

Section 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 052. In addition to these specifications, the participating CTU's must adhere to the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* and the Pharmacy Establishment Plan approved by the Pharmaceutical Affairs Branch (PAB). The protocol document should serve as the primary source of information regarding the study.

8.2 Study Product

HPTN 052 study product refers to ALL antiretroviral provided by the study.

The antiretrovirals provided by the study include lamivudine 300mg (3TC, Epivir®), tenofovir disoproxil fumarate 300mg (TDF, Viread®), lamivudine 150mg/zidovudine 300mg (3TC/ZDV, Combivir®), nevirapine 200mg (NVP, Viramune®), efavirenz 600mg (EFV, Sustiva®, Stocrin®), atazanavir (ATV, Reyataz®), didanosine delayed-release capsules (ddI-EC, Videx EC®), stavudine (d4T, Zerit®), lopinavir/ritonavir (LPV/r, Kaletra®/Aluvia®), and emtricitabine/tenofovir (FTC/TDF, Truvada®). Non-study-provided ART (including generic agents that are or become approved or tentatively approved by the U.S. FDA) may also be used in secondary and salvage regimens if approved by the HPTN 052 CMC. Once LoA#4 to V. 3.0 of the protocol is implemented at a site, non-study provided ART may also be used for the primary regimen with the approval of the 052 CMC. If non-study ART is used during the study, it must be provided by non-study prescription. Sites may choose to use other ART drugs to manage toxicity and virologic failure if they can provide them via non-National Institutes of Health [NIH] resources, or if participants can afford to buy them.

8.3 Study Product Acquisition

8.3.1 Procedures for Ordering and Receiving Study Product from the CRPMC

3TC, TDF, 3TC/ZDV, ATV, NVP, EFV, ddI-EC, d4T, FTC/TDF and LPV/r are available through the NIAID Clinical Research Products Management Center (CRPMC). An LPV/r (Kaletra®/Aluvia®-) based regimen is the preferred regimen for women to receive if they become pregnant while enrolled in the study; however, please note that LPV/r supplies are being donated only for these women and not for other purposes such as toxicity management or drug resistance. Sites are asked to use this drug only for treatment during pregnancy. Site pharmacists are expected to order accordingly.

After receipt of all necessary importation documents at the CRPMC and the protocol registration procedure is completed at each site, study product can be ordered.

To order study product from the CRPMC, the Pharmacist of Record must complete a *Study Product Request Form* and send it by fax or e-mail to the CRPMC. The *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* contains a blank form, as well as, instructions for completion.

Upon receipt of each shipment, the Pharmacist of Record will verify the content of the shipment against the *Investigational Agent Request Packing Slip*. Once verified, the pharmacist will sign that it was received and fax the slip back to the CRPMC, the same day. If there is study product missing, damaged or inconsistent with the information on the packing slip, the pharmacist should contact the CRPMC immediately by phone, fax or email. The contact information is at the end of this section. If the study product appears damaged, the pharmacist should not dispense it until s/he has been notified by the Protocol Pharmacist or the CRPMC that study product is acceptable for use. A hard copy of such notification and the signed verification of receipt should be retained in the site pharmacy records.

CRPMC (Clinical Research Products Management Center)
BIO.CRPMC.PH@thermofisher.com
Tel: (01) 301-294-0741
Fax: (01) 301-294-2905

8.3.2 Procedures for ordering ART Not Provided by the Study

Medication not provided by the study should be obtained using the mechanism specific for the site.

8.4 Study Product Accountability

The Pharmacist of Record is responsible for maintaining detailed records regarding all study products used in HPTN 052, whether they are provided through the CRPMC, from the site, or come from another source.

The accountability records may include, but are not limited to, logs for product received, returned, dispensed and stored. The Pharmacist of Record is responsible for documenting all information related to study product dispensing.

Each time a study product is dispensed to a participant, received from the CRPMC or other source; it should be documented in the Study Product Accountability Record. The inventory balance documented in the Study Product Accountability Record should match the actual study product inventory on hand at all times. An example of this form can be found in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*. This section also includes instructions for its completion. The site may develop its own form or use an

electronic record; however, the alternative form must contain the same information as shown in this example.

The Pharmacist of Record is responsible for maintaining all study product-related documents, for example original prescriptions, shipping invoices, study product return receipts, study drug destruction log, etc. DO NOT send originals or copies of accountability records to CRPMC or to DAIDS unless requested.

Important: Study Product Accountability Record and Participant Specific Dispensing Records are highly confidential and must be stored in a secure location within the pharmacy. These records should be accessible to authorized pharmacy staff only

8.5 Study Product Storage

Security

To provide adequate security, all study product used for HPTN 052 must be stored in a limited-access area. This area is locked when not in use and only accessible to the Pharmacist of Record and back-up pharmacist. The study products should be stored in a separate area of the pharmacy, if possible, or in a manner that segregates it from other medication stored in the pharmacy. Study product should be clearly labeled and identified.

Temperature

All study products must be stored in accordance with the storage conditions outlined in the protocol.

8.6 Study Product Dispensing, Dosing Regimen, and Adherence Measurement

Each participant must provide written informed consent for study participation and be determined eligible for the study prior to the pharmacist dispensing any study product.

Study Product will be dispensed by the HPTU pharmacist only upon the written/signed order of the Investigator of Record or other clinician listed on the current FDA Form 1572 who is authorized to prescribe in the CTU site's jurisdiction.

Upon enrollment of a study participant, a prescription order will be written and forwarded to the CTU pharmacist. The prescription should include the following: participant ID Number (PTID), date, product name and dose, quantity to dispense, instructions for use, the prescriber's signature, and any other information required by the site's jurisdiction.

Study product will be provided to study participants in full, unopened bottles each containing a 1 month supply of drug. Each participant should receive enough study product until the next targeted visit date. No partial dispensing of study

product should be necessary. In the event that a participant will need more than a 3-month supply of medication due to missed visits, travel, etc.; full, unopened bottles should be dispensed to accommodate this need. For example, if a participant will not return to the clinic for a study visit for 4 months, 4-5 bottles of study product each containing a 1 month supply should be dispensed to the participant.

A new prescription order may be written for each dispensing or the original prescription should indicate the number of refills allowed for the study product, for subsequent dispensing.

A new prescription order should be written and provided to the pharmacist for any medication changes, for example changes in quantity, strength, treatment modification, etc.

Each bottle should be clearly labeled and follow the guidelines outlined for each site's jurisdiction as well as those in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks. The site is responsible for providing containers, such as a mini cooler, that can keep the medication at the proper temperature if needed. The site should purchase these transport containers with their study-specific funds and, if possible, re-use them. All study product dispensed should be documented using a *Participant Specific Pharmacy Dispensing Record* (an example is included at the end of this section). This information should correlate with the *Study Product Accountability Record* for each study product.

The Pharmacist of Record is responsible for the monitoring of expiration dates of all study products, and ensuring that any expired study product is not dispensed to the participant and separated from the remaining stock.

The recommended starting regimen for the study includes lamivudine/zidovudine (3TC/ZDV) plus efavirenz (EFV) or atazanavir (ATV), except for pregnant women for whom a Kaletra/Aluvia (LPV/r) based regimen is the preferred regimen. An LPV/r-based regimen is preferred for pregnant women with CD4+ cell counts > 250 cells/mm³, and an LPV/r-based or a nevirapine (NVP) based regimen may be used for women with CD4+ cell counts < 250 cells/mm³. However, the study clinician may prescribe another regimen which includes study provided ART after obtaining permission from the HPTN 052 CMC. Once LoA#4 to V. 3.0 of the protocol is implemented at a site, non-study provided ART may also be used with the approval of the 052 CMC. Site investigators will be responsible for recommending an alternative starting regimen and should take into consideration the following factors:

- The side-effect profile for each drug
- Concomitant medications
- Whether a participant is of child-bearing age

If a study participant experiences drug-related toxicity or there is clinical evidence of virologic failure, the Investigator of Record or sub-investigator may modify or replace the regimen according to the protocol and the site's SOP for ART management.

Study participants are to be asked to bring their ART drugs with them to each study visit. The site is responsible for counting the pills as a measurement of participant adherence. At each study visit where medication will be dispensed, all bottles and pills will be returned to the pharmacy.

Medications brought in by the study participants to the pharmacy:

- **Count the number of pills brought in by the study participant and record the number on a *Participant Specific Pharmacy Dispensing Record* or equivalent/similar record.**
- **Check to see if the study participant is to continue taking the medication and that the medication is labeled correctly before giving the medications back to the study participant.**
- **Record the quantity that is given back to the study participant on the associated accountability records.**
- **Dispense additional full, unopened bottles to the study participant if additional supplies will be needed before the next study visit.**

The participant may then receive back at this next visit the partial bottle of study product returned and a full unopened bottle of medication.

Any empty bottles or bottles with remaining pills returned, but *not* given back to the participant should be documented as returned product and separated from the remaining stock. These bottles should be clearly identified as study product returns not to be dispensed.

8.7 Study Product Return and Destruction

All returned, expired, and unused study product should be quarantined and retained at the pharmacy until a destruction visit can be scheduled. The DAIDS/PAB SOP for product destruction must be followed. A DAIDS authorized witness will perform study drug accountability. Please refer to the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks for additional information regarding this process. "Returned" drug is study product that was dispensed to a participant and returned to the clinic, used or unused. "Unused" study products can include patient returns, expired product or product that remains in the pharmacy after the study is completed.

The destruction of all study products must be documented in the *Study Product Accountability Form*.

For any questions regarding the destruction process, please contact the CRPMC or the Protocol Pharmacist (Ana Martinez, am30c@nih.gov).

When a participant returns empty bottles (containing no study drug) to the site, these bottles may be discarded once the pharmacy logs have been updated appropriately.

HPTN 052 Participant/Patient- Specific Dispensing Record

Name of Institution:	Site Number:	Investigator of Record:	Investigator No.
Participant Initials or other Site Specific Identifier:		Participant ID Number (PTID):	

Line No.	Date	Rx No. <i>or other tracking # if applicable</i>	Study Product Name/ Strength/ Dosage Form:	Quantity Dispensed	Quantity returned	Initials	Comments
1.							
2.							
3.							
4.							
5.							
6.							
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8.8 Medication Code List

Table 8-1 contains the medication code list for use with the HPTN 052 DataFax forms.

Table 8-1 Medication Codes

Code	Medication
01	Abacavir (ABC, Ziagen)
02	Abacavir/Lamivudine (ABC/3TC, Epzicom)
03	Amprenavir (APV, Agenerase)
04	Atazanavir (ATV, Reyataz)
05	Combivir (Lamivudine/Zidovudine, 3TC/ZDV)
06	Delavirdine mesylate (DLV, Rescriptor)
07	Didanosine (ddI, Videx)
08	Didanosine Delayed Release Capsules (ddI-EC, Videx-EC)
09	Efavirenz (EFV, Sustiva, Stocrin)
10	Emtricitabine (FTC, Emtriva, Coviracil)
11	Emtricitabine/Tenofovir (FTC/TDF, Truvada)
12	Enfuvirtide (ENF, Fuzeon)
13	Fosamprenavir (FPV, Lexiva)
14	Indinavir (IDV, Crixivan)
15	Lamivudine (3TC, Epivir)
16	Lamivudine/Zidovudine/Abacavir (3TC/ZDV/ABC, Trizivir)
17	Lopinavir/Ritonavir (LPV/RTV, Kaletra/Aluvia)
18	Nelfinavir (NFV, Viracept)
19	Nevirapine (NVP, Viramune)
20	Ritonavir (RTV, Norvir)
21	Saquinavir Hard-Gel Capsules (SQV, Invirase)
22	Saquinavir Soft-Gel Capsules (SQV, Fortovase)
23	Stavudine (d4T, Zerit)
24	Stavudine Extended Release Capsules (d4T XR, Zerit XR)
25	Tenofovir Disoproxil Fumerate (TDF, Viread)
26	Zalcitabine (ddC, Hivid)
27	Zidovudine (AZT or ZDV, Retrovir)