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 4.0
February 10, 2021

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 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.

Upon receiving IRB/EC approvals and any other applicable regulatory entity approvals, all sites are required to submit an amendment registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. 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; **approval is required prior to implementation of Version 4.0 of the protocol**. Note that re-consent for specimen storage and future research, genetic testing, and the DXA subset (where applicable) is not required.

This Summary of Changes, Protocol Version 4.0, 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 3.0 have been incorporated to Version 4.0. The content of Letter of Amendment #2, July 01, 2020; Letter of Amendment #3, July 23, 2020; and Clarification Memo #3, May 04, 2020, are included. Letter of Amendment #1, May 19, 2020, provides unblinding instructions for sites and a participant letter to inform participants of preliminary study results, but does not contain edits to protocol text. Changes from Clarification Memo #1, February 10, 2020 are not included because Clarification Memo #3 supersedes it. Clarification Memo #2, April 02, 2020, and Clarification Memo #4, February 05, 2021, provide guidance to sites for participant follow-up during the COVID-19 pandemic but do not contain edits to protocol text. The rationale for each item included in these documents is not repeated below (refer to the respective final document for each); however, the modifications to protocol text are included in this document under the "implementation" section.

The following revisions are new to Version 4.0; that is, they do not appear in the Letters of Amendment and Clarification Memos listed above:

2. The Title Page, footer, and Protocol Signature Page are updated to reflect the new version number and date.

3. The Table of Contents is updated to reflect the new version.

4. The Protocol Roster is updated to remove Leslie Cottle and add Priyanka Agarwal.

5. Appendix IV, the Sample Screening and Enrollment Informed Consent Form used in the blinded part of the study, has been updated to reflect the new version number and date only – there are no other changes as this sample informed consent form is no longer applicable to the unblinded portion of the study. As such, these minor modifications are not depicted in this summary of changes. An updated Addendum to the Main Sample Informed Consent Form for this full amendment Version 4.0 is included in Appendix V, Section F. As outlined in the Addendum, participants will choose whether to continue or initiate cabotegravir or TDF/FTC and sign the form accordingly as to whether to take part in this next part of the study under Version 4.0.

6. Appendix V is a new section. The purpose of Appendix V is 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.

   On 14 May 2020, the NIAID Multinational Data & Safety Monitoring Board (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. 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 specified immediate procedures as an interim approach until additional cabotegravir study product was available to all participants, and included a Dear Participant Letter to this effect.

The 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. The relevant procedures from LoA # 1 are included in Appendix V. Appendix V expands on LoA # 1 to outline the procedures to offer cabotegravir or TDF/FTC and follow participants who choose to continue or initiate cabotegravir or choose to continue or initiate TDF/FTC and includes an addendum to the main informed consent form.

Appendix VI is a new section. The purpose of Appendix VI is to provide guidance to sites for participant follow-up during the COVID-19 pandemic per Clarification Memo (CM) #2, April 02, 2020, and CM #4, February 05, 2021.

Implementation of Modifications

Modifications of protocol text are described 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.

Revision 2: Title Page, footer, and Protocol Signature Page

Updated to Version 4.0, dated February 10, 2021

Revision 3: Table of Contents

Updated to reflect the contents of Version 4.0

Schema

CM #3, May 04, 2020

Exploratory Objectives:

- To perform secondary laboratory assessments that may include evaluation of factors related to HIV infection, hepatitis infection, or ~~sexually transmitted infections (STIs)~~ **other**

infections; antiretroviral (ARV) drug use; pharmacogenomics; characterization of HIV in infected participants; and evaluation of laboratory assays related to the study objectives

2.4 Exploratory Objectives

CM #3, May 04, 2020

- To perform secondary laboratory assessments that may include evaluation of factors related to HIV infection, hepatitis infection, or ~~sexually transmitted infections (STIs)~~ **other infections**; antiretroviral (ARV) drug use; pharmacogenomics; characterization of HIV in infected participants; and evaluation of laboratory assays related to the study objectives

5.8 Week 153, Last Visit of Step 2/ Day 0, First Visit of Step 3

CM #3, May 04, 2020

Only the "Note" at the bottom of Section 5.8 of Version 3.0 the protocol is impacted and depicted below.

NOTE: If a participant in Step 2 transitions prematurely to Step 3, or misses the Week 153 visit **for any reason**, **or if the Week 153 visit already occurred under Version 2.0 of the protocol and the participant now needs to move to Step 3 under Version 3.0 of the protocol,** the procedures listed above will be performed as part of the last visit of Step 2 (whenever that occurs)/Day 0 of Step 3 to the extent possible. All assessments are identical to Week 153/Day 0 listed above with the following exceptions:

- Behavioral assessment – do not administer if done within the last month before entering Step 3. **Refer to SSP Sections 6 and 13 and SSP Appendix III – Schedule of Forms.**
- Acceptability assessment (not listed above) – this should be administered at this visit if it was not done in the last 6 months before entering Step 3. **Refer to SSP Sections 6 and 13 and SSP Appendix III – Schedule of Forms.**
- Urine collection and testing for GC/CT – do not collect/do not perform test if testing occurred within 3 months prior to entering Step 3
- Rectal swab collection and testing for GC/CT – do not collect/do not perform test if testing occurred within 3 months prior to entering Step 3
- Syphilis testing – do not perform test if testing occurred within 3 months prior to entering Step 3
- **ECG – do not perform procedure if done within 3 months prior to entering Step 3**
- **Urine collection for urinalysis – do not collect/do not perform test if testing occurred within 3 months prior to entering Step 3**

- **HCV – do not perform test if testing occurred within 3 months prior to entering Step 3**

As mentioned above, any scenarios that do not fit into these exceptions or any other questions about the requirements for the last day of Step 2/first day of Step 3 (Week 153/Day 0), whenever that visit may occur, should be directed to the CMC.

7.6 Sample Size and Interim Monitoring

LoA #2, July 01, 2020

The third paragraph in this section is impacted and is therefore the only paragraph depicted below.

Interim monitoring will be conducted by an independent DSMB on a regular schedule, with safety review approximately every 6 months, and at least annually. Formal interim analyses will be planned approximately 4 times during the study, using the Lan-DeMets modification of the O'Brien-Fleming stopping bounds to control alpha spending. ~~Superiority~~ **Non-inferiority** bounds will be used for early stopping for favorable risk-to-benefit ratio for CAB LA **compared to TDF/FTC.** ~~; non-inferiority bounds will be used for early stopping for unfavorable risk-to-benefit ratio. Thus, the study will continue if non-inferiority is established but superiority remains plausible, however the study may end early if non-inferiority is ruled implausible or if inferiority is established.~~ **Stopping will also be advised if there is early evidence that CAB LA is clearly not as effective as TDF/FTC (i.e., early evidence that HR>1.0).**

7.11.1 Analyses of Primary Efficacy Objective

LoA #3, July 23, 2020

The first paragraph under the first bullet is impacted and is depicted below.

MITT: A modified intent-to-treat will be used as the primary assessment for the efficacy comparison, thus all participants ~~who receive at least one dose of oral study product~~ will contribute to the primary analyses. Any participant determined to be HIV infected prior to receiving study product will be omitted from the analysis.

The last paragraph and accompanying bullets are impacted and depicted below.

On blinded study product ~~Per protocol~~: An on blinded study product ~~A per protocol~~ estimate of treatment efficacy will be conducted as a secondary analysis in the non-inferiority context of active control, as a verification that a similar HR estimate is obtained ~~in the compliant population~~ in participants who are HIV-uninfected at the time of the first injection, while participants are compliant to the injection schedule. Compliance will be defined as~~:~~ **receiving the second injection within 6 weeks of the first injection and all subsequent injections within 10 weeks of the prior injection.** ~~Adherent by administration and plasma TDF~~

~~concentrations: In CAB LA arm, from the time of receipt of the injection the participant is considered adherent for 8 weeks. In the TDF/FTC arms, from time of dispensing pills the participant is considered adherent if plasma TDF concentrations are detectable at 8 weeks. Each HIV testing interval (time period between determining HIV status through study testing) will be defined as compliant if participant has TDF levels consistent with 4 or more doses per week by appropriate pharmacokinetic laboratory assays.~~

~~Estimates will be computed as follows:~~

- ~~Time varying compliance: Compliance will be a time-dependent covariate, and the HR for efficacy CAB-LA vs TDF/FTC during periods of compliance will be estimated using Cox proportional hazards with an interaction term between study arm and compliance. The estimate of efficacy will be the HR for CAB-LA vs TDF/FTC in the compliant periods.~~
- ~~Estimate in the compliant cohort: The compliant cohort is defined as those participants who were adherent >80% of their time on study. The same methods as detailed for the primary analysis will be used for estimating effectiveness on the compliant cohort. Evidence of confounding in this cohort will result in an analysis that is adjusted for additional baseline risk covariates.~~

Per protocol: A per protocol estimate of treatment efficacy, excluding participants with major protocol violations, or participant time after a major protocol violation, will be conducted as a secondary analysis in the non-inferiority context of an active control, as a verification that a similar HR estimate is obtained.

9.2.1 Virology

CM #3, May 04, 2020

The HPTN LC will perform QA testing, including testing to determine HIV infection status in selected cases. Additional assays may be performed at the HPTN LC or a laboratory designated by the HPTN LC. This testing may include the following tests for participants who acquire HIV infection: HIV viral load, HIV resistance testing, HIV subtyping, and other tests to characterize HIV viruses and/or the host response to HIV infection. Results will not be returned to the sites or study participants, with the exception of HIV testing (if results obtained at the HPTN LC do not agree with site results).

Resistance testing will be performed at the HPTN LC or a laboratory designated by the HPTN LC. This testing will be performed ~~retrospectively at the end of~~ **periodically during** the study. Results of this testing will not be returned to study sites. Because real-time resistance testing may be needed for clinical management in the event of HIV infection, each site will have an SOP as to how they will accomplish real-time local or regional resistance testing to assist with clinical decision making; separate specimens should be collected for that testing.

Appendices IB and IC

CM #3, May 04, 2020

Appendix IB: Schedule of Procedures and Evaluations - Step 2 – Blinded Injections + Blinded Daily Oral Pills

WEEKS (shaded column = injection/ dispense pills visit)	5	6	9	10	17	19	25	27	33	35	41	43	49	51	57	59	65	67	73	75	81	83	89	91	97	99	105	107	113	115	121	123	129	131	137	139	145	147	Week 153/ Day 0*
ADMINISTRATIVE, BEHAVIORAL, REGULATORY																																							
Locator Information	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV Counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Condoms and lubricant	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Acceptability Assessment*					X						X						X						X												X				
Behavioral Assessment	X		X		X		X		X		X		X		X				X				X				X				X				X				X*
Adherence Counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CLINICAL EVALUATIONS & PROCEDURES																																							
History, concomitant medications, physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight, blood pressure, pulse data entry to Medidata Rave	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
ECG															X												X										X		X*
DXA (subset only, 175 per arm)[1]															X												X												
Blood Collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine collection for urinalysis testing															X												X												X*
Urine collection for GC/CT testing									X						X						X						X						X						X*
Rectal swab for GC/CT testing[2]									X						X						X						X						X						X*
Injection/Dispense pills	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X[8]
ISR evaluation		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	
LOCAL LABORATORY EVALUATIONS & PROCEDURES																																							
HIV testing[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV testing[4]															X												X												X*

WEEKS (shaded column = injection/ dispense pills visit)	5	6	9	10	17	19	25	27	33	35	41	43	49	51	57	59	65	67	73	75	81	83	89	91	97	99	105	107	113	115	121	123	129	131	137	139	145	147	Week 153/ Day 0*
CBC with differential		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry testing[5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver function tests[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting glucose and fasting lipid profile[7]															X												X											
Syphilis serologic testing									X						X						X						X						X						X*
Urine GC/CT testing									X						X						X						X						X						X*
Rectal swab GC/CT									X						X						X						X						X						X*
Urinalysis															X												X												X*
Plasma storage	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DBS storage			X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X

FOOTNOTES FOR APPENDIX IB

*~~See Appendix IC and corresponding footnotes for Step 3 Day 0~~ **For participants who transition to Step 3 at Week 153, the first day of Step 3 begins at Week 153 and is also considered Day 0 of Step 3. The timeline for Step 3 continues whether or not a participant attends the Week 153/Day 0 visit or any subsequent visits.**

For participants who are already beyond Week 153 of Step 2 in their follow-up schedule, the timeline for Step 3 begins 8 weeks following their last injection and continues whether or not a participant attends the Day 0 visit or subsequent visits.

For participants who transition to Step 3 prematurely, the timeline for Day 0 begins 8 weeks after that participant's last injection, even if the participant does not report to the Day 0 visit (or the Week 12 visit, etc.). Sites may contact the CMC for questions regarding participants who transition to Step 3 prematurely who are then subsequently missing, though it is not required to do so.

Per Section 5.8 of the protocol, note the following:

- **Do not perform the following tests/procedures if they occurred within the last three months prior to either prematurely transitioning to Step 3, or the Week 153/Day 0 visit was missed for any reason, or if the Week 153 visit already occurred under Version 2.0 of the protocol and the participant now needs to move to Step 3 under Version 3.0 of the protocol: ECG; urine collection for urinalysis and GC/CT testing; rectal swab for GC/CT testing; HCV testing; and syphilis testing, and perform these requirements only at Weeks 24 and 48 (except for HCV testing, which is not required at Weeks 24 and 48). Refer to Appendix IC.**
- **For participants who either prematurely transition to Step 3, or the Week 153/Day 0 visit was missed for any reason, or if the Week 153 visit already occurred under Version 2.0 of the protocol and the participant now needs to move to Step 3 under Version 3.0 of the protocol, administer the acceptability assessment at the Week 153/Day 0 visit (whenever it occurs) as the final assessment if not done in the previous 6 months prior to transitioning, to include a brief preference assessment.**

- **Regarding the behavioral assessment, for participants who either prematurely transition to Step 3, or the Week 153/Day 0 visit was missed for any reason, or if the Week 153 visit already occurred under Version 2.0 of the protocol and the participant now needs to move to Step 3 under Version 3.0 of the protocol, do not administer at Week 153 and instead administer the behavioral assessment at Week 12 if it was done within the last month prior to transitioning, (see Appendix IC).**

[1] To include dietary calcium and Vitamin D assessment
[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 Appendices IE-G and 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] Required chemistry testing: BUN/Urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.
[6] Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.
[7] Required for lipid profile: Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection
[8] Per Section 5.8 of Protocol V3.0 and Appendix IB, the last injection in Step 2 will occur at the Week 145 visit. An injection will not be administered at the Step 2 Week 153/Step 3 Day 0 visit; any remaining blinded oral study product will be collected from the participant, and open-label TDF/FTC will be dispensed.

Appendix IC: Schedule of Procedures and Evaluations - Step 3 – Open Label Daily Oral TDF/FTC Post-Last Injection

Procedures*	~~Week 153/ Day0*~~	Week 12	Week 24	Week 36	Week 48
ADMINISTRATIVE, BEHAVIORAL, REGULATORY					
Locator Information	~~X~~	X	X	X	X
HIV Counseling	~~X~~	X	X	X	X
Offer Condoms and lubricant	~~X~~	X	X	X	X
~~**Acceptability Assessment**[2]~~	~~X~~				
Behavioral Assessment* ~~(if done in last 4 weeks, skip D0 and start at W12)~~	~~X~~		X		X
Adherence Counseling	~~X~~	X	X	X	
CLINICAL EVALUATIONS & PROCEDURES					
History, concomitant medications, physical exam	~~X~~	X	X	X	X
Weight, blood pressure, pulse data entry to Medidata Rave	~~X~~	X	X	X	X
Blood Collection	~~X~~	X	X	X	X
Urine collection for GC/CT testing	~~X~~[1]		X		X
Rectal swab for GC/CT testing[31]	~~X~~[1]		X		X
Dispense pills	~~X~~	X	X	X	
LOCAL LABORATORY EVALUATIONS & PROCEDURES					
HIV testing[42]	~~X~~	X	X	X	X
Chemistry testing[53]			X		X
Liver function tests[64]			X		X
Syphilis serologic testing	~~X~~[1]		X		X
Urine GC/CT testing	~~X~~[1]		X		X
Rectal swab GC/CT testing	~~X~~[1]		X		X
Plasma storage	~~X~~	X	X	X	X

FOOTNOTES FOR APPENDIX IC

***See Week 153/Day 0 of Appendix IB for Step 3 Day 0 procedures. If the behavioral assessment was not done at Day 0, administer at Week 12.** ~~For participants who transition to Step 3 prematurely, the timeline for Day 0 begins 8 weeks after that 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 3 continues whether or not a participant attends visits. Sites may contact the CMC for questions regarding participants who transition to Step 3 prematurely who are then subsequently missing, though it is not required to do so. For participants who transition to Step 3 at Week 153, the first day of Step 3 begins at Week 153 and is also considered Day 0 of Step 3.~~

[1] ~~Skip Day 0 if testing has occurred within last 3 months of Day 0 and do only at Weeks 24 and 48.~~

~~[2]Administer acceptability assessment at Day 0 as final assessment if not done in the previous 6 months on Step 2, to include a brief preference assessment~~
[31] If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).
[42] The HIV testing algorithm is provided in Appendices IE-G and the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.
~~[5]~~[53] Required chemistry testing: BUN/Urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.
~~[6]~~[64] Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.

APPENDIX V: PROCEDURES FOR INITIAL OFFERING OF OPEN LABEL CABOTEGRAVIR – THE NEXT PART OF HPTN 083

A. Background, Purpose and Overview, Description of Steps

1. Background

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.

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 12 incident cases of HIV were in the CAB arm, and 39 incident cases in the TDF/FTC arm. Four CAB arm and three TDF/FTC arm participants were found to have HIV prior to administration of any study products (prevalent). The CAB arm incidence rate in this post-hoc analysis was 0.38 per 100 PY; an HIV incidence rate of 1.22 per 100 PY was observed for participants randomized to TDF/FTC, demonstrating a superior 66% (primary analysis), 70% (post-hoc analysis) reduction in incident HIV infections in participants randomized to CAB compared to TDF/FTC. Among the 12 incident HIV infections in the CAB arm, four 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, 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 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.

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

2. Purpose and Overview

The purpose of this Appendix is to provide instructions for when an additional supply of oral and injectable cabotegravir is available for currently-enrolled HPTN 083 participants. The Appendix provides guidance for participants who choose to continue or initiate CAB-LA or choose to remain on TDF/FTC.

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 1) all required IRB/EC/other regulatory entity approvals 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 amendment protocol registration process; 3) an **additional supply of cabotegravir for this purpose has been received at the site;** and 4) the site has confirmed that training of all active personnel for Version 4.0 has been completed. **The HPTN Leadership and Operations Center (LOC) will issue an approval notice to begin implementation of Version 4.0 upon confirmation that all items outlined above are in place.**

3. Description of Steps 4 and 5

Sites will discuss with participants what the options are for ongoing study participation as outlined in the Steps below. An addendum to the main informed consent form is included in this Appendix and will document the participant's continued participation in the study. A site may opt to have the discussion regarding this choice via telephone or telemedicine at the discretion of the IoR and with approval from

all relevant IRB/ECs/other regulatory entities. If this 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 addendum informed consent form. Contact the CMC for guidance if there are other 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.

Contact the CMC for guidance for other cases that do not fit this description or the criteria above.

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

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

This step - for participants who opt to participate in it (or if the IoR or the IRBs/ECs/other review bodies require it) - is only for those originally randomized to oral TDF/FTC who choose to initiate cabotegravir for the first time. If a participant participates in Step 4a, and since it is deemed optional from the central management standpoint of the study, it will be at the discretion of the site Investigator of Record (or designee) as to what level of adherence to daily oral cabotegravir (if any) will be required by self-report prior to receiving injections. There are no pill counts in this Step; however, a site may choose to perform pill counts for documentation in the participant chart. Contact the CMC for guidance regarding cases or situations not outlined here.

See Table 1 for the schedule of procedures and evaluations for Step 4a.

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

This is a one-visit step for participants who are initiating cabotegravir for the first time (and have either completed Step 4a or not) or for participants who have been on cabotegravir during the study but have had a long absence of visits (> 15 weeks since prior injection) and require a reload of cabotegravir injections (two injections, 4 weeks apart). The first of these two injections is considered Step 4b. The

participant will then transition to Step 4c four weeks later. Contact the CMC for guidance regarding cases or situations not outlined here.

See Table 2 for the schedule of procedures and evaluations for Step 4b.

c. Step 4c: Cabotegravir Injections

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

Participants in Step 4c who no longer wish to continue receiving cabotegravir injections before Week 48 occurs will move to Step 5. Participants who complete Week 48 will also 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. Contact the CMC for guidance regarding cases or situations not outlined here.

See Table 3 for the schedule of procedures and evaluations for Step 4c.

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

This Step is for participants who choose to remain on or switch to oral TDF/FTC.

Participants who were originally randomized to oral TDF/FTC and choose to remain on oral TDF/FTC will complete the procedures of this Step until three years from the time of enrollment.

Participants who were originally randomized to cabotegravir who choose to switch to TDF/FTC will complete the procedures of this Step for 48 weeks from the last injection; that is, Step 5 Day 0 begins 8 weeks after that participant's last injection.

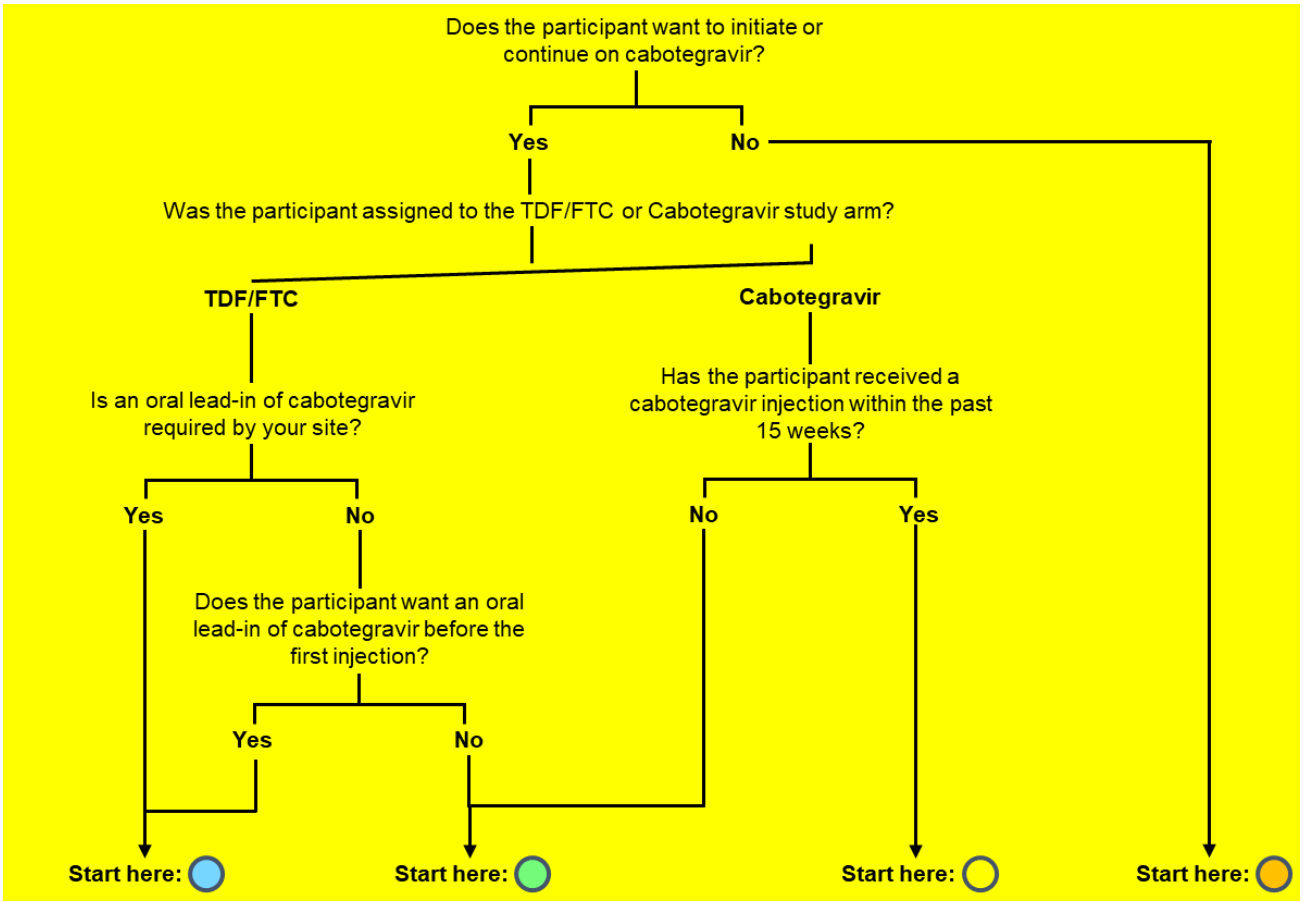
Contact the CMC for guidance regarding cases in which Day 0 of Step 5 would occur beyond 48 weeks from the time the participant received their last injection, or for other cases or situations not outlined here.

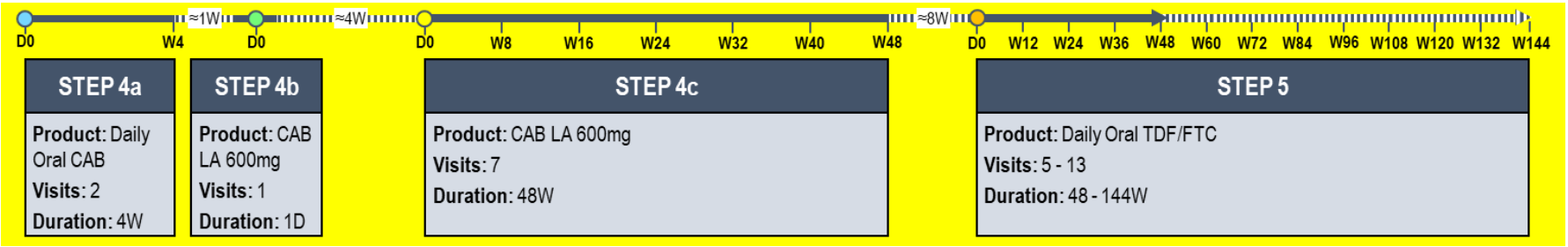
See Table 4 for the schedule of procedures and evaluations for Step 5.

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 1 below for a decision tree regarding the step sequences based on a participant's choice.

Figure 1: Decision Tree





B. Information in the Main Protocol that is Not Included in Appendix V

The sections listed below from the main protocol are no longer applicable to the procedures described in this Appendix or they pertain to the original study design and therefore are not applicable to the Appendix. Information from sections not listed here are outlined under "C" below.

Information from the following sections of the protocol are **not** included in this Appendix:

- Front matter such as the protocol roster, table of contents, schema, etc. An updated Protocol Signature Page is included in the body of the main protocol and should be signed and dated by the Investigator of Record.
- Section 1.0 in full
- Section 2.0, in full
- Section 3.0; Section 3.1; Section 3.2, Section 3.3
- Section 4.1
- Section 5.0 - Section 5.9; Section 5.11; Section 5.13; Section 5.13.1; Section 5.14.1; Section 5.18; Section 5.20. In order to reduce inconsistencies, specific listings of Steps 4, 5 and 6 procedures and assessments are not repeated as was done for Steps 1, 2 and 3 in the main protocol, and appear in this Appendix only in Tables.
- Section 7.0 in full (analyses from endpoints outlined are ongoing and pertain to the original study design and are not repeated in this Appendix)
- Section 9.0 in full (all relevant information from this section of the protocol is included in the updated SSP section pertaining to this Appendix – which is identified as Appendix VIII of the SSP)

C. Information in the Main Protocol that is Included Or Modified in Appendix V

Several sections from the main protocol still apply in full or in part to the procedures outlined in this Appendix and are outlined below and updated where necessary:

1. **Co-Enrollment (from Section 3.4 of the main protocol, with modifications):** Participants may participate in COVID-19 vaccine or treatment studies, provided that participant study burden and American Red Cross-mandated limitations on per-unit-time phlebotomized blood volumes are not exceeded. There is no need to consult the CMC for participation in these studies. The CMC should be consulted for participation in other COVID or non-COVID related biomedical intervention studies.

2. **Participant Retention (from Section 3.5 of the main protocol with modifications):** Sites will continue to implement existing retention strategies.

3. **Participant Withdrawal (from Section 3.6 of the main protocol):** Participants may voluntarily withdraw from the study for any reason at any time. Participants also may be withdrawn if the study sponsor, government or regulatory authorities (including Office for Human Research Protections [OHRP] and the FDA) or site IRBs terminate the study prior to its planned end date. Every reasonable effort will be made to complete a final evaluation of participants who terminate from the study prior to the final protocol-dictated study week, and study staff will record the reason(s) for all withdrawals from the study in participants' study records.

4. **Premature Termination Visits (from Section 3.6.1 of the main protocol, with modifications):** In general, for participants who withdraw consent from the study prematurely during a study visit, the requirements for that visit should be completed to the extent possible **except for provision of study product** and will be considered their final visit. When possible, a plan should be made to provide final laboratory results from site testing to the participant. For participants on oral TDF/FTC who inform the site in between visits that they wish to withdraw consent from the study, sites should make every effort to have the participant return any unused study product. It is at a site's discretion to terminate participants who have been lost to follow-up for a minimum of 6 months or who have relocated to an area where there is no HPTN 083 site. The timeline for the 6 months lost to follow-up or relocation begins at the participant's first missed visit (which may have occurred longer than 6 months ago by the time Version 4.0 of the protocol is in effect at the site).

5. **Study Product Considerations (from Section 4.0 of the main protocol, with modifications):**

The CAB study product (oral and LA injectable) being tested in this study is investigational and not yet approved by the US FDA for the prevention of HIV-1 infection. Further information on the study product is available in the Investigator's Brochure (IB), which will be 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.

Oral Study Products

Cabotegravir (CAB) 30 mg tablets are formulated as white to almost white oval-shaped coated tablets for oral administration. The tablets are packaged in high density polyethylene (HDPE) bottles with child-resistant closure that include an induction seal. The bottles contain 30 tablets and a desiccant. The tablets must be stored in the original container. The bottles are to be stored up to 30° C (86^{O} F) and protected from moisture.

TDF 300 mg/FTC 200 mg tablets (open-label) are capsule-shaped, film-coated blue tablets that must be stored in the original container. Each bottle contains a silica gel desiccant canister to protect the product from humidity. The bottles are to be stored at 25° C (77° F). Excursions are permitted between 15° to 30°C (59 to 86°F). The TDF/FTC fixed dose combination tablet containing 300 mg of tenofovir disoproxil fumarate (TDF) and 200 mg of emtricitabine (FTC) is available as Truvada® and is approved by the U.S. FDA for treatment and prevention of HIV-1 infection. Further information on Truvada® is available in the current package insert.

Injectable Study Product

Cabotegravir Long-Acting (CAB LA) is formulated as a sterile white to slightly pink colored suspension containing 200 mg/mL of CAB LA for administration by IM. The product is packaged in a 2 mL or 3 mL glass vial. Each vial is for single use containing 2 mL (400 mg) or 3 mL (600 mg) and does not require dilution prior to administration. CAB LA injectable suspension is to be stored up to 30°C (86°F), do not freeze.

Prescription

A prescription for unblinded study product (oral active CAB, oral active TDF/FTC or injectable CAB-LA) signed by an authorized prescriber must be provided to the site pharmacist prior to preparation of study product. The prescription must include the Step number (4a, 4b, 4c or 5) and a notation if the participant is switching between CAB arm and TDF/FTC arm.

Study Product Preparation**:**

The site pharmacist should consult the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations.

CAB 30 mg Oral Product

- The pharmacist will take the following steps to prepare and dispense un-blinded active oral CAB to the participant:
  1) Retrieve oral active CAB 30mg tablet bottle with two part-label from Step 2 supply.
  2) Retain both the un-blinded part and the blinded part of the two-part label on the CAB bottle. Do not tear off the un-blinded part of the two-part label from the bottle.
  3) Place pharmacist-prepared participant- specific un-blinded label in such a way that the blinded part of the two-part label on the bottle is covered.

- The pharmacist prepared, participant-specific, un-blinded oral active CAB bottle will have the manufacturer's unblinded part of the two-part label and site pharmacist generated participant specific un-blinded label visible on the prepared bottle before dispensation.

The participant specific label must be in accordance with the local regulations and the DAIDS Pharmacy Guidelines manual.

The pharmacist will prepare the participant-specific study product and dispense sufficient quantity to last until the next follow-up visit plus approximately one-month buffer supply. Pharmacists will record dispensations on the Pharmacy Accountability Logs.

TDF/FTC (300 mg/200mg) Oral Product

- The pharmacist will take the following steps to prepare and dispense un-blinded active oral TDF/FTC to the participant:
  1) Retrieve oral active TDF 300 mg/FTC 200 mg (open-label) bottle from Step 3 supply.
  2) Place pharmacist prepared participant-specific un-blinded label in such a way that the manufacturer's unblinded label on the bottle is not covered.

- The pharmacist-prepared, participant-specific, un-blinded oral active TDF/FTC bottle will have the manufacturer's unblinded label and site pharmacist generated participant-specific un-blinded label visible on the prepared bottle before dispensation.

The participant specific label must be in accordance with the local regulations and the DAIDS Pharmacy Guidelines manual.

The pharmacist will prepare the participant-specific study product and dispense sufficient quantity to last until the next follow-up visit plus approximately one-month buffer supply. Pharmacists will record dispensations on the Pharmacy Accountability Logs.

Injectable CAB LA 600 mg/3mL

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

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

Materials required for preparation and administration of CAB LA 600mg; 3 mL dose:

- One CAB LA 600 mg/3 mL vial or two CAB LA 400 mg/2 mL vials
- Becton Dickenson (BD) 3-mL syringe, Luer-Lok Tip, Product No.: 309657 or equivalent
- Becton Dickinson (BD) 5-mL Syringe, Luer-Lok Tip, Product No.: 309646 or equivalent
- Needle for aspiration: BD general use sterile hypodermic needle, 21G x 1½ inch (e.g. PrecisionGlide Needle, Product No.: 305165 or equivalent)
- Needle for intramuscular injection: BD IM sterile hypodermic needle, 23G x 1½ inch (e.g. PrecisionGlide Needle, Product No.: 305194 or equivalent). Refer to the HPTN 083 SSP for further details on appropriate needle gauge size and length to use for IM administration.

Preparation Steps:

- Remove two vials of CAB LA (400 mg/2 mL per vial) or one vial of CAB LA (600 mg/3 mL per vial) from storage. If the vials are stored in the refrigerator (2°C to 8°C), remove vial(s) from the refrigerator and wait at least 15 minutes to equilibrate to room temperature.

- Vigorously shake the vial(s) for a full 10 seconds by shaking the vial(s) with long arm movements.

- Invert the vial(s) and inspect to ensure uniform suspension. If solid remains undispersed, repeat vigorous shaking and inversion until all material is uniformly suspended.

    - NOTE: It is normal to see small air bubbles at the end of shaking the vial for re-suspension.

- Using aseptic technique under a pharmacy BSC/isolator, flip off the plastic cap from the vial. Wipe the top of the vial with an alcohol pad (isopropyl alcohol 70% or similar) and allow to dry. Do not touch the rubber stopper at any time.

- Remove a 3 mL or 5 mL size syringe and 21G x 1½ inch (or equivalent) needle for aspiration. Attach the needle to the Luer connection of the syringe.

- With the needle sheath on, pull the syringe plunger rod to allow approximately 1 mL of air into the syringe. Remove the needle sheath.

- With the vial in the inverted position and the syringe with the needle in the upright position, push the needle through the vial stopper and inject approximately 1 mL of air into the vial.

- While keeping the syringe with the needle in the upright position, withdraw needed volume of CAB LA suspension from the vial(s) into the syringe.

- Withdraw total of 3 mL (600 mg) of CAB LA suspension from the vial(s) into a syringe.
    - If using two CAB LA 400 mg/2 mL vials to prepare the dose, a second new aspiration needle should be used to withdraw suspension from the second vial. Remove the first needle that was used to withdraw the suspension out of the first vial and discard properly. Attach the new 21G x 1½ inch needle (or equivalent) to the syringe already containing suspension per instructions above to withdraw the remaining needed volume from the second vial.

    - Since the suspension can contain some air after having shaken the vial, withdraw enough suspension from the vial in order to be able to de-aerate the syringe properly.

- Remove the needle that was used to withdraw the suspension out of the vial and discard the needle properly.

- Attach a 23G x 1½ inch (or equivalent) needle to the Luer connection of the prepared CAB LA syringe for IM injection for the participant. Alternatively, the site pharmacist can attach a syringe cap to the prepared syringe. The study staff can then attach the appropriate needle for administration to the prepared syringe in the clinic before administration.

    - NOTE: The participant-specific prepared CAB LA in a syringe is to be de-aerated by administrator prior to injection so that the correct volume can be administered.

        - De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in an upright position until the first drop of suspension appears. Remove the excess suspension in order to administer the correct volume (3 mL). If needed, collect the excess suspension in a beaker to avoid spilling.

- Record the time that the suspension was withdrawn from the vial and into the syringe in the participant's pharmacy log. This is the time of preparation.

- Label the prepared syringe containing 3 mL (600 mg) of CAB-LA as "CAB LA 600 mg per 3 mL", including the volume (3 mL), route (IM), participant's PTID, date and time of preparation, and date and time of expiration. Follow the DAIDS Pharmacy guidelines and local regulations for preparing the participant specific label.

  After withdrawal of the CAB-LA suspension from the vial into a syringe, it is recommended to inject the suspension immediately. Do not exceed 2 hours between withdrawing the contents of the vial(s) into a syringe (see above) and administration to the study participant.

  The prepared CAB LA study product in a syringe must be stored at controlled room temperature between 20°C to 25°C (68°F-77°F) from the time it is withdrawn into a syringe to the time it is administered.

  Any entered vials or expired filled syringes should be disposed of in accordance with institutional or pharmacy policy.

Study Product Acquisition and Accountability

All study products will be supplied by the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Research Products Management Center (CRPMC). The study site pharmacist can obtain all the study products through the CRPMC by following the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trial Networks*, and instructions in the SSP Manual.

The site pharmacist is required to maintain complete records of all study products received from the CRPMC and subsequently dispensed to study participants. All study products must be stored in the pharmacy. At US clinical research sites, all unused study products must be returned to the CRPMC after the study is completed, terminated or otherwise instructed by the study sponsor. The procedures to be followed are provided in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks. The site pharmacist at non-US clinical research sites must follow the instructions in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks DAIDS Pharmaceutical Affairs for the destruction of unused study products.

Concomitant, Prohibited, and Precautionary Medications

The precautionary and prohibited medications are:

Cabotegravir:

- Not to be administered concurrently:
  - Cytotoxic chemotherapy or radiation therapy
  - barbiturates
  - carbamazepine

- oxcarbazepine
- phenytoin
- pheonobarbital
- rifabutin
- rifampin
- rifapentine
- St. John's wort

NOTE: Systematically administered immunomodulators is removed

- Prohibited within 7 days before and 7 days after an injection
  - high dose aspirin (>325 mg per day)
  - anagrelide
  - apixaban
  - argatroban
  - bivalirudin
  - clopidogrel
  - dabigatran
  - dalteparin
  - enoxaparin
  - fondaparinux
  - heparin
  - lepirudin
  - prasugrel
  - rivaroxaban
  - ticagrelor
  - ticlopidine
  - warfarin
- Oral formulation precautions
  - Antacid products containing divalent cations (e.g., aluminum, calcium, and magnesium) must be taken at least 2 hours before or at least 4-6 hours after the oral CAB administration

Truvada®:

- Medications containing the following ingredients should not be administered concurrently:
  - emtricitabine or tenofovir disoproxil fumarate (e.g. ATRIPLA®, COMPLERA®, EMTRIVA, GENVOYA®, ODEFSEY®, STRIBILD®, or VIREAD, Descovy).
  - lamivudine (e.g. Combivir, Dutrebis, Epivir, Epivir-HBV, Epivir A/F, Epzicom, Triumeq, or Trizivir)
  - adefovir (e.g. HEPSERA®)

- tenofovir alafenamide (e.g. Vemlidy)
- didanosine (e.g. Videx EC)
- atazanavir (e.g. Reyataz, Evotaz (atazanari/cobicistat))
- ledipasvir/sofosbuvir (e.g. HARVONI®)
- darunavir (e.g. Prezista)
- lopinavir/ritonavir (e.g. Kaletra)
- orlistat (e.g. Alli, Xenical)

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

All concomitant medications/preparations (prescription and non-prescription) including alternative/complementary medications/preparations (e.g., herbs, vitamins, etc.) will be collected in the study participant's chart and on study case report forms (CRFs). Alcohol and recreational or street drug use reported by a participant during the study will be recorded in the participant's study chart only (and not captured on the concomitant medication log for inclusion in the study database).

Refer to SSP Appendix VIII for NSAIDS and considerations for co-administration of precautionary and prohibited medications.

Other Study Product Dispensing Considerations

While it is not required, it is recommended that sites dispense an additional bottle of study product (TDF/FTC or CAB) to ensure an extra month supply between visits. For example, for participants initiating cabotegravir, sites should dispense two bottles of oral CAB to cover the 4- week period prior to the first injection. Participants should be advised to bring open bottles to appointments, finish an open bottle before opening a new one, and should not combine or transfer pills between open bottles. Formal pill counts will not occur under the procedures of this Appendix.

6. **Procedures for Steps 4 and 5 (originally Steps 1 – 3 from Section 5.0, with modifications):** Procedures and evaluations for Steps 4 and 5 are outlined in Tables 7 – 10 and are not repeated here. The HIV testing algorithm for follow-up visits is shown in Figure 2.

7. **Visit Windows (from Section 5.10 of the main protocol, with modifications):** 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 that they are a minimum of 6 weeks and a maximum of 15 weeks from the prior injection, and for the Step 4c Day 0 injection, when it is a minimum of 3 weeks and a maximum of 11 weeks from the Step 4b Day 0 injection. It is required to contact the CMC for guidance in cases outside of these parameters.

   It is not required to contact the CMC for out of target window safety visits no matter when they occur; however, an injection visit may never be completed without preceding safety laboratory assessments being completed and all the assessments being resulted and protocol-allowable.

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

Participants in Step 4a of the study who are unable to transition to Steps 4b and 4c for any reason – including HIV infection - will be referred to local care and terminated from the study.

Participants in Step 4b or 4c of the study who prematurely stop receiving injections will be asked to transition to Step 5 of the study 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 will be asked to be followed per Table 5 below. Participants who prematurely stop receiving injections for an AE or condition where open label TDF/FTC is contraindicated will be asked to continue follow-up for 48 weeks off study product.

9. Procedures for Suspected or Confirmed HIV Infection (from Section 5.14.2 of the main protocol, with modifications): Refer to the updated Appendix VIII of the SSP for guidance regarding suspected or confirmed HIV infection during Steps 4 and 5.

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.

10. Sexually Transmitted Infections (from Section 5.15 of the main protocol): Testing for GC/CT and syphilis will continue under this amendment. Testing will be performed at the local laboratory. For rectal swabs, if testing cannot be performed at the local laboratory, testing at another laboratory may be arranged (see SSP Manual). Testing may be adjusted or prioritized at the discretion of the site investigator if there is a potential for shortage of supplies for collection and testing. Please see CDC recommendation September 8 2020. https://www.cdc.gov/std/general/DCL-Diagnostic-Test-Shortage.pdf

Participants will be referred for treatment of STIs as per local guidelines. Symptomatic screening for STIs beyond what is required by the protocol will be performed at a site's discretion and costs associated may come out of each site's respective per participant study reimbursements.

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

Sites will continue to report STIs into the study database on the Adverse Event e-CRF as well as the STI e-CRF.

11. Hepatitis C (from Section 5.16 of the main protocol, with modifications)

Participants on Step 4c will have HCV antibody testing performed approximately annually (per Table 3). Incident HCV infection during follow-up will not mandate discontinuation of study product absent other requirements per Section E below - Toxicity Management.

12. Interim Contacts and Visits and Missed Visits (from Section 5.17 of the main protocol, with modification): Refer to SSP Appendix VIII for information.

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

Plasma and dried blood spots (DBS) will be collected for pharmacokinetic assessments. Results of this testing will not be provided to study sites or participants.

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

Study site staff will document in source documents and the appropriate e-CRF AEs (Grade 2 and higher clinical and laboratory AEs, 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.

Relatedness is an assessment made by a study clinician of whether or not the event is related to the study agent. The relationship of all AE to study product will be assessed as specified in Version 2.0, January 2010 of the DAIDS Expedited Adverse Event (EAE) Reporting Manual.

Requirements, definitions, and methods for expedited reporting of adverse events are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the DAIDS Regulatory Support Center (RSC) website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids.

The DAIDS Adverse Event Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE form. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting. For questions about DAERS, please contact CRMSSupport@niaid.nih.gov. Site queries may also be sent with the DAERS application itself.

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, will be used for determining and reporting the severity of adverse events. The DAIDS grading table is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

For questions about EAE reporting, please contact the RSC at DAIDSRSCSafetyOffice@tech-res.com.

The Serious Adverse Event (SAE) Reporting Category, as defined in Version 2.0 of the DAIDS EAE manual, will be used for this study (the definition of an SAE is also included in the manual).

In addition to SAEs, sites will report in an expedited manner the following results:

- ALT≥3xULN AND total bilirubin≥2xULN (must be both in order to require expedited reporting)

- Any seizure event

These reporting requirements are required for each study participant from enrollment until their follow-up in the study ends. 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.

The study agents for the purposes of EAE reporting are: Oral CAB 30 mg oral tablet; CAB LA injectable suspension (200mg/mL); TDF/FTC fixed dose combination tablet containing 200 mg of FTC and 300 mg of TDF.

In addition to submitting EAE information to the DAIDS Safety Office via DAERS, the site investigator may be required to submit AE and EAE information to local regulatory agencies or other local authorities.

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. 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 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.

15. Human Subjects Considerations (from Section 8.0 of the main protocol, with modifications):

The protocol, site-specific informed consent form, participant education and recruitment materials, and other requested documents — and any subsequent modifications — will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study site.

Study sites will follow all applicable local and national requirements for required reporting and continual renewal of the protocol. Study sites are responsible for the submission of continuing review to the DAIDS Protocol Registration Office, in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual.

Written informed consent will be obtained from each study participant. Each study site is responsible for developing study informed consent forms for local use, based on the template in this **Error! Reference source not found.**that describes the purpose of the amendment, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. If applicable, the study site also is responsible for translating the template form into local languages and verifying the accuracy of the translation by performing an independent back-translation.

Participants will document their provision of informed consent by signing their informed consent forms per site SOPs. 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.

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All laboratory specimens, reports, study data collection, process, and administrative forms will be identified by a coded number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by the NIAID and/or its contractors; pharmaceutical sponsors; representatives of the HPTN LOC, SDMC, and/or LC; the US FDA, OHRP, other U.S., local and international regulatory entities, and/or site IRBs.

For sites located in the US, the HPTN has obtained a Certificate of Confidentiality from the US Department of Health and Human Services that is applicable for this study. This Certificate protects study staff from being compelled to disclose study-related information by any Federal, State or local civil, criminal, administrative, legislative, or other body.

Study staff will comply with all applicable local requirements to report communicable diseases identified among study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.

The study may be discontinued at any time by NIAID, the HPTN, the pharmaceutical sponsors, the US FDA, other government or regulatory authorities (OHRP), or site IRBs/ECs.

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

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. 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; approval is required prior to implementation of Version 4.0 of the protocol. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which can be found at https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration.

DAIDS holds the Investigational New Drug (IND) application for this study. Copies of all regulatory documents submitted to this IND by DAIDS will be forwarded to ViiV Healthcare and Gilead Sciences, Inc. for cross-referencing with the company's other INDs for the study product(s). Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed by DAIDS and ViiV Healthcare, and DAIDS and Gilead Sciences, Inc.

Implementation of Version 4.0 will be directed by Appendix V of this protocol as well as SSP Manual Appendix VIII. The SSP Manual includes links to the DAIDS SOPs for Source Documentation and Essential Documents, Manual for Expedited Reporting of Adverse Events to DAIDS and the DAIDS Toxicity Tables.

Sites will continue to use the MediData Rave data management system. Quality control reports and queries routinely will be generated and distributed to the study sites for verification and resolution.

Study monitoring will continue to be performed as specified by and in accordance with DAIDS policies. Study monitors will:

- verify compliance with human subjects and other research regulations and guidelines;
- assess adherence to the study protocol, study-specific procedures manual, and local counseling practices; and
- confirm the quality and accuracy of information collected at the study site and entered into the study database.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures, as applicable. Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN LOC, HPTN SDMC, HPTN LC, NIAID, ViiV Healthcare, Gilead Sciences, Inc., site IRBs/ECs, and other US, local, and international regulatory authorities. A site visit log will be maintained at each study site to document all visits (including virtual visits).

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and DAIDS Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s) and the DAIDS Regulatory Support Center (RSC) prior to implementing the amendment.

The Investigator will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. In accordance with Federal regulations, for each of the investigational products tested, the Investigator will retain all study records for at least two years following the date of marketing approval for the study product for the indication in which it was studied and at least three years after the completion of research. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the US FDA is notified that the IND

is discontinued. Study records include administrative documentation — including protocol registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened and/or enrolled in the study — including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents.

Completion of a clinical research study occurs when the following activities have been completed:

- All research-related interventions or interactions with human subjects (e.g. when all subjects are off study);
- All protocol-required data collection of identifiable private information described in the IRB/EC-approved research plan;
- All analysis of identifiable private information described in the IRB/EC-approved research plan;
- Primary analysis of either identifiable private or de-identified information.

Publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be submitted by the Investigator to the HPTN Manuscript Review Committee, DAIDS, ViiV Healthcare, Gilead Sciences, Inc. for review prior to submission.

17. Appendices from the main body of the protocol have been modified accordingly to reflect this open label part of the study.

D. Schedules of Procedures and Evaluations for Steps 4 a-c and 5

See Tables 7 – 10 for corresponding Schedules of Procedures and Evaluations for Steps 4 a-c and 5, as well as Table 5 for participants who become infected with HIV during the time of this amendment. Refer to the Schedule of Forms (in SSP Section VIII) as well as instructions on the forms for whom and when to administer forms.

Table 1: STEP 4a Schedule of Procedures and Evaluations – Daily Oral Cabotegravir – OPTIONAL for participants initiating CAB injections

Procedures	DAY 0	WEEK 4
Informed consent/Product Choice discussion	X	
Product choice assessment questionnaire (Interviewer-administered)	X	
Locator information	X	X
HIV counseling	X	X
Offer condoms and lubricant	X	X
Interviewer-administered assessment (SMSQ)	X	
CASI-administered assessment (behavioral assessment)	X	
Adherence counseling	X	X
Self-reported pill adherence		X
Directed history, con meds, directed physical exam	X	X
Blood collection	X	X
Dispense pills (enough for 8 weeks)	X	
HIV testing[1]	X	X
Chemistry testing	X[2]	X
Liver function tests	X[3]	X
Plasma storage	X	X

FOOTNOTES FOR TABLE 7:

[1] The HIV testing algorithm is provided in Figure 2 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.

[2] The only chemistry required is creatinine. If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.

[3] Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase. If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.

Table 2: STEP 4b Schedule of Procedures and Evaluations – Loading Dose Cabotegravir Injection – for participants initiating or restarting CAB injections

Procedures*	DAY 0
Informed consent/ Product Choice discussion[1]	X
Interviewer-administered Product Choice assessment questionnaire [1]	X
Locator Information	X
HIV counseling	X
Condoms and lubricant	X
Interviewer-administered assessment (SMSQ)[2]	X
CASI-administered assessment (behavioral assessment)[2]	X
Adherence counseling	X
Directed history, concomitant medications, directed physical exam	X
Blood collection	X
Injection	X
ISR evaluation	X
HIV testing[3]	X
Plasma storage[4]	X
Chemistry testing[5]	X
Liver function tests[6]	X

FOOTNOTES FOR TABLE 8:
*Participants who opted into Step 4a must complete Step 4b Day 0 and receive their first injection within 8 weeks of starting Day 0 of Step 4a.
[1] For participants who transition from Step 4a to Step 4b and completed this assessment as part of Step 4a, do not repeat upon entry to Step 4b.
[2] Refer to instructions in the interviewer-administered and CASI assessments as well as the Schedule of Forms for whom and when these assessments should be administered.
[3] The HIV testing algorithm is provided in Figure 2 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] Blood collected for plasma storage must be collected prior to the loading dose.
[5] The only chemistry required is creatinine. If it was performed during Step 4a, do not perform at Day 0 of Step 4b
[6] Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.

Table 3: STEP 4c Schedule of Procedures and Evaluations – Cabotegravir Injections

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						
Locator Information	X	X	X	X	X	X	X
HIV counseling	X	X	X	X	X	X	X
Condoms and lubricant	X	X	X	X	X	X	X
Interviewer-administered assessment (SMSQ)	X		X				X
CASI-administered assessment (behavioral assessment)	X		X				X
Adherence counseling	X	X	X	X	X	X	X
Directed history, concomitant medications, directed physical exam	X	X	X	X	X	X	X
Weight data entry to Medidata Rave			X				X
Blood collection	X	X	X	X	X	X	X
Urine collection for GC/CT testing				X			X
Rectal swab for GC/CT testing[2]				X			X
Injection	X	X	X	X	X	X	X
ISR evaluation	X	X	X	X	X	X	X
HIV testing[3]	X	X	X	X	X	X	X
HCV testing[4]							X
Chemistry testing[5]	X			X			X
Liver function tests[6]	X			X			X
Syphilis serologic testing				X			X
Urine GC/CT testing				X			X
Rectal swab GC/CT				X			X
Plasma storage[7]	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. Participants who complete Step 4c will then 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.

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

[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 2 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. If it was performed during Step 4a or 4b, do not perform at Day 0 of Step 4c.

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

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

Table 4: STEP 5 Schedule of Procedures and Evaluations – Open Label Daily Oral TDF/FTC

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	X		
Interviewer-administered Product Choice assessment	X		
Locator information	X	X	X
HIV counseling	X	X	X
Offer condoms and lubricant	X	X	X
Interviewer-administered assessment (SMSQ)	X		X
CASI-administered assessment (behavioral assessment)	X		X
Adherence counseling	X	X	X
Directed history, concomitant medications, directed physical exam	X	X	X
Weight for entry to Medidata Rave	X	X	X
Blood collection	X	X	X
Urine collection for GC/CT testing and urinalysis	X[1]		X
Rectal swab for GC/CT testing[2]	X[1]		X
Dispense pills	X	X	X
HIV testing[3]	X	X	X
Chemistry testing[4]	X		X
Liver function tests[5]	X		X
Urinalysis	X		X
Syphilis serologic testing	X[1]		X
Urine GC/CT testing	X[1]		X
Rectal swab GC/CT testing	X[1]		X
HCV[6]			X
Plasma storage	X	X	X
DBS	X	X	X

FOOTNOTES FOR TABLE 10:

*Participants originally randomized to oral TDF/FTC who choose to continue TDF/FTC will be followed until three years from date of enrollment. 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 complete Step 4c, and participants who transition to Step 5 prematurely from Step 4c will be followed for 48 weeks. 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.

[1] If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.

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

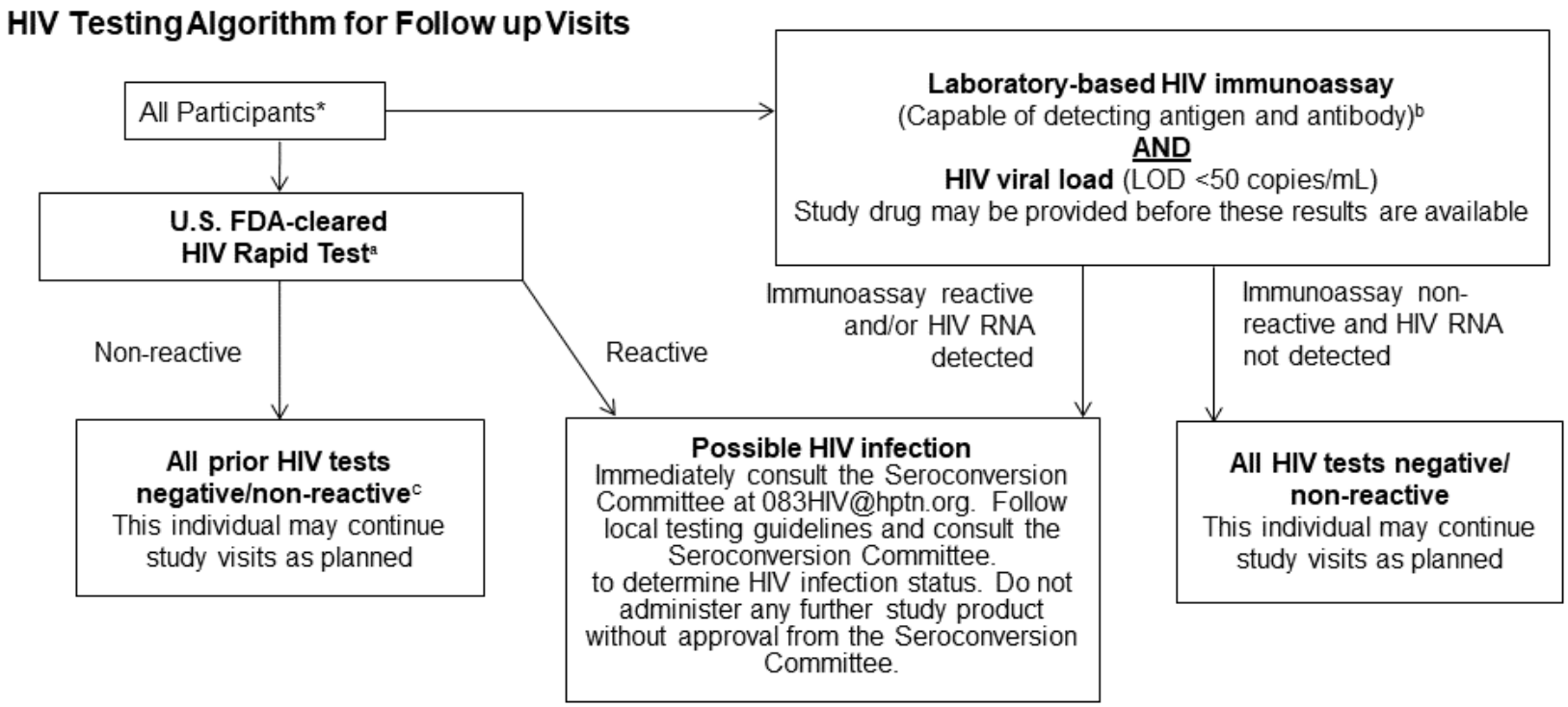
[3] The HIV testing algorithm is provided in Figure 2 below and Appendix VIII of the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.

[4] The only required chemistry test is creatinine. If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.

[5] Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase. If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.

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

Figure 2: HIV Testing Algorithm for Follow up Visits:



NOTES:

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

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

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

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

Table 5: Schedule for Additional Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result (including HIV confirmatory visit)

Note 1: The procedures listed for the HIV Confirmation Visit apply to participants who become infected during Steps 4 a-c and 5. The procedures listed for Weeks 12, 24, 36, and 48 apply only to participants with confirmed HIV infection during Steps 4b and 4c of the study. Participants with confirmed HIV infection in Step 5 of the study may undergo similar procedures as listed in Weeks 12, 24, 36, and 48, and will be determined by the members of 083CMC@hptn.org. Participants with confirmed HIV infection in Step 4a will be terminated from the study and referred to local care.

Note 2: Procedures for discordant or discrepant HIV test results are outlined in the SSP.

	HIV Confirmation Visit	Week 12	Week 24	Week 36	Week 48[7]
ADMININISTRATIVE, BEHAVIORAL, REGULATORY					
Locator information	X	X	X	X	X
Offer condoms and lubricant	X	X	X	X	X
HIV counseling	X				
CLINICAL EVALUATIONS AND PROCEDURES					
History, con meds, physical exam	X	X	X	X	X
Blood collection	X	X	X	X	X
LOCAL LABORATORY EVALUATIONS					
HIV testing[1]	X				
CD4 cell count	X		X		X
HIV viral load testing	X		X		X
HIV resistance testing[2]	X				
Chemistry testing[3]			X		X
Liver function testing[4]			X		X
Plasma storage[5]	X	X	X	X	X
DBS storage[6]	X				

[1] The HIV confirmation visit procedures, sample collection, and testing are to be performed on a different day from day of sample collection where the participant had an initial reactive/positive HIV test result. Procedures for the HIV Confirmation Visit are provided in the SSP Manual. If HIV rapid testing is included in the HIV testing algorithm, this testing may be performed in the clinic or the laboratory.

[2] Sites will collect specimens for resistance testing at a local laboratory to assist with clinical management; results from resistance testing performed at local laboratories will not be reported to the SDMC. Stored plasma cannot be used for real-time/local resistance testing.

[3] The only required chemistry test is creatinine.

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

[5] Stored plasma will be used for Quality Assurance testing at the HPTN LC and for other assessments described in the SSP. Assessments will be performed retrospectively; results will not be returned to study sites or participants.
[6] Stored DBS will be used for pharmacokinetic assessments. Assessments will be performed retrospectively; results will not be returned to study sites or participants.
[7] The Week 48 visit should be timed as closely as possible to 52 weeks after the participant received their last injection.

E. Toxicity Management General Guidance

In general, the IoR has the discretion to hold study product at any time if she/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary according to the judgment of the IoR. Throughout this appendix are examples of AEs that require consultation with the CMC; in all such cases, the CMC should be notified as soon as possible and ideally within 72 hours of site awareness of the AE in question. Investigators also should consult the CMC for further guidance in restarting study product or progressing to permanent discontinuation.

The following general guidance refers to all AEs except for ALT, creatinine clearance (absolute and change from baseline), and CPK. Refer to the tables below for specific guidance about these laboratory abnormalities.

Grade 1 or 2

In general, participants who develop a Grade 1 or 2 AE regardless of relatedness to study product, and that is not specifically addressed in the Table below may continue use of the study product per protocol.

Grade 3

Any grade 3 or higher clinical or laboratory AE observed prior to their first injection of active CAB (i.e. in STEP 4a) will prompt consultation with the CMC prior to any injectable dosing.

At any time, participants who develop a Grade 3 AE or toxicity that is not specifically addressed in the Table below and is judged to be related to study product by the Investigator, study product use should be temporarily discontinued. In general, the investigator should re-evaluate the participant until resolution of the toxicity. For Grade 3 AEs deemed related to study product, the study product should be permanently discontinued if improvement to severity ≤Grade 2 cannot be documented within 4 weeks of receipt of the initial result. If study product is resumed after holding for a Grade 3 AE and the same Grade 3 AE recurs without alternative explanation, study product should be permanently discontinued. For Grade 3 AEs deemed unrelated to study product, study product may continue with appropriate clinical management by the site, per local standards of care.

Grade 4

Any grade 4 or higher clinical or laboratory AE observed prior to first injection (i.e. in STEP 4a) will prompt permanent study product discontinuation. Participants who develop a Grade 4 AE or toxicity that is not specifically addressed below (regardless of relationship to study product) should have the study product temporarily discontinued. Study product use will not be resumed (i.e. product hold will be permanent) if the Grade 4 AE is considered by the IoR to be related to study product use. If study product use is resumed and the same Grade 4 AE recurs at Grade 4 level at any time, study product must then be permanently discontinued, unless an alternative explanation for the recurrence is clearly documented.

General Criteria for Discontinuation of Study Product

Participants may voluntarily discontinue the study products for any reason at any time. Investigators will permanently discontinue participants from study product per protocol for any of the specific criteria below, which may be further clarified in the SSP Manual. Investigators also may permanently discontinue participants for reasons not shown here or in the SSP Manual (e.g., to protect participants' safety and/or if participants are unable or unwilling to comply with study product use procedures). In such cases, the IoR or designee must first query the CMC for review. The CMC will provide a written response to the site indicating whether the CMC has recommended permanent discontinuation of study product based on careful review of all relevant data. It should be noted that the safety of the participant should always take precedence, and therefore, an IoR may determine that study product be permanently discontinued before the CMC has time to respond. This is acceptable, and in such cases, the CMC should be notified as soon as possible regarding the nature of the case and the course of action taken.

The criteria for permanent discontinuation of study product use for an individual participant are:

- Study product-related toxicity requiring permanent discontinuation of study product per the guidelines above and below
- Completion of regimen as defined in the protocol
- Request by participant to terminate study product
- Clinical reasons determined by the IoR
- Acquires HIV infection

Participants in Step 4c who prematurely and permanently discontinue study product should be asked to continue to be followed according to the applicable Schedule of Evaluations and Procedures of Step 5.

Study product will be temporarily withheld from a participant for any of the following reasons:

- Report of use of prohibited concomitant medications as described in the SSP Manual and protocol. Study product use may resume when the participant reports that he/she is no longer taking the prohibited medication, provided other reasons for temporary study product hold/permanent discontinuation do not apply.
- The participant is unable or unwilling to comply with required study procedures such as HIV testing and routine laboratory assessments, or otherwise might be put at undue risk to their safety and well-being by continuing study product use, according to the judgment of the IoR.
- The participant has one or more reactive HIV test results or expresses a concern about having acute HIV infection. Criteria for resuming use of study product in these circumstances are defined in the protocol and SSP Manual.

Participants who temporarily or permanently discontinue study product during the CAB oral phase (STEP 4a) will be instructed to return all study products as soon as possible.

Guidance on Toxicity Management for Specified Toxicities:

Nausea, Vomiting, and Diarrhea

CONDITION AND SEVERITY	IMMEDIATE ACTION	FOLLOW-UP AND MANAGEMENT
Nausea, Vomiting, and Diarrhea		
Grade 1 and 2	Continue study product (reminder to take study product with food)	Treat symptomatically with hydration, oral antiemetic therapies or antiemetic suppositories at the discretion of the Investigator. The Investigator should order any clinically relevant laboratory analyses (per judgment of the Investigator).
Grade ≥ 3	Discontinue study product temporarily	Participants with Grade ≥ 3 nausea, vomiting, or diarrhea, for which an alternative etiology is not established, must discontinue the study product temporarily until Grade 2 or lower and be treated symptomatically. Should condition(s) not improve to Grade ≤ 2 within 7 days, the Investigator should consult the CMC for guidance on continuing the temporary discontinuation or progressing to permanent discontinuation of study product.

Guidance on Toxicity Management for Specified Toxicities:

ALT

CONDITION AND SEVERITY	STUDY PRODUCT USE	FOLLOW-UP AND MANAGEMENT
ELEVATIONS in ALT		
Grade 3 and higher		**Oral CAB (Step 4a):** A Grade 3 or higher ALT abnormality reported at Week 4, regardless of relatedness to the study product, will prohibit a participant from entering the injection phase (Step 4b) of the study, and the participant will be permanently discontinued from the study. All such cases must be reported to the CMC. Prior to discontinuation, participants will be followed every two weeks for ALT assessments until they return to ≤ Grade 1. If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up, or return to clinical care.
Grade 3 and higher		**Injectable CAB (Step 4c)**: For Grade 3 and higher ALT, study product will be permanently discontinued. Repeat testing should be performed as soon as possible, and participants should be followed every two weeks until levels are ≤ Grade 1. **If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up, or in rare cases where alternative etiology has been identified and ALT has resolved to Grade 1 or lower, restart of study product.** Participants who are permanently discontinued from study product will be transitioned to local clinical care for clinical management and local prevention services and terminated from the study per CMC direction. **Open label TDF/FTC (Step 5):** Participants will be followed per the Schedule of Procedures and Evaluations for Step 5; for participants who have transitioned to Step 5 from Step 4c, the decision whether it is safe to provide oral TDF/FTC will be made with guidance from the CMC. When Step 5 concludes in these cases, the participant will be referred to local prevention services. Note that Step 5 concludes at Week 48 for all participants transitioning from Step 4c.

Guidance on Toxicity Management for Specified Toxicities:

Note for all grades: All study participants will be negative for HBsAg at study entry, and participants who enter the study without evidence of immunity to HBV will be referred for HBV vaccination. Therefore, pre-existing HBV infection is not likely to be a cause of AST/ALT elevations, however incident HBV infection may occur and should be considered in cases of otherwise unexplained ALT elevations.

Careful assessments should be done to rule out the use of alcohol, lactic acidosis syndrome, non-study medication-related product toxicity, herbal medications/supplements, or viral hepatitis as the cause of elevation in AST or ALT of any grade. The participant must be carefully assessed for any symptoms or signs of hepatotoxicity, including fatigue, malaise, anorexia and nausea, jaundice, acholic stools, right upper quadrant pain, or hepatomegaly. If the AST/ALT elevation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent, if possible, should be undertaken. If symptoms or signs of clinical hepatitis are present, study product must be held or discontinued. In addition, all participants with elevated values should be considered for testing for Hepatitis A, B, and C infection, as well as autoimmune and toxin-mediated conditions. A standardized work-up will be recommended by the CMC in such cases.

Guidance on Toxicity Management for Specified Toxicities:

Creatinine Clearance, only applicable to TDF/FTC recipients

Changes in creatinine clearance, in CAB recipients should be managed per clinical standards of care, unless attributed by the IoR to SP, in which case the below toxicity management guidelines should apply.

NOTE: Adverse events related to creatinine clearance should be based on examination of BOTH the absolute creatinine clearance AND the change in creatinine clearance from baseline (Enrollment/ Visit 2.0). When gradable, only the higher grade of these two assessments should be entered on the Adverse Event e-CRF. Clinical Management of Grade 3 and Grade 4 changes in creatinine clearance should follow the "Toxicity Management General Guidance" ONLY when the absolute creatinine clearance is < 90 mL/min. That is, changes in creatinine clearance of >30% from baseline that DO NOT result in an absolute creatinine clearance < 90 mL/min do NOT need to be reported to the CMC or more frequent clinical monitoring. Additionally, changes in creatinine clearance of > 30% that are accompanied by a creatinine that remains within normal limits also do not need to be reported to the CMC and do not require more frequent clinical monitoring.

CONDITION AND SEVERITY	STUDY PRODUCT USE	FOLLOW-UP AND MANAGEMENT
CREATININE CLEARANCE		
Estimated CrCl< 60 mL/min	Discontinue study product temporarily	If the calculated creatinine clearance is <60mL/min, it should be confirmed within 1 week of the receipt of the results, and the CMC should be consulted for adjudication and recommendation for further testing and follow-up.
Confirmed CrCl< 60 mL/min	Permanently discontinue study product	If the calculated creatinine clearance is confirmed to be <60 mL/min, the study product must be permanently discontinued and the CMC notified. Participants who fail to have a confirmed test within 2 weeks of receiving the initial result, should be discontinued from use of the study product until CMC adjudication and recommendation for further testing and follow-up.
Re-testing result is ≥60 mL/min	Consult CMC for guidance	If re-testing yields a result ≥ 60 mL/min, the Investigator must consult the CMC for further guidance on resuming study product use, continuing the hold temporarily, or progressing to permanent discontinuation. If the investigator in consultation with the CMC has determined that the case has

		stabilized, it may be possible to decrease the frequency of follow-up laboratory testing in addition to resumption of study product.

Guidance on Toxicity Management for Specified Toxicities:

Guidance for Injection Site Reactions (ISRs)

ISR discomfort can be managed symptomatically (e.g. cold/warm compress, acetaminophen, ibuprofen) if the reaction is interfering with the participant's ability to perform activities of daily living. Recommended interventions include:

- Pre-treatment (prior to injection administration) warm compresses
- Topical or oral pre-treatment with NSAID preparations, unless contraindicated
- Immediate post-injection massage to injection location
- Post-treatment warm or cold compresses
- Post-treatment NSAID or other analgesic preparations, topically or orally

A proactive and comprehensive approach to mitigating ISRs should be undertaken, with premature transition from Step 4c to Step 5 being reserved for refractory cases in extreme circumstances. The CMC should be notified of such transitions.

Guidance for Allergic Reactions

Participants may continue to receive oral or injectable study product for Grade 1 or 2 allergic reactions at the discretion of the IoR or designee. The participant should be advised to contact the study site staff immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Participants with Grade ≥3 allergic reactions that are considered related to study product should permanently discontinue study product and continue to be followed on study/off study product. Participants should be treated as clinically appropriate and followed until resolution of the AE.

F. Addendum To The Main Sample Informed Consent Form

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
February 10, 2021
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 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
- 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

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 place 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. We will tell you when your 3 years in the study will end.

IF YOU PREMATURELY STOP GETTING INJECTIONS

If you choose to continue or start receiving CAB injections and have to stop getting them because of a side effect or if you choose to stop getting them, 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.

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 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, and 5 below.

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, to check your general health, the health of your liver and kidneys, and for storage	X	X
Give you study pills, explain how to take them and any side effects they may cause	X	

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, to check your general health, the health of your liver and kidneys, and for storage	X
Administer the first shot in your buttocks	X

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	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 (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
Give you a shot in the buttocks	X	X	X	X	X	X	X

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	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 LEAVE THE STUDY BEFORE YOUR FINAL VISIT:

If you leave the study before your final visit, 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.

CAB protected people in this study from getting HIV infection about 70% 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, and we will ask you to come back for a visit every 3 months for about a year.

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

February 10, 2021

[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, and you voluntarily agree to continue in this part of the study, please sign your name or make your mark below. Also, please indicate by providing your initials in the spaces below the additional sample collection, genetic testing, or long-term storage that you agree to.

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

_____ I do not agree to take part 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

APPENDIX VI: OPERATIONAL GUIDANCE DURING THE COVID-19 PANDEMIC

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

PRIORITIZATION OF STUDY VISIT PROCEDURES

- Sites with full capacity to conduct study visits in-person at the study clinic should continue to do so in full compliance with the protocol.
- Sites with limited capacity to conduct in-person study visits should prioritize assessments as determined by the site Investigator of Record (IoR) (e.g., urgent safety testing, HIV testing, provision of study product, etc.).
- Sites with no capacity to conduct in-person visits may conduct telephonic or video-based assessments remotely at the discretion of the IoR (and following all institutional approval requirements), and may include targeted medical history (including ascertainment of AEs), HIV and adherence counseling, interviewer-administered surveys, etc. The content of these visits should be determined by the site IoR.

  NOTE: If locally available, feasible, and at the discretion of the IoR, home HIV self-tests can be sourced and distributed to participants for participant use, and results demonstrated by video or photo-sharing to study sites as corroborative evidence of testing and test results. Such photos should be placed in the participant research record. Absence of home-testing results will NOT be considered a protocol deviation, nor reportable.
- Sites that are able may also conduct study visits — in full or in part — off-site if permitted by applicable government, health authority, and institutional policies. This is including but not limited to home-based visits. Where this option is permitted, site staff should communicate with participants to determine in advance where and when such visits will take place, with adequate protections for safety, privacy, and confidentiality. Off-site visit procedures should be conducted by site staff who are adequately qualified and trained to conduct the procedures, as determined by the site Investigator of Record (IoR), with attention paid to occupational health, biohazard containment, and specimen and data chain of custody. These staff should also be adequately qualified and trained to immediately assess and/or manage any adverse events or social impacts that may occur during the visits. If adverse events requiring further evaluation or management are identified during an off-site visit, staff conducting the visit should arrange for appropriate clinical management, in consultation with the IoR or designee as needed.

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

GUIDANCE FOR STEP 4a, STEPs 4b AND 4c, AND STEP 5

For participants in Step 4a: Continuation on daily oral Cabotegravir would be appropriate – meaning, for participants who cannot report for the Week 4 visit, study product would continue, and where possible, study product potentially shipped or couriered to participants directly from PAB DAIDS established site pharmacies. If this is not feasible, participants should be instructed to protect themselves against HIV infection and exposure by all means available to them until they can return to study participation, and participants should document as carefully as possible the dates of exhaustion of their Step 4a study product medication supplies. Investigators of Record should use their clinical judgement regarding ongoing dispensation of oral Cabotegravir in these extraordinary circumstances absent interim safety monitoring.

For participants in Steps 4b and 4c: The same advice above would apply - that participants should protect themselves against HIV infection and exposure by all means available to them until they can return to study participation.

All sites should emphasize multi-modal HIV prevention activities – including social distancing, HIV status discussion, condom use, PEP and PrEP clinical services, HIV and STI testing (and treatment), clean needle use (if applicable), and other locally available in-person and/or on-line HIV prevention resources.

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

Sites that are able may provide PrEP services through NON-STUDY clinical services, or through referral to PrEP services as a bridging mechanism while study product injections are unable to be administered.

For sites that are not be able to provide PrEP services through NON-STUDY clinical services:

Additional open-label TDF/FTC supply was provided by Gilead Sciences, Inc., for the purpose of a bridging mechanism while study injections are unable to be provided as a result of the global COVID-19 pandemic, and is available for ordering through the DAIDS Clinical Research Product Management Center.

- Open-label Truvada for oral bridge therapy is available from the CRPMC now.
- The site team should communicate closely and notify the site pharmacist on which participants in Steps 4b and 4c will need study provided open-label Truvada for oral bridge therapy.
- The site pharmacist should place an order into the CRPMC for appropriate quantity of open-label Truvada supply for applicable participants in Steps 4b and 4c.
- The site pharmacist at US sites can place an order into the CRPMC for up to three-month supply of open-label Truvada for applicable participants in Steps 4b and 4c.
- The site pharmacist at international sites can place an order into the CRPMC for up to six-month supply of open-label Truvada for applicable participants in Steps 4b and 4c.

For participants in Step 5: Continuation on daily oral TDF/FTC would be appropriate; (if oral study product is ongoing for that participant) – meaning, for participants who cannot report for the quarterly visits, study product would continue, and where possible, study product potentially shipped or couriered to participants directly from PAB DAIDS established site pharmacies. If this is not feasible, participants should be instructed to protect themselves against HIV infection and exposure by all means available to them until they can return to study participation, and participants should document as carefully as possible the dates of exhaustion of their Step 5 study product medication supplies. Investigators of Record should use their clinical judgement regarding ongoing dispensation of oral study product in these extraordinary circumstances absent interim safety monitoring, given known previous creatinine clearance and adherence reported trajectories.

It is acceptable to provide a 3-month supply plus 1 additional month for overage for each quarterly dispensation (again, provided quarterly only if the IoR determines ongoing dispensation is acceptable as stated above).

STUDY PRODUCT CONSIDERATIONS

- For emergency cases, the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* permits shipment or courier of oral study product from the site directly to participants. The pharmacist should refer to the section on "Shipping Study Product to a Participant" in this manual for detailed procedures. If this method is to be implemented, each site pharmacist must develop appropriate procedures for the shipment or courier of oral study product to identified participant in accordance with these guidelines and must include appropriately documented chain of custody. This method should only be used if permissible per local institutional and IRB/EC policies.
- All questions related to study product management should be directed to Katie Shin – kashin@niaid.nih.gov.

DOCUMENTATION

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for HPTN 083.
- Participant-specific documentation should be entered in participant study charts in real-time to the extent possible.
- Specific guidance regarding coding visits and instructions has been provided from SCHARP in a separate communication to all sites (Data Communique #5 - Corrected, dated April 2, 2020).
- Sites will continue to document deviations related to study visits and procedures impacted by the global COVID-19 pandemic just as would be done in the absence of the pandemic.