Appendix VIII: SSP Manual Updates Per the Open Label Extension (OLE) in Appendix V of the Protocol

1.1 Overview of Appendix VIII

This Appendix includes specific updates, guidance, and considerations for the implementation of the Open Label Extension (OLE) in Appendix V of the Protocol and provides guidance for participants who choose to continue or initiate CAB-LA or choose to remain on TDF/FTC. Unless instructed by the HPTN Leadership and Operations Center (LOC), if there is an inconsistency between Appendix VIII of the SSP manual and the Protocol, the Protocol's specifications take precedence. Please alert the HPTN LOC of any such inconsistencies.

The updates outlined in this Appendix apply to all SSP Manual sections. **That is, updates to the individual SSP sections impacted by the OLE are not being made; rather, this SSP Appendix VIII serves as the document that outlines the updates. It is important to note that the content of the current version of each section of the SSP manual still applies and includes information that is still relevant under the current version of the Protocol. This Appendix VIII replaces or clarifies language already included in those sections accordingly.**

There are some sites that have not obtained approval for Version 4.0 of the Protocol, and will therefore begin the OLE under Version 5.0 of the Protocol. As such, sites are divided into two categories – Category A and Category B – as described below:

Category A Sites: Implemented OLE procedures under Version 4.0

The primary purpose of Step 6 for sites in Category A is to allow for continued access to CAB LA while participants transition to local CAB LA or other available clinical PrEP prevention services. Step 6 is the continuation of Step 4c, adding up to 48 weeks (Weeks 56 up to 96) of CAB.

For sites in Category A, the HPTN Leadership and Operations Center (HPTN LOC) already provided official notification to each site to implement the OLE under Version 4.0; therefore, official notification for the continued implementation of Appendix V under Version 5.0 will NOT be issued. Sites in this category should implement Version 5.0 **immediately upon obtaining IRB/EC/other regulatory entity approvals**. Sites should also submit for DAIDS Protocol Registration Office approval; however, sites should not wait for this notification to implement Version 5.0. Sites in this category are also responsible for ensuring that adequate study product supply is available for participants who will continue study product use under Version 5.0.

Category B Sites: Implementing OLE procedures for the first time under Version 5.0

The primary purpose of the updated Protocol Appendix V at Category B sites is to allow participants to make their initial choice regarding whether to continue to receive CAB LA or TDF/FTC through Steps 4a-c and 5 as initially described in Version 4.0 and below. Given the extended time it has taken to implement the OLE at Category B sites, Step 6 may also be utilized for participants if necessary but not required (based primarily on whether in-country approval of CAB LA has been obtained).

For sites in Category B, the following items are required prior to implementation of Appendix V of the Protocol and Appendix VIII of the SSP manual:

- IRBs/ECs/other regulatory entities overseeing the research approval of Protocol Version 5.0.
- DAIDS Protocol Registration Office notification of the protocol registration process for Version 4.5 of the Protocol.
- Confirmation that an adequate supply of study product is available at the site.
- Site staff has completed and documented training for Version 5.0 of the Protocol.

Once these items are completed, inform the LOC and the LOC will then issue an approval notice to implement Version 5.0 of the Protocol.

A Category B site cannot implement Protocol Version 5.0 until this notice is issued.

With the release of the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual, references to DAIDS policies are updated as follows:

HPTN 083 SSP Manual Section		**Please refer to the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual in place of the following DAIDS SOP links**
Section 1: Introduction	1.4 Investigator Responsibilities	The DAIDS Policy for Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials (DWD-POL-RA-03.00) DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (*DWD-POL-CL-04.00*)
Section 3: Document Requirements	3.2 Essential Documents	The DAIDS Policy for Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials (*DWD-POL-RA-03.00*) DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (*DWD-POL-CL-04.00*)
	3.3 Investigator Responsibilities	DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (*DWD-POL-CL-04.00*)
	3.3.1 Concept of Source Documentation	DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (*DWD-POL-CL-04.00*)
	3.3.3.1 Clinic Notes	DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (*DWD-POL-CL-04.00*)

HPTN 083 SSP Manual Section		Please refer to the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual in place of the following DAIDS SOP links
Section 4: Recruitment, Screening, and Enrollment	4.5.1 Informed Consent Process	DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (*DWD-POL-CL-04.00*)
	4.5.1.4 Document the Process	DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (*DWD-POL-CL-04.00*)
	4.6.2 Screening and Enrollment Logs	The DAIDS Policy for Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials (*DWD-POL-RA-03.00*)
Section 5: Study Procedures	5.5 Participant Transfers	DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (*DWD-POL-CL-04.00*)

1.2 Updates to SSP Manual Sections

1.2.1 Section 1: Introduction

Updates to Section 1.2 – Source of Procedural Information: The contact information table has been updated as follow:

HPTN LOC Clinical Research Managers	Marybeth McCauley (primary contact) Tel: ~~202-884-8340~~ 301-461-7797 Email: mmcCauley@fhi360.org Kailazarid Gomez-Feliciano Tel: 919-321-3486 ~~919-544-7040 ext. 11282~~ Email: kgomez@fhi360.org Andrea Jennings Tel. 919-544-7040, ext 11566 919-321-3617 Email: ajennings@fhi360.org

HPTN LOC ~~Research Specialist~~ Clinical Trial Assistant ~~Research Manager~~	Maxine Awekey Tel: 1-202-884-8072 Email: mawekey@fhi360.org ~~Busola Akingbade~~ ~~Tel: 1-919-544-7040~~ ~~Email: bakingbade@fhi360.org~~ ~~Leah Schrumpf~~ ~~Tel: 1-919-544-7040 ext 11909~~ ~~Email: lschrumpf@fhi360.org~~
HPTN SDMC Protocol Manager	Richard Berman Email: rberman@scharp.org ~~Priyanka Agarwal~~ ~~Tel: 206.667.4384~~ ~~Leslie Cottle~~ ~~Tel: 206-667-7405~~

Updates to Section 1.4: Investigator Responsibilities

The following text is added to the end of the third paragraph: Additionally, site investigators must promptly report to the IRBs/ECs any changes in the study and must comply with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108(b) for promptly reporting the following: unanticipated problems involving risks to participants or others; serious or continuing noncompliance with applicable regulations or the requirements or determinations of their IRBs/ECs; and any suspension or termination of IRB approval.

1.2.2 Section 2: Protocol

The following protocol documents were added to the table in Section 2 of the SSP (please note, the documents listed below only include those that were issued after LoA#3 to Version 3.0 of the protocol dated 23 July 2020)

Document	Date
• Clarification Memo (CM) #4 to Version 3.0 of the Protocol	05 February 2021
• Version 4.0 of the Protocol	10 February 2021
• Clarification Memo # 1, to Version 4.0	03 March 2021
• Letter of Amendment # 1 to Version 4.0 of the Protocol	25 April 2021
• Letter of Amendment # 2 to Version 4.0 of the Protocol	02 November, 2021
• Letter of Amendment # 3 to Version 4.0 of the Protocol	01 December, 2021
• Version 5.0 of the Protocol	28 April 2022

1.2.3 Section 3: Documentation Requirements

Updates to Section 4.3: Protocol Deviations

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

Under Appendix V of the protocol, examples of reportable protocol deviations include:

- 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 083 HIV testing algorithms were not followed as per protocol and Section 11 of the SSP manual, including Figure 11.4 of this SSP Appendix. This is applicable even if a commercial or external laboratory made the error or omission.
- 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. This does not apply to situations where the required laboratory test is part of a testing panel.
- Use of prohibited medications as specified in Section 1.2.9 below, 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.

NOTE: Missed study visits are not considered reportable deviations. All missed visits will be documented on the Missed Visit eCRF and followed per site's SOP. Similarly, missed study procedures due to conducting remote visits are not considered reportable deviations. Any procedure conducted remotely should be documented on participant's chart, including the date, rational, and any visit findings.

The DAIDS Critical Event (CE) policy is no longer applicable; therefore, sites will not need to report critical events to DAIDS. Investigators will report to the IRBs/ECs any changes in the study and must comply with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108(b) for promptly reporting the following: unanticipated problems involving risks to participants or others; serious or continuing noncompliance with applicable regulations or the requirements or determinations of their IRBs/ECs; and any suspension or termination of IRB approval.

Note: Sites <u>WILL</u> continue to report reportable deviations per the HPTN 083 protocol deviation instructions already in place in Section 3.4 of the SSP.

1.2.4 Section 4: Recruitment, Screening, and Enrollment

Updates to Section 4.5 – Eligibility Determination

Only participants who enrolled in HPTN 083 are eligible to participate in the OLE.

- Participants who previously discontinued under Step 2 or Step 3 of protocol Version 3.0, but are otherwise eligible for injectable CAB, are eligible to un-terminate and restart under Protocol Appendix V.
    - An un-termination form is available ONLY for participants who were terminated before 15May2020 and the termination form is now locked. Sites should email the SCHARP Data Managers (sc.083cdm@scharp.org) requesting the form to be added for the participant.

- For participants who terminated after 15May2020, the data on the previous Termination form will need to be removed and updated on the corresponding Date of visit / Interim visit form.

The following participants will not be able to continue study participation under the OLE:

- Participants who permanently discontinued study products during the blinded portion of the study due to:
  - HIV infection
  - HBV infection
  - study product-related AE that would deem the continuation or initiation of cabotegravir unsafe

    NOTE: The CMC may be contacted for questions related to study product AEs of concern for participants interested in continuing or initiating cabotegravir and whether it is safe to do so.

- Participants originally-randomized to TDF/FTC who choose to continue receiving TDF/FTC **and** have passed three years from the date of enrollment will not enter Step 5 (open-label TDF/FTC). These participants will be referred to local standard of care for HIV prevention services. However, these participants need to be consented so that they may receive the new information about cabotegravir contained in the addendum informed consent form and to document that they will not take part in the OLE.
- Participants who are otherwise not eligible to join the OLE or who do not wish to participate in the OLE will be consented so that they may receive the new information about cabotegravir contained in the addendum consent form, and to document that they will not take part in the OLE.
- Participants who already left the study prior to Version 5.0 because they were ineligible to continue in the OLE, did not wish to participate in the OLE, or were lost to follow up more than six months of initial OLE implementation at their site, will not be allowed to be reconsented to Version 5.0.
- As outlined in the consent form, participants who continue in the OLE but then leave the study before their last scheduled study visit will be asked to complete a final visit based on the OLE schedule if available to do so. These participants will be told that this will be considered their final study visit and will be asked to complete the procedures listed for participants who are not continuing under the OLE.

  Note: Participants may participate in COVID-19 vaccine or treatment studies, provided that participant study burden and American Red Cross-mandated limitations on per-unit-time phlebotomized blood volumes are not exceeded. There is no need to consult the CMC for participation in these studies. The CMC should be consulted for participation in other COVID or non-COVID-related biomedical intervention studies.

  Note: Participants who are in the process of completing 48 weeks of open-label TDF/FTC as part of prior Step 3 "coverage" of their final active CAB injection, who do NOT wish to or are not eligible to resume CAB, will complete those 48

*weeks of open-label TDF/FTC *EVEN IF* this extends past 3 years from their original enrollment. Please refer Data Communique #15 for further information.*

Updates to Section 4.5.1 – Informed Consent Process

Protocol Version 5.0 Appendix V includes two addendums to the main informed consent form. Sites will administer the respective informed consent form based on site's category (A or B) as participants present to the site. As a reminder, sites in Group B will administer the relevant informed consent after receiving notification from the LOC to implement Protocol Version 5. This form will document that the participant has received the new information about cabotegravir contained in the addendum consent form, and to document their choice about participating in the OLE.

The informed consent discussion can take place in the study clinic, and by telephone or telemedicine at the IoR or designee's discretion. It is important to note that if the discussion takes place by telephone or telemedicine, the site must obtain all relevant approvals from the IRB/EC/other regulatory entities for the use of these remote or e-consent processes as required. Sites that use e-consent will need to meet DAIDS SCORE Manual requirements for e-consenting and obtain all required IRB/EC/Regulatory approvals. Participants who did not provide consent using an electronic system will need to provide written informed consent once they report to the study site to continue participation and before study product is dispensed.

Contact the CMC for guidance if there are other consent-related scenarios not outlined here or in the protocol.

Participants who have not initiated any procedures under Appendix V in either Version 4.0 or Version 5.0 who wish to continue study participation under the OLE must be consented within six months of HPTN LOC notification to the site to begin OLE implementation. Participants will not be allowed to transition to the OLE beyond six months from date of HPTN LOC notification to implement. This includes participants who have indicated that they need time to decide whether they want to participate in the OLE. If a participant returns to a site more than six months after LOC notification to implement the OLE, the participant will be provided the new information in the informed consent form and will mark that they are not eligible to participate on the consent signature page.

Participants in the OLE who have been on TDF/FTC throughout the study and choose to stay on it, or participants who have been on CAB and choose to switch to TDF/FTC, will be permitted to change their mind once up to 6 months after making their choice at their initial OLE visit and switch to CAB. **There will be no switches allowed during Step 6.**

Contact the CMC for guidance if there are other consent-related scenarios not outlined here or in the protocol.

1.2.5 Section 5: Study Procedures Overview

Refer to the Protocol, Appendix V, Tables 7-11 for procedures for Steps 4a-c, 5, and 6; Table 12 for procedures for participants who are not continuing under the OLE; and Table 13 of the protocol details the procedures for participants who have a reactive or positive HIV test result for detailed information about study procedures.

Updates to Section 5.2 – Study Overview

HPTN 083 participants, in Category A or B sites, who choose to participate in the OLE will follow these steps:

Step 4a: Oral Cabotegravir Lead-In (Optional) for Participants Originally Randomized to TDF/FTC

This Step is optional and applies only to participants originally randomized to oral TDF/FTC who choose to initiate cabotegravir for the first time. Participants will decide, in consultation with the IoR or designee, if they want to take daily oral cabotegravir for approximately 4 weeks before receiving injections.

Considerations for Step 4a:

This Step is not to be used for any participant who has ever received CAB LA injections in the past.

Although this is an optional step, the local IRB/EC/other review bodies may require oral lead-in participation before receiving injections. Site-specific ICF should specify if this Step is required per IRB/EC/regulatory body.

There is no required pill count in this Step, and therefore no CRF is to be completed. It is at the discretion of the site IoR or designee to determine the level of adherence to daily oral cabotegravir (if any) that is required before participants receive injections. To determine the level of adherence, sites may choose to use participant self-report adherence or perform a pill count. Whatever method the site decides to use, it should be standard for all participants at the site.

Participants in Step 4a will take a daily oral cabotegravir pill up to the day before their Step 4b Day 0 visit. The Step 4b Day 0 injection visit can occur as soon as the Step 4a Week 4 laboratory tests are resulted (including but not limited to the entire HIV testing algorithm, including viral load), and ideally should occur within one week from the Step 4a Week 4 visit. There are no safety concerns if a participant takes their daily pill on the day of their first injection.

Contact the CMC for guidance regarding cases or situations not outlined here.

Step 4b: Loading Dose Visit for Injectable Cabotegravir for Participants Initiating or Restarting CAB Injections

Participants on this Step will have one visit for initiating or restarting cabotegravir injections. This Step applies to:

- Participants originally-randomized to TDF/FTC who completed Step 4a
- Participants originally randomized to TDF/FTC who chose not to complete Step 4a but will initiate CAB LA for the first time
- Participants originally-randomized to CAB LA 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 injections (two injections, four weeks apart).

Contact the CMC for guidance regarding cases or situations not outlined here.

Step 4c: Cabotegravir Injections

This Step is for participants originally-randomized to cabotegravir who choose to continue it and do not need a reloading dose or for participants transitioning from Step 4b. This Step includes cabotegravir injections every eight weeks and will last for approximately one year. Participants who are transitioning from Step 4b will have their first Step 4c visit conducted approximately four weeks following the Step 4b visit.

Participants who complete Week 48 of Step 4c and live in a country where CAB LA is approved for PrEP will be prioritized to transition to local CAB LA as soon as possible instead of moving to Step 5. If necessary, and if Version 5.0 approval is in place, these participants may continue CAB LA injections through the study up to Week 96 in Step 6 while this transition occurs. **Priority must be given to transitioning these participants to local CAB LA once they complete Step 4c and wish to remain on CAB LA**.

If Version 5.0 approval is not in place by the time the next injection (Week 56) is scheduled AND local CAB LA is not available, these participants will move to Step 5 until Version 5.0 approval is obtained; such participants will be allowed to enter Step 6 when Version 5.0 approvals and applicable implementation requirements are in place.

Note: Cases of significant delay of approval of Version 5.0 that would otherwise result in a lapse in the PrEP coverage for the duration of Step 5 will be considered on a case-by-case basis by the CMC.

There have also been cases at some sites where Version 5.0 approval in place and a participant has expressed that they will complete Step 4c through Week 48 but then wish to be terminated from the study. These participants should be consented to Version 5.0 and asked to mark the first option to continue in the study so that they may complete Step 4c through Week 48 and then be terminated from the study. Participants should do this even if the Week 48 is the last visit they are completing after signing the Version 5.0

informed consent form. (In general, when terminating a participant, sites are encouraged to wait to submit the termination form until test results from the participant's last visit are available and that no concerning AEs are present as deemed by the Investigator of Record.)
Contact the CMC for guidance regarding cases or situations not outlined here.

Step 5: Participants Who Choose to Remain On or Switch To Oral TDF/FTC

This Step is for:

- Participants who have had at least one injection in Step 4b or Step 4c who then choose not to or cannot continue receiving cabotegravir injections before Week 48 of Step 4 occurs will move to Step 5.
- Participants who were originally-randomized to oral TDF/FTC and choose to remain on oral TDF/FTC. They will complete the procedures for Step 5 until three years from the time of enrollment.
- Participants who were originally randomized to CAB LA and choose to switch to TDF/FTC. They will complete the procedures for Step 5 for approximately one year from the last injection. In other words, Day 0 begins 8 weeks after participant's last injection and ends 48 weeks after Day 0.
- Participants in Step 4b or Step 4c who decide they no longer wish to receive CAB LA or experience an AE that no longer allows them to receive CAB LA. These participants will complete the procedures for Step 5 for approximately one year from the last injection. In other words, Day 0 begins 8 weeks after participant's last injection and ends 48 weeks after Day 0.
- Participants who complete Step 4c and wish to continue receiving CAB LA and Version 5.0 is not approved yet and CAB LA is not available locally. These participants will temporarily move to Step 5 until site receives approval for Version 5.0 of the protocol. After Version 5.0 is approved, these participants will move to Step 6 while transitioning to local CAB.

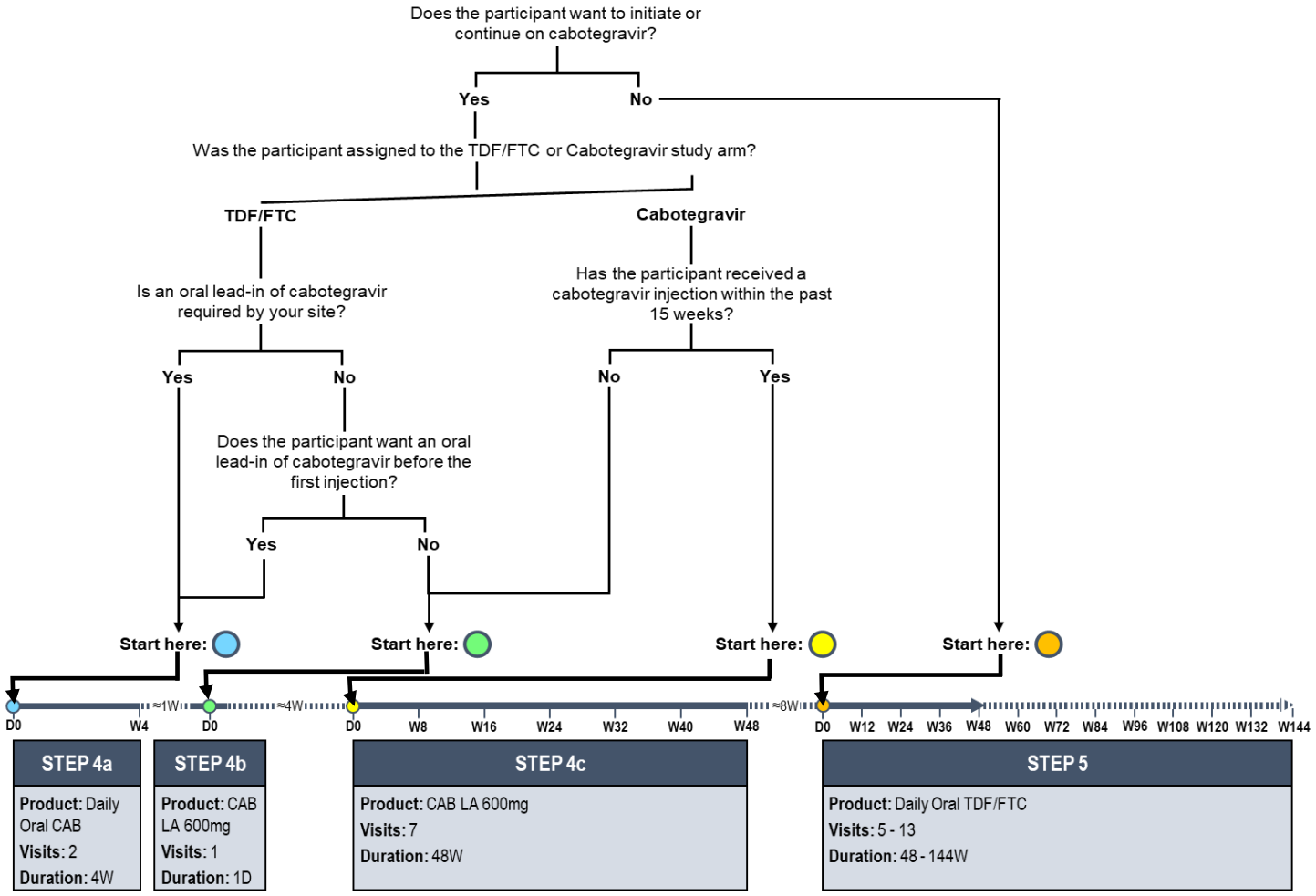
In cases where a participant in Step 5 – who completed Week 48 of Step 4 – under Version 4.0 of the protocol, do not want to transition to Step 6 under Version 5.0 of the protocol, will complete the remaining visits for Step 5 under Version 5.0 and then be terminated from the study and referred to local PrEP services.

Participants may also be moved to Step 5 if Version 5.0 is not approved by the time the next injection (Week 56) is scheduled AND local CAB LA is not available. Once Version 5.0 is approved applicable implementation requirements are in place, these participants will be allowed to enter Step 6.

Contact the CMC for guidance regarding cases in which Day 0 of Step 5 will occur beyond 48 weeks from the time the participant received their last injection or for other cases or situations not outlined here.

Figure 1: Decision Tree

NOTE: This decision tree outlines step sequences based on a participant's initial choice when first joining the OLE, which applies mainly to participants at Category B sites. This decision tree applies only to a participant's initial choice when starting the OLE and therefore only includes Steps 4a, 4b, 4c and 5. Note that Step 6 is the continuation of Step 4c.



Step 6: Participants Transitioning to Local CAB LA (Week 56 to Week 96)

Step 6 is a new Step under Version 5.0 and is only for participants who complete follow-up in Step 4c and who wish to continue CAB LA while awaiting transition to local CAB LA. The provision of CAB LA in Step 6 is for up to an additional 48 weeks (Weeks 56 – 96). **However, the priority should be given to transition participants to local CAB LA as soon as possible after a participant completes Week 48 of Step 4c.**

Participants on Step 6 who no longer want to receive injections or who can no longer receive injections due to an AE will be terminated from the study and referred to local prevention services. That is, these participants will not transition to Step 5 (TDF/FTC tail coverage).

Participants on Step 6 who become infected with HIV will complete the HIV confirmation visit as per Table 13 of the protocol and the visit checklist, then be terminated from the study and referred to HIV treatment services.

NOTE: As noted above, participants who completed Step 4c at a site that does not have Version 5.0 approved and who wish to remain on CAB LA but have not completed the transition to local CAB LA will move to Step 5. Once Version 5.0 is approved (and the participant has still not transitioned to CAB LA) the participant may move to Step 6 until they are able to transition to local CAB LA access or other prevention services.

Updates to Section 5.1 – Study Visits

Target and allowable windows for all visits are outlined in Section 1.2.13 below. Below are some considerations for visit windows:

- If injections that are scheduled or intended to be 4 weeks apart take place 12 or more weeks since the last injection, a 4-week interval should be used for the next injection after returning, followed by 8-week intervals.

- If injections that are scheduled or intended to be 8 weeks apart take place 16 or more weeks since the last injection, a 4-week interval should be used for the next injection after returning, followed by 8-week intervals.

I**t is no longer required to contact the CMC regarding late injections.**

NOTE: All safety laboratory assessments should be completed, and results confirmed to be within the protocol-allowable parameters before proceeding with an injection visit.

Visits are considered contiguous and therefore all visits are allowable; that is, a visit conducted outside of a target or allowable window is not considered a protocol deviation.

Updates to Section 5.3.1 – Follow-up Visit Procedures

Some important general considerations for study visits include:

- While it is not required, it is recommended that sites dispense an additional bottle of study product (TDF/FTC or CAB) to ensure an extra month supply between visits. 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. Also, although it's not required in the OLE, sites may choose to perform a formal pill count. If sites perform a pill count, the information should be documented in the participant's file; there is no CRF for this purpose.
- Participants in Step 4a of the study who are unable to transition to Steps 4b and 4c for any reason – including HIV infection - will be referred to local care and terminated from the study.
- Participants who completed Step 4c under Version 4.0 and moved to Step 5 have the option under Version 5.0 to finish Step 5 or start Step 6 if CAB is not yet approved and locally available.
- Participants who complete Step 4c under Version 5.0 and want to continue CAB will move from Step 4c to Step 6 if CAB is not yet approved and locally available.
- Participants who complete Step 4c under Version 5.0 but do not want to or cannot continue CAB in Step 6 are not eligible to enter Step 5 and will be terminated from the study and referred to local PrEP services.
- Considerations for participants who have a positive or reactive HIV test result during follow-up:
    - Participants who became infected with HIV under Version 3.0 or Version 4.0 of the protocol and are being followed on the HIV infection quarterly visit schedule when Version 5.0 is implemented will complete their visits under Version 5.0. For example, if they completed the HIV confirmation visit, Weeks 12, and 24 under Version 3.0 or Version 4.0 and Version 5.0 is now approved at the site, the participant will complete Weeks 36 and 48 under Appendix V of Version 5.0 and then be terminated from the study.
    - Participants that received <u>only</u> oral TDF/FTC and/or oral CAB but never CAB LA who have a positive or reactive HIV test result at Step 4a, Step 5, or at their final visit, and are not continuing in the OLE will be referred to local care.
    - Participants in Step 6 will only undergo the procedures in the HIV Confirmation Visit. Participants with confirmed HIV infection will be terminated from the study and referred to local care.
    - The procedures listed in Table 13 for the HIV Confirmation Visit apply to all participants that have a reactive or positive HIV test during Steps 4-6, or at their final study visit if not continuing participation under the OLE.

- Participants who have a positive or reactive HIV test during Steps 4b and 4c, Step 5, or at their final visit if not continuing in the OLE and received CAB LA at any time during the study, will be followed according to Table 13.
- The procedures listed in Table 13 for Weeks 12, 24, 36, and 48 apply to participants with confirmed HIV infection during Steps 4b and 4c of the study. Participants with confirmed HIV infection in Step 5 of the study may undergo similar procedures as listed in Weeks 12, 24, 36, and 48, and will be determined by the members of 083CMC@hptn.org.
- Sites will continue to contact the 083HIV@hptn.org email alias any time a participant has a reactive HIV test result for guidance regarding clinical management or other questions.

1.2.6 Section 6: Visit Checklists

The visit checklists are templates based on procedures outline in Appendix V of the Protocol. Sites should modify, as needed, to reflect site-specific study operations.

Participant ID ☐☐☐ ☐☐☐☐ ☐ ☐

Visit Date ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 4a: (Daily Oral Cabotegravir – OPTIONAL for participants initiating CAB injections) Day 0			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Confirm participant identity and PTID per site SOPs.	
_____	☐	Discuss with participants the options for ongoing study participation and the Steps under the OLE	
_____	☐	Obtain written informed consent for Version 5.0 of the Protocol. *Note: Participants should be followed under the appropriate Steps contained in Appendix V of the Protocol*	
_____	☐	Administer Product Choice Assessment Questionnaire (Interviewer Administered)	
_____	☐	Review/update locator information	
_____	☐	Complete Interviewer-administered assessment (SMSQ) *Refer to instructions in the interviewer-administered assessments as well as the Schedule of Forms for whom and when these assessments should be administered*	
_____	☐	Administer CASI (behavioral assessment) *Refer to instructions in the CASI assessments as well as the Schedule of Forms for whom and when these assessments should be administered*	
_____	☐	Collect directed medical history (including concomitant medications)	
_____	☐	Perform directed physical exam	

Participant ID ☐☐☐ ☐☐☐☐ ☐☐

Visit Date ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 4a: (Daily Oral Cabotegravir – OPTIONAL for participants initiating CAB injections) **Day 0**			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Provide HIV counseling	
_____	☐	Offer condoms and lubricant	
_____	☐	Collect blood for: ☐ HIV Testing (please refer to the HIV testing algorithm found in Figure 11-4 of Appendix VIII of the SSP for detailed information) o HIV Rapid test o Laboratory-based HIV immunoassay o **HIV viral load** (<50 copies/mL) ☐ Creatinine *NOTE: If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.* ☐ LFTs (AST, ALT, total bilirubin, alkaline phosphatase) *NOTE: If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator* ☐ Plasma storage ☐ Syphilis serologic testing *NOTE: Perform testing at Day 0 if not done within the last 6 months*	
_____	☐	Collect urine for GC/CT testing	
_____	☐	Collect rectal swab for GC/CT testing	

Participant ID ☐☐☐ ☐☐☐☐ ☐ ☐

Visit Date ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 4a: (Daily Oral Cabotegravir – OPTIONAL for participants initiating CAB injections) Day 0			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Dispense sufficient pills to last until the next follow-up visit plus approximately one-month buffer supply)	
_____	☐	Provide adherence counseling	
		Provide site contact information and instructions to report symptoms and/or clarify any questions	
_____	☐	Schedule next appointment, if applicable	
_____	☐	Provide reimbursement, if applicable	

Notes for Step 4a: Please refer to Table 7 of the Protocol for further guidance.

Comments: _____
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Participant ID ☐☐☐ ☐☐☐☐ ☐ ☐

Visit Date ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 4a: Daily Oral Cabotegravir – OPTIONAL for participants initiating CAB injections Week 4			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Confirm participant identity and PTID per site SOPs.	
_____	☐	**<u>If not done at Day 0</u>**: Obtain written informed consent for Version 5.0 of the Protocol *Note: Participants should be followed under the appropriate Steps contained in Appendix V of the Protocol*	
_____	☐	Review/update locator information	
_____	☐	Obtain self-reported pill adherence	
_____	☐	Pill count and document in the participant chart **(optional procedure)**	
_____	☐	Collect directed medical history (including concomitant medications)	
_____	☐	Perform directed physical exam	
_____	☐	Provide HIV counseling	
_____	☐	Offer condoms and lubricant	
_____	☐	Collect blood for: ☐ HIV Testing (please refer to the HIV testing algorithm found in Figure 11-4 of Appendix VIII of the SSP for detailed information) o HIV Rapid test o Laboratory-based HIV immunoassay o **HIV viral load** (<50 copies/mL) ☐ Creatinine	

Participant ID ☐☐☐ ☐☐☐☐ ☐ ☐ **Visit Date** ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 4a: Daily Oral Cabotegravir – OPTIONAL for participants initiating CAB injections Week 4			
Initial/date	**Completed**	**Procedures**	**Comments**
		NOTE: If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator ☐ LFTs (AST, ALT, total bilirubin, alkaline phosphatase) *NOTE: If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator* ☐ Plasma storage (Must be collected prior to injection)	
_____	☐	Provide adherence counseling regarding attending first CAB injection visit	
_____	☐	Provide site contact information and instructions to report symptoms and/or clarify any questions	
_____	☐	Schedule next study visit, if applicable	
_____	☐	Provide participant reimbursement, if applicable	

Notes for Step 4a: Please refer to Table 7 of the Protocol for further guidance.

Comments:
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Participant ID ☐☐☐ ☐☐☐☐ ☐☐

Visit Date ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 4b: Loading Dose Cabotegravir Injection – for participants initiating or restarting CAB injections Day 0			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Confirm participant identity and PTID	
_____	☐	Obtain written informed consent for Version 5.0 of the Protocol **ONLY** if not obtained at a previous study visit. *Note: Participants should be followed under the appropriate Steps contained in Appendix V of the Protocol.*	
_____	☐	Applicable **only** to participants who did not complete Step 4a: ☐ Discuss with participants the options for ongoing study participation and the Steps under OLE**)** ☐ Administer Product Choice Assessment Questionnaire (Interviewer Administered)	
_____	☐	Review/update locator information	
_____	☐	Interviewer-Administered, SMSQ *Note: Refer to form instructions and the Schedule of Forms for whom and when these assessments should be administered*	
_____	☐	Administer CASI *Note: Refer to instructions in the CASI assessments and the Schedule of Forms for whom and when these assessments should be administered*	
_____	☐	Collect directed medical history (including concomitant medications)	
_____	☐	Perform directed physical exam	

Participant ID ☐☐☐ ☐☐☐☐ ☐ ☐ **Visit Date** ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 4b: Loading Dose Cabotegravir Injection – for participants initiating or restarting CAB injections Day 0			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Provide HIV counseling	
_____	☐	Offer condoms and lubricant	
_____	☐	Collect blood for: ☐ HIV Testing (please refer to the HIV testing algorithm found in Figure 11-4 of Appendix VIII of the SSP for detailed information) o HIV Rapid test o Laboratory-based HIV immunoassay o **HIV viral load** (<50 copies/mL) ☐ Creatinine *NOTE: Do not perform if it was done during Step 4a* ☐ LFTs (AST, ALT, total bilirubin, alkaline phosphatase) ☐ Plasma Storage (must be collected prior to the loading dose) ☐ Syphilis serologic testing *NOTE: Perform if not done within the last 6 months*	
_____	☐	Collect urine for GC/CT testing *NOTE: Perform testing at Day 0 if not done within the last 6 months*	

Participant ID ☐☐☐ ☐☐☐☐ ☐ ☐

Visit Date ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 4b: Loading Dose Cabotegravir Injection – for participants initiating or restarting CAB injections Day 0			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Collect rectal swab for GC/CT testing *NOTE: Perform testing at Day 0 if not done within the last 6 months* *NOTE: If testing cannot be done locally, it may be done at another laboratory. Consult the LC for guidance.*	
_____	☐	Collect unused product	
_____	☐	Administer CAB injection	
_____	☐	ISR Evaluation *NOTE: Do not actively solicit this information from participants.* *NOTE: If an ISR is reported, document on the ISR eCRF.* *NOTE: Symptoms experienced immediately at the time of an injection are NOT considered ISRs. No ISR assessment is required at the visit at which the injection is provided.*	
_____	☐	Provide adherence counseling regarding attending CAB injection visits	
_____	☐	Offer condoms and lubricant	
_____	☐	Provide site contact information and instructions to report symptoms and/or clarify any questions	
_____	☐	Schedule next study visit, if applicable	
_____	☐	Provide participant reimbursement, if applicable	

Participant ID | **Visit Date**

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Notes for Step 4b: Please refer to Table 8 of the Protocol for further guidance.
Comments: _____
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Participant ID ☐☐☐ ☐☐☐☐ ☐ ☐ **Visit Date** ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 4c: Cabotegravir Injections **Day 0, Weeks 8, 16, 24, 32, 40, and 48** *Circle applicable visit week*			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Confirm participant identity and PTID	
_____	☐	Obtain written informed consent for Version 5.0 of the Protocol **ONLY** if not obtained at a previous study visit. (**Day 0)** *Note: Participants should be followed under the appropriate Steps contained in Appendix V of the Protocol.*	
_____	☐	Applicable **only** to participants who did not complete Step 4b (**Day 0**): ☐ Discuss with participants the options for ongoing study participation and the Steps under OLE**)** ☐ Administer Product Choice Assessment Questionnaire (Interviewer Administered) *NOTE: Do not repeat for participants who transition from Step 4b or Step 5 and completed these procedures in Steps 4a, 4b, or 5*	
_____	☐	Review/update locator information	
_____	☐	Interviewer-Administered, SMSQ (**Day 0, Weeks 16 and 48**) *Refer to instructions in the interviewer-administered assessments as well as the Schedule of Forms for whom and when these assessments should be administered*	
_____	☐	Administer CASI (**Day 0, Weeks 16 and 48**) *Refer to instructions in the CASI assessments as well as the Schedule of Forms for whom and when these assessments should be administered*	
_____	☐	Provide HIV counseling	
		Offer condoms and lubricant	

Participant ID ☐☐☐ ☐☐☐☐ ☐ ☐

Visit Date ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 4c: Cabotegravir Injections **Day 0, Weeks 8, 16, 24, 32, 40, and 48** *Circle applicable visit week*			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Collect directed medical history (including concomitant medications)	
_____	☐	Perform directed physical exam	
_____	☐	Enter weight data to applicable CRF (**Weeks 16 and 48**)	
_____	☐	Collect blood for: <u>At all visits:</u> ☐ HIV Testing (please refer to the HIV testing algorithm found in Figure 11-4 of Appendix VIII of the SSP for detailed information) o HIV Rapid test o Laboratory-based HIV immunoassay o **HIV viral load** (<50 copies/mL) ☐ Plasma storage (Must be collected prior to injection) <u>At Day 0, Weeks 24 and 48 visits</u> ☐ Creatinine *Note: If it was performed during Step 4a or 4b, do not perform at Day 0 of Step 4c.* ☐ LFTs (AST, ALT, total bilirubin, alkaline phosphatase ☐ Syphilis serology *Note: Perform testing at Day 0 if not done within the last 6 months; perform testing at all other visits as per Table 9 of the protocol* <u>At Week 48 visit:</u> ☐ HCV Ab Testing *Note: Do not to be repeat if infection was documented at a prior visit.*	

Participant ID ☐☐☐ ☐☐☐☐ ☐ ☐

Visit Date ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 4c: Cabotegravir Injections **Day 0, Weeks 8, 16, 24, 32, 40, and 48** *Circle applicable visit week*			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Collect urine for GC/CT testing (**Day 0, Weeks 24 and 48**) *NOTE: Perform testing at Day 0 if not done within the last 6 months*	
_____	☐	Collect rectal swab for GC/CT testing (**Day 0, Weeks 24 and 48**) *NOTE: Perform testing at Day 0 if not done within the last 6 months* *NOTE: If testing cannot be done locally, it may be done at another laboratory. Consult the LC for guidance.*	
_____	☐	Administer CAB injections	
_____	☐	Adherence counseling regarding attending CAB injection visits *NOTE: At Week 48 adherence counseling should be tailored to each participant. For example:* • *A participant who wants to continue CAB injections either in Step 6 or through local PrEP services should be reminded of the importance of receiving their next injection within 8 weeks of Week 48.* • *A participant who does not want to continue CAB injections should be told where they can go locally for other PrEP services and reminded of the importance of continuous PrEP coverage.*	

Participant ID ☐☐☐ ☐☐☐☐ ☐ ☐

Visit Date ☐☐ ☐☐☐ ☐☐

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NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 4c: Cabotegravir Injections **Day 0, Weeks 8, 16, 24, 32, 40, and 48** *Circle applicable visit week*			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	ISR Evaluation and reporting *NOTE: Do not actively solicit this information from participants.* *NOTE: If an ISR is reported, document on the ISR eCRF.* *NOTE: Symptoms experienced immediately at the time of an injection are NOT considered ISRs. No ISR assessment is required at the visit at which the injection is provided.*	
_____	☐	Provide site contact information and instructions to report symptoms and/or clarify any questions	
_____	☐	Schedule next study visit, if applicable	
_____	☐	Provide participant reimbursement, if applicable	

Note for Step 4c: Please refer to Table 9 of the Protocol for further guidance.

Comments:

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Participant ID ☐☐☐ ☐☐☐☐ ☐ ☐ **Visit Date** ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 5: (Open Label Daily Oral TDF/FTC) **Day 0, Week 12, 24, 36, 48 (Weeks 60, 72, 84, 96, 108, 120, 132, 144 if required)** *Circle applicable visit week*			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Confirm participant identity and PTID	
_____	☐	Obtain written informed consent for Version 5.0 of the Protocol **ONLY** if not obtained at a previous study visit. *Note: Participants should be followed under the appropriate Steps contained in Appendix V of the Protocol.*	
_____	☐	Applicable **only** to participants who did not complete Steps 4a – 4c: ☐ Discuss with participants the options for ongoing study participation and the Steps under OLE**)** ☐ Administer Product Choice Assessment Questionnaire (Interviewer Administered)	
_____	☐	Review/update locator information	
_____	☐	Interviewer-Administered, SMSQ (**Day 0, Weeks 24 and 48** (72, 96,120, 144, if required)) *Refer to instructions in the interviewer-administered assessments as well as the Schedule of Forms for whom and when these assessments should be administered*	
_____	☐	Administer CASI (**Day 0, Weeks 24 and 48 (**72, 96,120, 144, if required)) *Refer to instructions in the CASI assessments as well as the Schedule of Forms for whom and when these assessments should be administered*	
_____	☐	Collect directed medical history (including concomitant medications)	
_____	☐	Perform directed physical exam	
_____	☐	Enter weight data to applicable CRF	

Participant ID ☐☐☐ ☐☐☐☐ ☐☐

Visit Date ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 5: (Open Label Daily Oral TDF/FTC) **Day 0, Week 12, 24, 36, 48 (Weeks 60, 72, 84, 96, 108, 120, 132, 144 if required)** *Circle applicable visit week*			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Provide HIV counseling	
_____	☐	Offer condoms and lubricant	
_____	☐	Collect blood for: <u>At all visits:</u> ☐ HIV Testing (please refer to the HIV testing algorithm found in Figure 11-4 of Appendix VIII of the SSP for detailed information) o HIV Rapid test o Laboratory-based HIV immunoassay o **HIV viral load** (<50 copies/mL) ☐ Plasma storage ☐ DBS storage <u>At Day 0, Weeks 24 and 48 visits</u> (72, 96, 120, 144, if required) ☐ Creatinine *NOTE: Defer testing at the discretion of the investigator if it was done within the last month prior to Day 0* ☐ LFTs (AST, ALT, total bilirubin, alkaline phosphatase) *NOTE: If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.* ☐ Syphilis serology *NOTE: Perform testing at Day 0 if it was not done within the last 6 months: perform testing at all other visits required.* <u>At Weeks 24 and 48</u> (72, 96, 120, 144, if required) ☐ HCV Ab Testing *NOTE: Do not repeat if infection was documented at a prior visit*	

Participant ID ☐☐☐ ☐☐☐☐ ☐☐

Visit Date ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 5: (Open Label Daily Oral TDF/FTC) **Day 0, Week 12, 24, 36, 48 (Weeks 60, 72, 84, 96, 108, 120, 132, 144 if required)** *Circle applicable visit week*			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Collect urine for GC/CT testing and urinalysis (**Day 0, Weeks 24 and 48** (72, 96, 120, 144, if required)) *NOTE: Perform STI testing at Day 0 if not done within the last 6 months: perform testing at all other visits required.*	
_____	☐	Collect rectal swab for GC/CT testing (**Day 0, Weeks 24 and 48**) (72, 96, 120, 144, if required) *NOTE: Perform testing at Day 0 if not done within the last 6 months; perform testing at all other visits as noted*	
_____	☐	Dispense pills	
_____	☐	Provide adherence counseling *Adherence counseling at participant's last Step 5 study visit:* • *Participants ending study participation: counseling should include information about locally available PrEP services and a reminder of the importance of continuous PrEP coverage.* • *Participants moving to Step 6: these participants should receive adherence counseling as per site's SOP.*	
_____	☐	Provide site contact information and instructions to report symptoms and/or clarify any questions	
_____	☐	Schedule next study visit, if applicable	
_____	☐	Provide participant reimbursement, if applicable	

Notes for Step 5: Please refer to Table 10 of the Protocol for further guidance.

Comments: _____
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Participant ID ☐☐☐ ☐☐☐☐ ☐☐

Visit Date ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 6: Cabotegravir Injections Weeks 56, 64, 72, 80, 88, 96 *Circle applicable visit week*			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Confirm participant identity and PTID	
_____	☐	Obtain written informed consent for Version 5.0 of the Protocol **ONLY** if not obtained at a previous study visit. *Note: Participants should be followed under the appropriate Steps contained in Appendix V of the Protocol.*	
_____	☐	Review/update locator information	
_____	☐	Provide HIV counseling	
_____	☐	Offer condoms and lubricant	
_____	☐	Collect directed medical history (including concomitant medications)	
_____	☐	Perform directed physical exam	
_____	☐	Enter weight data to applicable CRF (**Weeks 72 and 96**)	

Participant ID **Visit Date**

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 6: Cabotegravir Injections Weeks 56, 64, 72, 80, 88, 96 *Circle applicable visit week*			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Collect blood for: <u>At all visits:</u> ☐ HIV Testing (please refer to the HIV testing algorithm found in Figure 10 of the Protocol and figure 11-4 of Appendix VIII of the SSP for detailed information) o HIV Rapid test o Laboratory-based HIV immunoassay o **HIV viral load** (<50 copies/mL) ☐ Plasma storage (Must be collected prior to injection) <u>At Weeks 72 and 96 visits</u> ☐ LFTs (AST, ALT, total bilirubin, alkaline phosphatase <u>At Weeks 56, 72, and 96 visits</u> ☐ Syphilis serology *NOTE: Perform testing at Week 56 if not done within the last 6 months; perform testing at all other visits as noted* <u>At Week 96 visit:</u> ☐ Creatinine ☐ HCV Testing *NOTE: Testing does not need to be repeated if infection was documented at a prior visit. HCV Ab testing is required.*	
_____	☐	Collect urine for GC/CT testing (**<u>Weeks 56, 72, and 96</u>**) *NOTE: Perform testing at Week 56 if not done within the last 6 months; perform testing at all other visits as noted*	

Participant ID ☐☐☐ ☐☐☐☐ ☐ ☐

Visit Date ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 6: Cabotegravir Injections Weeks 56, 64, 72, 80, 88, 96 *Circle applicable visit week*			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Collect rectal swab for GC/CT testing (**Weeks 56, 72, and 96**) *NOTE: Perform testing at Week 56 if not done within the last 6 months; perform testing at all other visits as noted*	
_____	☐	Administer CAB injections	
_____	☐	Provide adherence counseling *NOTE #1: Adherence counseling at Week 96 should be tailored to each participant and include a reminder of the importance of receiving their next CAB injection or other PrEP through local services within 8 weeks of last injection.* *NOTE #2: A participant's final visit in Step 6 may occur before Week 96 if CAB is approved and available locally, or if a participant does not want to or cannot continue receiving CAB injections*	
_____	☐	ISR Evaluation and reporting *NOTE #1: Only report on an eCRF an ISR that meets the definition of an SAE (others ISR should be documented in source documents). An ISR typically begins 24-48 hours after an injection.* *NOTE #2: Do not actively ask participants about IRS sign and symptoms; these should be reported by the participant and documented for the visit at which that injection occurred.* *REMINDER: symptoms experienced immediately at the time of an injection are NOT considered ISRs.*	

Participant ID ☐☐☐ ☐☐☐☐ ☐☐

Visit Date ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Step 6: Cabotegravir Injections Weeks 56, 64, 72, 80, 88, 96 *Circle applicable visit week*			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Provide site contact information and instructions to report symptoms and/or clarify any questions	
_____	☐	Schedule next study visit, if applicable	
_____	☐	Provide participant reimbursement, if applicable	

Notes for Step 6: Please refer to Table 11 of the Protocol for further guidance.

Comments: _____
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Participant ID ☐☐☐ ☐☐☐☐ ☐ ☐

Visit Date ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Procedures and Evaluations – For Participants Who Are Not Continuing Under the OLE			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Confirm participant identity and PTID	
_____	☐	Discuss with participants the new information per Version 5.0 of the Protocol	
_____	☐	Obtain written informed consent for Version 5.0 of the Protocol **ONLY** if not obtained at a previous study visit.	
_____	☐	Review/update locator information	
_____	☐	Provide HIV counseling	
_____	☐	Offer condoms and lubricant	
_____	☐	Collect blood for: ☐ HIV Testing (please refer to the HIV testing algorithm found in Figure 10 of the Protocol and Figure 11-4 of Appendix VIII of the SSP for detailed information) ○ HIV Rapid test ○ Laboratory-based HIV immunoassay ○ **HIV viral load** (<50 copies/mL) ☐ Plasma storage ☐ DBS storage ☐ Syphilis serology*	
_____	☐	Collect urine for GC/CT* testing	
_____	☐	Collect rectal swab for GC/CT* testing *NOTE: If testing cannot be performed at the local laboratory, testing at another laboratory will be considered*	

Participant ID **Visit Date**

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Procedures and Evaluations – For Participants Who Are Not Continuing Under the OLE			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Schedule next study visit, if applicable	
_____	☐	Provide participant reimbursement, if applicable	

Notes: Please refer to Table 12 of the Protocol for further guidance.
**Perform testing only if not done within the last 6 months*

Comments: _____
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Participant ID ☐☐☐ ☐☐☐☐ ☐ ☐

Visit Date ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result* **(HIV confirmation visit, Week 12, 24, 36, 48)** *Circle applicable visit week*			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Confirm participant identity and PTID	
_____	☐	Review/update locator information	
_____	☐	Collect directed medical history (including concomitant medications)	
_____	☐	Perform directed physical exam	
_____	☐	Provide HIV counseling (**HIV confirmation visit only**)	
_____	☐	Collect blood for: <u>At all visits:</u> ☐ Plasma storage <u>At HIV Confirmation visit</u> ☐ HIV Testing (please refer to the HIV testing algorithm found in Figure 11-4 of Appendix VIII of the SSP for detailed information) o HIV Rapid test o Laboratory-based HIV immunoassay o **HIV viral load** (<50 copies/mL) ☐ HIV resistance testing ☐ DBS storage <u>At Confirmation Visit, Weeks 24 and 48 visits</u> ☐ CD4 cell count ☐ HIV viral load <u>At Weeks 24 and visits</u> ☐ Creatinine ☐ LFTs (AST, ALT, total bilirubin, alkaline phosphatase)	

Participant ID ☐☐☐ ☐☐☐☐ ☐☐

Visit Date ☐☐ ☐☐☐ ☐☐

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive, and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why (if not self-explanatory), initial and date this entry.

NOTE: Please refer to Protocol Appendix V for specific details.
For a listing of forms required at each visit, please refer to the updated Scheduled of Forms found in Appendix VIII of the SSP

Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result* **(HIV confirmation visit, Week 12, 24, 36, 48)** *Circle applicable visit week*			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Offer condoms and lubricant	
_____	☐	Provide site contact information and instructions to report symptoms and/or clarify any questions	
_____	☐	Schedule next study visit, if applicable	
_____	☐	Provide participant reimbursement, if applicable *NOTE: The Week 48 visit should be timed as closely as possible to 52 weeks after the participant received their last injection.*	

Note for Reactive or Positive HIV Test Results: Please refer to Table 12 of the Protocol for further guidance.

**HIV Confirmation Visit procedures apply to participants with a reactive or positive HIV test during Steps 4 a-c and 5, or at their final study visit (if not continuing under the OLE). Participants with a positive or reactive HIV test during the OLE or at their final study visit (if not continuing under the OLE) and have ever received an active CAB injection at any time during previous study conduct, will be followed according to Table 13 of the Protocol. Participants who have a positive or reactive HIV test during the OLE or at their final study visit (if not continuing under the OLE) and have only ever received oral TDF/FTC and/or oral CAB will be referred to local care. Procedures listed for Weeks 12, 24, 36, and 48 apply only to participants with confirmed HIV infection during Steps 4b and 4c of the study. Participants with confirmed HIV infection in Step 5 may undergo similar procedures as determined by the members of 083CMC@hptn.org. Participants with confirmed HIV infection in Step 4a will be terminated from the study and referred to local care.*

Comments: _____
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1.2.7 Section 7: Participant Retention

Updates to Section 7.8: Participant Withdrawal

Sites will continue to implement existing retention strategies as per site's SOP; however, priority must be given to transitioning participants to local CAB LA for participants who have completed Step 4c and wish to continue receiving it.

Participants may voluntarily withdraw from the study for any reason at any time. Participants also may be withdrawn if the study sponsor, government or regulatory authorities (including Office for Human Research Protections [OHRP] and the FDA), or site IRBs terminate the study before its planned end date. Sites should make every reasonable effort to complete a final evaluation of participants who terminate from the study before the final protocol-dictated study week. Study staff will record the reason(s) for all withdrawals from the study in participants' study records.

In general, for participants who withdraw consent from the study prematurely during a study visit, all the study procedures required for that visit should be completed to the extent possible, except for the provision of study product, and will be considered their final visit. When possible, a plan should be made with the participant about how they'll receive laboratory test results from the final visit. For participants on oral TDF/FTC who withdraw consent from the study, every effort should be made to collect any unused study product.

Participants who decline to participate in the OLE or who are not eligible to participate in cases where they are beyond 3 years from enrollment and wish to remain on TDF/FTC should be consented to the OLE addendum consent form in order to document their decline and that the new information related to CAB was provided to them. It is recommended to perform the procedures listed under Step 5 Day 0 of the Schedule of Procedures and Evaluations as the participant's final study visit. Please refer to Data Communique #16 for further information. Sites should discuss with participants any last contact to provide test results or follow-up on any AEs. The contact plan should be included in the participant's chart.

An IoR or designee may decide to terminate a study participant if the participant has been lost to follow-up (i.e., not been to the study site) for over 6 months, or if the participant has relocated to an area where there is no HPTN 083 site. The timeline for the 6 months lost to follow-up or relocation begins at the participant's first missed visit (which may have occurred longer than 6 months ago by the time the OLE is in effect at the site).

1.2.8 Section 8: Study product considerations

Updates to Section 8.4: Dispensing, Labeling, and Study Product Return

The CAB study product (oral and LA injectable) being tested in this study has been approved by the US FDA for the prevention of HIV-1 infection. Further information on the study product is available in the current prescribing information. An Investigator's Brochure (IB), dated January 12, 2022 (OR LATER VERSION OF THE IB WHEN AVAILABLE), is provided by the DAIDS Regulatory Support Center (RSC), for sites that require it for submission to IRBs/ECs/other regulatory entities.

Participants in Step 4

Step 4a (Oral CAB Lead-In)

CAB 30 mg tablet, one tablet orally once daily for approximately 4 weeks 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.

- When the participant in the TDF/FTC arm wishes to switch to CAB, a new prescription for unblinded oral active CAB signed by an authorized prescriber must be provided to the site pharmacist if the prescriber wishes to start the participant on oral CAB.
- The pharmacist will take the following steps to prepare and dispense unblinded active oral CAB to the participant:
    - Retrieve oral active CAB bottle with two part-label from Step 1 supply.
    - 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.
    - 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.

Step 4b (CAB-LA Loading Dose)

CAB-LA600 mg administered as one 3 mL (600 mg) IM at the 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 and

require a reload of cabotegravir injection. See "Updates to Section 5.1- Study Visits" of Appendix VIII of the SSP for further details on dosing frequency.

- 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:
    - Retrieve injectable CAB-LA vial(s) from storage.
    - 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.
    - Place pharmacist-prepared participant-specific un-blinded label on the prepared syringe.

Step 4c (CAB-LA Maintenance Dose)

CAB-LA 600 mg administered as one 3 mL (600 mg) IM every 8 weeks for approximately one year. 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. See "Updates to Section 5.1- Study Visits" of Appendix VIII of the SSP for further details on dosing frequency.

- 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:
    - Retrieve injectable CAB-LA vial(s) from storage.
    - 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.
    - Place pharmacist-prepared participant-specific un-blinded label on the prepared syringe.

Participants in Step 5:

TDF/FTC, one tablet orally once daily. This Step is for participants who choose to remain on or switch to oral TDF/FTC.

Participants who were originally randomized to oral TDF/FTC and choose to remain on oral TDF/FTC will be on TDF/FTC for three years from the time of enrollment.

Participants who were originally randomized to cabotegravir who choose to switch to TDF/FTC will be on TDF/FTC for 48 weeks from the last CAB-LA injection starting on

Day 0 in Step 5 which begins 8 weeks after that participant's last injection, or for three years from the time of enrollment, whichever is longer.

Participants in Step 5 can change their mind and switch back from TDF/FTC to CAB once at any time during the remainder of the study.

- When the participant has been informed of their randomized assignment to the TDF/FTC arm and the participant wishes to continue TDF/FTC or participant in CAB arm wishes to switch to TDF/FTC, 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:
    - Retrieve open-label oral active TDF/FTC bottle from Step 3 supply.
    - Place pharmacist prepared participant-specific un-blinded label on the bottle and dispense.

Participants in Step 6:

CAB-LA 600 mg administered as one 3 mL (600 mg) IM every 8 weeks for up to an additional 48 weeks (Weeks 56 – 96). This is for participants who complete follow-up in Step 4c and who wish to continue CAB LA while awaiting transition to local commercial CAB LA. See "Updates to Section 5.1- Study Visits" of Appendix VIII of the SSP for further details on dosing frequency.

- 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:
    - Retrieve injectable CAB-LA vial(s) from storage.
    - 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.
    - Place pharmacist-prepared participant-specific un-blinded label on the prepared syringe.

Prescriptions

A prescription for unblinded study product (oral active CAB, oral active TDF/FTC or injectable CAB-LA) 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, 5, or 6), study product name, dose, strength, formulation, route, and

volume (if applicable). For participants making their choice and initiating the OLE for the first time, the prescription should include a notation if the participant is switching between their original CAB arm or original TDF/FTC arm. For participants who wish to switch study product regimen after initiating the OLE, then the prescription should include a notation accordingly. See further details on prescription requirements in the manual, *Pharmacy Guidelines and Instructions for DAIDS Clinical Trial Networks.*

Study Product Labeling

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.*

1.2.9 Section 9: Clinical considerations

Updates to Section 9.3.5.3: Neurologic Symptoms

It is not required to actively assess neurologic symptoms (seizure, trouble sleeping, vivid/strange dreams, dizziness, problems concentrating, lightheaded, tremor, vision changes, weakness, numbness/tingling, fainting). However, these symptoms will be assessed as part of the targeted physical exam as needed.

Updates to Section 9.4: Concomitant medications

The precautionary and prohibited medications are:

Cabotegravir:

- Not to be administered concurrently:
  - Cytotoxic chemotherapy or radiation therapy
  - carbamazepine
  - phenytoin
  - rifabutin
  - rifapentine
  - barbiturates
  - oxcarbazepine
  - phenobarbital
  - rifampin
  - St. John's wort

NOTE: Systemically administered immunomodulators is removed as a prohibited medication; that is, they can be administered to a participant on CAB.

- Prohibited within seven days before and seven days after an injection

    - high dose aspirin (>325 mg per day)
    - apixaban
    - bivalirudin
    - dabigatran
    - enoxaparin
    - heparin
    - prasugrel
    - ticagrelor
    - warfarin
    - anagrelide
    - argatroban
    - clopidogrel
    - dalteparin
    - fondaparinux
    - lepirudin
    - rivaroxaban
    - ticlopidine

- Oral formulation precautions:
    - Antacid products containing divalent cations (e.g., aluminum, calcium, and magnesium) must be taken at least 2 hours before or at least 4-6 hours after the oral CAB administration

Truvada®:

- Medications containing the following ingredients should not be administered concurrently:
    - emtricitabine or tenofovir disoproxil fumarate (e.g., ATRIPLA®, COMPLERA®, EMTRIVA, GENVOYA®, ODEFSEY®, STRIBILD®, or VIREAD, Descovy).
    - lamivudine (e.g. Combivir, Dutrebis, Epivir, Epivir-HBV, Epivir A/F, Epzicom,
    - Triumeq, or Trizivir)
    - adefovir (e.g., HEPSERA®)
    - tenofovir alafenamide (e.g. Vemlidy)
    - didanosine (e.g., Videx EC)
    - atazanavir (e.g. Reyataz, Evotaz (atazanari/cobicistat))
    - ledipasvir/sofosbuvir (e.g. HARVONI®)
    - darunavir (e.g., Prezista)
    - lopinavir/ritonavir (e.g. Kaletra)
    - orlistat (e.g., Alli, Xenical)

Additional information regarding recommended, prohibited, and precautionary concomitant medications can be found in the cabotegravir IB and the Truvada® PI.

Site staff will document all concomitant medications/preparations (prescription and non-prescription), including alternative/complementary medications/preparations (e.g., herbs, vitamins, etc.) in the study participant's chart and on relevant CRFs. Alcohol and recreational or street drug use reported by a participant during the study will be

documented in the participant's chart only. Do not document it on the concomitant medication log.

Updates to Section 9.4.2: Considerations for Co-administration of Precautionary and Prohibited Medications

- Site clinician should clinically monitor co-administration of precautionary and prohibited medications, as per considerations below:
    - Drugs that are eliminated by active tubular secretion (e.g., acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose (please refer to Table 9-1 below) or multiple NSAIDS), as these may increase concentrations of emtricitabine, tenofovir, and/or the co-administered drug.
        - Please report to the CMC if a participant takes a total daily dose of NSAIDS that meets or exceeds high dose, as designated in the Table 9-1 below, for MORE than 72 consecutive hours.
        - Acyclovir and valacyclovir may be used when indicated. If needed for treatment – sites do NOT need CMC permission for the use of these products, but sites should counsel the participant to increase hydration to avoid additive nephrotoxicity; no additional laboratory monitoring is required per protocol.
    - Drugs that decrease renal function (e.g., cause nephrotoxicity) as these may increase concentrations of emtricitabine and/or tenofovir.

Table 9-1: Comparable NSAID Dose Levels*

Nonselective NSAIDs	Low Dose	Medium Dose	High or Max Dose
Diclofenac potassium	50mg bid	50mg tid	50mg qid (in OA/RA only)
Diclofenac sodium	50mg bid	75mg bid	50mg qid or 100mg SR bid (in RA only)
Fenoprofen	200-300mg qid	600mg tid-qid	800mg qid
Flurbiprofen	50mg bid	50mg tid-qid	100mg tid
Ibuprofen	400mg tid	600mg tid-qid	800mg qid
Ketoprofen	25–50mg tid	75mg tid	IR =300mg/day (divide), SR =200mg/day
Naproxen	250mg tid	500mg bid	1250mg/day (divided)
Naproxen sodium	275mg tid	550mg bid	1375mg/day (divided)
Oxaprozin	600mg qd	1,200mg qd	1,200mg qd
Sulindac	150mg bid	200mg bid	200g bid
Piroxicam	10mg qd	20mg qd	40mg per day (not indicated for OA or RA)
Partially-selective NSAIDs	**Low Dose**	**Medium Dose**	**High or Max Dose**
Etodolac	200mg tid	400mg bid	1,200mg max (IR or SR divided doses)
Meloxicam/Mobic	7.5mg qd	7.5mg qd	15mg qd
Nabumetone	1,000mg qd	1,000mg bid	2,000mg/day (qd or divided bid)
Cox-2 inhibitors	**Low Dose**	**Medium Dose**	**High or Max Dose**
Celecoxib/Celebrex	200mg qd	200mg bid	200mg bid

COX = cyclo-oxygenase; IR = immediate release; NSAID = nonsteroidal antiinflammatory drug; OA = osteoarthritis; RA = rheumatoid arthritis; SR = sustained release
*This table does not represent exact or equivalent dosing conversions. It is based on U.S. Food and Drug Administration approved dosing ranges and comparative doses from clinical trials.
Source: www.ashp.org/emplibrary/NSAIDsConversiontools.pdf

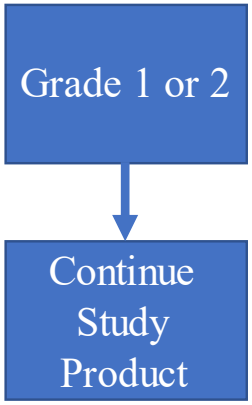
- Consult the CMC for guidance when a participant or provider decides it is in the participant's best interest to initiate PEP or if use of a prohibited medication is needed for treatment of a condition, including but not limited to TB or LTBI.

Updates to Section 9.8: Toxicity Management

Sites should regularly consult the HPTN 083 protocol Appendix V and the Toxicity Management Diagrams in this section for guidance related to toxicities. It should be noted that the Toxicity Management Guidance in Appendix V of the Protocol refers to several instances where the CMC must be contacted in the case of AE management and grading. AEs that require CMC consultation, the CMC should be notified as soon as possible, ideally within 72 hours of site's awareness.

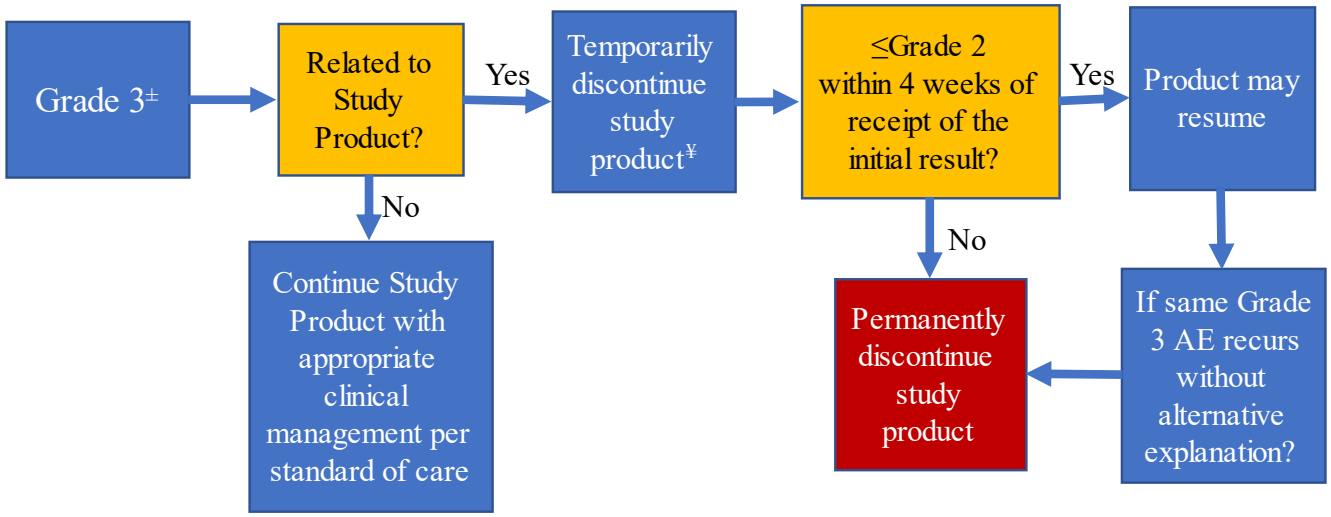
All toxicity management must be fully documented in participant study records. When the CMC is consulted in relation to toxicity management, all communication should be filed in participant study records.

General Guidance*



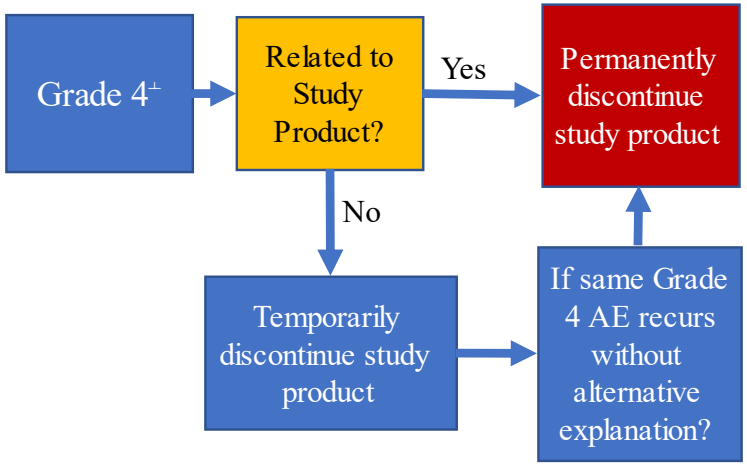
*General Guidance applies only to toxicities not addressed under *Guidance on Toxicity Management for Specified Toxicities*

General Guidance*



* General Guidance applies only to toxicities not addressed under *Guidance on Toxicity Management for Specified Toxicities*
± Any grade 3 or higher clinical or laboratory AE observed prior to their first injection of active CAB (i.e. in STEP 4a) will prompt consultation with the CMC prior to any injectable dosing
¥ Investigator should re-evaluate the participant until resolution of the toxicity.

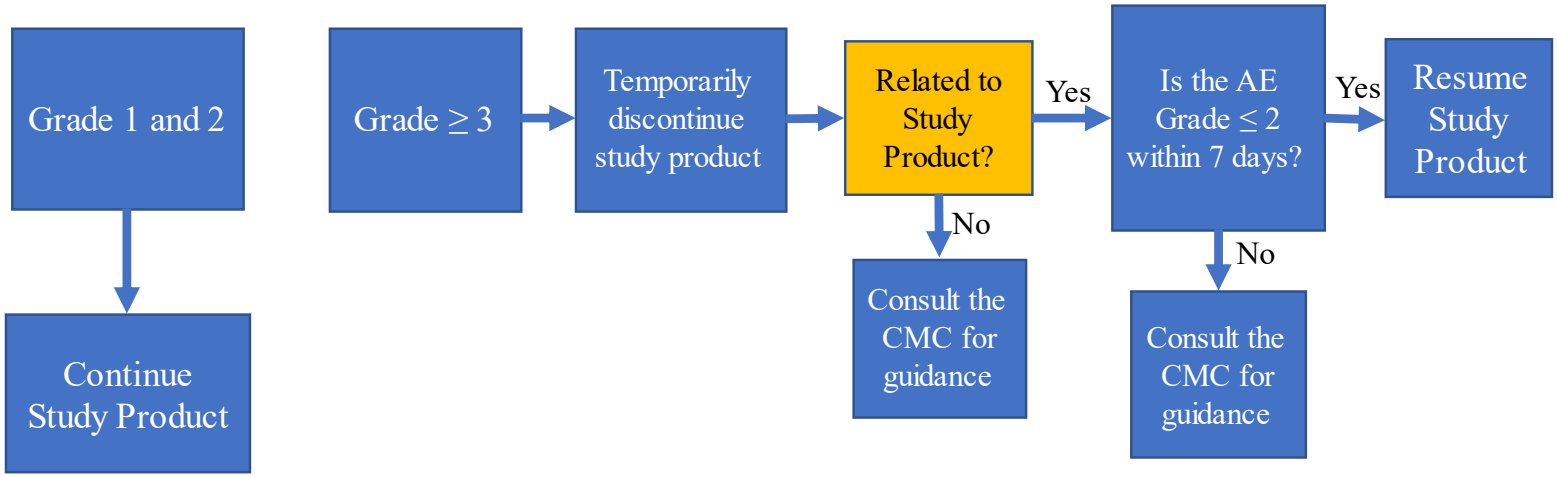
General Guidance*



*General Guidance applies only to toxicities not addressed under *Guidance on Toxicity Management for Specified Toxicities*

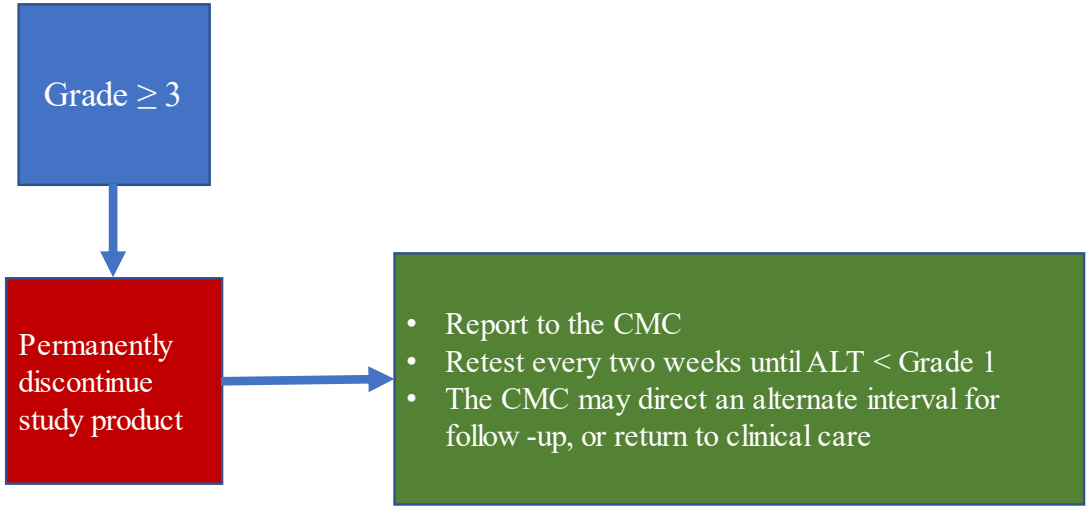
±Any grade 4 or higher clinical or laboratory AE observed prior to their first injection of active CAB (i.e. in STEP 4a) will prompt permanent study product discontinuation.

Guidance on Toxicity Management for Specified Toxicities
Nausea, Vomiting, and Diarrhea*

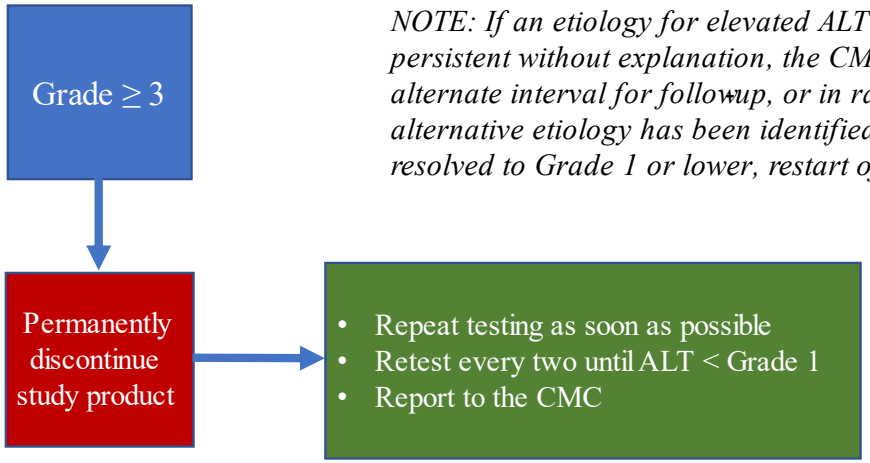


*For all grade levels, treat symptomatically

Guidance on Toxicity Management for Specified Toxicities
ALT Elevations
Oral CAB (Step 4a)

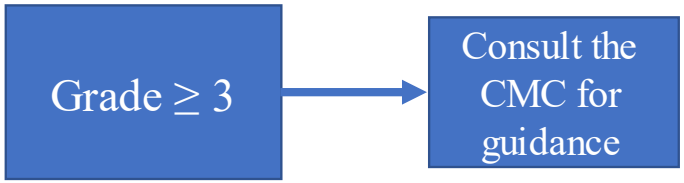


Guidance on Toxicity Management for Specified Toxicities
ALT Elevations
Injectable CAB (Steps 4b, 4c, and 6)

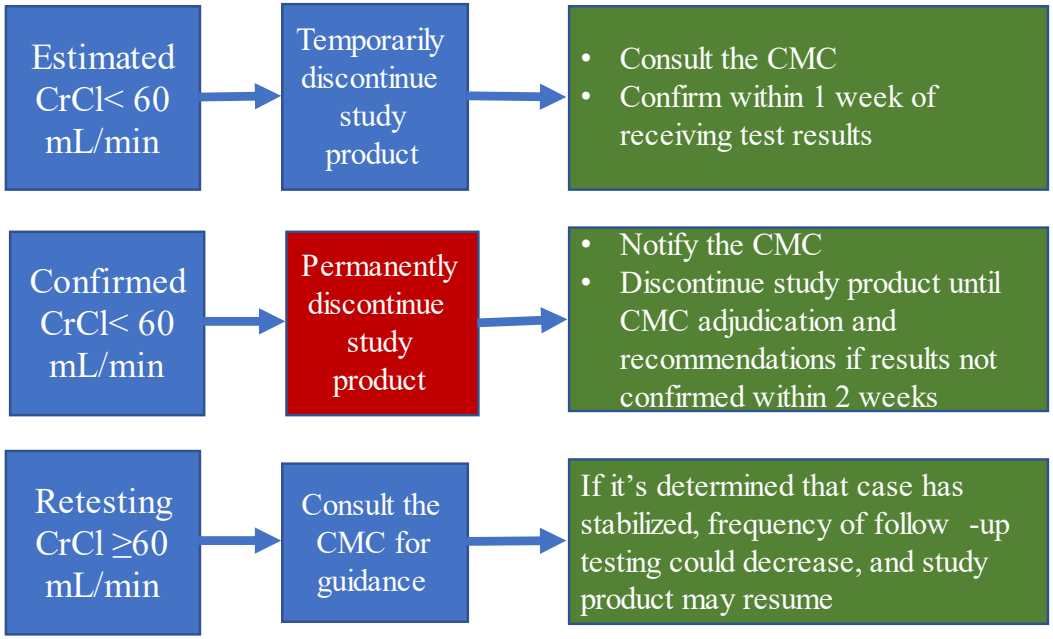


NOTE: If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up, or in rare cases where alternative etiology has been identified and ALT has resolved to Grade 1 or lower, restart of study product

Guidance on Toxicity Management for Specified Toxicities
ALT Elevations
Oral label TDF/FTC (Step 5)



Guidance on Toxicity Management for Specified Toxicities
Creatinine Clearance
Oral label TDF/FTC (Step 5)

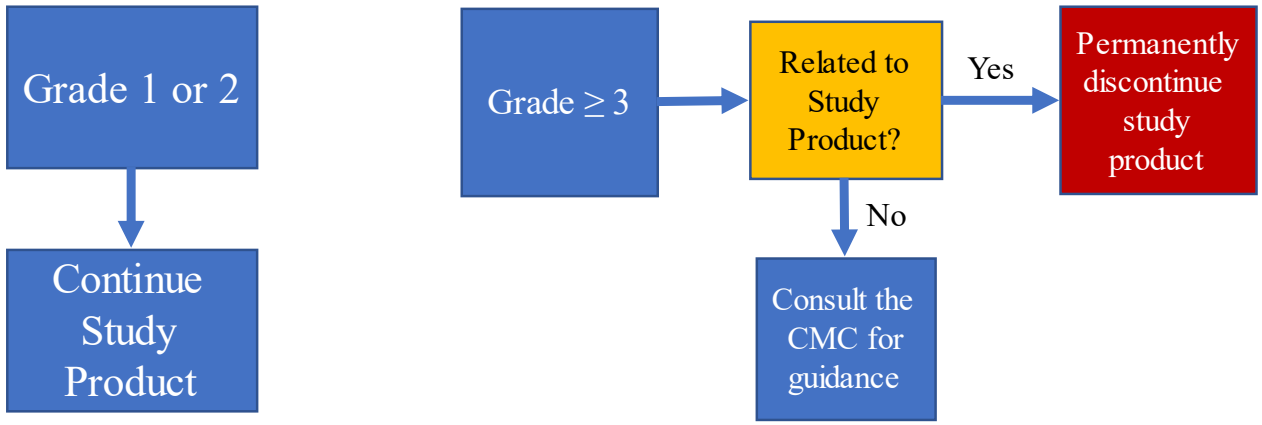


Adverse events related to creatinine clearance should be based on examination of BOTH the absolute creatinine clearance AND the change in creatinine clearance from baseline (Enrollment/ Visit 2.0).

Guidance on Toxicity Management for Specified Toxicities
Injection Site Reactions (ISRs)

- Manage ISR discomfort symptomatically (e.g. cold/warm compress, acetaminophen, ibuprofen) Recommended interventions include:
  - Pre-treatment (prior to injection administration) warm compresses
  - Topical or oral pre-treatment with NSAID preparations, unless contraindicated
  - Immediate post-injection massage to injection location
  - Post-treatment warm or cold compresses
  - Post-treatment NSAID or other analgesic preparations, topically or orally
- Notify the CMC of extreme circumstance of an ISR that warrant premature transition from Step 4c to Step5.
- During Step 6, only ISRs meeting the definition of an SAE or leading to discontinuation of study product will be entered into the database and such participants should be discontinued from the study. No need to contact the CMC in these cases. ISRs that are Grade 3 or higher that do not meet the above criteria do not need to be entered into the database.

Guidance on Toxicity Management for Specified Toxicities
Allergic Reactions



Updates to Section 9.10: Sexually Transmitted Infections (STIs)

Testing for GC/CT and syphilis will continue under the OLE. Participants who test positive will be referred for treatment of STIs as per local guidelines. Symptomatic screening for STIs beyond what is required by the Protocol will be performed at a site's discretion. The costs associated may come out of each site's respective per participant study reimbursements.

Sites will determine if syphilis testing meets the criteria for incident infection and will document on the relevant eCRF. Sites no longer need to consult the CMC regarding syphilis testing results. Syphilis infections deemed incident by the site IoR should continue to be documented on the STI and AE eCRFs.

Upon initial entry into the OLE, any participant who has not had asymptomatic STI screening in the previous 6 months should have STI testing performed at that OLE initial visit.

Sites will document all STIs on the Adverse Event e-CRF and the STI e-CRF.

Updates to Section 9.10.1: Hepatitis B and Hepatitis C

Participants on Step 4c and Step 6 will have HCV antibody testing performed approximately annually (per Tables 9 and 11 of the Protocol). During follow-up, HCV infection will not require discontinuation of study product unless otherwise indicated per the Toxicity Management Guidance in Appendix V of the Protocol.

1.2.10 Section 10: Adverse Event Reporting and Safety Monitoring

Updates to Section 10.3: Documenting Adverse Events

Study site staff will document all AEs reported or observed in study participants, regardless of presumed attribution, seriousness, or severity, in the study source documentation.

Updates to Section 10.6: Reporting Adverse Events to the HPTN SDMC

Site staff will document in source documents and the appropriate e-CRF AEs all Grade 2 and higher clinical and laboratory AEs, and all AE (clinical or laboratory) that leads to a study product hold (temporary or permanent) regardless of severity and presumed relationship to study product. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.1 corrected, July 2017. STIs will be dually reported on the AE e-CRF as well as the STI e-CRF.

For participants in Step 6: Grade 3 and higher study drug related clinical and laboratory AEs, any AE related to study drug discontinuation (temporary or permanent), and any SAE will be captured on the AE e-CRFs. These include AEs reported by or observed in enrolled (defined as after randomization has occurred) study participants. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.1 corrected, July 2017. STIs will be dually reported on the AE e-CRF as well as the STI e-CRF.

Updates to Section 10.10: Social Impact Reporting

Sites will continue to document on the applicable CRF any social impact reported by the participant in Steps 4a-c and 5 only. "Social Impact" reporting will not take place for participants in Step 6. It is possible that participants' involvement in the study could become known to others and that a social impact may result (i.e., because participants could be perceived as being HIV-infected or at risk or "high risk" for HIV infection). For example, participants could be treated unfairly or have problems being accepted by their families and/or communities. A social impact reported by the participant and judged by the IoR/designee to be serious or unexpected will be reported to the responsible site's IRBs annually or per IRB/EC requirements. Sites will provide appropriate care, counseling, and appropriate referral to any participant that reports a social impact. All actions taken by the site to address social impacts must be documented in the participants' study chart. While maintaining participant confidentiality, study sites may engage their CAB in exploring the social context surrounding instances of social impacts to minimize the potential occurrence of such an impact.

Updates to Section 10.11: AE Reporting

HIV acquisition (seroconversion) is the primary study endpoint and is thus not considered an AE for data collection or reporting purposes. "HIV infection" should not be reported as an AE or written anywhere on an AE Log CRF.

However, primary HIV infection is often symptomatic, and a constellation of symptoms may best be summarized as primary HIV infection illness. In this case, as in other cases when symptoms are best expressed as a unifying diagnosis, it is important to use that summary diagnosis. Thus, if a participant seroconverts and develops one or more signs or symptoms of acute HIV-infection, it is appropriate to report these sign(s)/symptom(s) as a single AE using ONLY the term "viral infection" for Item 1 within the AE Log CRF. Use the alternative etiology section of the AE Log CRF to describe each HIV-related sign/symptom (e.g., fatigue, pharyngitis, etc.).

Complete the other items on the AE Log CRF per the general form instructions. The onset date should be completed using the date on which the participant first reported experiencing the first sign/symptom of acute HIV-infection. If there is more than one

HIV-related sign/symptom, record the highest severity grade. A viral infection AE is considered 'resolved' when all the associated signs/symptoms have resolved or returned to baseline per participant report, and medications for the symptoms are no longer indicated. Mark any medications indicated and taken for the associated symptoms, if applicable.

If one or more signs/symptoms reported on separate AE Log entries are later attributed to acute HIV-infection, change the earliest reported sign/symptom page to the "viral infection" diagnosis and list any other signs or symptoms in the alternative etiology section of the AE Log page. Inactivate the applicable AE log line within Medidata Rave.

1.2.11 Section 11: Lab Considerations

The following schedules will be followed for participants in the OLE:

Table 11-6: Schedule of Study Visits and Specimen Collection – Step 4a

Step 4a		
	Day 0	**Week 4**
HIV testing[1]	X	X
Chemistry testing (creatinine only)[2]	X	X
LFT [2] (AST, ALT, total bilirubin, alkaline phosphatase)	X	X
Plasma Storage[3]	X	X
Syphilis serologic testing[4]	X	
Urine GC/CT testing[4]	X	
Rectal swab GC/CT testing[4]	X	

[1] Following the HIV algorithms described in SSP figure 11-4. HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates).
[2] If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.
[3] See section 11.4 for plasma processing and storage instructions.
[4] Perform testing at Day 0 only if not done within the last 6 months

Table 11-7: Schedule of Study Visits and Specimen Collection – Step 4b

Step 4b	
	Day 0
HIV testing[1]	X
Chemistry testing (creatinine only)[2]	X
LFT (AST, ALT, total bilirubin, alkaline phosphatase)	X
Plasma Storage[3]	X
Syphilis serologic testing[4]	X
Urine GC/CT testing[4]	X
Rectal swab GC/CT testing[4]	X

[1] Following the HIV algorithms described in SSP figure 11-4. HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates).
[2] If testing was performed during step 4a, do not perform at Day 0 of step 4b.
[3] See section 11.4 for plasma processing and storage instructions. Blood must be collected prior to the loading dose.
[4]Perform testing at Day 0 only if not done within the last 6 months

Table 11-8: Schedule of Study Visits and Specimen Collection – Step 4c

Step 4c							
	Day 0	**Week 8**	**Week 16**	**Week 24**	**Week 32**	**Week 40**	**Week 48**
HIV testing[1]	X	X	X	X	X	X	X
HCV antibody testing[2]							X
Chemistry testing (creatinine only)[3]	X			X			X
LFT (AST, ALT, total bilirubin, alkaline phosphatase)	X			X			X
Syphilis serological testing	X[5]			X			X
Urine GC/CT testing	X[5]			X			X
Rectal swab GC/CT testing	X[5]			X			X
Plasma Storage[4]	X	X	X	X	X	X	X

[1] Following the HIV algorithms described in SSP figure 11-4. HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates).
[2] Testing does not need to be repeated if infection was documented at a prior visit.
[3] If creatinine test was performed during Step 4a or 4b, do not perform at Day 0 of Step 4c.
[4] See section 11.4 for plasma processing and storage instructions. Must be collected prior to injection.
[5] Perform testing at Day 0 only if not done within the last 6 months

Table 11-9: Schedule of Study Visits and Specimen Collection – Step 5

Step 5			
	Day 0	**Weeks 12, 36, (60, 84, 108, 132, if required)**	**Week 24, 48 (72, 96, 120, 144, if required)**
HIV testing[1]	X	X	X
HCV antibody testing[2]			X
Chemistry testing (creatinine only)[3]	X		X
LFT[4] (AST, ALT, total bilirubin, alkaline phosphatase)	X		X
Syphilis serological testing	X[5]		X
Urine GC/CT testing	X[6]		X
Rectal swab GC/CT testing	X[7]		X
Urinalysis (protein and glucose)	X		X
Plasma Storage[8]	X	X	X
DBS storage[9]	X	X	X

[1] Following the HIV algorithms described in SSP figure 11-4. HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates).
[2] Testing does not need to be repeated if infection was documented at a prior visit.
[3] If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.
[4] If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.
[5] Perform testing at Day 0 only if not done within the last 6 months.
[6] Perform testing at Day 0 only if not done within the last 6 months
[7] Perform testing at Day 0 only if not done within the last 6 months
[8] See section 11.4 for plasma processing and storage instructions.
[9] See section 11.5 for DBS processing and storage instructions.

Table 11-10: Schedule of Study Visits and Specimen Collection – Step 6

Step 6						
	Week 56	**Week 64**	**Week 72**	**Week 80**	**Week 88**	**Week 96**
HIV testing[1]	X	X	X	X	X	X
HCV antibody testing[2]						X
Chemistry testing (creatinine only)						X
LFT (AST, ALT, total bilirubin, alkaline phosphatase)			X			X
Syphilis serological testing	X[3]		X			X
Urine GC/CT testing	X[3]		X			X
Rectal swab GC/CT testing	X[3]		X			X
Plasma Storage[4]	X	X	X	X	X	X

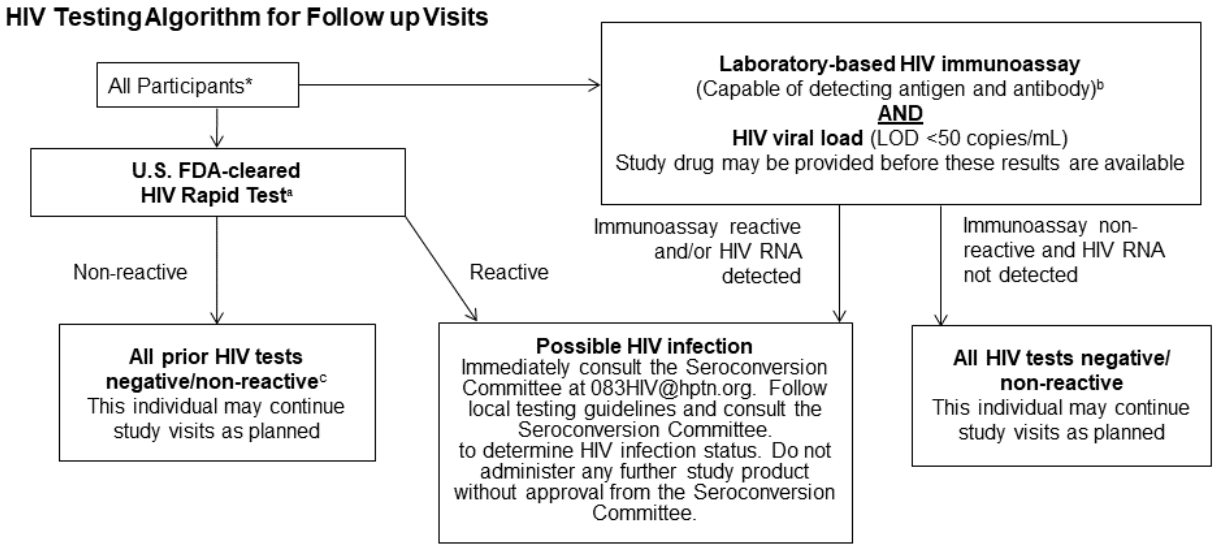
[1] Following the HIV algorithms described in SSP figure 11-4. HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates).
[2] Testing does not need to be repeated if infection was documented at a prior visit.
[3] Perform testing at Week 56 if not done within the last 6 months
[4] See section 11.4 for plasma processing and storage instructions. Must be collected prior to injection.

Table 11-11: Schedule of Specimen Collection – Participants Who Are Not Continuing Under the OLE

	Day 0
HIV testing[1]	X
Syphilis serological testing	X[2]
Urine GC/CT testing	X[3]
Rectal swab GC/CT testing	X[4]
Plasma Storage[5]	X
DBS storage[6]	X

[1] Following the HIV algorithms described in SSP figure 11-4. HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates).
[2] Perform testing if not done within the last 6 months.
[3] Perform testing if not done within the last 6 months.
[4] Perform testing if not done within the last 6 months.
[5] See section 11.4 for plasma processing and storage instructions.
[6] See section 11.5 for DBS processing and storage instructions.

Figure 11.4 HIV Testing Algorithm for Follow up Visits:



NOTES:

*If acute HIV infection is suspected, do not administer any further study product. Immediately consult the Seroconversion Committee. In addition to following the algorithm above, the site should send a sample for an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should use an assay that is FDA-cleared for early HIV diagnosis, such as the APTIMA HIV-1 RNA Qualitative Assay. The site should contact the Seroconversion Committee (083HIV@hptn.org) for additional guidance once all of the test results from this visit (including the HIV RNA test) are available.

[a] Sites that are not able to obtain HIV rapid test kits that are cleared by the US FDA may seek approval from the HPTN LC to use an alternate kit.

[b] This testing must be performed using a laboratory based, non-rapid HIV immunoassay that detects both HIV antigen and HIV antibody (either a 4th generation or 5th generation assay).

[c] At any visit where study product will be given, the site must ensure that the HIV rapid test from this visit, and all HIV results from prior study visits are negative or non-reactive.

Site laboratories should aim to have **HIV Viral Load** results back to the clinical team within approximately 5 working days.

Table 11-6: Schedule for Additional Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result (including HIV confirmatory visit)

The procedures listed for the HIV Confirmation Visit apply to participants who have a reactive or positive HIV test during Steps 4 a-c and 5, or at their final study visit if not continuing participation under the OLE. Participants who have a positive or reactive HIV test during the OLE or at their final study visit (if not continuing under the OLE) and have ever received an active CAB injection at any time during previous study conduct, will be followed according to Table 12. Participants who have a positive or reactive HIV test during the OLE or at their final study visit (if not continuing under the OLE) and have only ever received oral TDF/FTC and/or oral CAB but never an active CAB injection will be referred to local care. The procedures listed for Weeks 12, 24, 36, and 48 apply only to participants with confirmed HIV infection during Steps 4b and 4c of the study. Participants with confirmed HIV infection in Step 5 of the study may undergo similar procedures as listed in Weeks 12, 24, 36, and 48, and will be determined by the members of 083HIV@hptn.org. Participants with confirmed HIV infection in Step 4a will be terminated from the study and referred to local care.

	HIV Confirmation visit	**Week 12**	**Week 24**	**Week 36**	**Week 48**[1]
HIV testing[2]	X				
CD4 cell count.	X		X		X
HIV Viral Load Testing	X		X		X
HIV resistance testing[3]	X				
Chemistry Testing (creatinine only)			X		X
LFT (AST, ALT, total bilirubin, alkaline phosphatase)			X		X
Plasma Storage[4]	X	X	X	X	X
DBS storage[5]	X				

[1] The Week 48 visit should be timed as closely as possible to 52 weeks after the participant received their last injection.
[2] The HIV confirmation visit procedures, sample collection, and testing are to be performed on a different day from day of sample collection where the participant had an initial reactive/positive HIV test result. Procedures for the HIV Confirmation Visit are provided in the SSP Manual. If HIV rapid testing is included in the HIV testing algorithm, this testing may be performed in the clinic or the laboratory.
[3] Sites will collect specimens for resistance testing at a local laboratory to assist with clinical management; results from resistance testing performed at local laboratories will not be reported to the SDMC. Stored plasma cannot be used for real-time/local resistance testing.
[4] See section 11.4 for plasma processing and storage instructions.
[5] See section 11.5 for DBS processing and storage instructions.

Shipping of Samples to the HPTN Laboratory Center

Quarterly shipments of plasma and dried blood spots (DBS) will not take place for specimens collected in the OLE.

Samples for shipment will be specifically requested by the HPTN LC or the SDMC.

Sites may continue to store specimens as requested in Version 3.0 of the SSP or may adopt a storage system that is suitable to the individual site needs and meets study requirements.

1.2.12 Section 12: Counseling Considerations

Sites should continue to provide HIV pre- and post-testing counseling per site SOPs, as well as the appropriate adherence counseling based on the participant's choice under the OLE (initiate or continue on CAB or TDF/FTC), also per site SOPs. Additionally, the relevant information from the HPTN 083 Adherence Counseling Manual may be utilized and can be found in the Microsoft Teams site here: HPTN Study Documents - HPTN 083\Trainings\Version 1.0. Note that some elements of the manual are geared toward the blinded, randomized portion of the study; however, there are several elements that remain relevant and useful.

1.2.13 Section 13: Data Management

Open-label Extension (OLE) Visit Scheduling: Target Days and Visit Windows

Whenever possible, visits should be completed on the target day, which is based on Day 0 of the Step chosen for the participant, or within the target visit window. Allowable visit windows are an extension of the target windows and are contiguous; therefore, any visit is allowable. When necessary, visits may be completed inside the allowable window.

The following tables list the HPTN 083 visit codes, target days and visit windows for each study visit in the OLE for scheduling guidance. All windows are listed in days.

Participants originally randomized to oral TDF/FTC who choose to continue on TDF/FTC will be followed until three years from the date of enrollment. Participants originally randomized to CAB who choose to initiate TDF/FTC, as well as participants who transition from Step 4b or Step 4c (after completion or prematurely) to Step 5 will be followed for 48 weeks (until Visit 105 or Visit 125) or for three years from enrollment, whichever is longer. The timeline for Day 0 begins 8 weeks after participant's last injection, even if the participant does not report to the Day 0 visit (or the Week 12 visit, etc.). The timeline for Step 5 continues whether a participant attends visits or not.

Whenever possible, visits should be completed on the target day, which is based on the Day 0, or within the target visit window. Visits conducted outside of the target visit windows are allowable without restriction. Allowable visit windows are an extension of the target windows and are contiguous. When necessary, visits may be completed inside the allowable window.

Week	Visit Code	Target day	Target visit window (±varies days)	Allowable visit window (± varies days)	Allowable visit window
Step 4a					
Step 4a - Day 0	61	0	(0, 3)	+13	(0, 13)
Step 4a - Week 4	62	28	(25, 31)	-14 / +3	(14, 31)
Step 4b - Day 0*	63	35**	(32, 38)	-3/ +13	(32, 48)

* Once this visit is completed, please refer to the visit windows table for Step 4b.
** The participant can be scheduled as soon as the test results are back from Step 4a - Week 4.

Week	Visit Code	Target day	Target visit window (±varies days)	Allowable visit window (± varies days)	Allowable visit window
Step 4b					
Step 4b - Day 0	63	0	(0, 3)	+13	(0, 13)
Step 4c - Day 0*	64	28	(25, 31)	-14/+27	(14, 55)

* Once this visit is completed, please refer to the visit windows table for Step 4c.

Week	Visit Code	Target day	Target visit window (±varies days)	Allowable visit window (± varies days)	Allowable visit window
Step 4c					
Step 4c - Day 0	64	0	(0, 3)	+27	(0 , 27)
Step 4c - Week 8	65	56	(49, 63)	-28 / +27	(28, 83)
Step 4c - Week 16	66	112	(105, 119)	-28 / +27	(84, 139)
Step 4c - Week 24	67	168	(161, 175)	-28 / +27	(140, 195)
Step 4c - Week 32	68	224	(217, 231)	-28 / +27	(196, 251)
Step 4c - Week 40	69	280	(273, 287)	-28 / +27	(252, 307)
Step 4c - Week 48	70	336	(329, 343)	-28 / +27	(308, 363)
Step 6 - Week 56*	71	392	(385, 399)	-28 / +27	(364 , 419)
Step 5 – Day 0**	101	<8 weeks from the last injection	(0 , 14)	+42	(0 , 42)

***** If site has Protocol Version 5.0 approval, continue from Step 4c - Week 48 to Step 6 – Week 56.
****** If site does not have Protocol Version 5.0 approval, continue from Step 4c - Week 48 to Step 5 – Day 0.

Week	Visit Code	Target day	Target visit window (±varies days)	Allowable visit window (± varies days)	Allowable visit window
Step 5					
Step 5 - Day 0	101	0	(0, 14)	+42	(0, 42)
Step 5 - Week 12	102	84	(70, 98)	-41 / +42	(43, 126)
Step 5 - Week 24	103	168	(154, 182)	-41 / +42	(127, 210)
Step 5 - Week 36	104	252	(238, 266)	-41 / +42	(211, 294)
Step 5 - Week 48	105	336	(322, 350)	-41 / +42	(295, 378)
Step 5 - Week 60	106	420	(406, 434)	-41 / +42	(379, 462)
Step 5 - Week 72	107	504	(490, 518)	-41 / +42	(463, 546)
Step 5 - Week 84	108	588	(574, 602)	-41 / +42	(547, 630)
Step 5 - Week 96	109	672	(658, 686)	-41 / +42	(631, 713)

NOTE: If participant moved from Step 4c - week 48 to Step 5 before Version 5.0 approval, continue from Step 5 to Step 6 - Week 56 at first visit after IRB approval.

Week	Visit Code	Target day	Target visit window (±varies days)	Allowable visit window (± varies days)	Allowable visit window
Step 6					
Step 6 - Week 56*	71	0	(0, 33)	+27	(0, 27)
Step 6 - Week 64	72	56	(49, 63)	-28 / +27	(28, 83)
Step 6 - Week 72	73	112	(105, 119)	-28 / +27	(84, 139)
Step 6 - Week 80	74	168	(161, 175)	-28 / +27	(140, 195)
Step 6 - Week 88	75	224	(217, 231)	-28 / +27	(196, 251)
Step 6 - Week 96	76	280	(273, 287)	-28 / +27	(252, 307)

*If participant moves to Step 6 from a Step 5 visit, Step 6 – Week 56 functions as the Day 0 visit for calculating Step 6 windows. Otherwise, continue to calculate targets based on the Step 4c schedule.

Open-label Extension (OLE): Step Transitions

At a participant's first visit under protocol Appendix V, the participant chooses whether to continue in the OLE. If the participant opts to continue, record the choice by marking either TDF/FTC or CAB-LA on the Product Choice form. A Product Hold/Discontinuation form should NOT be completed when a participant moves to the OLE.

It is mandatory to complete the Product Choice form for any participant who has not terminated when the OLE is approved for the site.

If the participant does not opt to move to the OLE, they should be terminated. An interim visit should be completed based on the last visit that was recorded in Rave (either attended or missed) and the Termination form completed in that interim visit folder.

If CAB-LA is selected, the applicable Step should be selected in the next response:

Oral CAB (Step 4a)
Loading Dose (4-week interval CAB-LA (Step 4b)
Standard Dose (8-week interval CAB-LA (Step 4c)

Oral CAB (Step 4a) is an optional Step. Please refer to the Protocol Appendix V Part A Section 3a for details on the requirements for this step. If the participant's decision is to start Step 4a, please complete the Product Choice form to record this decision. Once this form is saved the first visit for Step 4a, V61 - Step 4a - Day 0 is populated.

Loading Dose (Step 4b) consists of only one visit. Please refer to the Protocol Appendix V Part A Section 3b for details on the requirements for this step. If the participant's decision is to start Step 4b, please complete the Product Choice form to record this decision. Once this form is saved, the first visit for Step 4b, V63 - Step 4b - Day 0 is populated.

Standard Dose (Step 4c): Please refer to the Protocol Appendix V Part A Section 3c for details on the requirements for this step. If the participant's decision is to start Step 4c, please complete the Product Choice form to record this decision. Once this form is saved the first visit for Step 4c, V64 - Step 4c - Day 0 is populated.

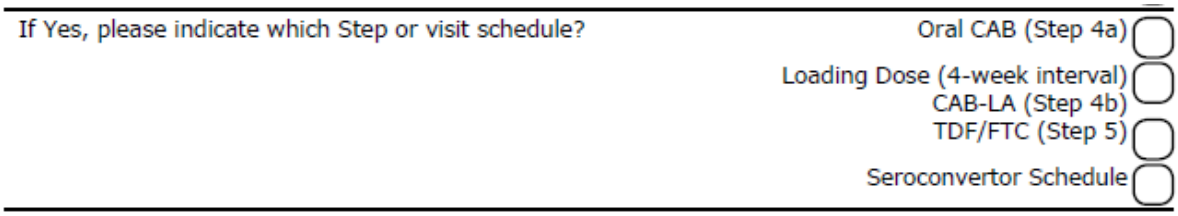
TDF/FTC (Step 5): Please refer to the Protocol Appendix V Part A Section 3d for details on the requirements for this step. If the participant's decision is to start Step 5, please complete the Product Choice form to record this decision. Once this form is saved the first visit for Step 5, V101 - Step 5 - Day 0 is populated.

Participants who start at either Step 4a or Step 4b will automatically move onto the next Step after the last visit in that cycle has been completed. This would not be considered a change in Step and should not be marked as such on the Date of visit or Interim visit form.

Step 4a ➔ Step 4b ➔ Step 4c ➔ Step 5

Open-label Extension: Switching Steps

Once OLE visits have been initiated, participants can choose to switch regimens one time. This change is documented on the Date of Visit - OLE or Interim visit – OLE form. Mark "Yes" for "Is the participant moving to a new step or visit schedule?", then select the applicable Step on the next question.



Selecting the next Step will populate the first visit in the new regimen. Future visits in the original Step will no longer be populated.

Note that a participant cannot move directly from TDF/FTC (Step 5) to Step 4c. Based on the site's requirement, the participant should first have either oral CAB visits or a loading dose visit before progressing to Step 4c.

Once a participant moves from CAB (Step 4a, 4b or 4c) to TDF/FTC (Step 5), they cannot move back to CAB. If the participant started on CAB, they should complete 48 weeks of TDF/FTC (Visit 105) unless there is an early termination. Once the participant has completed Visit 105, the Termination form should be recorded.

If a participant starts on TDF/FTC (Step 5) and switches to CAB-LA, they still have the option of switching back to TDF/FTC before all the CAB-LA visits are completed. In this scenario, "TDF/FTC Step 5" should be selected on the Date of Visit-OLE or Interim visit-OLE form. Once this form is saved the first visit for Step 5b, V121 - Step 5b - Day 0 is populated.

Open-label Extension (OLE II): Switching Steps

If a participant signs a Version 5.0 consent by the time they complete the Step 4c -Week 48 visit (v70), they move to Step 6 by changing Steps at that visit. Mark "Yes" for "Is the participant moving to a new step or visit schedule?", then select "Standard Dose CAB-LA (Step 6)" in the next response. This will populate the first Step 6 visit (v71/Step 6-week 56).

If a site doesn't have Protocol Version 5.0 approval by the time a participant completes the Step 4c-Week 48 visit (v70), they automatically move to Step 5 – Day 0 (v101). At the first visit after Version 5.0 approval is obtained, if they sign a consent, they move from Step 5 to Step 6. Mark "Yes" for "Is the participant moving to a new step or visit schedule?," then select "Standard Dose CAB-LA (Step 6)" in the next response. This will populate the first Step 6 visit (v71/Step 6-week 56)

HPTN 083 Schedule of Forms and CASI Surveys

Step 4a

CRF Name	Day 0 V61.0	Week 4 V62.0
Date of Visit - OLE	x	x
Specimen Storage	x	x
HIV Test Results	x	x
Local Laboratory Results	x	x
Vital Signs	x	x
SMSQ-OLE	x	
Interviewer Administered - OLE	x	
CASI Survey Sexually Transmitted Infections	x x*	

*Not required at Day 0 if done within the last 6 months.

Step 4b

CRF Name	Day 0 V63.0
Date of Visit - OLE	x
Specimen Storage	x
HIV Test Results	x
Injection Administration	x
Vital Signs	x
SMSQ-OLE	x
Interviewer Administered - OLE	x

CRF Name	Day 0 V63.0
Local Laboratory Results	x
CASI Survey Sexually Transmitted Infections	x x*

*Not required at Day 0 if done within the last 6 months.

Step 4c

CRF Name	Day 0 V64.0	Week 8 V65.0	Week 16 V66.0	Week 24 V67.0	Week 32 V68.0	Week 40 V69.0	Week 48 V70.0
Date of Visit - OLE	x	x	x	x	x	x	x
Vital Signs	x	x	x	x	x	x	x
Injection Administration	x	x	x	x	x	x	x
HIV Test Results	x	x	x	x	x	x	x
Local Laboratory Results	x			x			x
Specimen Storage	x	x	x	x	x	x	x
SMSQ-OLE	x		x				x
Interviewer Administered - OLE	x		x				x
Sexually Transmitted Infections	x*			x			x
Hepatitis Test Results							x
CASI Survey	x		x				x

*Not required at Day 0 if done within the last 6 months.

Step 5

CRF Name	Day 0 V101.0	Week 12 V102.0	Week 24 V103.0	Week 36 V104.0	Week 48 V105.0	Week 60 V106.0	Week 72 V107.0	Week 84 V108.0	Week 96 V109.0
Date of Visit - OLE	x	x	x	x	x	x	x	x	x
Vital Signs	x	x	x	x	x	x	x	x	x
Sexually Transmitted Infections	xxx*		x		x		x		x
HIV Test Results	x	x	x	x	x	x	x	x	x
Local Laboratory Results	x		x		x		x		x
Specimen Storage	x	x	x	x	x	x	x	x	x
SMSQ-OLE	x		x		x		x		x
Interviewer Administered - OLE	x		x		x		x		x
Hepatitis Test Results			x		x		x		x
CASI Survey	x		x		x		x		x

*Not required at Day 0 if done within the last 6 months.

Step 5b

CRF Name	Day 0 V121.0	Week 12 V122.0	Week 24 V123.0	Week 36 V124.0	Week 48 V125.0	Week 60 V126.0	Week 72 V127.0	Week 84 V128.0	Week 96 V129.0
Date of Visit - OLE	x	x	x	x	x	x	x	x	x
Vital Signs	x	x	x	x	x	x	x	x	x
Sexually Transmitted Infections	xxx*		x		x		x		x
HIV Test Results	x	x	x	x	x	x	x	x	x
Local Laboratory Results	x		x		x		x		x
Specimen Storage	x	x	x	x	x	x	x	x	x
SMSQ-OLE	x		x		x		x		x
Interviewer Administered - OLE	x		x		x		x		x
Hepatitis Test Results			x		x		x		x
CASI Survey	x		x		x		x		x

*Not required at Day 0 if done within the last 6 months.

Step 6

CRF Name	Week 56 V71.0	Week 64 V72.0	Week 72 V73.0	Week 80 V74.0	Week 88 V75.0	Week 96 V76.0
Date of Visit - OLE	x	x	x	x	x	x
Vital Signs	x	x	x	x	x	x
Injection Administration	x	x	x	x	x	x
HIV Test Results	x	x	x	x	x	x
Local Laboratory Results			x			x
Specimen Storage	x	x	x	x	x	x
Sexually Transmitted Infections	x*		x			x
Hepatitis Test Results						x

*Not required at v56 if done within the last 6 months.

Reactive or Positive HIV Test Result Schedule

CRF Name	**Week 12 V91.0**	**Week 24 V92.0**	**Week 36 V93.0**	**Week 48 V94.0**
Date of Visit - HIV	x	x	x	x
Vital Signs	x	x	x	x
Specimen Storage	x	x	x	x
Local lab Test Results		x		x
CD4		x		x
CASI Survey				

Additional / As Needed CRFs: Found in Ongoing Logs Folder

Concomitant Medications Y/N
Adverse Event Y/N
ART Medication Y/N
Protocol Deviation Y/N
Social Impact Y/N
Product Hold Y/N
Injection Site Reaction Y/N
Log Revisions
Product Hold - OLE Y/N

Found in Participant Unblinding Folder

Participant Unblinding

Found in Product Choice Folder

Product Choice - OLE
Informed Consent – Version 5.0

Found in "Add Event" function

Yearly Visit
Interim Visit
Interim Visit - OLE
V91.0 – Week 12
Long Term Consent Update

Additional Forms

Participant Transfer
Participant Receipt
Supplemental HIV Results