratory testing and study procedures. Sample test results should only be used (once) to meet the requirements of one visit and not duplicated for a second visit on the same day. Meaning, one sample test results cannot have two different visit codes. The safety visit should be considered missed and documented as such.

Because of the nature of study procedures required to be performed during the study, all visits are expected to be completed at the study clinic only. Sites should contact the Clinical Management Committee (CMC) regarding any questions about procedures performed outside of the study clinic if the situation arises (e.g., participant is incapacitated and cannot report to the clinic). Details regarding the CMC are described in SSP manual Section 9.

5.3.1 Follow-up Visit Procedures

- Refer to Protocol Appendices I, II, III and IV for details on follow-up procedures.

- In general, participants should not be withdrawn from the study except in the case of a) explicit withdrawal of consent by the participant; b) death; c) extreme/unusual circumstances to protect participant safety; or d) if they are unwilling or unable to comply with required study procedures. Any such safety-related participant terminations should only be implemented after consultation with the Protocol Chair, Division of AIDS (DAIDS) Medical Officer, Statistical and Data Management Center (SDMC) Protocol Statistician, representatives from the Laboratory Center (LC), the Leadership and Operations Center (LOC) Clinical Research Manager (CRM), and others.

  In general, for participants who withdraw consent from the study prematurely during a study visit, the requirements for that visit should be completed to the extent possible **except for provision of study product** and will be considered their final visit. When possible, a plan should be made to give final laboratory results to the participant. For participants who inform the site in between visits

that they wish to withdraw consent from the study, sites should make every effort to have the participant return any unused study product.

- While it is not required, it is recommended that sites dispense:
    - Week 0 in Step 1: Two bottles of study product (CAB oral)

    Participants should be advised to bring open bottles to appointments, finish an open bottle before opening a new one, and should not combine or transfer pills between open bottles.

5.4 HIV Considerations During Follow-Up

At all follow-up visits, HIV test results from previous visits and at least one HIV test result from the current visit must be available and reviewed by designated staff. HIV test results must be confirmed to be negative/non-reactive prior to study product administration. Sites must ensure the HIV testing algorithm at follow-up visits (Appendices I, II and III of the Protocol and Figure 11.3 of the SSP) is being followed without deviation and all required samples are collected. To avoid missing a required test, site-specific tracking documents of study procedures (e.g. visit checklists) must include all the required HIV tests per algorithm. If a participant has a reactive or positive HIV test, product will be held. Further testing for confirmation will be done per Appendix IV of the Protocol. Procedures for participants with discordant or discrepant HIV test results are outlined in Appendix III of this SSP. Procedures for participants who test positive during follow-up are described in Section 5.11 of the Protocol and Table 11.4 of Section 11 of this SSP.

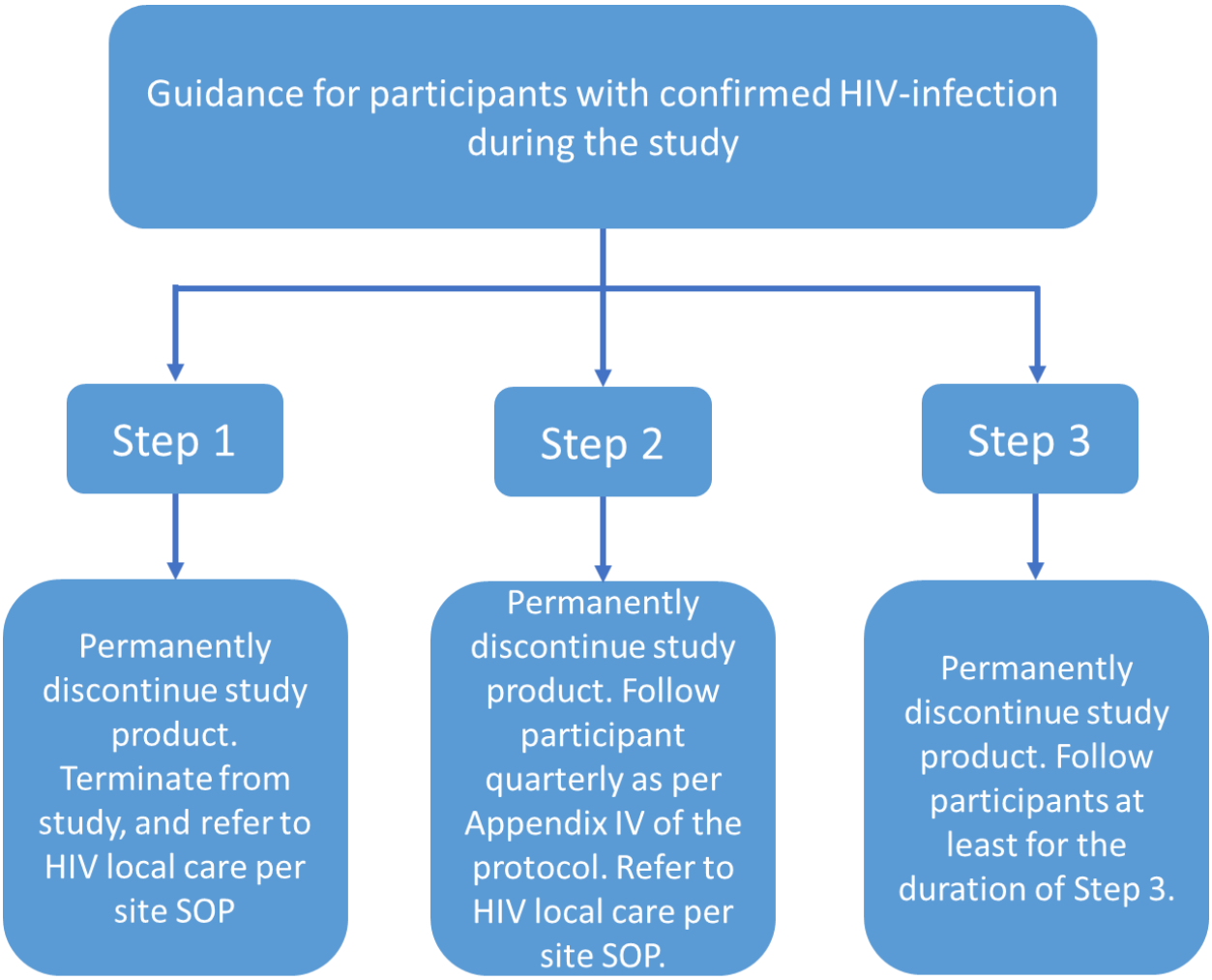
Further considerations for participants that have confirmed HIV-infection during each study Step include:

- Step 1: Permanently discontinue study product and terminate participant from the study. Refer participant for HIV-related care as per site-specific SOP.

- Step 2: Permanently discontinue study product and follow participant according to Appendix III (Step 3).

- Step 3: Permanently discontinue study product and follow participants at least for the duration of Step 3.

Please refer to the diagram below for a visual of how to proceed with participants confirmed to be HIV infected during each Step of the study.



5.5 Participant Transfers

During the course of the study, participants may leave the area where they enrolled. If they move to the vicinity of another HPTN 084-01 study site, they should be encouraged to transfer to that study site and continue study participation. To accomplish this, study staff at both sites will complete the participant transfer process. The same process should be followed for temporary or permanent transfers. If there is no way that the participant can return to the clinic where he enrolled and he is not close to another HPTN 084-01 clinic to transfer, the participant should remain in the study in case the situation changes and the participant returns or moves to a location where there is an HPTN 084-01 site.

Upon identifying the need for a participant transfer to another site, the transferring site is responsible for notifying the HPTN 084-01 LOC Clinical Research Managers, HPTN 084-01 SDMC Protocol Manager, the HPTN 084-01 LC Representatives, and the DAIDS Protocol Pharmacist (see Section 1.2 of the SSP manual for contact information). Also, the alias list 'sc.084-01cdm.org' should be included on the email. Data managers included on the alias will facilitate the process within MediData Rave.

Sites should allow 2-3 U.S. business days after the Transfer form has been completed and the IoR has signed off on all forms for the participant casebook to be transferred to the receiving site. Please refer to Appendix II of the SSP - 'Participant Transfer and Receipt Process within Medidata Rave' – for further information. The transferring site is also responsible for contacting the site to which the participant wishes to transfer (the "receiving site"). After the logistical details of the transfer have been agreed upon, the following steps will be completed:

- The transferring site will explain the transfer arrangements to the participant and obtain written permission for the release of information that will authorize the transfer of his study records to the receiving site.
- Both the transferring and receiving sites should follow the instructions for participant transfers within Medidata Rave in Appendix II of the SSP manual.
- For all other study records not found in Medidata Rave, the transferring site will ship **certified copies*** (see below) of all the participant's study records to the receiving site via courier or overnight mail service. The transferring site will track the shipment and the receiving site will confirm receipt of the shipment with the HPTN LOC, SDMC, and the transferring site. The receiving site will verify receipt of said materials with the transferring site. At this point in time, follow-up of the participant becomes the receiving site's responsibility.
- The transferring site will email the HPTN LC representative confirming transfer to the new site. The transferring site will retain archived samples for the participant unless otherwise instructed by the HPTN LC.
- Study drug supply should be discussed with the DAIDS Protocol Pharmacist in cases of participant transfer.
- The receiving site will establish contact with the participant, obtain a copy of the original screening and enrollment consent (and any others), along with his/her informed consent to continue in the study (have the participant sign a consent at the receiving site).
- Upon receipt of the Participant Transfer form and confirmation that the transferring IoR has signed off on the participant's eCRF casebook, the SDMC will re-map the participant's ID number (PTID) and any e-CRFs in the study database to reflect the change in study site follow-up responsibility. This will ensure that future questions and/or QCs will be sent to the appropriate site. The participant's original ID number and follow-up visit schedule will remain unchanged.
- The receiving site will complete a Participant Receipt eCRF to complete the transfer process.
- If the participant returns to the clinic where she enrolled, the same process should be followed to complete the transfer process. However, the certified copies to be sent to the enrolling site will only include those applicable to the visits conducted at the non-enrolling site. This is because the original records are at the enrolling site and the only records needed would be those for visits conducted at the non-enrolling site.

* See Appendix 1 of Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf) listed under Copies: Certified) for requirements for certification.