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 3.0, October 31, 2019

DAIDS Document ID: 20725

THE AMENDED PROTOCOL IS IDENTIFIED AS:

Final Version 5.0
April 28, 2022

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.

Most sites are operating under Version 4.0 of the protocol and have already started the Open Label Extension (OLE); however, there are a few sites that are still operating under Version 3.0 and therefore have not yet started the OLE. For operational ease of implementing this full amendment Version 5.0, sites have been divided into two categories: Category A Sites, which are sites currently implementing the OLE under Version 4.0, and Category B Sites, which are sites currently implementing Version 3.0. Category B sites will not implement Version 4.0 and will start the OLE with implementation of Version 5.0.

For Category A Sites (sites currently implementing Version 4.0): 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.

For Category B sites (sites currently implementing Version 3.0): These sites will not implement Version 4.0, and instead implement the initial OLE under this full amendment Version 5.0. These sites WILL have their IRB/EC approved site-specific consent forms 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; registration approval by the DAIDS PRO is required prior to implementation of Version 5.0 of the protocol at Category B sites.

Also required before implementation of Version 5.0 at Category B sites, the sites are required to confirm with the HPTN LOC that several tasks have been completed in preparation of consenting participants to the next part of the study before implementation. Once confirmed, the HPTN LOC will issue an OLE implementation memo to the site. **Once the site receives the implementation memo from the HPTN LOC, they will implement Version 5.0.**

This Summary of Changes, Protocol Version 5.0, 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. Revisions from Letters of Amendment and Clarification Memos to Version 4.0 have been incorporated into Version 5.0. The content of Clarification Memo #1, March 03, 2021; Letter of Amendment #1, April 25, 2021; and Letter of Amendment #3, December 01, 2021, are included. Letter of Amendment #2 was withdrawn and was not implemented by sites. Letter of Amendment #3 replaced Letter of Amendment #2 in full. The revisions from Version 4.0 Letters of Amendment and Clarification Memo are not included in this summary, as they are detailed in each of those protocol documents.

2. 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. There are no other significant changes to the main protocol.

3. 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. Since the time that Version 4.0 of the protocol was finalized, the US FDA approved CAB LA for PrEP in December 2021, and ViiV Healthcare has applied for approval in other countries where HPTN 083 is being conducted. In time, it is anticipated

that CAB LA will be available to participants outside of the study and participants will transition off study to local PrEP services that may include CAB injections.

This full amendment is an update to Appendix V to include new study data and information regarding US FDA approval, and to transition participants off study to local PrEP services. A new Step 6 is added to provide up to an additional year of access to CAB LA for participants who complete Step 4c Week 48 and wish to continue CAB LA but are unable to access it outside of the study because it is not yet approved in the country, or it is not yet available in the local area. Sites will prioritize participants' transition to local PrEP services as soon as feasible.

Additionally, as described above, sites are designated as Category A sites – those that already started the OLE under Version 4.0, and Category B sites – those that will start the OLE under Version 5.0, to distinguish implementation requirements and consent form utilization for this amendment.

The Addendum to the Main Sample Informed Consent Form is updated for this full amendment Version 5.0 in Appendix V, Part F, and now includes Consent F1 for use by Category A sites and Consent F2 for use by Category B sites.

References to Version 4.0 are updated to read Version 5.0 or OLE where applicable.

4. Appendix VI is updated to include Step 6.

5. 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 5.0, dated April 28, 2022.

2. APPENDIX V: PROCEDURES FOR ~~INITIAL OFFERING OF~~ THE OPEN LABEL EXTENSION OF CABOTEGRAVIR~~— THE NEXT PART OF HPTN 083~~

3. Background, Purpose and ~~Overview~~ Implementation, Description of Steps~~, Objectives/Endpoints~~

4. Part A, Section 1, Background

Only the modified part of this section is depicted:

~~On 14 May 2020, the NIAID Multinational DSMB overseeing HPTN 083 was in agreement that the primary question of whether long-acting cabotegravir prevents HIV infection was answered in the~~

~~affirmative and was highly statistically significant, and subsequently deemed superior. Because of these results, the DSMB recommended that the trial results be made available as soon as possible. Letter of Amendment (LoA) # 1, dated May 19, 2020, to Version 3.0, dated October 31, 2019, was issued to end the blinded portion of the study and is in effect at each participating site per local and national IRB/EC/other regulatory entity approvals. LoA # 1 specified immediate procedures as an interim approach until additional cabotegravir study product was available and included a Dear Participant Letter to this effect.~~

~~This full protocol amendment Version 4.0, dated February 10, 2021, is considered the next part of the study and is separate from the blinded, randomized part of the study. It includes an updated Protocol Signature Page (in the main body of the protocol), a new Appendix V, which expands on LoA # 1 in order to outline procedures for offering cabotegravir and following participants who choose to continue or initiate cabotegravir or remain on TDF/FTC, an addendum to the main informed consent form, and a new Appendix VI which provides operational guidance during the COVID-19 pandemic from Clarification Memo (CM) #2, dated April 2, 2020, and CM #4, dated February 5, 2021. The relevant procedures from LoA # 1 are included in Appendix V. Modifications under Version 3.0 of the protocol that are included in Clarification Memo (CM) # 3, dated May 4, 2020, and LoA # 2 and # 3, dated July 1, 2020, and July 23, 2020, respectively, pertain to the original randomized, blinded portion of the study, and have been incorporated into the main body of the protocol accordingly. No other substantive changes have been made to the main body of the protocol.~~ **The majority of the HPTN 083 sites initiated the open-label extension (OLE) part of HPTN 083 under Appendix V of Version 4.0. Some sites have not, due to regulatory reasons, and will initiate the procedures of Appendix V under Version 5.0.**

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 5.0) 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 Version 4.0 as follows (for ease of reference, refer 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, ~~F~~f**our 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 ~~0.38~~**0.44** per 100 PY; an HIV incidence rate of ~~1.22~~**1.29** per 100 PY was observed for participants randomized to TDF/FTC,

demonstrating a **consistent result of** superior 66% (**in both the** primary ~~analysis), 70% (~~**and** post-hoc ~~analysis)~~**analyses),** reduction in incident HIV infections in participants randomized to CAB compared to TDF/FTC. ~~Among the~~ **Genotypic resistance testing has been completed for the original** 12 incident HIV infections in the CAB arm~~, four~~**; 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 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 for Version ~~4.0~~ **5.0** has been updated to include this information to assist participants in making a fully informed decision about the risks and benefits of each PrEP option.

5. **Part A, Section 2, Purpose and ~~Overview~~ Implementation**

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 ~~provide instructions~~ **allow** for ~~when~~ **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 ~~supply of oral and injectable cabotegravir~~ **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 ~~083 participants. The~~ **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 continuation of implementation of** Appendix V~~provides guidance~~ **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 ~~choose to~~**will** continue ~~or initiate CAB~~ **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 ~~choose to remain on~~ 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.**

~~This Appendix includes procedures for new Steps of the study, referred to as Steps 4 (optional oral and long-acting cabotegravir) and 5 (oral TDF/FTC), the respective visit schedule for each participant group, updated toxicity management instructions, an updated sample informed consent form, and other relevant information from the original protocol that pertains to study procedures under this Appendix.~~

~~Implementation of this Appendix will go into effect at a site when~~**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) ~~an additional~~**confirmation that adequate supply of ~~cabotegravir for this purpose has been received~~study products are in place at the site;** and 4) the site has confirmed that training of all active personnel for Version ~~4.0~~**5.0** has been completed. **The HPTN Leadership and Operations Center (LOC) will issue an approval notice to begin implementation of Version ~~4.0~~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 a 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.

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

Sites will discuss with participants ~~what the~~**their** options are for ongoing study participation as outlined in the Steps below. ~~An addendum~~ **Two addendums** to the main informed consent form ~~is included in this Appendix and will document the participant's continued participation~~ **are included for continuation** in the study~~. A~~**, based on which category of site (A or B) and the status of each participant still in follow-up. In either case, a** site may opt to ~~have the discussion regarding this choice~~**conduct informed consent discussions** via telephone or telemedicine at the discretion of the IoR and **in accordance** with ~~approval from~~ all relevant IRB/ECs/other regulatory entities. If ~~this~~**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 can only occur after signature of the **applicable** addendum informed consent form. Contact the CMC for guidance if there are other **consent-related** scenarios ~~for a discussion about choice and obtaining informed consent that are~~ not outlined here.

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 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 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~~, as well as other participants who are otherwise not eligible to join the open-label extension (OLE) or who do not wish to participate in the OLE,~~ will still be consented ~~to Version 4.0~~ so that they may receive the new information about cabotegravir contained in the ~~Version 4.0~~**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 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 be reconsented to Version 5.0.** As outlined in the consent form, participants who **continue in the OLE but then** leave the study before their last scheduled study visit will be asked to complete a final visit based on the ~~Version 4.0~~**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 ~~Version 4.0~~**the OLE**.

~~All participants~~**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 ~~Version 4.0~~**the OLE** must be consented within six months of HPTN LOC notification to the site to begin **OLE** implementation ~~of Version 4.0~~. Participants will not be allowed to transition to the OLE beyond six months from date of HPTN LOC notification to implement ~~Version 4.0~~. 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 ~~Version 4.0~~**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 ~~Version 4.0~~ consent signature page.

NOTE: Participants in the first 48 weeks of the OLE who have been on TDF/FTC throughout the study and choose to stay on it, or participants who have been on CAB and choose to switch to TDF/FTC, will be permitted to change their mind once up to 6 months after making their choice at their initial OLE visit and switch to CAB. There will be no switches allowed during Step 6.

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

7. **Part A, Section 3a, Step 4a: Oral Cabotegravir Lead-In (Optional) for Participants Originally Randomized to TDF/FTC**

   Only the modified part of this section is depicted:

   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.**

8. **Part A, Section 3c, Step 4c: Cabotegravir Injections**

   Only the modified part of this section is depicted:

   Participants **who have had at least one injection** in Step **4b or Step** 4c ~~who no longer wish to~~ **who then choose not to or cannot** continue receiving cabotegravir injections before Week 48 **of Step 4** occurs will move to Step 5.

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

   If Version 5.0 approval is not in place by the time the next injection (Week 56) is scheduled AND local CAB LA is not available, these participants will move to Step 5~~. 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.~~ **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 lapse in the PrEP coverage for the duration of Step 5 will be considered on a case-by-case basis by the CMC.

9. **Part A, Section 3d, 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 will complete the procedures of this step for three years from the time of enrollment or for one year since their last injection of CAB, whichever is longer.~~

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 ~~cabotegravir who choose~~**CAB LA and choose to switch to TDF/FTC. They** will complete the procedures of this Step 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. They will complete the procedures of this Step 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 4.0, and then does not want to or cannot continue CAB injections in Step 6 when consenting to Version 5.0, they will complete the remaining visits of Step 5 under Version 5.0 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 Table 10 for the schedule of procedures and evaluations for Step 5.

~~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 choose 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 permitted 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).~~

See Figure 9 below for a decision tree regarding the step sequences based on a participant's **initial** choice~~.~~ **when first joining the OLE, which 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 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.

10. Part A, Section 3e, Step 6: Participants Transitioning to Local CAB LA (Week 56 to Week 96)

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

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

Participants on Step 6 who become infected with HIV will complete the HIV confirmation visit in Table 13, 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 Table 11 for the schedule of procedures and evaluations for Step 6.

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

Only the modified parts of this section are depicted:

~~Open-Label Extension Objectives/Endpoints/Statistical Analysis~~ **Note: The OLE objectives, endpoints, and statistical analysis refer to participants in the first 48 weeks of the OLE only and will not include any data collected on participants during Step 6, Weeks 56 – 96. Step 6 is in place only as a transitional mechanism to allow time to access local CAB LA.**

Objectives

#12: **Provide on-going access to CAB LA to eligible participants as a bridge to local CAB LA.**

Endpoints

#2: Grade 2 and higher clinical or laboratory adverse events (AEs). Grade ~~1~~ **2** and higher injection site reactions.

#12: **Number of participants transitioned to local CAB LA.**

Statistical Analysis

#12: **Describe number of participants who transitioned to local CAB LA.**

12. Part C, Section 2, Participant Retention

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

13. Part C, Section 5, Study Product Considerations

Only the modified parts of this section are depicted:

The CAB study product (oral and LA injectable) being tested in this study ~~is investigational and not yet~~ **has been** approved by the US FDA for the prevention of HIV-1 infection. Further information on the study product is available in the **current prescribing information. An** Investigator's Brochure (IB), ~~which will be~~ **dated January 12, 2022, is** provided by the DAIDS Regulatory Support Center (RSC)~~. As of January 2021, the CAB study product plus rilpivirine (two injections once per month) is approved by the US FDA,~~ for ~~the treatment of HIV-1 infection.~~ **sites that require it for submission to IRBs/ECs/other regulatory entities.**

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 ~~5) and~~ **6). 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 ~~and~~ **or original** TDF/FTC arm.

14. Part C, Section 6, Procedures for Steps 4, 5, and 6

Procedures and evaluations for Steps 4**,** 5, **and 6** are outlined in Tables 7 – ~~10~~ **11** and are not repeated here. ~~Table 11~~ **Table 12** details final procedures and evaluations for participants who receive the new study information but do not continue follow up under ~~Version 4.0~~**the OLE** because they do not want to or are ineligible to do so. The HIV testing algorithm for follow-up visits is shown in Figure 10.

15. Part C, Section 7, Visit Windows

Target windows for all visits are outlined in Appendix VIII of the SSP Manual. ~~It is not required to contact the CMC for out of target visit window injection visits provided~~

For injections that ~~they~~ are ~~a minimum of 6~~ **scheduled or intended to be 4** weeks ~~and a maximum of 15~~**apart: If the planned return visit is 12 or more** weeks ~~from~~**since** the ~~prior~~**last injection, a 4-week interval should be used for the next** injection~~, and for the Step 4c Day 0 injection, when it is a minimum of 3~~ **after returning, and then 8-week intervals resumed.**

For injections that are scheduled or intended to be 8 weeks ~~and a maximum of 11~~**apart: If the planned return visit is 16 or more** weeks ~~from the Step 4b Day 0~~ **since the last injection, a 4-**

week interval should be used for the next injection **after returning, and then 8-week intervals resumed**.

I**t is no longer required to contact the CMC** ~~for guidance in cases outside of these parameters~~ **regarding late injections.**

An injection visit or a study **product** dispensation visit may never be completed without preceding safety laboratory assessments being completed and all the assessments being resulted and protocol allowable.

16. Part C, Section 8, Procedures for Participants Who Do Not Complete Step 4a

Only the modified part of this section is depicted:

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 and 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 **during Step 4b or 4c** will be asked to be followed per ~~Table 12~~**Table 13** 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 for 48 weeks off study product.

17. Part C, Section 9, Procedures for Suspected or Confirmed HIV Infection

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

Under this amendment, 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 **or Version 4.0** of the protocol and are being followed on the HIV infection quarterly visit schedule **when Version 5.0 is implemented** will complete their visits under ~~this~~ Version ~~4.0~~**5.0** ~~amendment~~. For example, if they completed Weeks 0, 12, and 24 under Version 3.0 **or Version 4.0** and Version ~~4.0~~**5.0** is now approved at the site, the participant will complete Weeks 36 and 48 under **Appendix V of** Version ~~4.0~~**5.0** and **then** be terminated from the study.

Participants who are found to have a positive or reactive HIV test during consent to or participation in ~~Version 4.0~~**Steps 4b-c or Step 5** and have ever received an active CAB injection at any time during previous study conduct will be followed according to ~~Table 12~~ **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 ~~Version 4.0~~**Step 4a or Step 5** and have received only oral TDF/FTC and/or oral CAB but never an active CAB injection at any time during previous study conduct will be referred to local **clinical** care ~~for ART~~ if HIV infection is confirmed based on testing performed at study sites; there will be no further study follow-up for these participants once HIV infection is confirmed.

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

18. Part C, Section 11, Hepatitis C

Participants on Step 4c **and Step 6** will have HCV antibody testing performed approximately annually ~~(per Table 9)~~. Incident HCV infection during follow-up will not mandate discontinuation of study product absent other requirements per ~~Section~~ **Part** E ~~below~~, Toxicity Management.

19. Part C, Section 13, Pharmacokinetic Monitoring

Plasma ~~and dried blood spots (DBS)~~ 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 for confirmation of HIV infection; participants will be informed of their HIV testing results. Stored plasma may be used for future analyses.**

20. Part C, Section 14, Adverse Event Reporting

Only the modified parts of this section are depicted:

For participants in Step 4a-c and Step 5: Study site staff will document in source documents ~~and the appropriate e-CRF~~ **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. STIs will be dually reported on the AE e-CRF as well as the STI e-CRF.

For participants in Step 6: 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. STIs will be dually reported on the AE e-CRF as well as the STI e-CRF.

These reporting requirements are required for each study participant from enrollment until their follow-up in the study ends **or as otherwise stated above**. After this time, sites must report to DAIDS serious, unexpected, clinical suspected adverse drug reactions, as defined in Version 2.0 of the DAIDS EAE manual, if the study site becomes aware of the event on a passive basis, i.e., from publicly available information.

Information on ~~Grade 1 and higher~~ AEs will be included in reports to the US FDA, and other government and regulatory authorities as applicable. Site staff will report information regarding AEs to their IRB in accordance with all applicable regulations and local IRB requirements.

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**. 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. ~~In the event that~~ **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.

21. Part C, Section 15, Human Subjects Considerations

Only the modified part of this section is depicted:

Participants will document their provision of informed consent by signing their informed consent forms per site SOPs (refer also to the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual). Site-specific reimbursement amounts will be specified in the study informed consent forms. All participants will be offered a copy of their informed consent form. **If applicable, sites should follow all SOPs and institutional requirements for off-site consent discussions.**

22. Part C, Section 16, Administrative Procedures

Only the modified parts of this section are depicted:

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.**

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

For Category B sites only, ~~S~~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 ~~4.0~~ **5.0** of the protocol. ~~A copy of the Amendment Registration Notification should be retained in the site's regulatory files.~~

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 make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. ~~Potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, direct access to Electronic Medical Record (EMR), and Medidata Rave Imaging Solution. Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).~~ **Sites should consult with their DAIDS Office of Clinical Site Oversight Program Officer for acceptable platform options.**

23. Part D, Schedules of Procedures and Evaluations for ~~Steps 4 a-c and 5,~~ the OLE and for Participants who are Not Continuing under ~~Version 4.0~~ the OLE

See Tables 7 – ~~11~~ **12** for corresponding Schedules of Procedures and Evaluations for Steps 4 a-c, Step 5, **Step 6,** and **for** participants not continuing under ~~Version 4.0~~**the OLE**, as well as ~~Table 12~~**Table 13** for participants who become infected with HIV during ~~the time of this amendment.~~**Steps 4-6 or at a final visit if not continuing in the OLE**. Refer to the Schedule of Forms (in SSP ~~Section~~**Appendix** VIII) as well as instructions on the forms for whom and when to administer forms.

24. Part D, Table 9: STEP 4c Schedule of Procedures and Evaluations – Cabotegravir Injections – Day 0 - Week 48

Only the modified parts of this section are depicted:

Procedures*	DAY 0	WEEK 8	WEEK 16	WEEK 24	WEEK 32	WEEK 40	WEEK 48
Informed consent/ Product "Choice" discussion[1]	X						
Interviewer-administered Product Choice assessment[1]	X						
Adherence counseling[11]	X	X	X	X	X	X	**X**

FOOTNOTES FOR TABLE 9

*Participants in Step 4c who no longer wish to continue receiving cabotegravir injections before Week 48 occurs will move to Step 5. 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.

Participants who completed Step 4c under Version 4.0 and moved to Step 5 have the option under Version 5.0 to finish Step 5 or start Step 6 if CAB is not yet approved and locally available.

Participants who complete Step 4c under Version 5.0 and want to continue CAB will move from Step 4c to Step 6 if CAB is not yet approved and locally available.

Participants who complete Step 4c under Version 5.0 but do not want to or cannot continue CAB in Step 6 are not eligible to enter Step 5 and will be terminated from the study and referred to local PrEP services.

[1] For participants who transition from Step 4b **or Step 5** and completed these procedures in Step**s** 4a ~~or Step,~~ 4b, **or 5** do not repeat upon entry to Step 4c.

[11] Adherence counseling at Week 48 should be tailored to each participant. A participant who wants to continue CAB injections either in Step 6 or through local PrEP services should be reminded of the importance of receiving their next injection within 8 weeks of Week 48. A participant who does not want to continue CAB injections should be told where they can go locally for other PrEP services and reminded of the importance of doing so within 8 weeks of Week 48.

25. Part D, Table 10: STEP 5 Schedule of Procedures and Evaluations – Open Label Daily Oral TDF/FTC

Only the modified parts of this section are depicted:

Procedures*	Day 0	*Weeks 12, 36 (60, 84, 108, 132, if required)	*Week 24, 48 (72, 96, 120, 144, if required)
Informed consent/ "Choice" discussion[9]	X		
Interviewer-administered Product Choice assessment[9]	X		

FOOTNOTES FOR TABLE 10:

* Participants **originally randomized to TDF/FTC who choose to continue TDF/FTC** will be followed in this step for three years from the time of enrollment ~~or for one year since their last injection of CAB, whichever is longer~~. Contact the CMC for guidance for participants originally randomized to TDF/FTC who have been missing to follow-up and wish to continue TDF/FTC on Step 5.

Participants originally randomized to CAB who choose to initiate TDF/FTC, as well as participants who **no longer want to or cannot continue CAB injections before Week 48 of** ~~complete Step 4c, and participants who transition to Step 5 prematurely from~~ Step 4c **occurs** will be followed for ~~48 weeks~~ **approximately one year from their last injection**. The timeline for Day 0 begins 8 weeks after a 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.

Participants who completed Step 4c under Version 4.0 and moved to Step 5 have the option under Version 5.0 to finish Step 5 or start Step 6 if CAB is not yet approved and locally available.

Participants who complete Week 48 of Step 4c under Version 5.0 are not eligible to enter Step 5 and will either enter Step 6 to continue CAB or be terminated from the study and referred to local PrEP services.

[9] ~~This procedure is required only if the participant did not complete Step 4.~~ **For participants who transition from Step 4 and completed these procedures in Step 4, do not repeat upon entry to Step 5.**

26. Part D, Table 11: STEP 6 Schedule of Procedures and Evaluations – Cabotegravir Injections – Weeks 56 to 96

Procedures	WEEK 56	WEEK 64	WEEK 72	WEEK 80	WEEK 88	WEEK 96
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
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

Procedures	WEEK 56	WEEK 64	WEEK 72	WEEK 80	WEEK 88	WEEK 96
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 11

[1]IMPORTANT NOTE: A participant should be consented to Version 5.0 at their next visit, and they should continue to be followed under the appropriate Steps contained in Appendix V. The "[X]" listed at Week 56 with a bracket is to signify that consenting to Version 5.0 may or may not occur at that visit but consent to Version 5.0 must occur before any procedures are undertaken for Step 6. If consent to Version 5.0 is obtained in a previous step before entering Step 6, do not repeat at entry to Step 6.

[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 Figure 10 below and Appendix VIII 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 56 if not done within the last 6 months; perform testing at all other visits as noted.

[10] Only report on an eCRF during Weeks 56 – 96 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 be reported by the participant, it should be reported as an ISR for the visit at which that injection occurred. If an ISR 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 final visit of Step 6 should be tailored to each participant and include a reminder of the importance of receiving their next CAB injection or other PrEP through local services within 8 weeks of last injection. A participant's final visit in Step 6 may occur before Week 96 if CAB is approved and available locally, or if a participant does not want to or cannot continue receiving CAB injections.

27. Part D, Table ~~11~~ 12: Schedule of Procedures and Evaluations – For Participants Who Are Not Continuing Under ~~Version 4.0~~ the OLE

This table is renumbered. There are no changes to the procedures or evaluations.

28. Part D, Table ~~12~~ 13: Schedule for Additional Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result (including HIV Confirmatory Visit)

This table is renumbered. 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 ~~a-c and 5~~ **6**, or at their final study visit if not continuing

participation under ~~Version 4.0~~**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 ~~12~~**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 ~~Version 4.0~~**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 ~~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 083CMC@hptn.org. **Participants in Step 6 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** will be terminated from the study and referred to local care.

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

Only the modified part of this section is depicted:

Grade 3 and higher, Injectable CAB (Steps **4b,** 4c**, and Step 6**)

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

Only the modified part of this section is depicted:

During Step 6, only ISRs meeting the definition of an SAE or leading to discontinuation of study product will be entered into the database and such participants should be discontinued from the study. No need to contact the CMC in these cases. ISRs that are Grade 3 or higher that do not meet the above criteria do not need to be entered into the database.

31. Part F1, 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~~**5.0**
~~February 10, 2021~~**April 28, 2022**
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. ~~You were told about the results of the blinded part of the study after an independent committee determined that participants getting TDF/FTC pills had three times the number of HIV infections than participants getting long-acting cabotegravir shots (real CAB, also called CAB LA). As a reminder, both CAB and TDF/FTC were very good at preventing new HIV infections, and both were safe and well tolerated.~~

You ~~have been told which medication~~**were offered to make a choice of being on CAB or TDF/FTC. As a reminder,** you ~~are on. We are now able to offer you~~**chose to do one of** the following~~ choices if you wish to continue in the next part of the study~~:

- Stay on CAB if you ~~are~~ **were** already on it
- Stay on TDF/FTC if you ~~are~~ **were** already on it
- Switch to getting CAB if you ~~are~~ **were** on TDF/FTC and it ~~is~~ **was** safe for you to do so
- Switch from CAB to TDF/FTC
- Receive CAB if you ~~are~~ **were** on the annual visit schedule ~~now~~ and it ~~is deemed~~ **was** safe for you to start CAB again or to start it for the first time
- If you are HIV infected and you ~~have~~ **had** been coming to this clinic already for a visit every 3 months, ~~you will complete~~ **completing** the remainder of these visits ~~in this next part~~ **for a total** of ~~the study~~ **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 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 ~~next part of this~~ **process for moving you off the** study ~~that will be discussed with you~~ **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 ~~next part~~ **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 ~~research~~ **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 next part of the study now or at any time without a loss of benefits to which you are otherwise entitled. ~~We will also review the information in the main consent form that you already signed again with you, if you would like to do so, and will review with you any changes as related to this next part of the study~~ [*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.

~~**New Steps of the Study**~~

~~If you decide to take part in the next part of the study, there are 4 new steps, and you will come in for visits similar to what you have already been doing throughout the study based on your choice of study medication.~~

~~If you are on oral TDF/FTC and decide to continue it, and then you change your mind and want to switch to CAB, you may do so at any point **but only once** during the rest of your time in the study. If~~

~~you are on CAB and choose to switch to TDF/FTC, and you change your mind and want to switch back to CAB, you may do so at any point **but only once** during the rest of your time in the study,~~

~~IF YOU CHOOSE TO START CAB FOR THE FIRST TIME:~~

~~Step 4a: You will have the **option** of taking CAB pills for 30 days before starting to get shots of CAB. During the blinded part of the study, you may remember that you had to take pills before getting shots. This was because we did not have enough information then about CAB to know if it was safe to start getting shots right away. Based on what we learned in the blinded part of the study, we now know that it is safe. But you may feel more comfortable taking 30 days of CAB pills first to be sure. We will talk with you about this and answer any questions that you have. [Note to sites: If your IRB/EC requires this step, or if the IoR requires this step, then update this language to make it non-optional].~~

~~If you choose to take CAB pills before starting injections and for any reason do not move to Step 4b and 4c, your participation in the study will end and we will refer you to local HIV prevention services.~~

~~Step 4b: This is a one-time visit where you will get your first CAB shot.~~

~~Step 4c: These are visits where you will continue to come to the clinic for approximately 1 year to receive CAB shots. The next shot you will get after the one you received in Step 4b will be 4 weeks later, followed by shots every 8 weeks.~~

~~Step 5: If you complete the one year of CAB shots, or you decide that you no longer want to receive CAB shots after having received at least one, you will be offered TDF/FTC pills for one year. If you switch to TDF/FTC, you will come to the clinic for visits every 3 months.~~

~~IF YOU CHOOSE TO CONTINUE ON CAB:~~

~~Step 4b: If you have been on real CAB but have not been to the clinic in over 15 weeks since your last injection, this is a one-time visit where you will get a CAB shot to get you back on track with getting shots.~~

~~Step 4c: These are visits where you will continue to come to the clinic for approximately 1 year to get CAB shots every 8 weeks.~~

~~Step 5: If you complete the one year of CAB shots, or you decide that you no longer want to receive CAB shots after having gotten at least one shot, you will be offered to take TDF/FTC pills for one year. You will come to the clinic for these visits every 3 months.~~

~~IF YOU CHOOSE TO STAY ON TDF/FTC OR START TDF/FTC:~~

~~Step 5: If you have been getting TDF/FTC pills and you choose to continue, or if you have been on CAB and choose to start TDF/FTC, you will come to the clinic for visits every 3 months for 3 years from the time that you enrolled in the study, or for one year since your last injection of CAB, whichever is longer.~~

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.

~~IF YOU PREMATURELY STOP GETTING INJECTIONS~~

If you continue CAB injections in Step 6:

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:

- ~~As explained above, y~~ **Y**ou experience a side effect and it is no longer safe for you to take it
- The ~~investigator of record~~ **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~~, which is explained further below~~

Steps and Procedures

~~No matter which new step you start in, w~~ **W**e will review the ~~information in this consent form~~ **Steps below** with you and answer any questions you may have. ~~We will discuss which study product you would like to choose and ask you questions about your decision. The new steps also include the procedures listed at each visit marked with an X in Steps 4a, 4b, 4c, and 5 below.~~

There may be special circumstances where your time in ~~this part of~~ 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 ~~choose to~~ 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	

* ~~If you have had s~~Syphilis, gonorrhea, and chlamydia testing ~~within 6 months of joining this part of the study, this testing~~ will ~~not~~ be done at Day 0 ~~unless~~ **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

* ~~If you have had s~~**S**yphilis, gonorrhea, and chlamydia testing ~~within 6 months of joining this part of the study, this testing~~ will ~~not~~ be done at Day 0 ~~unless~~ **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 4c: Schedule of Procedures and Evaluations – Cabotegravir Injections ~~– if you choose to continue CAB 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.

* ~~If you have had s~~Syphilis, gonorrhea, and chlamydia testing ~~within 6 months of joining this part of the study, this testing~~ will ~~not~~ be done at Day 0 ~~unless~~ **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 ~~choose to stay~~ are staying on or ~~switch~~ switching to TDF/FTC~~, or after you complete Step 4c~~

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

* ~~If you have had s~~ Syphilis, gonorrhea, and chlamydia testing ~~within 6 months of joining this part of the study, this testing~~ will ~~not~~ be done at Day 0 ~~unless~~ **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.

~~**Not continuing in this part of the study: Schedule of Procedures and Evaluations – If you decide you do not want to participate in this part of the study, or you have reached 3 years from your enrollment date and do not want to start CAB, or you are otherwise not eligible to participate in this part of the study**~~ **If you are not continuing 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

* ~~If you have had s~~ Syphilis, gonorrhea, and chlamydia testing ~~within 6 months of joining this part of the study, this testing~~ will ~~not~~ be done at **final visit (**Day 0**)** ~~unless~~ **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

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.

New Information about CAB

We went over the side effects of CAB and TDF/FTC with you when you joined the study. We can go over these again ~~in the main consent form~~ if you want~~ We do have some new information about CAB that we will share with you in order~~ to~~ help you make your choice about whether to continue on CAB or start CAB for the first time~~.

We 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 ~~70~~ **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.

~~In January 2021, CAB was approved by the US Food and Drug Administration (FDA) along with another drug called rilpivirine, for the **treatment** of HIV in adults. CAB for the **prevention** of HIV, which is what are studying in HPTN 083, has not yet been approved by the US FDA and so it is still called an investigational drug for this purpose.~~

~~**If you become infected with HIV during this part of the study**~~

~~If you get HIV during Step 4a, you will stop taking the CAB pills, and you will be referred for local care and treatment of HIV and will be discontinued from the study. If you get HIV during Step 4b or 4c (while you are getting shots), you will stop getting any further shots and we will ask you to come back for a visit every 3 months for about a year. If you get HIV during Step 5 of the study, you will stop taking the TDF/FTC pills and will be referred for local care and treatment of HIV. If you get HIV during Step 5 and you have ever had a CAB injection at any time during past study visits, we will ask you to~~

~~come back for a visit every 3 months for about a year; if you did not receive any CAB injections during past study visits, you will be discontinued from the study.~~

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 ~~4.0~~ 5.0

~~February 10, 2021~~April 28, 2022

[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

32. Part F2, Addendum to The Main Sample Informed Consent Form for Category B Sites (Sites That Have Not 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~~**5.0**
~~February 10, 2021~~**April 28, 2022**
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. You were told about the results of the blinded part of the study after an independent committee determined that participants getting TDF/FTC pills had three times the number of HIV infections than participants getting long-acting cabotegravir shots (real CAB, also called CAB LA). As a reminder, both CAB and TDF/FTC were very good at preventing new HIV infections, and both were safe and well tolerated.

Since that time, the United States Food and Drug Administration approved the use of CAB LA shots for PrEP in December 2021. ViiV Healthcare, the drug company that makes cabotegravir, has asked for approval from all of the other countries where the HPTN 083 study is being done. That means that CAB LA shots will become available in your country outside of this study.

You have been told which medication you are on. We are now able to offer you the following choices if you wish to continue in the next part of the study:

- Stay on CAB if you are already on it
- Stay on TDF/FTC if you are already on it **for up to three years from the time of enrollment**
- Switch to getting CAB if you are on TDF/FTC and it is safe for you to do so
- Switch from CAB to TDF/FTC
- Receive CAB if you are on the annual visit schedule now and it is deemed safe for you to start CAB again or to start it for the first time

- If you are HIV infected and you have been coming to this clinic already for a visit every 3 months you will complete the remainder of these visits in this next part of the study.

- **If there is a scenario that is not described here, we will discuss it with you.**

Once you make your choice, you can change your mind once during the first 6 months after you start this part of the study. For example, if you are on TDF/FTC and you are within 3 years from the time of enrollment, you can change your mind and switch to CAB. If you are on CAB and choose to switch to TDF/FTC, then you change your mind and want to switch back to CAB, you may do so only once during the first 6 months after you start this part of the study.

We will tell you how long we will follow you in this part of the study, based on the choice you make. We are doing this part of the study in order to learn more about why people in the study choose CAB or TDF/FTC. For participants who choose CAB, we want to learn more about how it works to prevent getting HIV.

Your participation is voluntary

This consent form gives information about the next part of this study that will be discussed with you. Once you understand the next part, 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 research 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 next part of the study now or at any time without a loss of benefits to which you are otherwise entitled. We will also review the information in the main consent form that you already signed again with you, if you would like to do so, and will review with you any changes as related to this next part of the study [*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.

New Steps of the Study

If you decide to take part in the next part of the study, there are ~~4~~ **5** new steps, and you will come in for visits similar to what you have already been doing throughout the study based on your choice of study medication.

~~If you are on oral TDF/FTC and decide to continue it, and then you change your mind and want to switch to CAB, you may do so at any point **but only once** during the rest of your time in the study. If you are on CAB and choose to switch to TDF/FTC, and you change your mind and want to switch back to CAB, you may do so at any point **but only once** during the rest of your time in the study.~~

IF YOU CHOOSE TO START CAB FOR THE FIRST TIME:

Step 4a: You will have the **option** of taking CAB pills for 30 days before starting to get shots of CAB. During the blinded part of the study, you may remember that you had to take pills before getting shots. This was because we did not have enough information then about CAB to know if it was safe to start getting shots right away. Based on what we learned in the blinded part of the study, we now know that

it is safe. But you may feel more comfortable taking 30 days of CAB pills first to be sure. We will talk with you about this and answer any questions that you have. **If you ever had a CAB shot during the blinded part of the study, you cannot restart CAB pills in Step 4a during this part of the study.** [Note to sites: If your IRB/EC requires this step, or if the IoR requires this step, then update this language to make it non-optional].

If you choose to take CAB pills before starting injections and for any reason do not move to Step 4b and 4c, your participation in the study will end and we will refer you to local HIV prevention services.

Step 4b: This is a one-time visit where you will get your first CAB shot.

~~Step 4c: These are visits where you will continue to come to the clinic for approximately 1 year to receive CAB shots. The next shot you will get after the one you received in Step 4b will be 4 weeks later, followed by shots every 8 weeks.~~

~~Step 5: If you complete the one year of CAB shots, or you decide that you no longer want to receive CAB shots after having received at least one, you will be offered TDF/FTC pills for one year. If you switch to TDF/FTC, you will come to the clinic for visits every 3 months.~~

IF YOU CHOOSE TO CONTINUE ON CAB:

Step 4b: If you have been on real CAB but have not been to the clinic in over 15 weeks since your last injection, this is a one-time visit where you will get a CAB shot to get you back on track with getting shots.

Step 4c: These are visits where you will continue to come to the clinic for approximately 1 year to get CAB shots every 8 weeks. The next shot you will get after the one you received in Step 4b will be 4 weeks later, followed by shots every 8 weeks.

Step 5: If you ~~complete the one year of CAB shots, or you decide that you no longer want to receive CAB~~ **stop getting** shots ~~after having gotten at least one shot~~ **before the end of Step 4c**, you will be offered to take TDF/FTC pills for one year **in Step 5. If you complete the one year of CAB shots in Step 4c and don't want to continue shots in Step 6, you will not start Step 5 and will instead be referred to local PrEP services and terminated from the study.**

Step 6: This is a continuation of Step 4c and will last for up to an additional year of shots (Weeks 56 up to 96) only if you wish to keep getting them 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 staff at the site 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.

IF YOU CHOOSE TO STAY ON TDF/FTC OR START TDF/FTC:

Step 5: If you have been getting TDF/FTC pills and you choose to continue, or if you have been on CAB and choose to start TDF/FTC, you will come to the clinic for visits every 3 months for 3 years from the

time that you enrolled in the study, or for one year since your last injection of CAB, whichever is longer. **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.** We will tell you when your time in the study will end.

IF YOU PREMATURELY STOP GETTING INJECTIONS

If you choose to continue or start receiving CAB ~~injections~~ **shots** and have to stop getting them because of a side effect or if you choose to stop getting them **during Steps 4b or 4c**, we will ask you to move to Step 5 of the study and receive 48 weeks of oral TDF/FTC. You may also experience a side effect that makes taking oral TDF/FTC not safe; if this is the case, you will be asked to move to Step 5 of the study but not receive TDF/FTC so that we can make sure you are healthy. **If you stop getting shots in Step 6 for any reason, you will be terminated from the study.**

REASONS YOU MAY HAVE TO STOP TAKING STUDY PRODUCT

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

- As explained above, you experience a side effect and it is no longer safe for you to take it
- The ~~investigator of record~~ **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, which is explained further below

Steps and Procedures

No matter which new step you start in, we will review the information in this consent form with you and answer any questions you may have. We will discuss which study product you would like to choose and ask you questions about your decision. The new steps also include the procedures listed at each visit marked with an X in Steps 4a, 4b, 4c, 5, **and 6** below.

There may be special circumstances where your time in this part of 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.

STEP 4a: Schedule of Procedures and Evaluations – Daily Oral Cabotegravir – OPTIONAL if you choose to 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	

* ~~If you have had s~~ Syphilis, gonorrhea, and chlamydia testing ~~within 6 months of joining this part of the study, this testing~~ will ~~not~~ be done at Day 0 ~~unless~~ **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 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

* ~~If you have had s~~ Syphilis, gonorrhea, and chlamydia testing ~~within 6 months of joining this part of the study, this testing~~ will ~~not~~ be done at Day 0 ~~unless~~ **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 4c: Schedule of Procedures and Evaluations – Cabotegravir Injections - if you choose to continue CAB 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.

* ~~If you have had s~~ **S**yphilis, gonorrhea, and chlamydia testing ~~within 6 months of joining this part of the study, this testing~~ will ~~not~~ be done at Day 0 ~~unless~~ **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 choose to stay on or switch to TDF/FTC, or after you complete Step 4c

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

* ~~If you have had s~~ Syphilis, gonorrhea, and chlamydia testing ~~within 6 months of joining this part of the study, this testing~~ will ~~not~~ be done at Day 0 ~~unless~~ **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.

~~**Not continuing in this part of the study: Schedule of Procedures and Evaluations – If you decide you do not want to participate in this part of the study, or you have reached 3 years from your enrollment date and do not want to start CAB, or you are otherwise not eligible to participate in this part of the study**~~ **If you are not continuing 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

* ~~If you have had s~~ Syphilis, gonorrhea, and chlamydia testing ~~within 6 months of joining this part of the study, this testing~~ will ~~not~~ be done at **final visit (**Day 0**)** ~~unless~~ **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.

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.

Other New Information about CAB

We went over the side effects of CAB and TDF/FTC with you when you joined the study. We can go over these again in the main consent form if you want. We do have some new information about CAB that we will share with you to help you make your choice about whether to continue CAB or start CAB for the first time.

CAB protected people in this study from getting HIV infection about ~~70~~ **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.

~~In January 2021, CAB was approved by the US Food and Drug Administration (FDA) along with another drug called rilpivirine, for the **treatment** of HIV in adults. CAB for the **prevention** of HIV, which is what are studying in HPTN 083, has not yet been approved by the US FDA and so it is still called an investigational drug for this purpose.~~

If you become infected with HIV during this part of the study

If you get HIV during Step 4a, you will stop taking the CAB pills, and you will be referred for local care and treatment of HIV and will be discontinued from the study. If you get HIV during Step 4b or 4c (while you are getting shots), you will stop getting any further shots and we will ask you to come back for a visit every 3 months for about a year.

If you get HIV during Step 5 of the study, you will stop taking the TDF/FTC pills and will be referred for local care and treatment of HIV. If you get HIV during Step 5 and you have ever had a CAB injection at any time during past study visits, we will ask you to come back for a visit every 3 months for about a year; if you did not receive any CAB injections during past study visits, you will be discontinued from the study.

If you get HIV during Step 6, your study participation will end, and you will be referred to local HIV clinical care.

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 ~~4.0~~ 5.0

~~February 10, 2021~~April 28, 2022

[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