

**Letter of Amendment #1 to:**

**HPTN 084-01:**

**Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV among Adolescent Females – A Sub-study of HPTN 084**

**Version 1.0, October 14, 2019**

**DAIDS Document ID: 38655**

**IND # 122, 744**

**FINAL LoA #1: 03 December 2020**

**Instructions to the Study Sites from the Sponsor**

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The following information impacts the HPTN 084-01 study and must be forwarded to all responsible Institutional Review Boards (IRBs)/Ethics Committees (ECs) and any other required regulatory authorities as soon as possible for their information, review and approval. It is expected that sites will submit the changes to the HPTN 084-01 study specified in this Letter of Amendment (LoA) for approval as soon as possible upon receipt. The content of the LoA is effective upon obtaining all required approvals.

This LoA has appended to it a Dear Participant Letter for all study participants (See LoA Appendix I). This Dear Participant Letter should accompany any enrollment to V1.0 of the HPTN 084-01 protocol.

Your site is required to submit an LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Your site will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. A LoA registration notification from the DAIDS PRO is ***NOT*** required prior to implementing the LoA. Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential document files for HPTN 084-01.

If the HPTN 084-01 protocol is fully amended in the future, this Letter of Amendment will be incorporated into the next version. Text appearing below in **bold** will be added, and text appearing in ~~strike-through~~ will be deleted.

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## Background and Summary of Modifications:

Some modifications included in this Letter of Amendment are changes made as a result of a pre-planned interim efficacy and safety review by the National Institute of Allergy and Infectious Diseases (NIAID) Multinational Data and Safety Monitoring Board (DSMB) of the parent protocol, HPTN 084. On 5 November 2020, the NIAID Multinational DSMB was in agreement that the primary question of whether long-acting cabotegravir prevents HIV infection has been answered in the affirmative and was highly statistically significant. The study's sponsor (NIAID) accepted the Board's recommendation and, thus, these and other changes to protocol HPTN 084-01 are listed below and in the Implementation Section of this document.

The immediate modifications are summarized below:

### 1. **Revision 1:** Title and Protocol Signature Pages

The title and protocol signature pages are updated for Letter of Amendment #1 (see Implementation Section of this LoA). NICHD has been removed from funders and BMGF has been added to supporters. Updated to reflect current date and version.

2. **Revision 2:** Section 1.2 is updated to replace reference to an outdated version of the cabotegravir Investigator's Brochure with the most recent version.
3. **Revision 3:** In Section 1.5.2, an unnecessary table (for this version) has been removed.
4. **Revision 4:** Section 1.7 is created to deliver HPTN 083 and HPTN 084 results, as they relate to this protocol.
5. **Revision 5:** Section 1.8 is edited to include the latest information on pediatric dosing. Section 1.8.1 is a new section which includes PK data on adolescents <50kg from the MOCHA Study (IMPAACT 2017).
6. **Revision 6:** Dolutegravir information regarding pregnancy, taken from the parent protocol HPTN 084, has been incorporated.
7. **Revision 7:** We have removed language from Section 2.3, Study Design and Overview, that is no longer relevant. This information stated that the team would broaden the sexual risk profile of participants in the future, if results show CAB LA is effective at preventing HIV. This is now the case, so this language has been removed. As is noted in number 18 below, we have also added the option for participants to join an open label CAB study instead of using Truvada during follow-up in Step 3.
8. **Revision 8:** Section 3.1, Inclusion Criteria, is updated in two areas. (See number 18 below for another minor change, not included in the implementation section following this section.)
  - 3.1.3 Decreased weight criterion from  $\geq 50$  kg (110 lbs) to  $\geq 35$  kg (77 lbs).
  - 3.1.10 Added new inclusion criterion: "If currently on PrEP from a non-study source, willing to stop said PrEP prior to enrollment and agree to switch to oral CAB for the lead-in period and CAB LA injections."
9. **Revision 9:** Section 3.2, Exclusion Criteria, is updated in two areas:
  - 3.2.2 "Currently receiving PrEP from a non-study source" has been removed.

- 3.2.5 Three exclusion criteria have been removed, to broaden the sexual risk profile for participants, due to the superiority results from HPTN 084.
10. **Revision 10:** Section 5, Study Procedures, has been updated in various ways. See Implementation Section for more details.
  11. **Revision 11:** Removal of description of SMC from Clinical Data Review section (Section 6.4).
  12. **Revision 12:** Updates to Section 7, Statistical Considerations.
  13. **Revision 13:** Section 8.1, Ethical Review: Removed inclusion of SRC and PSRC review of any subsequent modifications of the protocol and template informed consent forms.
  14. **Revision 14:** The Virology section (Section 9.3) now includes language permitting the HPTN Laboratory Center to periodically conduct resistance testing, instead of conducting it retrospectively. This was a change in the parent protocol, given DSMB feedback.
  15. **Revision 15:** Record Retention, in Section 10.6, was changed to incorporate potential European Medicines Agency (EMA) requirements.
  16. **Revision 16:** Appendix I has been changed to allow for collection of demographic information at Screening or Enrollment and administering the PHQ-9 at Enrollment and to clarify when to use urine samples and vaginal swabs.
  17. **Revisions 17 and 18:**
    - a. The fasting lipid requirement has been removed at every visit except Enrollment and Week 34 (Appendices II and III).
    - b. Appendix II: footnote changes include clarification to calculate BMI only at injection visits and instructions for fasting lipid requirement if participant does not receive all 5 injections.
    - c. Minor changes to Appendix III:
      - i. Inclusion of provision of a Hepatitis B vaccination (if needed) and Truvada® at early discontinuation.
      - ii. Period of qualitative interviews was extended to the +24 week last injection visit.
      - iii. Blood collection at Week +12 last injection was added.
  18. Other minor changes have been made (not included in the Implementation Section below):
    1. The Table of Contents has been updated to reflect corrected linked page numbers.
    2. Patient Health Questionnaire-9 (PHQ-9) has been added to and NICHD has been removed from the Acronyms list.
    3. “TENOFVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®)” has been replaced with “Trade name: TDF/FTC, Truvada®” throughout the protocol.

4. The Protocol Team Roster information is updated for Lynda Stranix-Chibanda, Lynda Emel, Jim Hughes, Sahar Zangeneh, and Marcus Bryan. Julie Ngo and Jean Paul Pease are added as protocol team members. Bill G. Kapogiannis, Heather Noble, and Lisa Hightow-Weidman were removed from the roster. External links to email addresses were removed.
5. Table and Section numbers have been updated.
6. The weeks in Step 2 have been changed from 34 to 29 in the Study Duration section of the Schema.
7. The 4<sup>th</sup> secondary objective on pharmacokinetics of CAB LA has been returned to Section 2.2 (formatting error).
8. Section 3.1.6: Platelet count is clarified to **cells/mm<sup>3</sup>**.
9. Section 4.4 (under the Truvada® section): Descovy® spelling error was corrected.
10. Various sections: Changes made to clarify that a participant may join an open-label CAB study during Step 3 if available in their area.
11. Two new references have been added.
12. References to Appendices numbers have been corrected, as necessary.
13. Minimal changes made to the Informed Consent Forms (ICFs)/Assents:
  - a. Date and version number have been changed.
  - b. Removal of *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and addition of Bill and Melinda Gates Foundation (BMGF) as funding sources on the title pages of the ICFs/assents.
  - c. Under reasons why a participant may not be allowed to participate further, “The study **staff** feels that staying in the study would be harmful to you.” has been changed to “The study **doctor** feels that staying in the study would be harmful to you.”
  - d. Since the results from HPTN 084 have been released, we have now included mention of efficacy instead of unknown efficacy of CAB LA in these ICFs/assents, as well as included the possibility for a participant to join and open label CAB study in Step 3 (if available locally and if desired and warranted).
  - e. Other changes have been made, in order to reflect recent changes made to the 083-01 ICFs/assents, regarding incentives, etc., by the HPTN’s sIRB, Advarra:
    - i. Added information on whether the participant’s samples would be used for profit or not.
    - ii. Added information about what test results will be returned to the participant.
    - iii. Added an additional reason why the participant may be released from the study.
    - iv. Added amount and frequency of incentives.

## **Implementation**

Revision 1. Title and Protocol Signature Page edits

**HPTN 084-01:  
Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention  
of HIV among Adolescent Females – A Sub-study of HPTN 084**

**DAIDS Document ID: 38655**

**A Study by the HIV Prevention Trials Network**

**Sponsored by:**

Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases  
(NIAID),  
US National Institutes of Health (NIH)

**Support Provided by:**

ViiV Healthcare  
Bill and Melinda Gates Foundation (BMGF)

**IND Holder:**

DAIDS, NIAID, NIH

**IND #:** 122,744

**Protocol Chair:**

Sybil Hosek, PhD

**Protocol Co-Chair:**

Lynda Stranix-Chibanda, MBChB, MMED

**Version 1.6  
03 December 2020**

**Protocol Signature Page**

**HPTN 084-01:  
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**DAIDS Document ID: 38655**

**Version 1.0 dated 14 October 2019**

**Letter of Amendment #1, 03 December 2020**

**I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.**

\_\_\_\_\_  
**Name of Investigator of Record**

\_\_\_\_\_  
**Signature of Investigator of Record**

\_\_\_\_\_  
**Date**

Revision 2: Section 1.2 - Removal of reference to outdated CAB IB.

## **1.2 Overview of Oral CAB and CAB LA**

The majority of information contained in this section of the protocol is a summary of information provided in the CAB Investigator's Brochure (IB) **V9.0, Effective Dated December 2019, ~~V8.0, Effective Dated 17 December 2018~~** unless otherwise noted.

Revision 3: Section 1.5.2 - Removal of unnecessary table.

### **1.5.2 CAB LA**

Through October 2018, approximately 4236 adult participants have been exposed to at least one dose of CAB (oral and/or LA) across 18 completed or ongoing Phase 1, 2 & 3 clinical trials. (~~see Table 4~~).

Revision 4: Section 1.7 is created to update the protocol with recent results from parent protocols, HPTN 083 and HPTN 084.

### **1.7 Results from HPTN 083 and 084**

**In May 2020 at a pre-planned interim review the DSMB recommended that the blinded portion of HPTN 083, a companion phase III trial of CAB LA for HIV prevention in MSM and transgender women (TGW), be stopped for evidence of efficacy. Subsequent analysis confirmed that CAB was superior to TDF/FTC (HR 0.35; 95% CI 0.18-0.62) in preventing HIV infection. Overall incidence was 0.81% (95% CI 0.61- 1.07). CAB and HPTN 084 LoA # 2 to V2.0, 6 Nov 2019 FINAL v1.0 10 September 2020 Page 4 of 7 TDF/FTC were both well tolerated; most adverse events were mild/moderate and balanced between arms. Injection site reactions were more common in the cabotegravir arm but were generally grade 1-2 and decreased with time on study. Injection intolerance led to discontinuation in 46 (2.2%) active CAB-LA recipients and was associated with the severity of the reaction. Grade 2+ events observed with significant higher frequency in the CAB LA arm included nasopharyngitis, increased blood glucose and pyrexia. These differences were not observed when compared grade 3+ events. There were no significant differences in serious adverse events between the two groups.<sup>42</sup>**

**On 5 November 2020, the international DSMB met to review the safety and efficacy data for the HPTN 084 trial. Overall, HPTN 084 enrolled 3,223 cisgender women at research sites in Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, and Zimbabwe. The average age of study participants was 26 years and 57% of participants were 18-25 years old. Eighty-two percent of the women enrolled were not living with a partner, 55% reported two or more partners in the past month, with 34% having a primary partner who is reported to be living with HIV or having an unknown HIV status. A total of 38 HIV infections occurred during follow-up, with four infections in the CAB LA arm (incidence rate 0.21%) and 34 infections in the FTC/TDF arm (incidence rate 1.79%). The hazard ratio in the CAB LA versus FTC/TDF arm was 0.11 (95% CI 0.04-0.32). Approximately nine times more incident HIV infections occurred in the FTC/TDF arm than in the CAB arm. These results meet the statistical criteria for superiority of CAB LA compared to FTC/TDF in the HPTN 084 study population.**

Revision 5: Section 1.8 is updated to include MOCHA (IMPAACT 2017) results.

## 1.8 Pediatric Dosing

Currently, there is no previous clinical trial experience with oral CAB or CAB LA in humans under 18 years of age. This protocol will enroll using a weight-based approach rather than age based. This allows for an eventual adolescent indication for LA CAB in adolescents at-risk, regardless of age. The supplemental adolescent indication for Truvada® was entirely weight-based (down to 35 kg) for adolescents at risk of HIV. Also, by not specifying a lower limit of age, this allows sites the flexibility to enroll participants that meet the behavioral and physical criteria necessary to qualify. Each site will have ethics review and will consider these criteria in light of community standards; and each investigator of record will be able to determine whether a candidate is appropriate for enrollment or not. These decisions will then be made with consideration for the local context of each site/community, rather than arbitrarily choosing what age should be the lower limit.

### 1.8.1 Preliminary Results MOCHA (IMPAACT 2017)

The IMPAACT 2017 trial began enrolling in April 2019. IMPAACT 2017 (NCT03497676) is a Phase I/II, multi-center, open-label, non-comparative study to confirm the dose and evaluate the safety, tolerability, acceptability, and PK of oral CAB, long-acting injectable CAB (CAB LA), and long-acting injectable RPV (RPV LA) administered monthly among up to 155 virologically suppressed HIV-1 infected children and adolescents aged 12 to <18.

As of January 2020, 7 adolescent HIV infected participants in IMPAACT 2017 (MOCHA) aged 12 to 17 years (40 to <50kg: n=4, >50 kg: n=3) had PK collected and analyzed following oral CAB 30 mg once daily and three injections of the CAB LA adult monthly regimen (600 mg IM initiation injection, followed by two monthly 400 mg IM injections). Median (range) CAB PK parameters were within the desired target ranges, specifically Week 2 oral AUC 167.0 (131.1-326.8) µg•h/mL and Week 16 IM trough 2.9 (1.2-6.2) µg/mL, and were similar to adult exposures (Table 1.2).

**Table 1.2: Pharmacokinetic Parameters following Cabotegravir Orally Once Daily and Initiation and Monthly Continuation Intramuscular Injections in Adults**

Dosing Phase	Dosage Regimen	Geometric Mean (5 <sup>th</sup> , 95 <sup>th</sup> Percentile) <sup>a</sup>	
		AUC <sub>(0-tau)</sub> <sup>b</sup> (mcg•h/mL)	C <sub>tau</sub> <sup>b</sup> (mcg/mL)
Oral Lead-In <sup>c</sup>	30 mg once daily	145 (93.5, 224)	4.6 (2.8, 7.5)
Initial Injection <sup>d</sup>	600 mg IM Initial Dose	1,591 (714, 3,245)	1.5 (0.65, 2.9)



Monthly Injection <sup>e</sup>	400 mg IM monthly	2,415 (1,494, 3,645)	2.8 (1.7, 4.6)
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<sup>a</sup> All pharmacokinetic parameter values based on pooled FLAIR and ATLAS individual post-hoc estimates from cabotegravir population pharmacokinetic model (n = 581, 2018N384611\_01).

<sup>b</sup> tau is dosing interval: 24 hours for oral administration; 1 month for IM injections of extended-release injectable suspension.

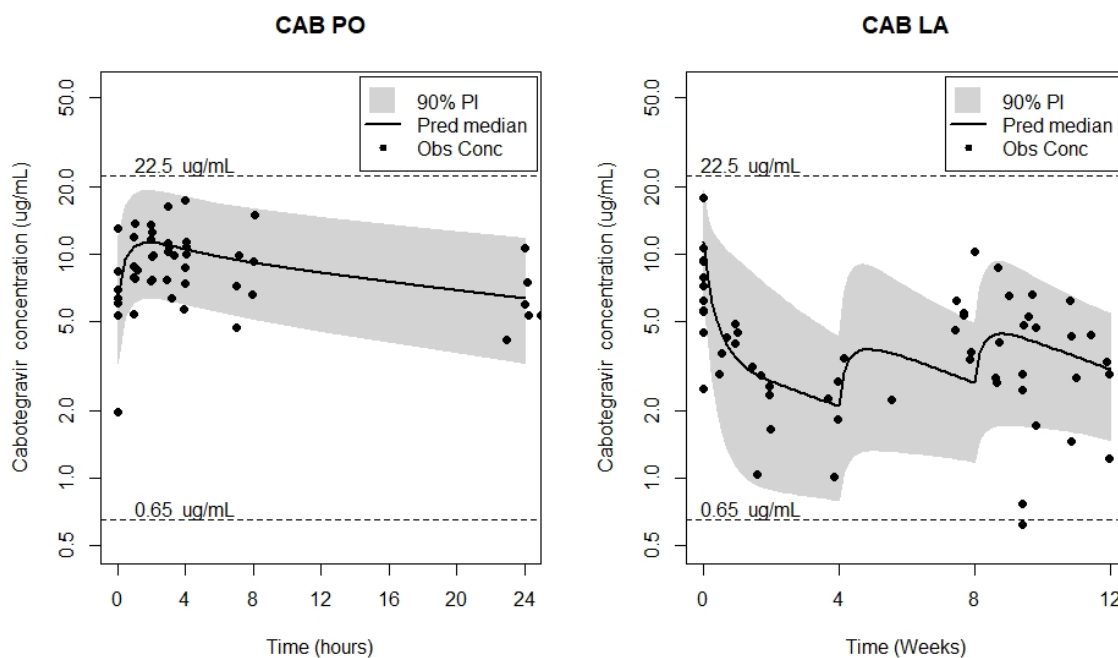
<sup>c</sup> Oral lead-in pharmacokinetic parameter values represent steady-state.

<sup>d</sup> Initial injection AUC<sub>(0-tau)</sub> value includes contribution following oral dosing because the initial injection was administered on the same day as the last oral dose; however, the C<sub>tau</sub> value at Week 4 reflects the initial injection.

<sup>e</sup> Monthly pharmacokinetic parameter values represent Week 48 data.

Preliminary CAB data observed in adolescent participants were compared to *a priori* predictions in adolescents from population PK (POP PK) modelling and simulation (Figure 1.2). The CAB POP PK model was developed utilizing exposure data from adult participants (n=1647) in clinical studies with efficacious dosing regimens having an acceptable safety profile with Q4W and Q8W injections, and simulations were conducted taking into account any potential age and weight related impact on PK, to recommend appropriate doses in adolescents that achieve comparable exposures to those seen in adults. The preliminary adolescent PK data are in agreement with the predicted exposure range and within thresholds (Figure 1.2). Given the strong agreement of observed data with predictions, the model is considered suitable to predict exposure in adolescents ≥35 kg for any dosing regimen. Predicted exposures following CAB LA Q8W administration in adolescents are shown in Table 1.2.

**Figure 1.2: Preliminary Observed CAB concentrations in adolescents compared to model predictions based on POP PK analyses from adult studies (IMPAACT 2017 Cohort 1C)**



Note: The plots represent the CAB systemic exposure: solid line and shaded band reflect the population pharmacokinetic model predictions (median and 90% interval); the dots represent the observed individual subject data. The dashed lines represent the maximum observed geometric mean exposure from the TQT study at (22.5 µg/mL) at suprathreshold doses following 150 mg q12h x 3 and the target threshold concentrations at trough (0.65 µg/mL).

**Table 1.3: Predicted Steady State CAB Parameters following CAB LA IM Q8W regimen compared with Observed and Estimated data in Adults**

		Predicted C <sub>τ</sub> (µg/mL) <sup>b</sup>	
		Post First Injection	Post Second Injection <sup>c</sup>
Adolescent Body weight	35 to <50kg	2.49 [0.98, 4.72]	2.34 [0.84, 3.98]
	≥50kg	1.76 [0.69, 3.49]	1.76 [0.77, 3.05]
Observed adult data		1.50 [0.65, 2.90] <sup>a</sup>	1.61 [0.80, 2.99] <sup>d</sup>
<p>a. Geometric mean [5<sup>th</sup> and 95<sup>th</sup> percentile] - Week 8 pre-dose concentrations were obtained following a CAB 600 mg IM dose.)</p> <p>b. Median [90% prediction Interval]</p> <p>c. C<sub>τ</sub> after second injection is 8 weeks post injection</p> <p>d. Geometric mean [5<sup>th</sup> and 95<sup>th</sup> percentile] - C<sub>τ</sub> at Week 48 with Q8W dosing regimen (ATLAS 2M, 207966)</p>			

Currently, there is no previous clinical trial experience with oral CAB or CAB LA in humans under 18 years of age. However, the IMPAACT 2017 began enrolling in April 2019. IMPAACT 2017 is a Phase I/II, multi-center, open-label, non-comparative study to confirm the dose and evaluate the safety, tolerability, acceptability, and PK of oral CAB, long-acting injectable CAB (CAB LA), and long-acting injectable RPV (RPV LA) administered monthly among up to 155 virologically suppressed HIV-1 infected children and adolescents aged 12 to <18.

In HPTN 077, 89 healthy females received an oral lead-in (OLI) of CAB 30 mg once daily x 4 weeks prior to initiating CAB LA injections. These participants had a median weight of 71 kg, and 6 weighed ≤ 50 kg. Therefore, administration of the OLI to participants ≥ 50 kg is expected to achieve exposures within the range of prior experience, and PK will not be evaluated following oral administration in this study. Following a 1-week washout, 40 of 89 female participants in HPTN 077 received the proposed CAB LA Q8W regimen (**Error! Reference source not found.**).

A population PK model (n=1647) that included data from HPTN 077 (n=134, 89 females, 45 males) and 15 other studies was used to predict exposures following the proposed CAB LA Q8W regimen in adolescents. Gender and BMI are significant covariates affecting the absorption rate following IM administration and were retained in the model to extrapolate to smaller adolescent females expected to enroll in HPTN 084-01. Model predicted concentrations in adolescent females (simulated with median weight and BMI of 59 kg and 22 kg/m<sup>2</sup>, respectively) to enroll in HPTN 084-01 are similar to adult females in HPTN 077 and below oral dosing, and therefore are expected to be safe in this population (Table 1). Greater than >95% are expected to achieve trough concentrations > 4x PA-IC<sub>90</sub> following the 5th injection. This regimen is currently being evaluated in uninfected adult males and females in

HPTN 083 and HPTN 084, respectively, and has maintained HIV suppression in infected adults when combined with RPV LA (LATTE-2).

**Table 1. Predicted CAB Parameters following Injection 5 of the CAB LA 600mg IM Q8W Regimen in Female Adolescents compared with Predicted and Observed Data in Female Adults in HPTN 077**

Plasma CAB Parameter ((µg/mL)	Female Participants in HPTN 077 Median (range)		Predicted Exposures Female Adolescents ≥50kg		
	Predicted Parameters 30 mg Once Daily	Observed Data 600mg IM Q8W (Injection 5)	Median (90% PI)	Peds:Adults Relative Exposure	
				Vs 30mg	Vs 600mg
Oral C <sub>max</sub> or C <sub>1</sub> Wk 34 (1-week post Inj5)	9.1 (4.4–18.1)	3.3 (1.7–8.2)	<b>3.9 (2.0, 6.8)</b>	<b>0.4</b>	<b>1.2</b>
Oral C <sub>τ</sub> or C <sub>1</sub> Wk 41 (8-weeks post Inj5)	5.4 (2.3–12.0)	2.1 (0.62–4.6)	<b>2.3 (1.3, 3.8)</b>	<b>0.4</b>	<b>1.1</b>

Plasma CAB concentrations are expected to be detectable in a majority of subjects for one year following the final injection.

Based on adult dosing data and pharmacokinetic modeling, oral CAB 30mg and CAB LA 600mg IM are expected to be safe in adolescents and have been selected as the initial regimen for IMPAACT 2017 study—the same as the adult CAB regimen in current Phase III studies. While somewhat higher CAB plasma concentrations are expected in lower weight adolescent participants, the safety and tolerability seen in adults at the higher oral CAB dose of 60 mg daily and CAB LA dose of 800mg q 8-weeks tempers any safety concerns.

This protocol will enroll using a weight-based approach rather than age-based. This allows for an eventual adolescent indication for LA CAB in adolescents at-risk, regardless of age. The supplemental adolescent indication for Truvada<sup>®</sup> was entirely weight-based (down to 35 kg) for adolescents at risk of HIV. Also, by not specifying a lower limit of age, this allows sites the flexibility to enroll participants that meet the behavioral and physical criteria necessary to qualify. Each site will have ethics review and will consider these criteria in light of community standards; and each investigator of record will be able to determine whether a candidate is appropriate for enrollment or not. These decisions will then be made with consideration for the local context of each site/community, rather than arbitrarily choosing what age should be the lower limit. Additionally, we need to acquire more data for use of this product in adolescents under 50 kg.

Dose adjustments are not anticipated for this protocol. However, a pre-specified weight-based analysis from Cohort 1 of IMPAACT 2017 is scheduled to compare dosing safety above and below 50kg (110 lbs.). The HPTN 084-01 protocol team will review these findings when data is available to determine

whether the dose of the oral and injectable CAB study products must be revised. In that case, the new doses will be specified in a letter of amendment.

**Table 2. Cumulative CAB Exposures from Phase 1 through Phase 3 Clinical Studies Through October 2018**

<b>Treatment Population/ Dose</b>	<b>Duration</b>	<b>Completed</b>	<b>Ongoing/ Concluded<sup>a</sup></b>	<b>Total</b>
<i>Healthy Volunteers/HIV-Uninfected</i>				
5 to 150 mg oral	Single dose	208	0	208
10 to 30 mg once daily oral	10 to 28 days	293	1694	1987
150 mg every 12 hours oral	3 doses	40	0	40
100–800 mg IM/SC LA	Max 763 days <sup>c</sup>	230 <sup>b</sup>	1377 <sup>e</sup>	1607
<b>Any dose</b>		<b>599</b>	<b>1694</b>	<b>2293</b>
<i>HIV infected patients</i>				
5 to 30 mg once daily oral (Ph 2a)	10 days	15	0	15
10 to 60 mg once daily oral (Ph 2b)	Max 2247 days <sup>h</sup>	0	181	181
30 mg once daily oral (Ph 2b)		0	1739	1739
Up to 800 mg IM LA <sup>d</sup>	Max 1477 days <sup>e</sup>	0	1745 <sup>e</sup>	1745
<b>Any dose</b>		<b>15</b>	<b>1928</b>	<b>1943</b>
<i>All participants</i>				
Single dose oral (5 to 150 mg)		208	0	208
Repeat dose once daily oral (5 to 60 mg)		308	3614	3922
150 mg oral every 12 hours x 3		40	0	40
Single or repeat dose LA injection (100 to 800 mg)		230 <sup>b</sup>	3122 <sup>f</sup>	3352
<b>Any dose</b>		<b>614</b>	<b>3622</b>	<b>4236</b>

a. Concluded studies: study completed through follow up; and/or clinical study report is in preparation

b. 172 participants received both oral and LA dosing

c. All participants received both oral and LA dosing

d. Includes 400 mg Q4W and 600 mg Q8W dosing

e. 1736 participants received both oral and LA dosing

f. 3113 participants received both oral and LA dosing

g. Detectable CAB concentrations can remain for up to 72 weeks following the last CAB injection

h. As of 28 Dec 2014, all participants had transitioned to CAB 30 mg in the Open Label phase of study LAI116482 (LATTE 1), therefore, the longer durations apply to the 30 mg dose only

Revision 6: Section 1.9 - Updates from the parent protocol, HPTN 084, have been included.

### 1.9.1 Dolutegravir and Pregnancy

Dolutegravir (DTG) is an integrase inhibitor in the same class of pharmaceuticals as CAB. Thus far, limited safety or efficacy data for DTG in pregnancy in humans have been published or presented. In May 2018, WHO and several other regulatory agencies released advisories regarding the safety of dolutegravir in early pregnancy **based on an interim review of data from the Botswana NICHD-funded Tsepamo Birth Outcomes Surveillance Study, in Botswana.**<sup>44</sup> This study was designed to evaluate adverse birth outcomes by maternal HIV status and ART regimen, and to determine whether there is an increased risk of neural tube defects (NTDs) among infants exposed to efavirenz (EFV) from conception. Botswana's HIV program moved to universal ART with DTG/TDF/FTC in first line for patients starting ART (including pregnant women) in May of 2016 (women already on other regimens were not switched to DTG). The previous first-line regimen was EFV/TDF/FTC. Almost all women on DTG-based and EFV-based ART took these drugs in combination with TDF/FTC.

**Since August 2014, the Tsepamo study collected information on 153,899 deliveries. An updated analysis including births since March 2019 reported seven neural tube defects among 3,591 women exposed to dolutegravir at conception (0.19, 95% CI 0.09%, 0.40%). In comparison, neural tube defects occurred in 21/19,361 (0.11%; 95%CI 0.07%, 0.17%) women on any non-dolutegravir regimen at conception. The prevalence of neural tube defects did not differ significantly between dolutegravir and any nondolutegravir antiretrovirals from conception (0.09% difference; 95%CI -0.03%, 0.30%). After a period of decline since the original safety signal, the prevalence of neural tube defects in infants born to women on dolutegravir around the time of conception appears to have stabilized at 2 per 1000.**<sup>46</sup>

~~This was based on information received from the Botswana NICHD-funded Tsepamo Birth Outcomes Surveillance Study, the largest body of data related to birth outcomes following the use of DTG in pregnancy. This study was designed to evaluate adverse birth outcomes by maternal HIV status and ART regimen, and to determine whether there is an increased risk of neural tube defects (NTDs) among infants exposed to efavirenz (EFV) from conception. Botswana's HIV program moved to universal ART with DTG/TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®) as first line treatment for patients starting ART (including pregnant women) in May of 2016 (women already on other regimens were not switched to DTG). The previous first line regimen was EFV/TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®). Almost all women on DTG-based and EFV-based ART took these drugs in combination with TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®). More than 95% of women in Botswana deliver in a hospital, and obstetric records were available for >99% of women. The Tsepamo surveillance study is conducted at 8 of the largest public maternity wards across Botswana (representing ~45% of the total births in the country). Research assistants abstract ART data from the maternity card for all consecutive in-hospital deliveries (both HIV-infected and HIV-uninfected women). Each newborn, whether stillborn or live-born, undergoes a systematic infant surface examination that is completed by trained nurse midwives. Reports and photographs (where available) of major abnormalities are reviewed by an experienced medical geneticist who is blinded to exposure information. During a preliminary unscheduled analysis of the Tsepamo data collected between August 15, 2014 and May 1, 2018, which was undertaken at the request of colleagues who were preparing for a WHO meeting, the investigators found 4 cases of neural tube defects in babies of 426 women who became pregnant while taking DTG (prevalence 0.9%). This rate compares to a 0.1% risk of neural tube defects in infants born to women taking other antiretroviral medicines at the time of conception. Data is expected on the pregnancy outcomes of an additional 600 women in the Tsepamo study who were taking DTG around the time of conception. A follow-up analysis of 1729 pregnant women in the same~~

observational cohort in Botswana found that there was no difference in the risk for any adverse birth outcome among children born to women on dolutegravir as compared to those on efavirenz (33.2% vs 35% for DTG and EFV, respectively; aRR 0.95, 95% CI 0.88-1.03). There was also no difference in the occurrence of any severe birth outcome (10.7% for women on DTG versus 11.3% for women on EFV; aRR 0.94, 95% CI 0.81-1.11).<sup>45</sup> More data are also expected to be forthcoming from other studies of DTG in pregnancy. These data will provide more information on the safety of DTG for women of childbearing age.

Revision 7: Section 2.3 - Removal of wording which is no longer applicable.

### 2.3 Study Design and Overview

We propose a single arm, open label, safety, tolerability, and acceptability study (n=50) in sexually-active, healthy adolescents assigned female sex at birth. ~~We have chosen to enroll an adolescent population that is sexually active, yet not at the highest risk for HIV exposure due to several reasons. First, this is the first protocol to study a new prevention product (CAB LA) among adolescent minors and the primary outcome of interest is safety. Safety studies within a new population with an unproven product typically enroll “healthy” volunteers. The adult safety study for CAB LA was HPTN 077, which enrolled lower risk adults in a manner similar to the approach adopted for these sub-studies. Second, adolescents are considered a vulnerable population and the efficacy of CAB LA has yet to be proven. Thus, a young person at very high risk would potentially benefit more from oral TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®), which is highly efficacious and approved for use by adolescents to prevent HIV infection. Finally, adolescent sexual activity is highly variable and we will likely see individual variation in sexual risk over the course of the study visits. Should promising efficacy data from adult populations become available during the implementation of this study, the protocol team will consult with the DSMB to consider broadening the sexual risk criteria to enroll high risk adolescents.~~

...for daily use for 48 weeks. **Participants may be offered the opportunity to join an open label CAB study instead, if such a study is being implemented in their area at the time.** Behavioral and acceptability data will be collected via computer-assisted self-interview (CASI).

Revision 8: Section 3.1, Inclusion Criteria - Two areas have been edited.

3.1.3 **At enrollment, body weight  $\geq$  5035 kg (11077 lbs.);\***

**3.1.10 If currently on PrEP from a non-study source, willing to stop said PrEP prior to enrollment and agree to switch to oral CAB for the lead-in period and CAB LA injections.**

Revision 9: Section 3.2, Exclusion Criteria, has been revised.

~~**3.2.2 Currently receiving PrEP from a non-study source;**~~

**3.2.5 In the last 6 months (at the time of screening):**

- ~~• self-reported unprotected anal or vaginal intercourse with someone known to be HIV-infected;~~

- ~~self-reported illicit injection drug use of any kind or stimulant use (including inhaled nitrate, cocaine in any form, methamphetamine, or non-physician prescribed pharmaceutical grade stimulants),~~
- active or planned use of any substance use which would, in the opinion of the site investigator, interfere with study participation (including herbal remedies), as described in the IB or listed in the SSP, and/ or Protocol Section 4.4,
- ~~self-report of greater than 5 different sexual partners (anal or vaginal), regardless of use of protection or knowledge of HIV status in last 6 months~~

Revision 10: Section 5, Study Procedures – Changes to various sections.

## 5.2 Enrollment

### Baseline/Enrollment/Week 0 Visit

Both clinical and laboratory evaluations will occur at this visit, along with behavioral and acceptability assessments, **including administration of the Patient Health Questionnaire-9 (PHQ-9).** (See **Appendix I Schedule of Evaluations for Oral Phase – Step 1 for details**).

All behavioral assessment measures will be programmed into CASI, **with the exception of the PHQ-9, which is an eCRF administered only at Enrollment.** Measures have been previously used either in adolescent biomedical prevention trials or in the Phase III adult trials of cabotegravir (HPTN 083/084).

### 5.3.1 Management of Participants with AEs during Step 1 – **Oral Phase**

#### 5.4 Transitioning from Step 1 to Step 2

- Any suspected or confirmed pregnancy (see SSP and Section 5.165);

#### 5.4.1 Early Discontinuation in Step 1

Participants who do not enter Step 2 will discontinue study follow-up (**except Step 1 participants with confirmed pregnancy, see Section 5.15**).

## 5.7 Step 3, Follow-up Phase

### Follow-up Phase

**All participants will be followed quarterly for 48 weeks following their last injection and provided with Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®). ~~{TRADE NAME: TDF/FTC, TRUVADA®}~~. Participants may also join a local open label CAB study, if available.**

~~All participants will be followed quarterly for 48 weeks following their last injection.~~

Step 3 will begin with the +8 Week Visit, in which participants who receive the Week 33 injection will return for a blood draw eight weeks afterwards, in order to monitor drug levels of CAB. Participants who do not receive the week 33 injection will have a +8 Week Visit after their last injection visit and continue to be followed per the Step 3 Follow-up Phase (see [Appendix III](#)).

Both clinical and laboratory evaluations will occur during follow-up phase visits as well as CASI administration for either behavioral or acceptability assessments (see [Appendix III. Schedule of Evaluations for Follow-up Phase – Step 3](#)). ~~Participants will also be monitored for increased HIV transmission risk behavior during this time and open label oral PrEP provided at the clinical sites.~~

### 5.8.1 HIV and Risk Reduction Counseling

HIV testing and risk reduction counseling will be provided at each study visit, in accordance with local SOC, and will include messaging about consistent condom use. Condoms will be offered to all participants at each study visit consistent with local standards **and oral PrEP referrals made as desired.**

#### Increase in Risk for HIV Infection

~~At any time during study participation, any participant whose risk for HIV increases such that they qualify for PrEP by local guidelines, and desire to start PrEP, will permanently discontinue study product and receive ongoing risk reduction counselling. Step 1 participants will be switched to open label TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®) PrEP and not transition to Step 2. They will be referred for further HIV prevention services and exit the study. Step 2 participants will switch to open label TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®) PrEP and remain in follow-up in Step 3. All cases should be communicated to the HPTN 084-01 CMC at 084-01cmc@hptn.org.~~

### 5.8.2 Adherence Counseling and Monitoring

The study will provide adherence support/counseling at baseline and at all follow-up visits for all participants and will be tailored to participants' current study Step. During Step 1, participants will receive counseling focused on adherence to the oral CAB and messages about ensuring adequate dosing for safety prior to proceeding to Step 2. During Step 2, the importance of returning for injection visits on or as close to the scheduled date as practical will be emphasized. During Step 3, the focus will be on adherence to oral Tenofovir/emtricitabine (Trade name: TDF/FTC, Truvada®) PrEP. ~~TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®) PrEP. Throughout the study, participants will be reminded that efficacy of CAB LA for HIV prevention has yet to be established.~~

### 5.9 Injection Visit Windows

The visit windows for all visits, including injection visits, are outlined in the SSP Manual. Refer to SSP for instruction on managing participants who report to clinic outside of injection window.

The target visit windows for all visits, including injection visits, are outlined in the SSP Manual. In brief, the target visit window for ~~for the Week 5 and 9 injections~~ **all** injection visits is +/- 3 days ~~and is +/- 7 days for all other injection visits.~~ Visits conducted outside of the target visit windows are allowable without restriction and are also defined in the SSP Manual for scheduling guidance. Each study visit, including the injection visit, should ideally be conducted within the target date range. When that is not possible, visits outside of the target dates may be completed.

### 5.10.2 After Study Enrollment

#### Step 2 – Injection Phase

HPTN 084-01, Letter of Amendment #1 to Version 1.0  
Date of Protocol Version 1.0: 14 October 2019  
Date of Letter of Amendment #1: 03 December 2020



Participants with confirmed HIV infection during Step 2 will not receive additional injections and will be followed per the SOE in Appendices III and IV quarterly for 48 weeks.

### Step 3 – Follow-up Phase

Participants with confirmed HIV infection during Step 3 will not receive oral **Tenofovir/emtricitabine (Trade name: TDF/FTC, Truvada®)** ~~TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®)~~ and will be followed per the SOE in Appendices ~~III and IV~~ quarterly through study exit.

### 5.18 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time (**or their parents/guardians may, if they are under the legal age of consent**). **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 to the participant. For participants 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.** Study staff will record the reason(s) for all withdrawals in participants' study records: **and consult procedures for early discontinuation.**

Revision 11: Section 6.4 - Removal of description of SMC from Clinical Data Review section.

### Clinical Data Review

A multi-tiered safety review process will be followed for the duration of this study. The study site investigators are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the CMC if unexpected concerns arise.

Participant safety data is also monitored by the SDMC Clinical Affairs staff who review incoming safety data for completeness and consistency on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification.

AE reports submitted in an expedited manner to the DAIDS Safety Office will be forwarded to the DAIDS Medical Officer for review and possible reporting to the FDA as a Safety Report.

~~The SDMC will prepare routine reports of study conduct for the Safety Monitoring Committee (SMC), which will meet by conference call approximately every 6 months and will review accrual and retention data, as well as other aspects of study conduct. More frequent or ad hoc reviews of safety data may be conducted by the SMC as needed.~~

This study ~~also~~ will be monitored by a NIAID Data and Safety Monitoring Board (DSMB), along with the parent protocols, which will meet at least annually to review safety and efficacy data. More frequent or *ad hoc* reviews of safety data may be conducted by the DSMB as needed.

Revision 12: Section 7, Statistical Considerations - Re-organization and additions.

### 7.2.2 Secondary Endpoints

- Plasma CAB pharmacokinetics
- Proportion of participants experiencing Grade 2 or higher clinical AEs and laboratory abnormalities in the **oral phase and the aggregate over the entire study period 48 weeks following final injection**
- Proportion of injection visits that occurred “on-time”
- Change from enrollment of self-reported sexual behavior (number of sexual partners, increased episodes of unprotected vaginal or anal intercourse) during the study period

### 7.6.1 Study Monitoring Committee

NIAID DSMB oversight is planned for this study. Monitoring guidance will be detailed in a separate Interim Monitoring Plan. In addition, approximately every six months the HPTN SMC will conduct interim reviews of study progress, including rates of participant accrual, visit retention, and completion of primary and main secondary endpoint collection. The frequency and content of SMC reviews will be determined prior to the start of the study as outlined in the HPTN Manual of Procedures (MOP).

**In addition, approximately every six months the HPTN SMC will conduct interim reviews of study progress, including rates of participant accrual, visit retention, and completion of primary and main secondary endpoint collection. The frequency and content of SMC reviews will be determined prior to the start of the study as outlined in the HPTN Manual of Procedures (MOP).**

### Secondary Analyses

#### Plasma Drug-Level Concentrations

**Descriptive analyses of plasma concentration of CAB LA will be performed using mean, median, standard deviation, coefficient of variation (%CV) and range, for example. Graphical displays of the data based on appropriate techniques (e.g., boxplots, histograms, kernel density estimates, probability plots, scatterplots) will be generated to visually explore distributional properties of the data. Statistics and graphical displays will be produced for plasma concentrations within and across timepoints. In addition, proportion of participants with plasma CAB concentrations <LLQ, between LLQ and PA-IC90, 1-4X PA-IC90, and >4X PA-IC90 will be calculated at pre-specified time points after the final injection. In addition to concentration summaries, parameters may be derived by non-compartmental pharmacokinetic methods.**

#### Safety Endpoints

**Secondary safety analyses will be summarized using the same method described in section 7.7.1, applied over the oral phase only (week 0 to week 4) and the aggregate oral+injectable+follow-up period.**

#### AEs and Serious Adverse Events (SAEs)

**AEs and SAEs will be summarized using the same method described in section 7.7.3, applied over the oral phase only (week 0 to week 4) and the aggregate oral+injectable+follow-up period.**

#### Injection adherence

**The number and the percent of injection visits that occur within the injection visit window will be tabulated.**

#### Sexual Risk Behaviors

**Change in sexual risk behavior (number of sexual partners, episodes of unprotected anal and/or vaginal intercourse) during the injection phase will be measured by summarizing the change from baseline by visit.**

## ~~7.7 Secondary Analyses~~

### ~~7.7.1 Sexual Risk Behaviors~~

~~Change in sexual risk behavior (number of sexual partners, episodes of unprotected anal and/or vaginal intercourse) during the injection phase will be measured by summarizing the change from baseline by visit. Sexual risk behavior will be analyzed in aggregate.~~

### ~~7.7.2 Plasma Drug Level Concentrations~~

~~Descriptive analyses of plasma concentration of CAB LA will be performed using mean, median, standard deviation, coefficient of variation (% CV) and range, for example. Graphical displays of the data based on appropriate techniques (e.g., boxplots, histograms, kernel density estimates, probability plots, scatterplots) will be generated to visually explore distributional properties of the data. Statistics and graphical displays will be produced for plasma concentrations within and across timepoints. In addition, proportion of participants with plasma CAB concentrations <LLQ, between LLQ and PA-IC90, 1-4X PA-IC90, and >4X PA-IC90 will be calculated at pre-specified time points after the final injection. In addition to concentration summaries, parameters may be derived by non-compartmental methods. Details of the analysis will be described in the study Reporting and Analysis Plan (RAP), separately.~~

Revision 13: Edit to Section 8.1.

## **8.1 Ethical Review**

This protocol and the template informed consent form contained in [Appendix IV](#)—~~and any subsequent modifications~~—will be reviewed and approved by the HPTN Scientific Review Committee (SRC) and DAIDS Prevention Science Review Committee (PSRC) with respect to scientific content and compliance with applicable research and human subjects regulations.

Revision 14: **Edit to Section 9.3, Virology Section.**

## 9.3 Virology

Resistance testing will be performed at the HPTN LC or a laboratory designated by the HPTN LC. This testing will be performed **periodically during** ~~retrospectively at the end of~~ the study.

Revision 15: Changes to Section 10.6 - updated to provide additional guidance regarding retention of study records following completion of a study.

## **10.6 Investigator's Records**

The IoR 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 IoR 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, or if other applicable laws,

regulations, policies, or other requirements (e.g., State, country-specific, and local laws, and sponsor or institutional policies) exist, the most stringent retention period will be followed. **European Medicines Authority (EMA) requirements, which will apply to the parent protocol (HPTN 083), were the most demanding identified by DAIDS at the study-wide level. Based upon EMA requirements, sites should therefore plan to retain files (and any other study documentation) for more than 15 years from the end of data collection, or longer if required by local regulations.**

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, or if other applicable laws, regulations, policies, or other requirements (e.g., State, country-specific, and local laws, and sponsor or institutional policies) exist, the most stringent retention period will be followed.

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. This includes informed consent forms, locator forms, CRFs, 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.**

Revision 16: Changes to Appendix I.

#### **APPENDIX I. SCHEDULE OF EVALUATIONS – ORAL PHASE (Step 1)**

<b>WEEKS in Study</b> (Shaded column = dispense oral product)	<b>Screening</b>	<b>WEEK 0 Enrollment</b>	<b>WEEK 2</b>	<b>WEEK 4</b>
<b>ADMINISTRATIVE, BEHAVIORAL, REGULATORY</b>				
Informed consent	X			
Locator information	X	X	X	X
Demographic information	X	X		
HIV prevention counseling	X	X	X	X
Offer condoms	X	X	X	X
<b>Patient Health Questionnaire-9 (PHQ-9)</b>		X		
Behavioral/Acceptability Assessment (CASI)		X		X
<b>CLINICAL EVALUATIONS &amp; PROCEDURES</b>				
Dispense study product (enough for 5 weeks)		X		
Observe participant take oral study product <sup>1</sup>		X	X <sup>1</sup>	X <sup>1</sup>

<b>WEEKS in Study</b> (Shaded column = dispense oral product)	<b>Screening</b>	<b>WEEK 0 Enrollment</b>	<b>WEEK 2</b>	<b>WEEK 4</b>
Adherence counseling/pill count (pill count Weeks 2 and 4 only)		X	X	X
Contraception counselling and provision or verification of use	X	X	X	X
Medical history, con meds, targeted physical exam (with weight) <sup>2</sup>	X	X	X	X
Hep B vaccination (if needed) <sup>3</sup>			X	
Blood collection	X	X	X	X
Urine and/or vaginal swab collection <sup>4</sup>	X	X	X	X
<b>Vaginal swab collection<sup>5</sup></b>	X			
<b>LOCAL LABORATORY EVALUATIONS &amp; PROCEDURES</b>				
HIV testing <sup>65</sup>	X	X	X	X
Pregnancy testing <sup>76</sup>	X	X	X	X
HBV and HCV testing <sup>87</sup>	X	X		
CBC with differential	X	X	X	X
Chemistry testing <sup>98</sup>	X	X	X	X
Liver function tests <sup>109</sup>	X	X		X
Fasting lipid profile <sup>1140</sup>		X		
Syphilis testing	X			
GC/CT testing (urine or vaginal swab)	X			
Urinalysis (protein and glucose)		X		
Plasma storage <sup>1244</sup>	X	X	X	X

**FOOTNOTES FOR APPENDIX I:**

<sup>1</sup> Staff are required to observe participants take one pill at Enrollment. If participants return with their pills at Weeks 2 & 4, staff will observe participant take one pill then as well, unless the participant has already taken oral study product that day. Participants must not be asked to take a second dose of oral study product for the sake of observation.

<sup>2</sup> Full physical exam is to be conducted during Enrollment. A targeted physical exam will be done at all other visits. Participant pulse, blood pressure and weight must be recorded at every visit. BMI is calculated at enrollment only.

<sup>3</sup> The initial dose of the Hep B vaccination will ideally be given at Week 2, though there is flexibility around the timing of the vaccination. Subsequent doses may be given at different visits than indicated in this SOE, as long as sites follow manufacturer guideline timing.

<sup>4</sup> **At screening: For the GC/CT test, if sites use urine for that assay, instead of a vaginal swab. At all visits: For the pregnancy test, if sites use urine for that assay, instead of blood or plasma. At Week 2: For the urinalysis.**

<sup>5</sup> **For the GC/CT test, if sites use a vaginal swab for that assay instead of urine.**

<sup>56</sup> The HIV testing algorithm is provided in the SSP Manual. Testing for acute HIV must be negative and must be performed within 14 days prior to enrolling the participant. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory. At least one HIV test must be available and reviewed the same day as sample collection and before product is administered.

<sup>67</sup> Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Confirmation of pregnancy at a subsequent visit at least 4 weeks after the initial pregnancy test is required. Participants with confirmed pregnancies will permanently discontinue oral CAB and will not transition to Step 2. They will skip to Step 3, be provided open label Tenofovir/emtricitabine (Trade name: TDF/FTC, Truvada®) as PrEP and be reviewed every 12 weeks until delivery. If pregnancy is not confirmed on subsequent testing, Step 1 participants will exit the study. Site staff will refer to their SOP for detailed management.

<sup>87</sup>-Participants will be tested for Hepatitis B surface antibody (HBsAb), and Hepatitis B core antibody (HBcAb, total) at Screening or Enrollment. HbsAg and HCV Ab must be resulted and reviewed prior to enrollment.

<sup>98</sup> At Screening: Creatinine. At and after enrollment: BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.

<sup>109</sup> At Screening: ALT and TBili. At and after Enrollment: AST, ALT, total bilirubin, and alkaline phosphatase.

<sup>4011</sup> Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants must have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. Do not collect or test if <8 hrs fasting.

<sup>412</sup> Stored plasma will be used for Quality Assurance testing and other assessments at the HPTN LC (see Section 9). Assessments will be performed retrospectively; results will not be returned to study sites or participants, except as noted in SSP. Samples cannot be used by site or other lab for local purposes without specific instructions from the LC w/CMC consult.

Revision 17: Changes to Appendix II.

## APPENDIX II. SCHEDULE OF EVALUATIONS – INJECTION PHASE (Step 2)

Fasting lipid profile <sup>7</sup>	X	X	X	X	X	X	X	X	X	X
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### FOOTNOTES FOR APPENDIX II:

<sup>1</sup> Medical history must include pulse, blood pressure, **and** weight. ~~and~~ Body Mass Index (BMI) is calculated at each **injection** visit (**weeks 5, 9, 17, 25 and 33**) **only**.

<sup>7</sup> Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants must have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. Do not collect or test if <8 hrs fasting. **For participants who switch to Step 3 early (without having completed all 5 injections), the fasting lipid profile will be taken at the first visit after they transition off injections.**

Revision 18: Changes to Appendix III.

## APPENDIX III. SCHEDULE OF EVALUATIONS –FOLLOW-UP PHASE (Step 3)

WEEKS SINCE LAST INJECTION	Wk +8	Wk +12	Wk +24	Wk +36	Wk +48	Early Discontinuation
ADMINISTRATIVE, BEHAVIORAL, REGULATORY						

Locator information	X	X	X	X	X	X
HIV prevention & risk reduction counseling	X	X	X	X	X	X
Condoms per local SOC	X	X	X	X	X	X
Behavioral/Acceptability assessment (CASI)		X	X	X	X	X
<b>CLINICAL EVALUATIONS &amp; PROCEDURES</b>						
Qualitative interviews <del>begin</del> <b>continue</b> (approximately)		X	X			
Contraception counselling and provision or verification of use		X	X	X	X	
Medical history <sup>1</sup> , concomitant medications, targeted physical exam		X	X	X	X	X
Hep B vaccination (if needed) <sup>2</sup>						X
Blood collection	X	X	X	X	X	X
Urine collection		X	X	X	X	X
Provision of <b>Tenofovir/emtricitabine (Trade name: TDF/FTC, Truvada®)</b> <b>TENOFOVIR/EMTRICITABINE</b> (TRADE NAME: TDF/FTC, TRUVADA®) (3 months' worth)		X	X	X		X
<b>LOCAL LABORATORY EVALUATIONS &amp; PROCEDURES</b>						
HIV testing <sup>3</sup>		X	X	X	X	X
Pregnancy testing <sup>4</sup>		X	X	X	X	X
CBC with differential		X	X	X	X	X
Chemistry testing <sup>5</sup>		X	X	X	X	X
Liver function testing <sup>6</sup>		X	X	X	X	X
<del>Fasting lipid profile<sup>7</sup></del>		<del>X</del>				
Syphilis testing				X		
GC/CT testing (urine or vaginal swab)		X	X	X	X	X
Urinalysis (protein, glucose)		X	X	X	X	
Plasma storage <sup>8</sup>	X	X	X	X	X	X
DBS storage		X	X		X	

**FOOTNOTES FOR APPENDIX III:**

<sup>7</sup>Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants must have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. Do not collect or test if <8 hrs fasting.

## APPENDIX I

### Sample HPTN 084-01 Participant Letter/Information Sheet

**PRINCIPAL INVESTIGATOR:** [Insert PI Name/Affiliation]

Dear HPTN 084-01 Participant:

The purpose of this letter is to share with you some important results from the HPTN 084 study, a study related to the HPTN 084-01 study, that have become available after a recent Data and Safety Monitoring Board (DSMB) meeting on 5 November 2020. The DSMB is an independent group that reviews studies and their results while they are happening to ensure the safety and well-being of the study participants. After reading this letter, if you have any questions about this information, we encourage you to talk to the site staff.

#### The HPTN 084 Study:

The HPTN 084 study is being done at 20 sites in South Africa, Botswana, Eswatini, Zimbabwe, Malawi, Uganda and Kenya and has enrolled 3,224 participants with **[X]** at this site.

The purpose of the study is to try to find out if a new drug called cabotegravir (CAB), is as safe and will work better than TDF/FTC in protecting you from getting HIV. As a reminder, TDF/FTC is approved by the U.S. Food and Drug Administration (FDA) **[and insert local country if applicable]** for the treatment of HIV and also to prevent people from getting HIV.

All participants in the HPTN 084 study were put into one of two groups by chance (like the flip of a coin):

- Group 1: Real CAB drug and TDF/FTC placebo (pill that does not have TDF/FTC)
- Group 2: Real TDF/FTC drug and CAB placebo (injections that do not have CAB)

#### Results of the DSMB review:

At the DSMB meeting on 5 November 2020, the DSMB found that both CAB and TDF/FTC were very good at preventing new HIV infections. They also found that both CAB and daily TDF/FTC pills were safe and well tolerated. They saw that CAB was much better at preventing HIV than TDF/FTC. Participants given daily TDF/FTC pills had approximately nine times the number of HIV infections than participants getting long-acting cabotegravir shots (real CAB, also called CAB LA). The DSMB recommended that the blinded part of the study be stopped, that participants be informed of their study group, and that the results be made public.

The HPTN 084 study will continue. In the near future, the HPTN 084-01 protocol will be amended to allow for slight changes to the information about HPTN 084 and you will be given the information and



asked to sign an updated consent/assent form at that time.

If you have any questions now or later about the information in this letter, you may ask the study staff or contact me directly. We will do our best to answer your questions or concerns.

Enrolling in this study, the HPTN 084-01 study, will help to increase our knowledge about how CAB LA works in adolescents, which is still an important question. Thank you for participating in HPTN 084.

Sincerely,

[Insert name and contact information of Investigator of Record]

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If you have read this letter, or have had it read and explained to you, and understand the information, please sign your name or make your mark below.

**Write your initials or make your mark below.**

\_\_\_\_\_  
Name of Participant (print)

\_\_\_\_\_  
Signature and Date

PARENT/GUARDIAN INFORMED CONSENT

\_\_\_\_\_  
Relationship to participant

\_\_\_\_\_  
Name (print)

\_\_\_\_\_  
Signature and Date

\_\_\_\_\_  
Study Staff Conducting  
Consent Discussion (print)

\_\_\_\_\_  
Study Staff Signature and Date

\_\_\_\_\_  
Witness Name (print)  
(As appropriate)

\_\_\_\_\_  
Witness Signature and Date