FINAL

SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:

HPTN 083

A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV Uninfected Cisgender Men and Transgender Women who have Sex with Men, Version 5.0, April 28, 2022

DAIDS Document ID: 20725

THE AMENDED PROTOCOL IS IDENTIFIED AS:

Final Version 6.0
May 24, 2023

IND #122,744

Information/Instructions to the Study Sites from the Division of AIDS

The information contained in this protocol amendment impacts the HPTN 083 study and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs), as well as any other national regulatory entities, as required as soon as possible for review and approval. This amendment impacts the study informed consent form (ICF); all study sites must prepare updated informed consent forms and obtain IRB/EC approval of the updated forms. Approval also must be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Possible exception to above: There are sites in the US that no longer have participants on study. In these cases, sites should follow their IRB/EC guidelines regarding whether it is required to submit the protocol for approval.

Implementation of this amendment will begin upon receiving IRB/EC approvals and any other applicable regulatory entity approvals. Simultaneous to local implementation, all sites are required to submit an amendment registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center.

This Summary of Changes, Protocol Version 6.0, corresponding site-specific informed consent forms, and all associated IRB/EC and regulatory entity correspondence should be retained in each site's essential document files for HPTN 083.

The Division of AIDS Regulatory Affairs Branch will submit this amendment to the United States Food and Drug Administration (FDA) for inclusion in Investigational New Drug application (IND) #122,744.

Summary of Revisions and Rationale

The modifications included in this protocol amendment and the rationale are summarized below and detailed in the 'implementation' section that follows. The modifications are presented generally in order of their appearance in the study protocol. The major items included in this protocol amendment are as follows:

1. The Title Page, footer, and Protocol Signature Page are updated to reflect the new version number and date. The Table of Contents is updated to reflect the content of the new version. The protocol team roster is updated to remove and add team members, as well as update contact information for some members. There are no other significant changes to the main protocol.

2. Appendix V was added to Protocol Version 4.0 to provide instructions to offer all currently enrolled HPTN 083 participants the option to choose to continue or initiate CAB LA or choose to continue or initiate TDF/FTC as part of an open label extension. Appendix V was updated again under Version 5.0 to add another year of CAB LA. The purpose of this full amendment is to update Appendix V to extend the availability of CAB LA once again to participants **at non-US sites only**, to inform participants in the study at all sites that the study will end on March 31, 2024, and to inform participants in the study about two new risks related to CAB.

   A new Step 7 – which is identical to Step 6 - is added to provide CAB LA for participants at **non-US sites only** who complete Step 6 and who wish to continue CAB LA but are unable to access it outside of the study because it is not yet available.

   The Addendum to the Main Sample Informed Consent Form (ICF) is updated for this full amendment Version 6.0 in Appendix V, Part F.

3. Appendix VI is updated to include Step 7 and made to apply to any pandemic or disruption (not just COVID).

4. Other minor edits are made for clarity and to correct typographical errors.

Implementation of Modifications

Modifications of protocol text are listed below. Modifications are generally listed in order of appearance in the protocol. Where applicable, modified protocol text is shown using strikethrough for deletions and bold type for additions.

1. Title Page, footer, Protocol Signature Page, and Table of Contents

Updated to reflect Version 6.0, dated May 24, 2023.

2. Protocol Team Roster

Only the team members removed or added are depicted here:

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3. Part A, Section 1, Background

The majority of the HPTN 083 sites initiated the open-label extension (OLE) part of HPTN 083 under Appendix V of Version 4.0 **and Version 5.0 of the protocol**. ~~Some sites have not, due to regulatory reasons, and will initiate the procedures of Appendix V under Version 5.0.~~ **The study team is updating the protocol to Version 6.0 to extend the provision of CAB LA under a new Step 7 in the open label extension until 31 March 2024. Accordingly, updates are included in this same Appendix V.**

Since the time that Version 4.0 of the protocol was finalized in February 2021, the US FDA approved the use of CAB LA for PrEP in December 2021. At the time this protocol amendment (Version 6.0) was finalized, ViiV Healthcare, the pharmaceutical manufacturer of cabotegravir products, had also applied for regulatory approval for CAB LA for PrEP in several other countries where HPTN 083 is being conducted. As such, it is anticipated that local CAB LA will become available outside of the study over time in other countries where HPTN 083 is taking place.

Further data have been analyzed and presented or published since **this amendment** ~~Version 4.0~~, **including the following** ~~as follows (for ease of reference, refer also to the Summary of Changes document that accompanies this full protocol amendment to see the updates):~~

In the randomized blinded portion of the HPTN 083 study, among 4570 participants enrolled, the primary pre-specified analysis found 13 incident cases of HIV in the CAB arm, and 39 incident cases in the TDF/FTC arm. Two CAB arm and three TDF/FTC arm participants were also found to have HIV prior to administration of any study products (prevalent). An HIV incidence rate of 0.41 per 100 person years (PY) was observed for participants randomized to CAB in the primary results. Post-hoc testing revised these metrics slightly. In post-hoc testing initially 12, and in the final analysis 14 incident cases of HIV were in the CAB arm, and initially 39, and in the final analysis 41 incident cases in the TDF/FTC arm. In addition, four CAB arm and three TDF/FTC arm participants were found to have HIV prior to administration of any study products (prevalent). The CAB arm incidence rate in this revised post-hoc analysis was 0.44 per 100 PY; an HIV incidence rate of 1.29 per 100 PY was observed for participants randomized to TDF/FTC, demonstrating a consistent result of superior 66% (in both the primary and post-hoc analyses), reduction in incident HIV infections in participants randomized to CAB compared to TDF/FTC. Genotypic resistance testing has been completed for the original 12 incident HIV infections in the CAB arm; six were found to have integrase strand transfer inhibitor (INSTI) resistance-associated mutations (RAMs); in addition, one of the four prevalent CAB-group HIV infections was found to have such mutations. These mutations were Q148R or Q148K in combination with additional INSTI RAMs, N155H, or R263K; these mutations would be expected to confer variable levels of resistance to DTG and BIC. Additionally, detection of HIV infection at study sites was delayed in CAB participants in all four prevalent cases and in 7 of the 12 incident infections, by a median 62 days (range 28-72) for the prevalent cases and 79 days (range 35-185 days) for incident cases. In most of these cases, infection would have been detected at the first HIV-positive visit using a sensitive viral load assay. These observations prompted the updating of the HIV testing algorithm in Version 4.0 **of the protocol** to include a viral load assay with a limit of detection of 50 c/mL or lower as part of the testing performed at all study visits. Participants who are receiving CAB LA or are in the CAB LA tail period (e.g., 48 months since their last injection) with RNA (viral load) evidence of HIV infection should be initiated on fully suppressive ART as rapidly as possible to avoid emergence of INSTI resistance. The sample informed consent **in** ~~for~~Version 5.0 **wh**as ~~been~~ updated to include this information to assist participants in making a fully informed decision about the risks and benefits of each PrEP option.

~~In the randomized, blinded portion of the study, no safety signal for hypersensitivity or other concerns were identified; therefore, these observations in combination with recently presented data from the CAB LA/RPV LA treatment program which did not include the oral lead-in phase without safety or efficacy concerns have allowed relaxation of the requirement for an oral lead-in period in this next part of HPTN 083.~~ The oral lead-in **is optional for** ~~participants, but~~**participants but** may still be **required** ~~employed~~ at the discretion of local IRBs/ECs **or,** ~~-~~investigators of record ~~or participants.~~

Refer to ViiV Healthcare's Version 13 of their Investigator Brochure for cabotegravir, where new risks - hypersensitivity reaction and suicidal thoughts/attempts - are included. These new risks also appear in the sample informed consent in this amendment.

4. Part A, Section 2, Purpose and Implementation

The purpose of this amendment is two-fold: 1) To add Step 7 for participants outside of the US who have not yet transitioned to locally available CAB by the time this amendment is implemented at a site; and 2) To provide an official end date for all participants in the study, which is 31 March 2024. Study participation will end for all participants (including any still on study in the US) as of that date, no matter where they are in the study. As of that date, participants will have ~~been~~ to be transitioned to locally available CAB through an access program or other protocol if they so choose or to other local HIV prevention services. In the unforeseen event that a local access program or protocol is not available or available earlier than 31 March 2024, a memo will be issued from the study team to each non-US site describing next steps for participants impacted by that circumstance.

Priority must be given to transitioning participants to locally available CAB as soon as possible before the end date of the study (31 March 2024, or date specified in a memo from the study team).

~~To avoid confusion, sites will herein be divided into two categories – Category A and Category B – as described below:~~

~~**Category A Sites: Implemented OLE procedures under Version 4.0 (majority of the sites)**~~

~~The primary purpose of this updated Appendix V at Category A sites is to allow for continued access to CAB LA while participants transition to local CAB LA or other available clinical PrEP prevention services by adding up to an additional 48 weeks (Weeks 56 up to 96) of CAB LA as a new Step 6. Step 6 is the continuation of Step 4c, beyond Week 48.~~

~~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. Similar official notification from the HPTN LOC for the continued implementation of Appendix V under Version 5.0 will NOT be issued for this amendment. Sites in this category should implement Version 5.0 immediately upon obtaining IRB/EC/other regulatory entity approvals (and submit for but not wait for DAIDS Protocol Registration Office approval). Sites in this category are also responsible for ensuring that adequate study product supply is available for participants who will continue study product under Version 5.0.~~

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

~~The primary purpose of this updated 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.~~

~~For sites in Category B, the following is required for implementation: 1) all required IRB/EC/other regulatory entity approvals for Version 5.0 are in place; 2) the site receives notification from the DAIDS Protocol Registration Office that the site-specific informed consent addendum is approved and indicates successful completion of the Version 5.0 amendment protocol registration process; 3) confirmation that adequate **supply of study products are in place at the site;** and 4) the site has~~

~~confirmed that training of all active personnel for Version 5.0 has been completed.~~ **~~The HPTN Leadership and Operations Center (LOC) will issue an approval notice to begin implementation of Version 5.0 upon confirmation that all items outlined above are in place; a Category B site cannot implement Version 5.0 until this notice is issued.~~**

~~For both categories of sites, Appendix V under Version 5.0 of the protocol includes an updated Protocol Signature Page (in the main body of the protocol) and updated procedures including new Step 6 (Weeks 56 – 96). Two sample addendum consent forms are also included – one for Category A sites and one for Category B sites.~~

5. Part A, Section 3 a - f, Description of Steps 4a-c, 5, and 6 and 7

As part of this amendment, an updated informed consent is provided. Sites will discuss with participants their options for ongoing study participation as outlined in the Steps below **and in the consent form, which makes it clear that the study will end on 31 March 2024, except as noted above.** ~~Two addendums to the main informed consent form are included for continuation in the study, based on w~~**~~which category of site (A or B) and the status of each participant still in follow-up. In either case,~~** AAs has been the case, ~~a~~ site may opt to conduct informed consent discussions via telephone or telemedicine at the discretion of the IoR and in accordance with all relevant IRB/Ecs/other regulatory entities. If the consent discussion occurs off-site and the participant chooses to continue in the study, once the participant reports to the study site, product dispensation **and study procedures** can only occur after signature of the applicable addendum informed consent form. Contact the CMC for guidance if there are other consent-related scenarios not outlined here.

The following three paragraphs apply only to sites in Peru:

NOTE: Participants who permanently discontinued study products during the blinded portion of the study due to HIV infection, HBV infection, or for a study product-related AE that would deem the continuation or initiation of cabotegravir unsafe are NOT eligible to restart or begin cabotegravir. The CMC may be contacted for questions related to study product AE~~s~~ 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 have passed three years from the date of enrollment will not be permitted to make the choice of entering Step 5 (open-label TDF/FTC), per the original study design and informed consent; such participants will be referred to local standard of care for prevention services. These participants will still be consented **(if they can be located)** 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. Additionally, participants who are otherwise not eligible to join the OLE or who do not wish to participate in the OLE will also 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 **6**~~5~~.0 because they were ineligible to continue in the OLE, or did not wish to participate in the OLE, or were lost to follow up beyond six months of initial OLE implementation at their site, will not be allowed to **participate under** ~~be reconsented to~~ Version **6**~~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. Participants who do not participate in the OLE 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.~~

~~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.~~

NOTE: Participants ~~in the first 48 weeks of the OLE~~ who **are joining the OLE for the first time and who** have been on TDF/FTC throughout the study and choose to stay on it~~,~~ or **who** ~~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 or 7.**

Contact the CMC for guidance for other cases that do not fit the descriptions or criteria described above.

a. Step 4a: Oral Cabotegravir Lead-In (Optional) for Participants Originally Randomized to TDF/FTC (This Step is ONLY open to participants who are initiating CAB for the first time during HPTN 083, upon entry into the OLE~~) (This Step will not apply to the majority of sites by the time Version 6.0 is implemented)~~

This step is optional and a decision as to whether to opt in and take daily oral cabotegravir for approximately 4 weeks prior to receiving injections will be made by the participant in consultation with the IoR (or designee). There also may be cases where the local IRB/EC/other review bodies require the participant to participate in the oral lead-in prior to receiving injections; either way, each site's local informed consent form will reflect the situation at the site.

This step – for participants who opt to participate in it (or if the IoR or the IRBs/Ecs/other review bodies require it) – is only for those originally randomized to oral TDF/FTC who choose to initiate cabotegravir for the first time. If a participant participates in Step 4a~~, and~~ since it is deemed optional from the central management standpoint of the study, it will be at the discretion of the site Investigator of Record (or designee) as to what level of adherence to daily oral cabotegravir (if any) will be required by self-report prior to receiving injections. There are no pill counts in this Step (that is, no Pill Count eCRF will be used); however, a site may choose to perform pill counts for documentation in the participant chart. **This Step is not to be used for any participant who has ever received CAB LA injections in the past.**

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

See **Error! Reference source not found.** for the schedule of procedures and evaluations for Step 4a.

b. Step 4b: Loading Dose Visit for Injectable Cabotegravir for Participants Initiating ~~or Restarting~~ CAB Injections (This Step is ONLY open to participants who are initiating CAB-LA for the first time during HPTN 083, upon entry into the OLE, or after prolonged (>15 week) hiatus since last CAB-LA injection upon entry into the OLE.)

This is a one-visit step for participants who are initiating cabotegravir for the first time (and have either completed Step 4a or not). ~~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 injections (two injections, 4 weeks apart).~~ The first of these two injections is considered Step 4b. The participant will then transition to Step 4c four weeks later.

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

See **Error! Reference source not found.** for the schedule of procedures and evaluations for Step 4b.

c. Step 4c: Cabotegravir Injections (Beginning the OLE at this Step will not apply to a majority of participants by the time Version 6.0 is implemented)

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 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 on this Step who have had a long absence of visits (> 15 weeks since prior injection) will require a reload of cabotegravir injections (two injections, 4 weeks apart). The CMC should be contacted in this situation.

Participants who complete Week 48 of Step 4c **may continue to Step 6 and then Step 7 if they wish to continue CAB LA up until 3l March** ~~31,~~ 2024, at which time they will transition to local CAB LA via an access program or another protocol if they wish to continue CAB LA. Exceptions to this **~~were~~are described earlier in the protocol .** ~~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.~~

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

See **Error! Reference source not found.** for the schedule of procedures and evaluations for Step 4c.

d. Step 5: Participants Who Choose to Remain ~~O~~on or Switch t~~T~~o Oral TDF/FTC (This Step will not apply to a majority of participants by the time Version 6.0 is implemented)

This Step is for:

- Participants who were originally randomized to oral TDF/FTC and choose to remain on oral TDF/FTC. They will complete the procedures of this Step until three years from the time of enrollment.
- Participants who were originally randomized to CAB LA and choose to switch to TDF/FTC **before the Step 4c/Week 48 visit**. They will complete the procedures of this Step for 48 weeks **or until 31 March 2024 – whichever occurs** first~~for approximately one year from the last injection; that is~~. Step 5 Day 0 begins 8 weeks after that participant's last injection ~~and is 48 weeks in duration~~.
- Participants in Step 4b or Step 4c who decide they no longer wish to receive CAB or experience an AE that no longer allows them to receive CAB **before the Step 4c/Week 48 visit.** They will complete the procedures of this Step **for 48 weeks or until 31 March 2024, whichever occurs first.** ~~for approximately one year from the last injection; that is,~~ Step 5 Day 0 begins 8 weeks after that participant's last injection ~~and is 48 weeks in duration~~.
- ~~Participants who complete Step 4c and wish to continue receiving CAB LA and Version 5.0 is not approved yet and local CAB is not available. These participants will temporarily move to Step 5 until Version 5.0 approval is in place and then move to Step 6 while transitioning to local CAB.~~

If a participant completed Week 48 of Step 4c AND started Step 5 under Version **64**.0, and then does not want to or cannot continue CAB injections in Step 6 **or** when consenting to Version **65**.0, they will complete the remaining visits of Step 5 under Version **65**.0 **until they reach 48 weeks or until 31 March 2024, whichever occurs first.** ~~and then be terminated from the study and referred to local PrEP services.~~

If a participant completes Week 48 of Step 4c ~~under Version 5.0,~~ and ~~then~~ does not want to or cannot continue CAB injections in Step 6, they will NOT enter Step 5 and will instead be terminated from the study and referred to local PrEP services.

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

See **Error! Reference source not found.** for the schedule of procedures and evaluations for Step 5.

~~See~~ **Error! Reference source not found. remains in this amendment for historical purposes only and pertains mainly to sites in Peru. The purpose of the Figure is to depict a** ~~below for a~~ decision tree regarding the step sequences based on a participant's initial choice when first joining the OLE, which **will only apply to very few, if any, participants by the time this amendment is implemented at a site.** ~~applies mainly to participants at Category B sites; that is, participants who have not yet been offered the **initial choice** of CAB or TDF/FTC.~~ This decision tree applies only to a participant's initial choice when starting the OLE **for the first time** and therefore only includes Steps 4a, 4b, 4c and 5. ~~Note that Step 6 is only to be used as a continuation of Step 4c.~~

e. Step 6: ~~Participants Transitioning to Local CAB LA~~Participants requiring ongoing access to CAB-LA (Week 56 up to ~~to~~ Week 96 or 31 March 2024, whichever occurs first)

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 **or 31 March 2024, whichever occurs first).** ; ~~**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) within the protocol.

Participants on Step 6 who become infected with HIV will complete the HIV confirmation visit in **Error! Reference source not found.**, 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.~~

See **Error! Reference source not found.** for the schedule of procedures and evaluations for Step 6.

f. Step 7: Participants at non-US sites requiring ongoing access to CAB-LA ~~Participants Transitioning to Local CAB LA~~ (Weeks 104 and every 8 weeks thereafter, up to 31 March 2024)

Step 7 visits are identical to Step 6 visits and are considered an extension of Step 6. The same stipulations as outlined under "e" above apply to Step 7.

See Error! Reference source not found. **for the schedule of procedures and evaluations for Step 7.**

6. **Part A, Section 4, Open-Label Extension Objectives/Endpoints/Statistical Analysis**

   Only the first paragraph of this section has been modified and is depicted here:

   Note: The OLE objectives, endpoints, and statistical analysis refer to participants in the first 48 weeks of the OLE only**.** ~~and will not include~~ **Descriptive analysis of** ~~any~~ data collected on participants during Step**s** 6 **and 7**~~, Weeks 56 – 96~~ **may be conducted**. Step**s** 6 **and 7 are** ~~is~~ **are also** in place ~~only as a transitional mechanism~~ to **serve as a mechanism to transition** ~~allow time to access~~ **to** local CAB LA.

7. **Part B, Information in the Main Protocol that is Not Included in Appendix V**

   Only one bullet item is modified in this section and is depicted here:

   - Section 5.0 - Section 5.9; Section 5.11; Section 5.13; Section 5.13.1; Section 5.14.1; Section 5.18; Section 5.20. To reduce inconsistencies, specific listings of Steps 4, 5, ~~and~~ 6 **and 7** procedures and assessments are not repeated as was done for Steps 1, 2 and 3 in the main protocol, and appear in this Appendix in Tables only.

8. **Part C, Section 2, Participant Retention (from Section 3.5 of the main protocol with modifications):**

   Sites will continue to implement existing retention strategies; however, **for participants on CAB LA,** priority must be given to transitioning **them to** ~~participants to~~ local CAB LA ~~for participants who have completed Step 4c and wish to continue receiving it.~~

9. **Part C, Section 3, Participant Withdrawal (from Section 3.6 of the main protocol):**

   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/ECs terminate the study prior to its planned end date. Every reasonable effort will be made to complete a final evaluation of participants who terminate from the study prior to **31 March 2024**~~the final protocol-dictated study week,~~ and study staff will record the reason(s) for all withdrawals from the study in participants' study records.

10. **Part C, Section 4, Premature Termination Visits (from Section 3.6.1 of the main protocol, with modifications:**

    In general, for participants who withdraw consent from the study prematurely during a study visit, the requirements for that visit should be completed to the extent possible **except for provision of study product** and will be considered their final visit. When possible, a plan should be made to provide final laboratory results from site testing to the participant. For participants on oral TDF/FTC who inform the site in between visits that they wish to withdraw consent from the study, sites should

make every effort to have the participant return any unused study product. **Sites must** ~~**It is at a site's discretion to**~~ **terminate participants who have been lost to follow-up for 6 months or more.** ~~**who have been lost to follow-up for a minimum of 6 months or who have relocated to an area where there is no HPTN 083 site.**~~ **The timeline for the 6 months lost to follow-up 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).~~

11. Part C, Section 5, Study Product Considerations

Only the three modified parts of this section are depicted:

The CAB study product (oral and LA injectable) being tested in this study has been approved by the US FDA**, as well as regulatory agencies in other countries,** for the prevention of HIV-1 infection. Further information on the study product is available in the current prescribing information. **The DAIDS Regulatory Support Center issues updated** ~~An~~ Investigator's Brochure (IB**) typically on an annual basis** ~~, dated January 12, 2022, is provided by the DAIDS Regulatory Support Center (RSC)~~, for sites that require it for submission to IRBs/ECs/other regulatory entities.

Prescription

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 **or 7**). 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.

Injectable CAB LA 600 mg/3mL

The site pharmacist(s) must be proficient in the preparation of injectable study products using aseptic technique under a pharmacy biological safety cabinet (BSC) Class II or better. Local regulations and site institutional policies and procedures for use of personal protective equipment, such as gloves, gowns, masks, and safety glasses, must be followed.

The site pharmacist will follow the steps below for preparation of active injectable study product, CAB LA injectable suspension. In Step 4b**,** ~~and~~ 4c**, 6 and 7** of the study, one syringe containing 3 mL (600 mg) of CAB-LA must be prepared using aseptic technique under a pharmacy BSC/Isolator.

12. Part C, Section 8, Procedures for Participants Who Do Not Complete Step 4a (originally Step 1 from Section 5.12 of the main protocol, with modifications):

Only the one paragraph with changes in this section is depicted here:

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 **up** ~~and receive~~ **to** 48 weeks of open label TDF/FTC **or until 31 March 2024, whichever occurs first (excluding** ~~unless the reason is~~ HIV infection or an AE or condition where open label TDF/FTC is contraindicated**)**. Participants with HIV infection during Step 4b or 4c will be asked to be followed per **Error! Reference source not found.** below.

Participants who prematurely stop receiving injections for an AE or condition where open label TDF/FTC is contraindicated during Step 4b or 4c will be asked to continue follow-up **off study product** for **up to** 48 weeks **or until 31 March 2024, whichever occurs first**~~off study product~~.

13. Part C, Section 9, Procedures for Suspected or Confirmed HIV Infection (from Section 5.14.2 of the main protocol, with modifications:

Only the first and last sentence in this section have been modified and are depicted here:

Refer to the updated Appendix **IX**~~VIII~~ of the SSP for guidance regarding suspected or confirmed HIV infection during Steps 4, 5, ~~and~~ 6 **and 7**.

Participants with suspected or confirmed HIV infection during Step 6 **or Step 7** will be terminated from the study and referred to clinical care.

14. Part C, Section 10, Sexually Transmitted Infections (from Section 5.15 of the main protocol):

Only the third paragraph in this section has been modified and is depicted here:

Sites will determine if syphilis testing meets the criteria for incident infection and will mark accordingly on the appropriate eCRF. Refer to Appendix **IX**~~VIII~~ in the SSP for guidance regarding syphilis titer adjudication. **The CMC no longer needs to be consulted regarding syphilis testing results. As has been the case in the study to date, syphilis infections deemed incident by the site IoR should continue to be reported into the study database via the STI and AE eCRFs.**

15. Part C, Section 11, Hepatitis C

Participants on Step 4c and Step**s** 6 **and 7** will have HCV antibody testing performed approximately annually. Incident HCV infection during follow-up will not mandate discontinuation of study product absent other requirements per Part E, Toxicity Management.

16. Part C, Section 12, Interim Contacts and Visits and Missed Visits (from Section 5.17.1 of the main protocol, with modification)

Refer to SSP Appendix **IX** ~~VIII~~ for information.

17. Part C, Section 13, Pharmacokinetic Monitoring (from Section 5.19 of the main protocol, with modifications):

Plasma will be collected for pharmacokinetic assessments during Steps 4a, 4b and 4c. Results of this testing will not be provided to study sites or participants. Plasma will be collected during Step 6 **and 7** for confirmation of HIV infection; participants will be informed of their HIV testing results. Stored plasma may be used for future analyses.

18. Part C, Section 14, Adverse Event Reporting (from Section 6.0 of the main protocol, with modifications):

Only the three paragraphs with modifications in this section are depicted here:

For participants in Step 4a-c and Step 5: Study site staff will document in source documents all AEs. Grade 2 and higher clinical and laboratory AEs **(**including SAEs), and any AE (clinical or laboratory) that leads to a study product hold (temporary or permanent) will be captured on AE e-CRFs) reported by or observed in enrolled (defined as after randomization has occurred) study participants 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. **Using these reporting guidelines**, STIs will be dually reported on the AE e-CRF as well as the STI e-CRF.

For participants in Step 6 **and Step 7**: Study site staff will document in source documents all AEs. 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 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. **Using these reporting guidelines,** STIs will be dually reported on the AE e-CRF as well as the STI e-CRF.

Sites will continue "Social Impact" reporting for participants in Steps 4a-c and 5 only. "Social Impact" reporting will not take place for participants in Step 6 **and 7**. 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 could have problems being accepted by their families and/or communities. A social impact that is reported by the participant and judged by the IoR/designee to be serious or unexpected will be reported to the responsible site's IRBs at least annually, or according to their individual requirements. Social impacts will be collected and reported on CRFs during regular visits. If a participant reports a social impact, every effort will be made by study staff to provide appropriate care and counseling to the participant as necessary, and/or referral to appropriate resources for the safety of the participant. Each site will provide such care and counseling in accordance with standardized guidance in the SSP Manual. 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.

19. Part C, Section 16, Administrative Procedures (from Section 10.0 of the main protocol, with modifications):

Only the five paragraphs with modifications in this section are depicted here:

Full protocol amendments require submission of a protocol registration packet to the DAIDS Protocol Registration Office (PRO). Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. A copy of the Amendment Registration Notification should be retained in the site's regulatory files. **Sites are not required to wait for DAIDS PRO registration to implement Version 6.0 of the protocol.**

~~Category A sites are not required to wait for DAIDS PRO registration to implement Version 5.0.~~

~~For Category B sites only, site-specific ICF(s) WILL be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification from the DAIDS PRO that approves the site specific ICFs and indicates successful completion of the amendment protocol registration process. Receipt of DAIDS PRO approval and the HPTN LOC implementation memo is required prior to implementation of Version 5.0 of the protocol.~~

Implementation of this amendment will be directed by Appendix V of this protocol as well as SSP Manual Appendix **IX** ~~VIII~~. The SSP Manual includes links to the DAIDS SCORE Manual, Manual for Expedited Reporting of Adverse Events to DAIDS and the DAIDS Toxicity Tables.

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID~~or other contractors~~. Remote monitoring visits may be performed in place of, or in addition to onsite visits to ensure the safety of study participants and data integrity.[93] The site ~~will~~ **must** make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. **The Data Management Center will configure Medidata Remote Source Review (RSR) and make it available to all sites. Sites are encouraged to use the Data Management Center-provided Medidata RSR platform, but other potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, and direct access to Electronic Medical Record (EMR). Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Oversight (OCSO).** ~~Sites should consult with their DAIDS Office of Clinical Site Oversight Program Officer for acceptable platform options~~

20. Part D, Schedules of Procedures and Evaluations for the OLE and for Participants who are Not Continuing under the OLE

See Tables 7 – 12 for corresponding Schedules of Procedures and Evaluations for Steps 4 a-c, Step 5, Step 6 **and Step 7**, and for participants not continuing under the OLE, as well as Table 13 for participants who become infected with HIV during Steps 4-~~6~~ **7** or at a final visit if not continuing in the OLE. Refer to the Schedule of Forms (in SSP Appendix **IX** ~~VIII~~) as well as instructions on the forms for whom and when to administer forms.

21. Part D, Tables 7 – 12:

Footnote # 3 is updated in each table as follows:

The HIV testing algorithm is provided in **Error! Reference source not found.** below and Appendix **IX** ~~VIII~~ of the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.

22. Part D, Table 13: Schedule for Additional Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result (including HIV Confirmation Visit)

Only the modified part of this section is depicted:

Note 1: The procedures listed for the HIV Confirmation Visit apply to all participants who have a reactive or positive HIV test during Steps 4-~~6~~ **7**, or at their final study visit if not continuing

participation under the OLE. Participants who have a positive or reactive HIV test during Version ~~4.0~~ Steps 4b and 4c, Step 5, or at their final visit if not continuing in the OLE and have ever received an active CAB injection at any time during previous study conduct, will be followed according to Table 13 - Schedule for Additional Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result. Participants who have a positive or reactive HIV test during Step 4a, Step 5, or their final visit if not continuing in the OLE and have received only 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 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. Participants in Step 6 **and Step 7** who have a reactive or positive HIV test will undergo the procedures in the HIV Confirmation Visit only. Participants with confirmed HIV infection in Step 4a, ~~and~~ Step 6 **and Step 7** will be terminated from the study and referred to local care.

23. Part D, Table 14, STEP 7 Schedule of Procedures and Evaluations – Cabotegravir Injections – Week 104 +:

This is a new table for inclusion of Step 7.

Table 1: STEP 7 Schedule of Procedures and Evaluations – Cabotegravir Injections – Week 104 +

IMPORTANT NOTE: Numbered weeks are only depicted below to avoid confusion about what procedures to perform at the visits every 8 weeks. The intention is for all participants to end their participation in the study well before Week 144 occurs (and on or before 31 March 2024). The study team will provide a memo with instructions to sites regarding the official end date in the participating country.

Procedures	Week 104 (if needed)	Week 112 (if needed)	Week 120 (if needed)	Week 128 (if needed)	Week 136 (if needed)	Week 144[12] (if needed)
Informed consent[1]	[X]					
Locator Information	X	X	X	X	X	X
HIV counseling	X	X	X	X	X	X
Condoms and lubricant	X	X	X	X	X	X
Adherence counseling[11]	X	X	X	X	X	X
Directed history, concomitant medications, directed physical exam	X	X	X	X	X	X
Weight data entry to Medidata Rave			X			X
Blood collection	X	X	X	X	X	X
Urine collection for GC/CT testing[9]	X		X			X
Rectal swab collection for GC/CT testing[2, 9]	X		X			X

Procedures	Week 104 (if needed)	Week 112 (if needed)	Week 120 (if needed)	Week 128 (if needed)	Week 136 (if needed)	Week 144[12] (if needed)
Injection	X	X	X	X	X	X
ISR evaluation[10]	X	X	X	X	X	X
HIV testing[3]	X	X	X	X	X	X
HCV testing[4]						X
Chemistry testing[5] (creatinine only)						X
Liver function tests[6] (AST, ALT, total bilirubin, alkaline phosphatase)			X			X
Syphilis serologic testing[9]	X		X			X
Urine GC/CT testing[9]	X		X			X
Rectal swab GC/CT testing[9]	X		X			X
Plasma storage[7]	X	X	X	X	X	X

FOOTNOTES FOR TABLE 14

[1]IMPORTANT NOTE: A participant should be consented to Version 6.0 at their next visit, and they should continue to be followed under the appropriate Steps contained in Appendix V. The "[X]" listed here with a bracket is to signify that consenting to Version 6.0 may or may not occur at that visit but consent to Version 6.0 must occur before any procedures are undertaken for Step 7. If consent to Version 6.0 is obtained in a previous step before entering Step 7, do not repeat at entry to Step 7.

[2] If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

[3] The HIV testing algorithm is provided in Error! Reference source not found. **and Appendix IX of the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.**

[4] Testing does not need to be repeated if infection was documented at a prior visit. HCV Ab testing is required.

[5] The only required chemistry test is creatinine.

[6] Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.

[7] Blood collected for plasma storage must be collected prior to injection.

[9] Perform testing at Week 108 if not done within the last 6 months; perform testing at all other visits as noted.

[10] Only report on an eCRF an ISR that meets the definition of an SAE (all others should still be documented in source documents). An ISR typically begins 24-48 hours after an injection. The "X" marked in each visit box pertains to reporting an ISR if a participant experiences signs and symptoms of one (e.g., pain, redness, swelling, etc.) as a result of the injection that occurred at that visit at any point later that day and onward (as reported by the participant). A participant may follow-up with the site before their next visit to report that they have experienced an ISR or they may report it at their next visit. Sites need not actively solicit this information from participants, either in-person or remotely. Should ISR symptoms that meet the definition of an SAE be reported by the participant, it should be reported as an ISR for the visit at which that injection occurred. If an ISR that meets the definition of an SAE is reported, use the Injection Site Reaction eCRF. As a reminder, 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.

[11] Adherence counseling at whatever may be the final visit in Step 7 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 their last injection.

[12] In the unforeseen circumstance where additional visits need to occur after the Week 144 visit, the schedule will repeat itself as such: Week 152 is the same as Week 104; Week 160 is the same as Week 112, and so on. Additional instructions will be provided by memo from the team in this rare and unexpected circumstance.

24. Part E, Guidance on Toxicity Management for Specified Toxicities: ALT

Only the modified part of this section is depicted in the Grade 3 and higher row:

Injectable CAB (Steps 4b, 4c, ~~and~~ Step 6 **and Step 7**)**:**

25. Part E, Guidance on Toxicity Management for Specified Toxicities: Guidance for Injection Site Reactions (ISRs)

Only the one paragraph with modifications is depicted here:

During Step 6 **and 7**, 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.

~~26.~~ Part F~~1~~, Addendum to the Main Sample Informed Consent Form ~~for Category A Sites (Sites That Have Implemented Version 4.0)~~

HPTN 083

Original Study Title: A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men

Version ~~4.0~~**6.0**
~~**April 28, 2022**~~ **May 24, 2023**
DAIDS Document ID: 20725

Sponsored by: Division of AIDS, United States (US) National Institute of Allergy and Infectious Disease, US National Institutes of Health. Study products are provided by ViiV Healthcare and Gilead Sciences, Inc.

PRINCIPAL INVESTIGATOR: *[Insert Name]*

PHONE: [Insert Number]

You are currently taking part in the above-named research study. **We have some new information about CAB to tell you. We also have a new visit schedule for participants who are in the study outside of the US.**

~~You were offered to make a choice of being on CAB or TDF/FTC. As a reminder, you chose to do one of the following:~~

~~Stay on CAB if you were already on it~~

~~Stay on TDF/FTC if you were already on it~~

~~Switch to getting CAB if you were on TDF/FTC and it was safe for you to do so~~

~~Switch from CAB to TDF/FTC~~

~~Receive CAB if you were on the annual visit schedule and it was safe for you to start CAB again or to start it for the first time~~

~~If you are HIV infected and you had been coming to this clinic already for a visit every 3 months, completing the remainder of these visits for a total of a year.~~

~~If there was another status that is not listed here, we will discuss it with you.~~

~~Since the time you made your choice, the United States Food and Drug Administration approved the use of CAB for prevention of HIV in December 2021. That means that participants in this study in the United States will soon be able to get CAB shots outside of this study and at a local provider.~~

~~ViiV Healthcare, the drug company that makes cabotegravir, has also applied for approval of CAB for HIV prevention in each country where this study is taking place. That means that CAB shots will also become available in [*non-US sites to insert name of country here*] outside of this study~~.

Since it may take a long time for CAB to be available in some of the countries participating in this study, this HPTN 083 study will go on until 31 March 2024. It will end on that date no matter where you are in the study.

[US sites only to add this paragraph]: For participants in the US, your participation may end sooner than that date because you will have reached the last study visit of the Step you are in before then. We will remind you where you are in the study and tell you when your participation will end.

[Non-US sites only to add this paragraph]: ViiV Healthcare, the company that makes CAB, is also developing a research protocol for participants outside of the US to go into once it is approved. Once the ViiV protocol is approved, you will move to that study if you want to and are eligible to do so, even if it is before 31 March 2024. You may also want to transition to locally available CAB when it is available in your country instead of staying in this study up to 31 March 2024 or joining the ViiV research protocol. If CAB is not available in your local area or the ViiV research protocol is not available before or by 31 March 2024, a memo from the study team will be sent to this site with plans for what will happen next for you. Whatever you decide, we will tell you when your participation in this HPTN 083 study will end.

~~Since CAB shots are or will become available at local providers in these countries, we need to work on completing this study and moving you to local prevention or clinical care, which may include access to CAB.~~

~~Also, we previously told participants that they could change their mind and choose the other study medication (CAB or TDF/FTC) one time at any point during this part of the study. Now that CAB is or will soon be available outside of the study, we need to work on completing this study. Therefore, we will allow you to change your mind only during the first 6 months after you started on this part of the study. We will tell you if you are already beyond this point.~~

Your participation is voluntary

~~This consent form gives information about the process for moving you off the study and into local prevention or clinical care, which may include access to CAB. We also provide some new information about CAB in this consent form.~~

Once you understand the **new information in this consent form,** ~~process, and if you agree to take part~~, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep. Your continued participation in this study is voluntary. If you decide not to take part, you will not lose any of the benefits to which you are otherwise entitled. You may decide to not take part in the **rest of** ~~next part of~~ the study now or at any time without a loss of benefits to which you are otherwise entitled. [*Instruction to sites: Include in your site-specific consent form any update to the participant reimbursement or any other relevant site-specific updates*]

You may also participate in COVID-19 vaccine or treatment studies while on this part of the study.

Process for Transition Off of the Study

If you are getting CAB now in Step 4:

- You will continue to get CAB pills (if you opted to) and shots until you complete the schedule for Steps 4a (if you opted to), 4b, and Step 4c. You also may have already completed the schedule of CAB shots in Step 4c. If so, you may have moved to TDF/FTC in Step 5 until you can get CAB shots again either through this study or at a local provider. These Steps have been explained to you before. Let us know if you want to go over them again.

- Once your current schedule of CAB shots ends or if it has already ended (Week 48 of Step 4c), we will work closely with you to move you off the study and to a local provider where you can keep getting CAB shots. While we do this, you can continue to get CAB shots every 8 weeks through this study for up to another year in a new Step 6. However, our priority will be to move you to a local provider as soon as possible.

- We told you before that if you stop getting shots after Step 4b or before the end of Step 4c for any reason other than getting HIV infection that you will move to Step 5. If you complete Week 48 of Step 4c, you will not move to Step 5 – you will have the option to continue CAB injections in Step 6 or be terminated from the study and referred to local PrEP services.

- We told you before that if you are in Step 4b or Step 4c and get HIV infection that you will stop getting CAB shots, be followed every three months for a year, and be referred for HIV clinical care.

- Step 6 is different: If you stop getting CAB shots in Step 6 for any reason, your participation in the study will end and we will refer you to local HIV prevention or clinical services. This is because Step 6 is being added only to allow participants who can continue CAB shots to do so while we move them off the study and to a local provider.

- We will continue to test you for sexually transmitted infections during Step 6.

- Step 6 has fewer procedures than Step 4c. We will review this with you.

- If you complete Week 48 of Step 4c and no longer wish to or cannot continue CAB shots, your participation in the study will end and we will refer you to local HIV prevention or clinical services. You will not have the option to enter Step 5.

If you are on oral TDF/FTC in Step 5:

- We told you before that at the time you made your choice to continue in the study and you chose to continue or switch to TDF/FTC, that you will complete your follow-up visits under Step 5 until three years from the time of enrollment. If you were originally randomized to TDF/FTC and have reached three years from enrollment, you cannot continue TDF/FTC in this part of the study. Then your participation in the study will end and we will refer you to local HIV prevention services.

- ~~If you were getting CAB shots and chose to or had to switch to TDF/FTC before finishing Step 4c, you will be followed for one year since your last CAB injection. Once that happens, your participation in the study will end and we will refer you to local HIV prevention services.~~

- ~~If you were getting CAB shots, have already finished Week 48 of Step 4c, and then moved to Step 5 before the time of this consent, you have the option to finish Step 5 or resume CAB shots in Step 6 if you are healthy and able to do so.~~

- ~~We will explain the options you can choose and tell you when your time in the study will end.~~

[INSTRUCTIONS TO US SITES ONLY: REMOVE THE FIRST THREE PARAGRAPHS IN THIS SECTION ABOUT STEP 7 AND THE STEP 7 TABLE

A new step – ~~If you continue~~ CAB injections in Step 7~~6~~:

We have told you before about all the Steps of this study, including what will happen if you get infected with HIV. We can go over those with you again if you wish. We will remind you at this visit which Step you are in.

Step 7 is a new step added to the study for participants outside of the US so that participants can keep getting CAB shots if they want them until CAB is available in the country, until the ViiV protocol is ready at this site, or until 31 March 2024, whichever occurs first. If you want to move to the ViiV protocol or to locally available CAB shots in your country before 31 March 2024, your participation in this study will end.

Step 7 is exactly like Step 6, where you get CAB shots every 8 weeks as well as STI testing at certain weeks. The schedule is below. Once you move to the ViiV protocol or if CAB shots become available in this country, your participation in this study will end.

[INSTRUCTIONS TO NON-US SITES ONLY: REMOVE THIS PARAGRAPH]: Step 7 is not available to participants in the US. CAB for prevention of HIV has been approved in the US since December 2021 as well as other regulatory agencies in other countries. Your study team is working to move you to getting CAB shots or the best HIV prevention services available outside of this study. US participants will complete the study as covered under the last version of the protocol. We can go over that with you again if you wish.

~~This is a continuation of Step 4c and will last for up to an additional year of shots only if you wish to keep getting them (Weeks 56 up to 96) and CAB is not yet approved or available in your local area. The main reason for this Step is to allow time for you and the site staff to help you get shots at a local provider once CAB is approved for PrEP in your country or if approved, available in your area. You will no longer be in this study once you start getting shots at a local clinic, which may happen before Week 96. If you stop getting the shots while in this Step, you will be terminated from the study and told where you can go for other HIV prevention services.~~

REASONS YOU MAY HAVE TO STOP TAKING STUDY PRODUCT

There are some reasons you may have to stop taking study product:

- You experience a side effect and it is no longer safe for you to take it
- The doctor in charge of the study at this site determines that it is not safe for you to take it
- ~~You complete the full course of taking the study product during this part of the study~~
- You get HIV infection

~~We will review the Steps below with you and answer any questions you may have.~~

~~There may be special circumstances where your time in the study may be different (shorter or longer) from what is outlined in this consent form to ensure your safety. We will tell you if this happens and how long you will be followed.~~

[Note to Category A sites: Sites where all participants are beyond their six-month window to change product choice may delete Step 4a]

STEP 4a: Schedule of Procedures and Evaluations – Daily Oral Cabotegravir – OPTIONAL if you start CAB for the first time

Procedures	DAY 0	WEEK 4
Confirm where you live and how to contact you	X	X
Talk with you about HIV and ways to protect yourself from getting it	X	X
Offer you condoms and lubricant	X	X
Ask you questions about your opinions of taking pills and getting injections	X	
Ask you questions about your sexual behavior	X	
Talk with you about ways to help you take your pills	X	X
Ask you to count the total number of pills you took		X
Give you a brief physical exam, to include measuring your weight, blood pressure, pulse, and ask you if you have experienced any side effects from the study drugs, and ask you about any other medicines you are taking	X	X
Collect ~XX mL (about x teaspoons) of blood for HIV testing, syphilis testing (Day 0 only)*, to check your general health, the health of your liver and kidneys, and for storage	X	X
Perform a swab of your rectum and collect urine for gonorrhea and chlamydia testing*	X	
Give you study pills, explain how to take them and any side effects they may cause	X	

* Syphilis, gonorrhea, and chlamydia testing will be done at Day 0 if you have not had this testing in the past 6 months of the study, or at any visit if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections.

[Note to Category A sites: Sites where all participants are beyond their six-month window to change product choice may delete Step 4b]

STEP 4b: Schedule of Procedures and Evaluations – Loading Dose Cabotegravir Injection – If you are initiating or restarting CAB injections

Procedures	DAY 0
Confirm where you live and how to contact you	X
Talk with you about HIV and ways to protect yourself from getting it	X
Offer you condoms and lubricant	X
Ask you questions about your opinions of taking pills and getting injections	X
Ask you to answer questions about your sexual behavior	X
Discuss with you any challenges of attending your injection visits and getting shots	X
Give you a brief physical exam, to include measuring your weight, blood pressure, pulse, and ask you if you have experienced any side effects from the study drug, and ask you about any other medicines you are taking	X
Collect ~XX mL (about x teaspoons) of blood for HIV testing, syphilis testing*, to check your general health, the health of your liver and kidneys, and for storage	X
Perform a swab of your rectum and collect urine for gonorrhea and chlamydia testing*	X
Administer the first shot in your buttocks	X

* Syphilis, gonorrhea, and chlamydia testing will be done at Day 0 if you have not had this testing in the past 6 months of the study, or if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections.

STEP 4c: Schedule of Procedures and Evaluations – Cabotegravir Injections

Procedures	DAY 0	WEEK 8	WEEK 16	WEEK 24	WEEK 32	WEEK 40	WEEK 48
Confirm where you live and how to contact you	X	X	X	X	X	X	X
Talk with you about HIV and ways to protect yourself from getting it	X	X	X	X	X	X	X
Offer you condoms and lubricant	X	X	X	X	X	X	X
Ask you questions about how you feel about getting injections	X		X				X
Ask you to answer questions about your sexual behavior	X		X				X
Discuss with you any challenges of attending your injection visits and getting shots[1]	X	X	X	X	X	X	X
Give you a brief physical exam, to include measuring your weight, blood pressure, pulse. Ask you if you have experienced any side effects from the shots you received, and ask you about any other medicines you are taking	X	X	X	X	X	X	X
Collect ~XX mL (about x teaspoons) of blood for HIV testing (every visit); to check your general health and the health of your liver and kidneys (Week 0, 24 and 48 only); for storage (every visit); HCV testing (Week 48 only); and Syphilis testing (Day 0*, Weeks 24 and 48 only)	X	X	X	X	X	X	X
Perform a swab of your rectum and collect urine to test for gonorrhea and chlamydia*	X			X			X
Give you a shot in the buttocks	X	X	X	X	X	X	X

[1] We will talk with you about how important it is to stay on schedule for your PrEP appointments.

* Syphilis, gonorrhea, and chlamydia testing will be done at Day 0 if you have not had this testing in the past 6 months of the study, or at any visit if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections.

STEP 5: Schedule of Procedures and Evaluations – Open Label Daily Oral TDF/FTC – If you are staying on or switching to TDF/FTC

Procedures	Day 0	Weeks 12, 36 (60, 84, 108, 132, if required)	Week 24, 48 (72, 96, 120, 144, if required)
Confirm where you live and how to contact you	X	X	X
Talk with you about HIV and ways to protect yourself from getting it	X	X	X
Offer you condoms and lubricant	X	X	X
Ask you questions about getting the injections and taking the study pills	X		X
Ask you to answer questions about your sexual behavior	X		X
Discuss with you any challenges of taking a pill every day (except at your final visit)	X	X	X
Give you a brief physical exam, to include measuring your weight, blood pressure, pulse, and ask you about any other medicines you are taking	X	X	X
Collect ~XX mL (about x teaspoons) of blood for HIV testing (every visit); syphilis testing (Day 0*, then every 6 months only); to check your general health and the health of your liver and kidneys (Day 0, then every 6 months only); the amount of the study drug in your blood, and for storage (every visit)	X	X	X
Perform a swab of your rectum; collect urine for urinalysis and gonorrhea and chlamydia testing*	X		X
Give you your study pills, and explain how to take them, and any side effects they may cause	X	X	X

* Syphilis, gonorrhea, and chlamydia testing will be done at Day 0 if you have not had this testing in the past 6 months of the study, or at any visit if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections.

STEP 6: Schedule of Procedures and Evaluations – Cabotegravir Injections – Weeks 56 – 96

Procedures	WEEK 56	WEEK 64	WEEK 72	WEEK 80	WEEK 88	WEEK 96
Confirm where you live and how to contact you	X	X	X	X	X	X
Talk with you about HIV and ways to protect yourself from getting it	X	X	X	X	X	X
Offer you condoms and lubricant	X	X	X	X	X	X
Discuss with you any challenges of attending your injection visits and getting shots[1]	X	X	X	X	X	X
Give you a brief physical exam, to include measuring your weight, blood pressure, and pulse. Ask you if you have experienced any side effects from the shots you received, and ask you about any other medicines you are taking	X	X	X	X	X	X
Collect ~XX mL (about x teaspoons) of blood for HIV testing (every visit); to check your general health and the health of your liver and kidneys (Week 72 and 96 for liver; Week 96 only for kidneys); for storage (every visit); HCV testing (Week 96 only); and Syphilis testing (Week 56*, Weeks 72 and 96 only)	X	X	X	X	X	X
Perform a swab of your rectum and collect urine to test for gonorrhea and chlamydia*	X		X			X
Give you a shot in the buttocks	X	X	X	X	X	X

[1] We will talk with you about how important it is to stay on schedule for your PrEP appointments.

* Syphilis, gonorrhea, and chlamydia testing will be done at Weeks 72 and 96. It will also be done at Week 56 if you have not had this testing in the past 6 months before the Week 56 visit, or at any visit if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections.

STEP 7: Schedule of Procedures and Evaluations – Cabotegravir Injections every 8 weeks

Step 7 visits are exactly like Step 6. The first visit of Step 7 will be 8 weeks after your last visit in Step 6. Visits will then be every 8 weeks after that, if needed, until you move to getting CAB outside of this study if you wish to, move to the ViiV protocol if you wish to, or 31 March 2024, whichever occurs first. The procedures of the Step 7 visits are here:

Procedures	+8 weeks after last visit in Step 6	+ 8 weeks later, if needed	+ 8 weeks later if needed	+ 8 weeks later if needed	+ 8 weeks later if needed	+ 8 weeks later if needed
Confirm where you live and how to contact you	X	X	X	X	X	X
Talk with you about HIV and ways to protect yourself from getting it	X	X	X	X	X	X
Offer you condoms and lubricant	X	X	X	X	X	X
Discuss with you any challenges of attending your injection visits and getting shots[1]	X	X	X	X	X	X
Give you a brief physical exam, to include measuring your weight at up to two visits, blood pressure, and pulse. Ask you if you have experienced any side effects from the shots you received, and ask you about any other medicines you are taking	X	X	X	X	X	X
Collect ~XX mL (about x teaspoons) of blood for HIV testing (every visit). Blood will also be collected at some visits to check your general health and the health of your liver and kidneys. Certain weeks you will also give blood for Syphilis, and HCV. Because we do not know how long you will be in Step 7, we will let you know when each of these tests will occur. You will have blood stored at every visit.	X	X	X	X	X	X
Perform a swab of your rectum and collect urine to test for gonorrhea and chlamydia*.	X		X			X
Give you a shot in the buttocks	X	X	X	X	X	X

[1] We will talk with you about how important it is to stay on schedule for your PrEP appointments.
* Syphilis, gonorrhea, and chlamydia testing will be done at the third and fifth visit in Step 7. It will also be done at the first visit in Step 7 if you have not had this testing in the past 6 months, or at any visit if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections.

~~IF YOU LEAVE THE STUDY BEFORE YOUR FINAL VISIT:~~

~~If you join this part of the study and then leave the study before the last visit of the study schedule, we will ask you to complete a final study visit if you are available to do so. The final study visit will include the requirements for the visit at which it is confirmed you are leaving the study, and you will not receive CAB or TDF/FTC study product at this visit. Also, if you are on TDF/FTC and leave the study prior to your final visit, we will ask you to return any unused study product.~~

If you decide to ~~are~~ not continue ~~ing~~in the study at the time of this consent, we will ask you to do these procedures as your final visit:

Procedures	Day 0
Confirm where you live and how to contact you	X
Talk with you about HIV and ways to protect yourself from getting it	X
Offer you condoms and lubricant	X
Collect ~XX mL (about x teaspoons) of blood for HIV testing, syphilis testing*, and storage	X
Perform a swab of your rectum and collect urine for gonorrhea and chlamydia testing*	X

* Syphilis, gonorrhea, and chlamydia testing will be done at final visit (Day 0) if you have not had this testing in the past 6 months of the study, or if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections.

New Information about CAB

We went over the side effects of CAB and TDF/FTC with you when you joined the study. **We have included the side effects of CAB here again, including new information.** ~~We can go over these again if you want to.~~ **We already told you about these side effects:**

- **Headache**
- **Diarrhea**
- **Fatigue**
- **Muscle aches**
- **Nausea**
- **Fever**
- **Dizziness**
- **Runny nose**
- **Sore throat**
- **Upper respiratory tract infection**
- **Vomiting (being sick)**

- **Difficulty sleeping**
- **Abnormal dreams/nightmares**
- **Depression***
- **Flatulence (gas or wind)**
- **Increase in the level of enzymes in the muscles (creatine phosphokinase)**
- **With the CAB that you get as a shot, some people in other studies have said they had pain, irritation, skin redness, bumps, swelling, itching, bruising in the area where they got the shot, some of which lasted a weeks before resolving.**

The following are new side effects that are uncommon but were reported in other studies of CAB and include:

Allergic reaction, of which signs include:

- **skin rash**
- **a high temperature (*fever*)**
- **lack of energy (*fatigue*)**
- **raised and itchy rash (*hives*)**
- **swelling, sometimes of the face or mouth (*angioedema*), causing difficulty in breathing**
- **muscle or joint aches.**

***Suicidal thoughts/suicide attempts reported mainly in people who have had or have depression**

If you experience any of these or any other unusual symptoms, get emergency care immediately and notify your study team.

~~e also went over with you the results from the first part of this study where you did not know whether you were getting real CAB shots or real TDF/FTC.~~

~~CAB protected people in this study from getting HIV infection about 66% better than TDF/FTC. The reason for this is that TDF/FTC works best when taken daily. The participants in HPTN 083 for whom TDF/FTC did not work was mostly because it was not being taken as prescribed (that is, it was not being taken every day). Both PrEP regimens work very well to prevent a person from getting HIV if taken as prescribed. In the participants who got HIV while getting CAB, about half of them had some resistance to CAB and likely other drugs like CAB (called integrase inhibitors). Resistance means that the drug, and sometimes other drugs like it, would not work as part of a treatment regimen ("cocktail") to control the HIV infection. If you get infected with HIV while on CAB, you might need a regimen ("cocktail") that contains other drugs that are not like CAB to treat the HIV infection. Just over 15% of HIV infections that occurred in participants taking TDF/FTC had resistance to one or both drugs in TDF/FTC as well. Some HIV infections that occurred in participants taking TDF/FTC had resistance to one or both drugs in TDF/FTC as well. If you become HIV infected while taking PrEP it is important to make sure~~

~~you tell your doctor or provider which PrEP drug you have been taking so that a treatment regimen can be given to you that will be able to control the HIV to undetectable levels.~~

Problems or Questions

If you ever have any questions about the study, or if you have a research-related injury, you should contact [*insert name of the investigator or other study staff*] at [*insert telephone number and/or physical address*].

If you have questions about your rights as a research participant, you should contact [*insert name or title of person on the IRB or other organization appropriate for the site*] at [*insert physical address and telephone number*].

If you have questions about who to contact at the research site, you should contact [insert name of the investigator or community educator or CAB member] at [insert physical address and telephone number].

SIGNATURE PAGE

HPTN 083

A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men

Version ~~5.0~~ 6.0

~~April 28, 2022~~ May 24, 2024

[Insert signature blocks as required by the local IRB:] If you have read this addendum to the main consent form, or had it read and explained to you, and you understand the information, please initial the one line that applies to you to note that you want to continue in the study, or you no longer want to continue in the study, or you are not eligible to continue in the study. Then sign your name or make your mark below.

_____ I voluntarily agree to continue to take part in this portion of the study.

_____ I do **not** agree to take part in this portion of the study, but I do agree to the procedures listed in the table for not continuing in this part of the study.

_____ I do **not** agree to take part in this portion of the study, and I do **not** agree to the procedures listed in the table for not continuing in this part of the study.

_____ I understand I am **not** eligible to take part in this portion of the study, and I do agree to the procedures listed in the table for not continuing in this part of the study.

_____ I understand I am **not** eligible to take part in this portion of the study, and I do **not** agree to the procedures listed in the table for not continuing in this part of the study.

_____ _____

Participant Name (print) Participant Signature and Date

_____ _____

Study Staff Conducting Consent Discussion (print) Study Staff Signature and Date

Witness Name (print) (As appropriate)	Witness Signature and Date

27. Part F2, Addendum to The Main Sample Informed Consent Form for Category B Sites (Sites That Have Not Implemented Version 4.0)

This entire consent is deleted and not depicted here.

28. APPENDIX VI: OPERATIONAL GUIDANCE DURING ~~THE~~ COVID-19 OR OTHER PANDEMIC ACTIVITY

Only the paragraphs or sentences with modifications are included here:

The extent to which site operations may be disrupted by ~~the~~ **a global** ~~COVID-19~~ pandemic may vary across sites and over time. **All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff.** Site investigators should continue to follow current protocol specifications for communication with the Protocol Team and/or Clinical Management Committee and should contact the protocol team leadership with any questions or concerns regarding management of study participants.

NOTE: Steps 4b, 4c, ~~and~~ 6 and 7 injectable Cabotegravir cannot be provided at an off-site visit.

GUIDANCE FOR STEP 4a, STEPs 4b, 4c, 5, ~~and~~ 6~~,~~ and 7

For participants in Steps 4b, 4c, ~~and~~ 6 and 7: The same advice above would apply - that participants should protect themselves against HIV infection and exposure by all means available to them until they can return to study participation or to local CAB LA if it is available.

If a site can no longer provide injectable Cabotegravir in Steps 4b, 4c, ~~and~~ 6 and 7:

DOCUMENTATION

- Sites will continue to document deviations related to study visits and procedures impacted by **a** ~~the~~ global ~~COVID-19~~ pandemic just as would be done in the absence **a** ~~the~~ pandemic.