8. Study Product Considerations

8.1 Overview of Section 8

This section provides instructions to the Pharmacist of Record and the study staff for the proper management of study products used in HPTN 083 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.

8.2 Chain of Custody

In addition to the requirements of the Pharmacist of Record 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. 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 IIa)
- Record of Return of Participant-Specific Study Product by Non-Pharmacy Staff (Appendix IIb)

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 083 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. They 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.

8.3 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 record 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.

8.4 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 temperatures 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 083 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 (68.0 to 77.0° F) 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 083 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 083 Clinical Management Committee (083CMC@hptn.org).

8.5 Step 1: Enrollment

The Pharmacist of Record 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 IIa) 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.

8.6 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 bottles at the Week 2 and Week 4 visits. Any returned study product still in the bottles 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 on the product accountability logs.

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

These participants will be asked to report for annual visits until all participants in the study have completed Step 2.

8.7 Step 2: Weeks 5, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 137 and 145

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 IIa) 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, 105, 113, 121, 129, 137 and 145**

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 4.3.2 of the protocol. Syringes will be covered with an overlay by the Pharmacist of Record prior to dispensing to the study clinic in order to maintain the blind.

The Pharmacist of Record 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 IIa) must be completed.

Injectable study product will be administered as one 3 mL (600 mg) injection IM 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, 105, 113, 121, 129, 137, 145)**

Note: Week 153 is the last visit of Step 2 and the first visit (Day 0) of Step 3. Refer to Section 5.8 of the protocol.

8.8 Step 3

Dispense oral study products in the original bottles only at Day 0, Weeks 12, 24, 36

The study is designed such that participants in Step 2 will continue to receive injections to Week 153, with the last injection occurring at Week 145. Step 3 will begin at Week 153, which is the last day of Step 2 and first day of Step 3. 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 then end of the randomized-blinded portion of the study for all participants 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 300 mg/FTC 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 three years from the time of their Enrollment.

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

8.9 Dispensing, Labeling, and Study Product Return

8.9.1 Study Product Quantity - Prescription and Dispensation

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.

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. A formal pill count for entry into the study database on the Pill Count e-CRF is only required at Weeks 2 and 4 during Step 1, and is not required in Step 2 or Step 3, but an open bottle can be used to assist with determining refill quantity (that is, whether there is sufficient remaining oral study product supply in the participant's possession that only two bottles need be dispensed and still maintain a three-month supply in the participant's possession).

It is important to dispense all study products at each visit at which study product dispensation is scheduled per protocol. For example, if during Step 2 a participant reports for an injection visit but refuses the injection or does not receive the injection for any other reason, oral study product should not be dispensed. Participants should either receive all study products at each visit where study product is scheduled to be dispensed, or no study products.

8.9.2 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 unblinded (open-label) 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*. The prepared syringes are to be labeled as stated above.

8.10 Emergency unblinding by CRS IoR or designee for Medical Reasons

Please see further instructions in Appendix VI in the SSP.

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, the CRS IoR may ask the CRS pharmacist to unblind the participant. 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 083 Clinical Management Committee (083CMC@hptn.org) and copy the PoR regarding the participant's emergency unblinding within 24 hours of the event.

The PoR must email the HPTN 083 protocol pharmacist (kashin@niaid.nih.gov) regarding the participant's emergency unblinding within 24 hours of the event.