

Section 8. Study Product Considerations

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8.1 Overview of Section 8

This section provides instructions to the Pharmacist of Record (PoR) and the study staff for the proper management of study products used in HPTN 084 including ordering, storage, randomization, dispensing, transport, administration, and record keeping of pharmacist- prepared, participant-specific study products. In addition to these specifications, the participating clinical research sites must adhere to the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trial Networks*, and the site Pharmacy Establishment Plan approved by the DAIDS Pharmaceutical Affairs Branch (PAB). These specifications and the protocol take precedence over this document.

8.1.1 Chain of Custody

In addition to the requirements of the PoR for maintaining the Study Product Accountability Record and participant specific study product accountability record, if the pharmacist is not dispensing study products directly to participants, the non-pharmacy study staff must help to ensure the chain of custody of study product by completing any applicable sections and/or the following documents in their entirety, as directed for each participant. The sites may choose to use the documents listed below for this purpose or develop their site-specific documents as long as these include all the required information.

- Record of Dispensation of Participant-Specific Study Product to Non-Pharmacy staff (Appendix 8c)
- Record of Return of Participant-Specific Study Product by Non-Pharmacy Staff (Appendix 8d)

In an instance when the participant returns their oral study products at any time during the study for reasons such as study product discontinuation, damage, spills, inappropriate storage, etc.; the return must be reconciled by documenting on the participant specific study product accountability record when applicable and by following the instructions in the DAIDS pharmacy guidelines.

Each study site must designate its dispensing method(s) in HPTN 084 Standard Operating Procedures (SOPs) for participant-specific study product supply during clinic visits. These SOPs should be developed with input from both pharmacy and clinic staff. If applicable, the chain of custody SOP must be provided to the DAIDS Protocol Pharmacist for review prior to study activation and may only be modified after consultation with the DAIDS Protocol Pharmacist.

8.1.2 Preparation of the Oral Study Product

The oral products for this study will be provided with customary two-part structure which includes a tear-off portion containing the blinded-product identification (i.e., active or placebo).

Prior to dispensing, the un-blinded portion of the tear-off label must be removed and attached to the participant specific pharmacy records such as participant prescription or participant specific study product accountability record. The permanently affixed section of the label will remain on the original container

The site pharmacist will label the bottle with a participant specific label prior to dispensing. The participant specific label must be in accordance with the local regulations and the DAIDS Pharmacy Guidelines manual.

The pharmacist will prepare the participant-specific study product and dispense sufficient quantity to last until the next follow-up visit. Pharmacists will record dispensations on the Pharmacy Accountability Logs.

8.1.3 Short-Term Storage of Participant-Specific Study Product in the Clinic

Oral Study Product:

If the PoR is not dispensing directly to participants and participant-specific study product is stored in the clinic for a short period of time (e.g., while the participant is undergoing the study visit procedures for a particular visit), it must be stored at the conditions described per protocol in an area that is always locked and is accessible only to pharmacists and authorized study staff as specified in the site's SOP and Pharmacy Establishment Plan.

If the participant or site staff believes that the study product storage temperature has reached outside the specified storage temperature range per protocol, the PoR at the site must be contacted immediately so that she/he can dispense the appropriate participant-specific study product again as needed. In addition, the HPTN 084 DAIDS Protocol Pharmacist must be notified by email that this occurred, the reason that it occurred, and the corrective mechanism in place to assure that it will not occur again. This email should come from the Investigator of Record or designee and should copy the PoR at the site. The PoR is responsible for ensuring that the temperature in the storage cabinet is reviewed and recorded daily. These records must be reviewed by the PoR on a monthly basis. The monthly temperature records must be provided to the PoR to be maintained in the pharmacy. These records must be available for review by site monitors.

Injectable Study Product:

Injectable study product will be prepared in the pharmacy and delivered to the study clinic. The product must be administered to a participant as soon as possible **or within two hours of preparation by the site pharmacist. The product must remain at controlled room temperature of 20 to 25° C from the time it is prepared to the time it is administered (within two hours).** If the injectable study product is unable to be administered within two hours from the time it was prepared, the PoR at the site must be contacted immediately so that she/he can prepare and dispense the appropriate participant-specific study product again as needed. In addition, the HPTN 084 DAIDS Protocol Pharmacist must be notified by email that this occurred, the reason that it occurred, and the corrective mechanism in place to assure that it will not occur again. This email should come from the Investigator of Record or designee and should copy the PoR at the site, as well as the HPTN 084 Clinical Management Committee (084CMC@hptn.org).

8.1.4 Step 1: Enrollment

The PoR will dispense the participant-specific labeled oral study product to the participant directly or will dispense it to the clinical staff to give to the participant. If the oral study product is given to the study participant by the clinical staff, the Record of Dispensation of Participant-Specific Study Product to Non-Pharmacy Staff (Appendix 8c) must be completed.

Each participant is to receive a 5-week supply of oral study product upon enrollment (and after randomization). Each bottle of oral study product contains 30 tablets per bottle. Therefore, two bottles of each oral study product (TDF/FTC or Placebo AND CAB or placebo) should be dispensed in Step 1. Dosing should begin on the day of Enrollment or no later than 24 hours of Enrollment.

8.1.5 Weeks 2 and 4

No additional dispensing procedures are noted for these visits unless at the Week 2 visit a participant requires additional oral study product (e.g., they lost or damaged the oral study product). Participants are to return with their bottle at the Week 2 and Week 4

visits. Any returned study product still in the bottle will be counted and that number will be captured in the participant's study chart and on the electronic case report form (e-CRF). Returned product at the Week 5 visit will also be counted and recorded by the PoR for product accountability logs.

If there is not a greater than 50% adherence seen via pill count at Week 4, the participant should not proceed to Step 2. The IoR or designee should contact the CMC.

8.1.6 Step 2: Weeks 5, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 97+8w, 185 +/- 4-8 w

Oral Product:

The PoR will dispense the participant-specific labeled oral study product to the participant directly or will dispense it to the clinical staff to give to the participant. If the oral study product is given to the participant by the clinical staff, the Record of Dispensation of Participant-Specific Study Product to Non-Pharmacy Staff (Appendix 8c) must be completed. The site pharmacist will dispense sufficient supply of the oral study product to last until their next scheduled study visit when injectable product will be administered at two time points four weeks apart and every 8 weeks thereafter beginning at Week 5 (Time points: **Weeks 5, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 97+8w, 185 +/- 4-8 w**)

The site pharmacist and site study staff should maintain close communication to ensure that adequate supply of participant's oral study products is prescribed and dispensed. The participant should have about one-month buffer oral study product supply in case the participant's next scheduled clinic visit date is rescheduled within the allowable study visit window per protocol.

Injectable Product:

Participant-specific labeled injectable study product will be prepared by the PoR as outlined in Section 8.7.4. Syringes will be covered with an overlay by the PoR prior to dispensing to the study clinic in order to maintain the blind.

The PoR will dispense the participant-specific labeled injectable study product to the clinic where it will be administered to the participant **within two hours from the time the syringe was prepared**. The Record of Dispensation of Participant-Specific Study Product to Non-Pharmacy Staff (Appendix 8c) must be completed.

Injectable study product will be administered as one 3 mL (600 mg) injection in the gluteal muscle at two time points four weeks apart and every 8 weeks thereafter beginning at Week 5 (Time points: **Weeks 5, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 97+8w, 185 +/- 4-8 w**)

8.1.7 Step 3:

Dispense tablets only at Day 0, Weeks 12, 24, 36

The study is designed such that participants in Step 2 will continue to receive injections until the last participant enrolled in the study completes their Week 65 visit or the required number of endpoints have been met. In either case, all participants still receiving injections on Step 2 will be transitioned to Step 3. Additionally, participants who permanently discontinue receiving injections before their Step 2 participation in the study ends will transition to Step 3 at the time that it is determined that they can no longer continue to receive injections (either due to an adverse event or participant decision). Any participant transitioning to Step 3 will receive open-label TDF/FTC 300 mg/200 mg fixed dose combination daily oral tablets, provided for up to 48 weeks.

Participants in Step 1 of the study who do not transition to Step 2 (that is, they never received an injection) will no longer receive any study product, will be referred to preventive care services, and will be followed on study for annual HIV testing until the end of Step 2.

Participants will begin Step 3 approximately 4-8 weeks after final injection in Step 2.

8.2 Dispensing, Labeling, and Study Product Return

8.2.1 Study Product Labeling

Under Step 1 and Step 2, the study products are to be labeled in a blinded fashion.

Under Step 3, the study products are to be labeled in an unblinded fashion.

The site pharmacist must place a participant-specific label on the prepared study product in accordance with the local regulations and by following instructions provided in the manual, *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

8.2.2 Emergency Unblinding by CRS IoR or designee for Medical Reasons

Please see additional information in SSP Section 9 for unblinding.

If, in the judgment of the CRS IoR or designee or in the judgment of the participant's medical provider and the CRS IoR or designee, a medical event is of sufficient extreme severity that it requires the immediate unblinding of a participant without CMC consultation, the CRS IoR or designee may ask the CRS PoR to unblind the participant. Emergency Unblinding is expected to be extremely rare, if it occurs at all. It should only occur in the setting of a potentially life threatening clinical event, and if knowing the participant's treatment assignment would affect decisions regarding the participant's immediate medical management. Both conditions must be satisfied.

Emergency Unblinding IoR or designee may use the unblinding feature in the Medidata system to perform emergency unblinding of a participant. If this feature is not available or the

IoR or designee is unable to perform this for any reason, the IoR or designee may ask the site pharmacist to unblind the participant.

The CRS IoR or designee must provide a written request to unblind the participant's treatment assignment to the PoR. The PoR must then provide the participant's treatment assignment in writing to the CRS IoR or designee.

In case of extreme medical emergency, the CRS IoR or designee may verbally request the PoR to unblind a participant's treatment assignment. However, in such cases, the verbal request must be followed by a written request to the PoR within 24 hours of the verbal request and must include a reason why the request to unblind participant's treatment assignment could not be provided to the PoR in writing initially.

The written request to unblind the participant's treatment assignment from the CRS IoR or designee and a copy of the written participant's treatment assignment provided by the PoR to the CRS IoR or designee must be filed in pharmacy records.

The CRS IoR or designee must email the HPTN 084 Clinical Management Committee (084CMC@hptn.org) and copy the PoR regarding the participant's emergency unblinding within 24 hours of the event.

The PoR must email the HPTN 084 protocol pharmacist (kashin@niaid.nih.gov) regarding the participant's emergency unblinding within 24 hours of the event.

Appendix 8a: Specific Updates to SSP Section 8 in relation to Unblinding and issuance of study products in when implementing Letter of Amendment 4, Protocol Version 2.0

Documentation to be Provided to the Site Pharmacist of Record and staff:

When the site has LoA # 4 to HPTN 084, Version 2.0 approved by their IRB/EC/other regulatory entities and the participant is informed of her randomized assignment, the site investigator or designated study staff must provide a written notification to the pharmacy that the participant has been informed of their randomized assignment for pharmacy record. This documentation can be in an email to the site Pharmacist of Record (PoR) from the site investigator or designee or on a prescription for un-blinded study product that is signed by an authorized prescriber. If the written notification was not provided prior to the implementation of unblinding in relation to LoA 4 for Protocol Version 2.0, then the site investigator or designee should provide retroactive written notification to the PoR of participant(s) who have been informed of their randomized assignment for pharmacy records.

Sections 8.1.2, 8.1.4, 8.1.5 and 8.1.6 Participants Assigned to the TDF/FTC Arm in Steps 1 and 2:

- When the participant has been informed of her randomized assignment to the TDF/FTC arm, a new prescription for un-blinded oral active TDF/FTC signed by an authorized prescriber must be provided to the site pharmacist.
- The pharmacist will take the following steps to prepare and dispense un-blinded active oral TDF/FTC to the participant:
 - 1) Retrieve oral active TDF/FTC bottle with two part-label from Step 2 supply.
 - 2) Retain both the un-blinded part and the blinded part of the two-part label on the TDF/FTC bottle. Do not tear off the un-blinded part of the two-part label from the bottle.
 - 3) Place pharmacist prepared participant-specific un-blinded label in such a way that the blinded part of the two-part label on the bottle is covered.
- The pharmacist-prepared, participant-specific, un-blinded oral active TDF/FTC bottle will have the manufacturer's unblinded part of the two-part label and site pharmacist generated participant-specific un-blinded label visible on the prepared bottle before dispensation.
- Alternatively, retrieve open-label oral active TDF/FTC supply from Step 3 supply if the site no longer has oral active TDF/FTC bottles with a two-part label from Step 2 supply due to no further supply of oral TDF/FTC from Step 2 supply available at the CRPMC to distribute to sites. Place pharmacist prepared participant-specific un-blinded label on the open-label oral active TDF/FTC bottle from Step 3 supply and dispense.
- If a participant assigned to the TDF/FTC arm in Step 2 wishes to switch to CAB, then the authorized prescriber will write a prescription for CAB once oral CAB is available from the CRPMC for these participants.

- The participant will initiate oral CAB 30 mg tablet, one tablet orally once daily for 5 weeks. After 5 weeks of oral CAB therapy, the participant will start injectable CAB-LA 600 mg administered as one 3 mL (600 mg) IM at two times points 4 weeks apart and every 8 weeks thereafter.

Sections 8.1.2, 8.1.4 and 8.1.5- Participants Assigned to the CAB Arm in Step 1:

- When the participant has been informed of their randomized assignment to the CAB arm, a new prescription for unblinded oral active CAB signed by an authorized prescriber must be provided to the site pharmacist.
- The pharmacist will take the following steps to prepare and dispense unblinded active oral CAB to the participant:
 - 1) Retrieve oral active CAB bottle with two part-label from Step 2 supply.
 - 2) Retain both the un-blinded part and the blinded part of the two-part label on the CAB bottle. Do not tear off the un-blinded part of the two-part label from the bottle.
 - 3) Place pharmacist-prepared participant- specific un-blinded label in such a way that the blinded part of the two-part label on the bottle is covered.
- The pharmacist prepared, participant-specific, un-blinded oral active CAB bottle will have the manufacturer’s unblinded part of the two-part label and site pharmacist generated participant specific un-blinded label visible on the prepared bottle before dispensation.

Section 8.1.6 Participants Assigned to the CAB Arm in Step 2:

- When the participant’s treatment assignment has been unblinded and the participant is assigned to the CAB arm, a new prescription for unblinded injectable CAB-LA signed by an authorized prescriber must be provided to the site pharmacist.
- The pharmacist will take the following steps to prepare and dispense unblinded active injectable CAB-LA to the participant:
 - 1) Retrieve injectable CAB-LA vial(s) from storage.
 - 2) Prepare the injectable CAB dose in a syringe per protocol. The overlay tape that covers the syringe barrel of the prepared unblinded, injectable CAB-LAB in a syringe is not required.
 - 3) Place pharmacist-prepared participant-specific un-blinded label on the prepared syringe.

Section 8.1.7 Participants in Step 3:

- Participants in Step 3 will continue to take open-label TDF/FTC from Step 3 supply per protocol.

Appendix 8b: Specific Updates to SSP Section 8 in relation to issuance of unblinded study products in when implementing Appendix VIII, HPTN 084 Protocol Version 3.0

Participants in Step 4

Participants who transition from TD/FTC or re-start CAB LA may choose from two options (Step 4a or Step 4b) before starting Step 4c.

Step 4a (Participants Initially Randomized to TDF/FTC Who Elect to Move to OL CAB LA with Optional Oral Lead-in first)

CAB 30 mg tablet, one tablet orally once daily for 4 weeks, with or without food, prior to initiating CAB-LA injection. This is an optional oral CAB lead-in prior to receiving CAB-LA injection for participants originally randomized to TDF/FTC.

Step 4b (Participants Initiating or Re-starting CAB LA without the Optional Oral Lead-in; the Initial Dose Visit, CAB LA Loading Dose)

CAB-LA 600 mg administered as one 3 mL (600 mg) IM in the gluteal muscle one time at Step 4b visit. The participant will then transition to Step 4c four weeks later. This is for participants who are initiating CAB for the first time with or without oral CAB (Step 4a) or for participants who have been on cabotegravir during the study but have had a long absence of visits (>15 weeks since prior injection) and require a reload of cabotegravir injection.

Step 4c (Participants on Maintenance Doses of CAB LA or TDF/FTC)

CAB LA Maintenance Doses

CAB-LA 600 mg administered as one 3 mL (600 mg) IM in the gluteal muscle every 8 weeks for no longer than a total of 48 weeks. This is for participants transitioning from Step 4b, or for participants originally randomized to cabotegravir who choose to continue it and do not need reloading dose.

TDF/FTC Maintenance Doses

TDF/FTC 300 mg/200 mg fixed dose combination tablet, one tablet orally once daily, with or without food for no longer than a total of 48 weeks.

Step 4d (Participants who become pregnant in Step 4 and first 8 weeks of Step 5, who have had at least one CAB LA injection ever and Participants who are Breastfeeding)

CAB-LA 600 mg administered as one 3 mL (600 mg) IM in the gluteal muscle every 8 weeks for no longer than a total of 48 weeks.

If participant declines to continue CAB LA during pregnancy or breastfeeding will be offered OL TDF/FTC. **TDF/FTC 300 mg/200 mg fixed dose combination tablet, one tablet orally once daily, with or without food for no longer than a total of 48 weeks per protocol.**

Step 5 (Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation)

TDF/FTC 300 mg/200 mg fixed dose combination tablet, one tablet orally once daily, with or without food for no longer than a total of 48 weeks per protocol.

This is for participants who received OL CAB LA in Step 4 and who discontinue CAB-LA early for safety or other reasons will have the option to transition to Step 5.

Study Product Preparation:

Prescription

A prescription for all unblinded study product signed by an authorized prescriber must be provided to the site pharmacist prior to preparation of study product. The prescription must include the Step number (4a, 4b, 4c, 4d or 5) and a notation if the participant is switching between CAB arm and TDF/FTC arm.

Study Product Preparation in Steps 4a, 4b, 4c, 4d, and 5

The site pharmacist must follow the study product preparation instruction in HPTN 084 protocol and comply with the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations.

Preparation of Unblinded Oral CAB Study Product

The pharmacist will take the following steps to prepare and dispense un-blinded active oral CAB to the participant:

- 1) Retrieve oral active CAB 30mg tablet bottle with two part-label from Step 1 supply.
- 2) Retain both the un-blinded part and the blinded part of the two-part label on the CAB bottle. Do not tear off the un-blinded part of the two-part label from the bottle.
- 3) Place pharmacist-prepared, participant- specific, un-blinded label in such a way that the blinded part of the two-part label on the bottle is covered.

The pharmacist prepared, participant-specific, un-blinded oral active CAB bottle will have the manufacturer's unblinded part of the two-part label and site pharmacist generated participant specific un-blinded label visible on the prepared bottle before dispensation.

The participant specific label must be in accordance with the local regulations, and the DAIDS Pharmacy Guidelines manual.

Preparation of Unblinded Oral TDF/FTC Study Product

The pharmacist will take the following steps to prepare and dispense un-blinded active oral TDF/FTC to the participant:

- 1) Retrieve oral active TDF 300 mg/FTC 200 mg with two-part label from Step 2 supply.
- 2) Retain both the un-blinded part and the blinded part of the two-part label on the TDF/FTC bottle. Do not tear off the un-blinded part of the two-part label from the bottle.
- 3) Place pharmacist prepared participant-specific un-blinded label in such a way that the blinded part of the two-part label on the bottle is covered.

The pharmacist-prepared, participant-specific, un-blinded oral active TDF/FTC bottle will have the manufacturer's unblinded part of the two-part label and site pharmacist generated participant-specific un-blinded label visible on the prepared bottle before dispensation.

Alternatively, retrieve open-label oral active TDF/FTC supply from Step 3 supply if the site no longer has oral active TDF/FTC bottles with a two-part label from Step 2 supply due to no further supply of oral TDF/FTC from Step 2 supply available at the CRPMC to distribute to sites. Place pharmacist prepared participant-specific un-blinded label on the open-label oral active TDF/FTC bottle from Step 3 supply and dispense.

The participant specific label must be in accordance with the local regulations and the DAIDS Pharmacy Guidelines manual.

Preparation of Unblinded Injectable CAB LA 600 mg/3mL

The pharmacist will take the following steps to prepare and dispense unblinded active injectable CAB-LA in a syringe to the participant:

- 1) Retrieve injectable CAB-LA vial(s) from storage.
- 2) Prepare the injectable CAB LA dose in a syringe using aseptic technique under a pharmacy BSC Class 2 or better as detailed in Appendix 8 of the protocol. The overlay tape that covers the syringe barrel of the prepared unblinded, injectable CAB-LA in a syringe is not required.
- 3) Place pharmacist-prepared participant-specific un-blinded label on the prepared syringe.

The participant specific CAB LA label must be in accordance with the protocol, local regulations and the DAIDS Pharmacy Guidelines manual.

Appendix 8c: HPTN 084 Record of Dispensation of Participant-Specific Study Product to Non-Pharmacy Staff

CRS Name:
CRS Number:

		STUDY STAFF						COMMENTS
Date Dispensed from Pharmacy (dd-MMM-yy), and Time Prepared (hh:mm)	Pharmacy Staff Initials	PTID	Date (dd-MMM-yy) and Time (hh:mm) Collected from Pharmacy	Number of oral tablet-Bottles	Number of CAB LA/Placebo Syringes	Prepared Syringes Should be Administered by hh:mm (to correspond within 2 hours of preparation, outlined in first column)	Staff Initials	

- Instructions:**
- Complete one row each time participant-specific study products are provided to a participant
 - Comments may be recorded in the designated column and, if additional space is needed, on the back of the record or chart notes.

Appendix 8d: HPTN 084 Record of Return of Participant-Specific Study Product by Non-Pharmacy Staff

CRS Name:
CRS Number:

STUDY STAFF								COMMENTS
Date Returned by study staff or participant (dd-MMM-yy)	PTID	Name of the oral study product returned	Number of oral tablets returned	Number of CAB LA/ placebo syringe Returned	Staff Initials	Date returned to pharmacy by Clinic Staff (dd-MMM-yy)	Clinic Staff Initials	

- Instructions:**
- Complete one row each time participant-specific study products are returned by study staff or study participants.
 - Comments may be recorded in the designated column and, if additional space is needed, on the back of the record or chart notes.