Appendix VIII: SSP Manual Updates Per Version 4.0 of the Protocol

1.1 Overview of Appendix VIII

This Appendix includes specific updates, guidance, and considerations for implementation of Version 4.0 of the HPTN 083 protocol. It complements Appendix V of Version 4.0 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 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 Version 4.0 are not being made; rather, this Appendix 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 Version 4.0**

of the protocol. This Appendix VIII replaces or clarifies language already included in those sections accordingly.

Implementation of Version 4.0 of the Protocol and Appendix VIII of the SSP manual will be implemented once the following items are completed:

- Site receives approval of Protocol Version 4.0 by the site's IRBs/ECs/other regulatory entities overseeing the research.
- Site receives notification from the DAIDS Protocol Registration Office indicating successful completion of the protocol registration process for Version 4.0 of the Protocol.
- Additional supply of cabotegravir has been received at the site.
- Site staff has completed and documented training for Version 4.0 of the protocol.

Once these items are completed, the LOC will issue a notification memo to the site to begin implementing Version 4.0 of the Protocol.

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*)
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 Research Specialist	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	Priyanka Agarwal Tel: 206.667.4384 Email: pagarwal@scharp.org ~~Leslie Cottle~~ ~~Tel: 206-667-7405~~ ~~Email: leslie@scharp.org~~

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	5 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

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 Version 4 of the protocol, examples of reportable protocol deviations include:

- Failing to administer the ICF at participant's first visit following IRB/EC approval. For example, an updated ICF is approved by the local IRB/EC on October 4th, a participant presents to the clinic on October 8th; however, the updated ICF is not obtained at this visit.
- 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. 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 9.3.4.7 of the SSP, 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, but should be discussed by the protocol team.

- Participant overdose of study product. For purposes of reporting, a study product overdose is defined as three or more occasions of taking more than the specified dose of study product during a 30-day period.

  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. 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 WILL 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 next part of HPTN 083 and continue/initiate open-label CAB-LA or TDF/FTC.

- 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 Version 4.0.
  - 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 Version 4.0:

- 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.

  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. Visits should follow the Step 5 visit schedule in these cases until a year of coverage is complete (e.g., if they had 3 visits remaining in Step 3, they will complete the first three visits of Step 5).*

Updates to Section 4.5.1 – Informed Consent Process

After receiving notification to implement Version 4.0 of the protocol, sites will administer the addendum to the main informed consent form as participants present to the site. This form will document the participant's continued participation in the study. As part of the consent discussion, sites should explain to participants the options for ongoing study participation as outlined in Appendix V of the Protocol.

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 scenarios for a discussion about choice and obtaining informed consent.

1.2.5 Section 5: Study Procedures Overview

Updates to Section 5.2 – Study Overview

HPTN 083 participants who choose to continue or initiate CAB-LA or decide to remain in TDF/FTC will follow these steps (please refer to Figure 1 below):

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:

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. 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 will move to Step 5:

- If they no longer wish to continue receiving cabotegravir injections before Week 48 occurs
- If they complete Week 48

The timeline for Step 5 Day 0 begins 8 weeks after a participant's last injection and continues whether a participant attends visits or not. 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 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 complete the procedures for Step 5 until three years from the time of enrollment.

Participants who were originally randomized to cabotegravir who choose to switch to TDF/FTC will complete the procedures of this Step for 48 weeks from the last injection or for three years from the time of enrollment, whichever is longer. The timeline for Step 5 Day 0 begins eight weeks after that participant's last injection.

- A participant who was in the process of completing 48 weeks of open-label TDF/FTC as part of prior Step 3 coverage of their final CAB injection under protocol Version 3.0, who does NOT wish to or is not eligible to resume CAB under Version 4.0, will complete the 48 weeks of open-label TDF/FTC in Step 5 even if this extends their study participation beyond three years from their original enrollment.

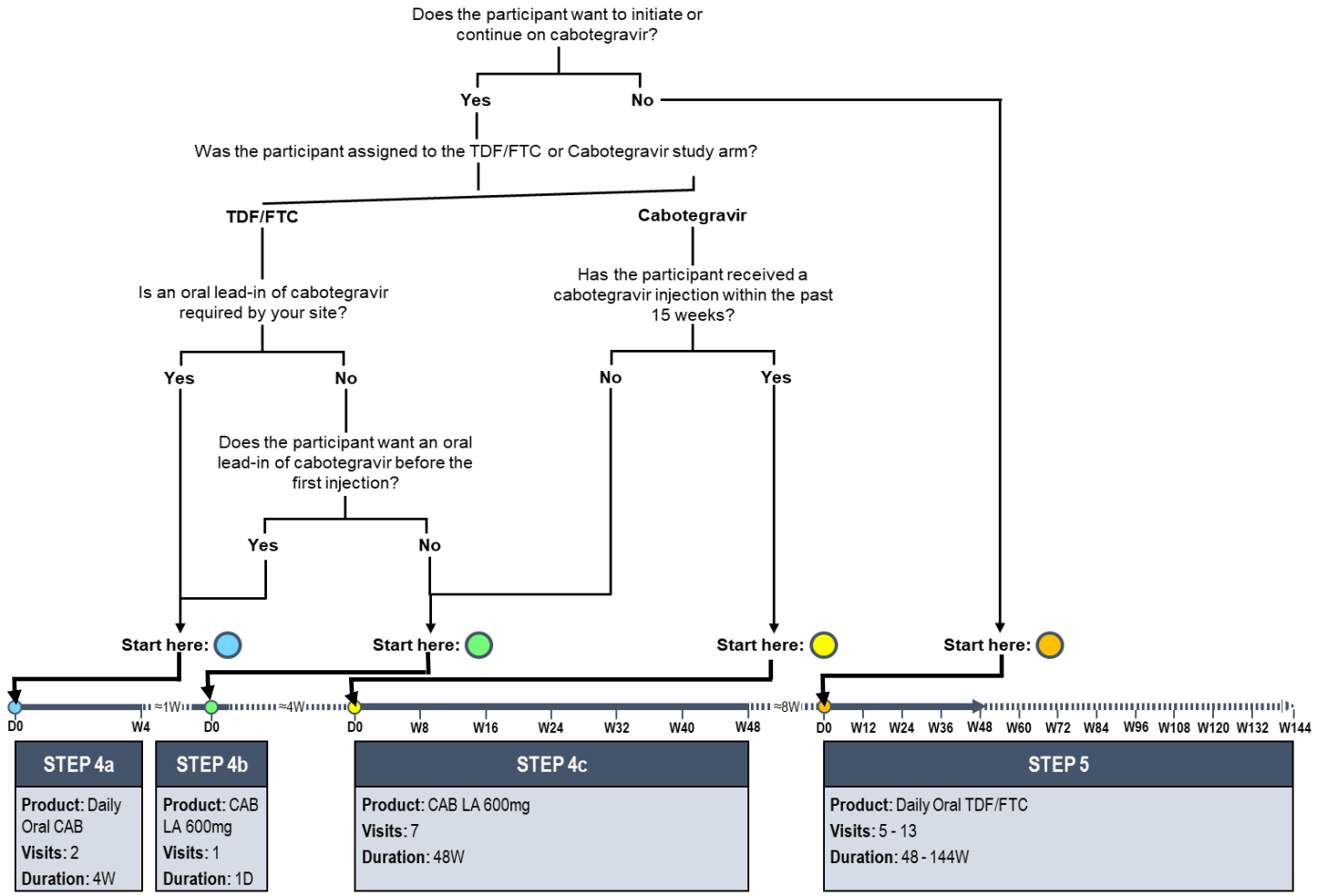
- A participant who was receiving CAB injections as part of Step 2 under protocol Version 3.0, who does NOT wish to or is not eligible to resume CAB under Version 4.0, will complete 48 weeks of open-label TDF/FTC in Step 5, then if not

yet at three years since their original enrollment, will be allowed to remain in Step 5 of the study on TDF/FTC until three years of study participation is reached.

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.

NOTE: Participants who have been on TDF/FTC throughout the study and choose to stay on it during this part of the study, or participants who have been on CAB and decide to switch to TDF/FTC, will be permitted to change their mind any time after making this choice and switch to CAB. That is, they will be allowed to switch to CAB at any point during the remainder of their study participation and be followed accordingly to the visit schedules for CAB. However, they will only be allowed the option to switch to CAB once. That is, if a participant's initial choice is to stay on or switch to TDF/FTC, and then change their mind and switch to CAB, and then change their mind again and switch back to TDF/FTC, they will not be allowed to switch back to CAB again (that is, only one switch is allowed).

Figure 1: Decision Tree



Updates to Section 5.1 – Study Visits

Target windows for all visits are outlined below and are provided for scheduling purposes, under updates to Section 13 of the SSP Manual. Sites are not required to contact the CMC for out-of-target visit windows for visits that are:

- For injection visits that happen a minimum of 6 weeks and a maximum of 15 weeks from the prior injection
- For the Step 4c Day 0 injection, if it is a minimum of 3 weeks and a maximum of 11 weeks from the Step 4b Day 0 injection

  NOTE: All safety laboratory assessments should be done and verify the results are within the protocol-allowable parameters before proceeding with an injection visit.

Sites must contact the CMC for any other out-of-target visits that don't meet these parameters.

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.

Information regarding interim and missed visits is found below, under updates to Section 13 of the SSP manual.

Updates to Section 5.3.1 – Follow-up Visit Procedures

Refer to Tables 7-10 of Version 4.0 of the Protocol, Schedule of Procedure, and Evaluation for Steps 4a-c, 5 for detailed information about study procedures. Table 11 of the protocol also details the procedures for participants who have a reactive or positive HIV test result.

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, 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 in Step 4b or 4c of the study, who prematurely stop receiving injections, will be asked to transition to Step 5 of the study. These participants will receive 48 weeks of open-label TDF/FTC unless the reason is HIV infection or an AE or condition where open-label TDF/FTC is contraindicated. Participants with HIV infection will be followed per Table 11: *Schedule for Additional Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result (including HIV confirmatory visit)* of the protocol. Participants who prematurely stop receiving injections for an AE or condition where open-label TDF/FTC is contraindicated will be asked to continue follow-up for 48 weeks off study product.

- 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.

- *Note: Participants who became infected with HIV under Version 3.0 of the protocol and are being followed on the HIV infection quarterly visit schedule will complete their visits under this Version 4.0 amendment. For example, if they completed Weeks 0, 12, and 24 under Version 3.0 and Version 4.0 is now approved at the site, the participant will complete Weeks 36 and 48 under Version 4.0 and then be terminated from the study.*

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 Version 4 of the protocol	
_____	☐	Obtain written consent for Version 4.0 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	
_____	☐	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 4a: (Daily Oral Cabotegravir – OPTIONAL for participants initiating CAB injections) Day 0			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	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* ☐ LFTs* (AST, ALT, total bilirubin, alkaline phosphatase) ☐ Plasma storage *Note: If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the investigator	
_____	☐	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: _____
_____

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.	
_____	☐	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 ☐ LFTs (AST, ALT, total bilirubin, alkaline phosphatase) ☐ Plasma storage	
_____	☐	Provide adherence counseling regarding attending first CAB injection 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

_____	☐	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:
_____
_____
_____

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 after hiatus*) Day 0			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	Confirm participant identity and PTID	
_____	☐	Applicable **only** to participants who did not complete Step 4a: ☐ Discuss with participants the options for ongoing study participation and the Steps under Version 4 of the protocol**)** ☐ Obtain written informed consent for Version 4.0 of the protocol ☐ Administer Product Choice Assessment Questionnaire (Interviewer Administered)	
_____	☐	Review/update locator information	
_____	☐	Interviewer-Administered, SMSQ (*Refer to form instructions and the Schedule of Forms for whom and when these assessments should be administered*)	
_____	☐	Administer CASI (*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	
_____	☐	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 4b: (Loading Dose Cabotegravir Injection – for participants initiating or restarting CAB injections after hiatus*) Day 0			
Initial/date	**Completed**	**Procedures**	**Comments**
_____	☐	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 (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)	
_____	☐	Collect unused product	
_____	☐	Administer CAB injection	
_____	☐	ISR Evaluation	
_____	☐	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	

Notes for Step 4b: Please refer to Table 8 of the Protocol for further guidance.
* Hiatus is defined as > 15 weeks since prior injection

Comments: _____
_____

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: (Every 8 week [Standard] 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	
_____	☐	Applicable **only** to participants who did <u>not</u> complete Step 4b: ☐ Discuss with participants the options for ongoing study participation and the Steps under Version 4 of the protocol**)** ☐ Obtain written informed consent for Version 4.0 of the protocol ☐ Administer Product Choice Assessment Questionnaire (Interviewer Administered)	
_____	☐	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	
_____	☐	Collect directed medical history (including concomitant medications)	
_____	☐	Perform directed physical exam	
_____	☐	Enter weight data to applicable CRF (**Weeks 16 and 48**)	

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: (Every 8 week [Standard] Cabotegravir Injections) **Day 0, Weeks 8, 16, 24, 32, 40, and 48** *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 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 ☐ LFTs (AST, ALT, total bilirubin, alkaline phosphatase <u>At Weeks 24 and 48</u> ☐ Syphilis serology <u>At Week 48 visit:</u> ☐ HCV Testing	
_____	☐	Collect urine for GC/CT testing (**Weeks 24 and 48**)	
_____	☐	Collect rectal swab for GC/CT testing (**Weeks 24 and 48**)	
_____	☐	Administer CAB injections	
_____	☐	Adherence counseling regarding attending CAB injection visits (**Weeks 8, 16, 24, 32, and 40)**	
_____	☐	ISR Evaluation	

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: (Every 8 week [Standard] Cabotegravir Injections) **Day 0, Weeks 8, 16, 24, 32, 40, and 48** *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	

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

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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 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	
_____	☐	Applicable **only** to participants who did <u>not</u> complete Steps 4a – 4c: ☐ Discuss with participants the options for ongoing study participation and the Steps under Version 4 of the protocol**)** ☐ Obtain written informed consent for Version 4.0 of the protocol ☐ 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	
_____	☐	Provide HIV counseling	
_____	☐	Offer condoms and lubricant	

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 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 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* ☐ LFTs* (AST, ALT, total bilirubin, alkaline phosphatase) ☐ Syphilis serology* <u>At Weeks 24 and 48</u> (72, 96, 120, 144, if required) ☐ HCV Testing (if infection was <u>not</u> documented at a prior visit)	
_____	☐	Collect urine for GC/CT* testing (**Day 0, Weeks 24 and 48** (72, 96, 120, 144, if required))	
_____	☐	Collect rectal swab for GC/CT* testing (**Weeks 24 and 48**) (72, 96, 120, 144, if required)	
_____	☐	Dispense pills	

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 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 adherence counseling *Adherence counseling is not conducted during a participant's final visit of Step 5*	
_____	☐	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.
*If done within last month prior to Day 0, testing may be deferred at the discretion of the investigator.
Comments: _____
_____
_____
_____

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 for Reactive or Positive HIV Test Results: Please refer to Table 11 of the protocol for further guidance.
Comments: _____
_____
_____

1.2.7 Section 7: Participant Retention

Updates to Section 7.8: Participant Withdrawal

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 under Version 4.0 of the protocol 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 Version 4.0 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. The visit code for this final visit should be based on the last visit attended or missed in Version 3.0. 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 may decide to terminate a study participant if the participant has been lost to follow-up (e.i. 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. However, depending on the situation, the IoR may decide not to terminate a study participant, even if participants have not attended a study visit for over 6 months. For example, if a participant's last study visit was over 6 months ago due to the COVID-19 pandemic, but they have been in contact with the site and have expressed interest in continuing the study, the IoR may decide not to terminate this participant.

1.2.8 Section 8: Study product considerations

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

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 (>15 weeks since prior injection) and require a reload of cabotegravir injection.

- 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.

- 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.

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
    - anagrelide
    - argatroban
    - clopidogrel
    - dalteparin
    - fondaparinux

- heparin
- prasugrel
- ticagrelor
- warfarin
- 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.

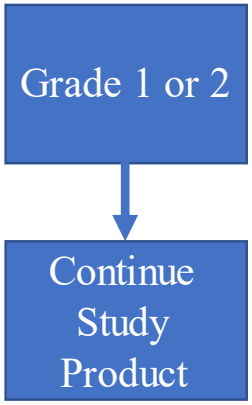
Updates to Section 9.8: Toxicity Management

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.

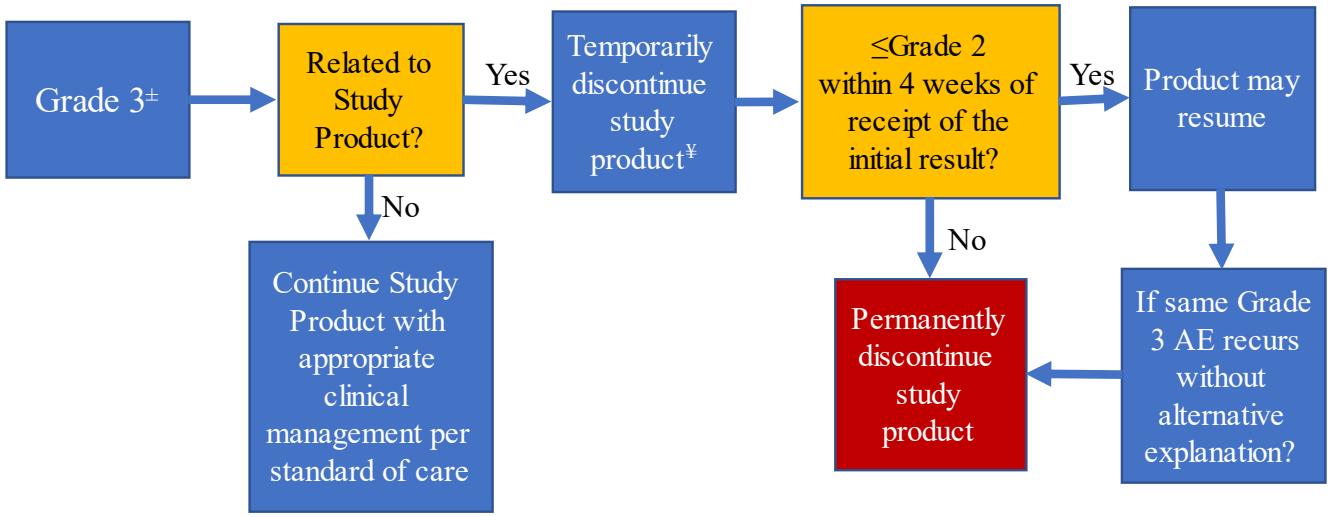
All toxicity management must be fully documented in participant study records. When the CMC is consulted in relation to toxicity management, all communication should be filed in participant study records.

General Guidance*



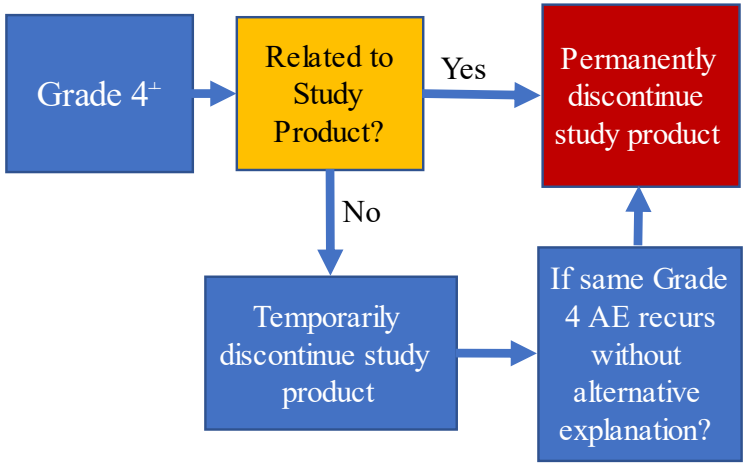
*General Guidance applies only to toxicities not addressed under *Guidance on Toxicity Management for Specified Toxicities*

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.

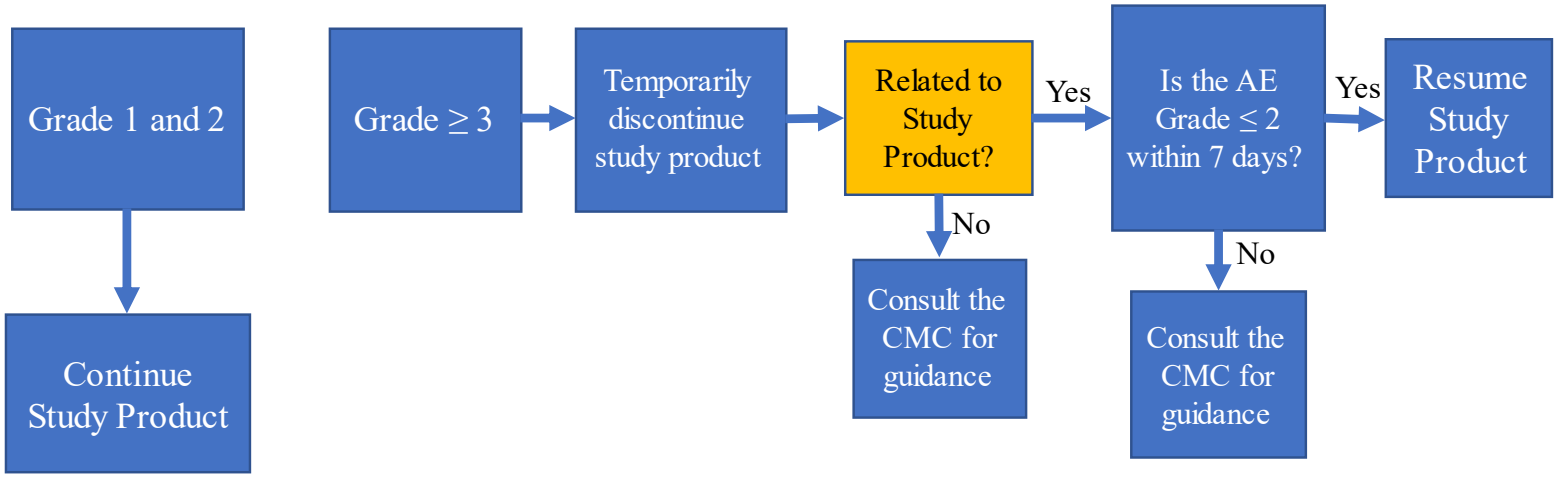
General Guidance*



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

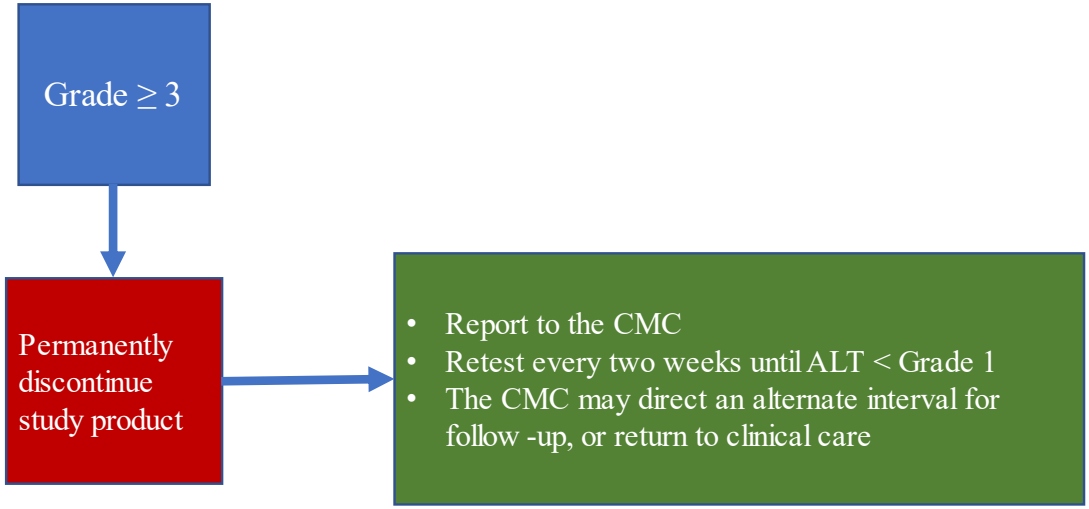
±Any grade 4 or higher clinical or laboratory AE observed prior to their first injection of active CAB (i.e. in STEP 4a) will prompt permanent study product discontinuation.

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

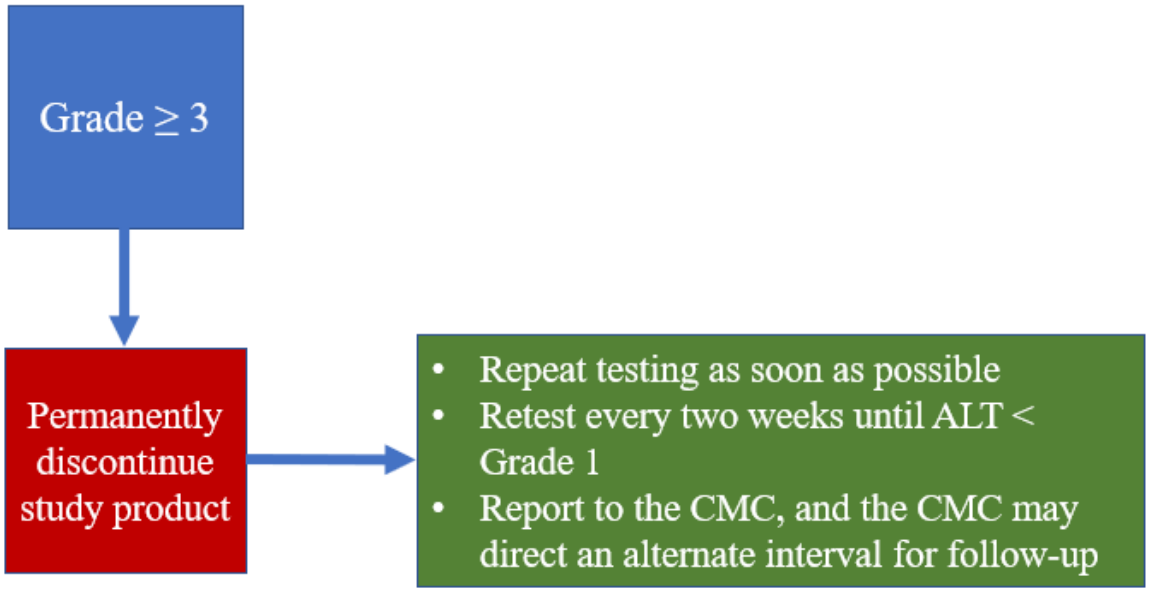


*For all grade levels, treat symptomatically

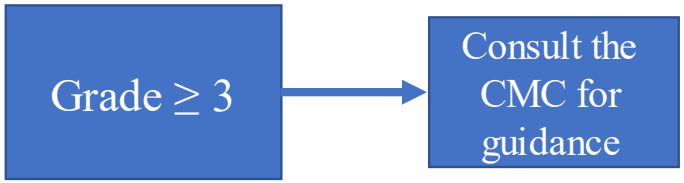
Guidance on Toxicity Management for Specified Toxicities
ALT Elevations
Oral CAB (Step 4a)



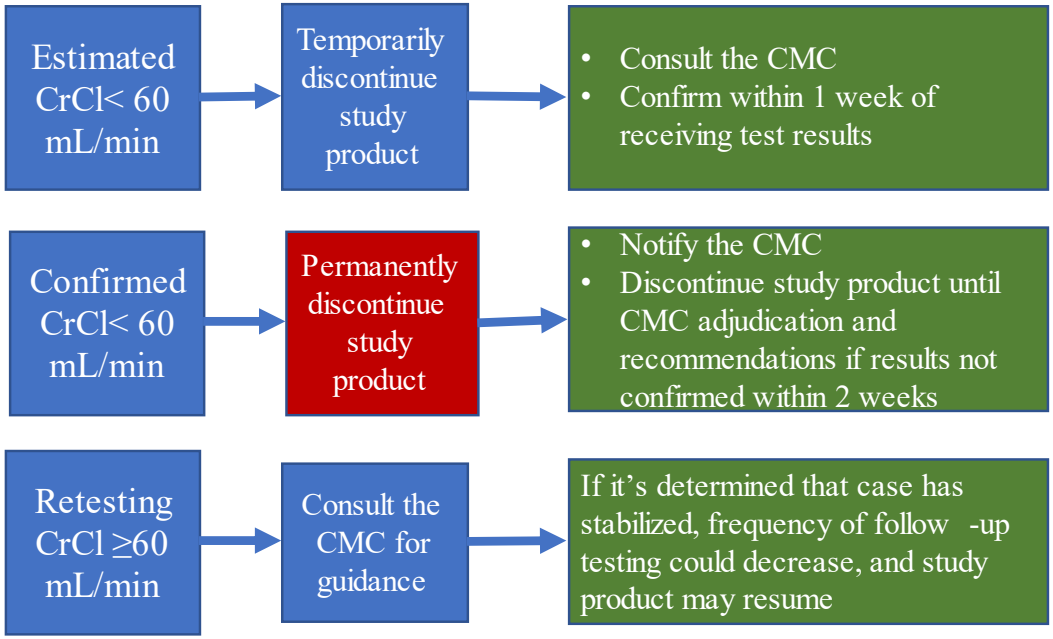
Guidance on Toxicity Management for Specified Toxicities
ALT Elevations
Injectable CAB (Step 4c)



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)

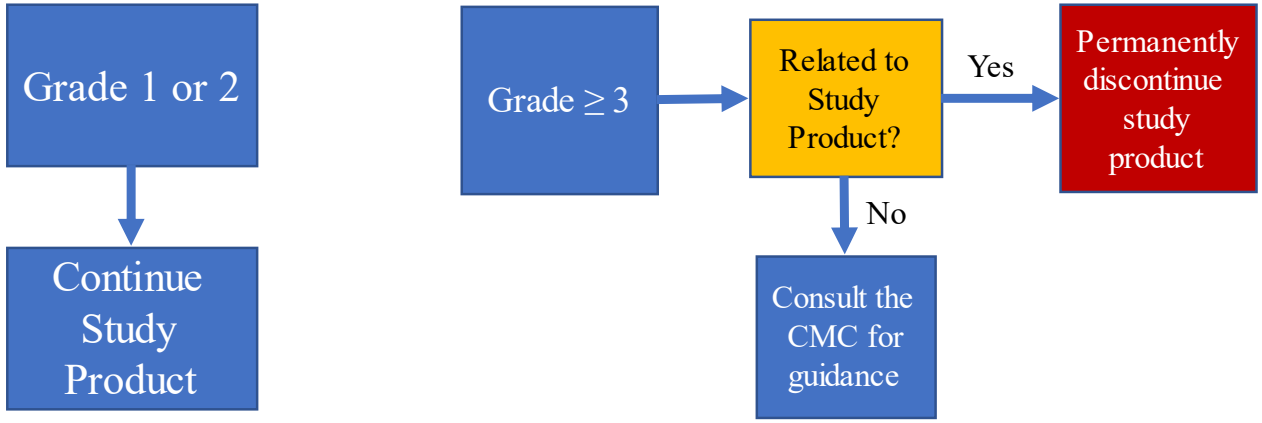


Adverse events related to creatinine clearance should be based on examination of BOTH the absolute creatinine clearance AND the change in creatinine clearance from baseline (Enrollment/ Visit 2.0).

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
- CMC should be notified of premature transition from Step 4c to Step 5 in extreme circumstances.

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 Version 4.0 of the Protocol. 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.

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 will have HCV antibody testing performed approximately annually (per Table 9 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 continue to 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.

Updates to Section 10.10: Social Impact Reporting

Sites will continue to document on the applicable CRF any social impact reported by the participant. 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.

1.2.11 Section 11: Lab Considerations

The following schedules will be followed for participants in Version 4.0:

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

Step 4a		
	Screening	**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

[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.

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

[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.

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			X
Urine GC/CT testing				X			X
Rectal swab GC/CT testing				X			X
Plasma Storage[4]	X	X	X	X	X	X	X

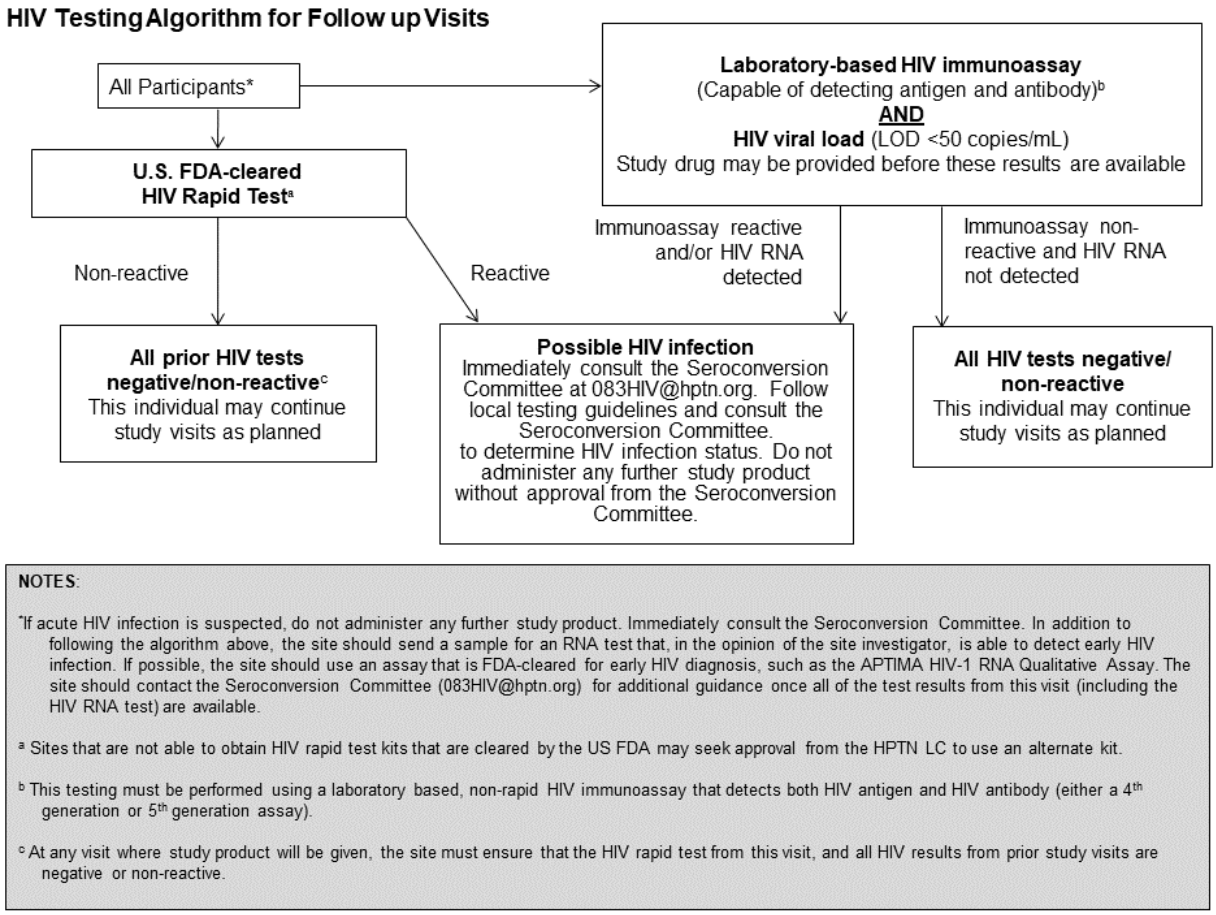
[1] Following the HIV algorithms described in SSP figure 11-4. HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates).
[2] Testing does not need to be repeated if infection was documented at a prior visit.
[3] If creatinine 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.

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] If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.
[6] If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.
[7] If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.
[8] See section 11.4 for plasma processing and storage instructions.
[9] See section 11.5 for DBS processing and storage instructions.

Figure 11.4 HIV Testing Algorithm for Follow up Visits:



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)

Note 1: The procedures listed for the HIV Confirmation Visit apply to participants who become infected during Steps 4 a-c and 5. 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 under Version 4.0 of the study.

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 Version 4.0 (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.

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 / +13	(14 , 41)
Step 4b - Day 0*	63	56	(53 , 59)	-14 / +13	(42 , 69)

* Once this visit is completed please refer to the visit windows table for Step 4b

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 5 - Day 0*	101	<8 weeks from last injection	(0 , 14)	+42	(0 , 42)

* Once this visit is completed please refer to the visit windows table for Step 5

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)

Open-label Extension (OLE): Step Transitions

At a participant's first visit under Version 4.0, the participant chooses whether to continue in the open-label extension (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 Protocol Version 4.0 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 Section 3 Subsection a 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 Section 3 Subsection b 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 Section 3 Subsection c 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.

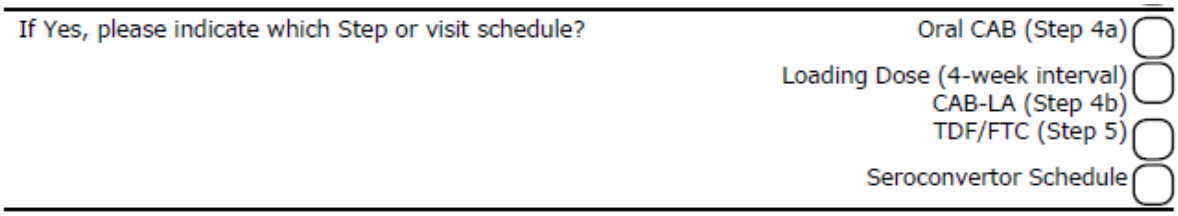
TDF/FTC (Step 5): Please refer to the Protocol APPENDIX V Section 3 Subsection d for details on the requirements for this step. If the participant's decision is to start Step 5, please complete the Product Choice form to record this decision. Once this form is saved the first visit for Step 5, V101 -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