HPTN 083-01:
Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV among Adolescent Males – A sub-study of HPTN 083

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A Study by the HIV Prevention Trials Network (HPTN)

Sponsored by:
Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases (NIAID), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD),
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LIST OF ABBREVIATIONS AND ACRONYMS

ABC/3TC	abacavir/lamivudine
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	Antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
BCRP	breast cancer resistance protein
βhCG	beta human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
C	Celsius
C_τ	trough concentration
CAB	cabotegravir, oral and LA formulations
CAB LA	long-acting injectable formulation of cabotegravir
CABG	coronary artery bypass grafting
CASI	computer-assisted self-interview
CBC	complete blood count
CD4	T-helper cells or T4 cells
CDC	(US) Centers for Disease Control and Prevention
CFR	(US) Code of Federal Regulations
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum or "peak" concentration of a drug observed after its administration
CMC	Clinical Management Committee
C_{min}	minimum or "trough" concentration of a drug observed after its administration and just prior to the administration of a subsequent dose
CPQA	Clinical Pharmacology Quality Assurance Committee
CPK	creatine phosphokinase
CRF	case report form
CRM	Clinical Research Manager
CRPMC	Clinical Research Products Management Center
CRS	Clinical Research Site
CT	*Chlamydia trachomatis*
CVb%	geometric mean
DAERS	DAIDS Adverse Event Reporting System
DAIDS	Division of AIDS
DAIDS PRO	DAIDS Protocol Registration Office
DAIDS RSC	DAIDS Regulatory Support Center
DBS	dried blood spot
DMPA	depot medroxyprogesterone acetate
DSMB	Data and Safety Monitoring Board

EAE	expedited adverse event
EC	Ethics Committee
ECLAIR	Phase IIa Safety and PK Study of Cabotegravir LA in HIV-Uninfected Men at Low Risk for Sexual Acquisition of HIV Infection
EFD	early fetal development
EFV	Efavirenz
EQA	external quality assurance
FDA	(US) Food and Drug Administration
FEM-PrEP	Pre-exposure Prophylaxis Trial for HIV Prevention among African Women
FTC	Emtricitabine
FTC-TP	emtricitabine triphosphate
GC	*Neisseria gonorrhoeae*
GCLP	Good clinical laboratory practice
GT	genital tract
HBcAb	hepatitis B virus core antibody
HBsAb	hepatitis B virus surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCAb	hepatitis C antibody
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HIV RNA	HIV test using a ribonucleic acid
HIV-1	human immunodeficiency virus type 1
HPTN	HIV Prevention Trials Network
HPTN LC	(HPTN) Laboratory Center
HPTN LDMS	(HPTN) Laboratory Data Management System
HPTN LOC	(HPTN) Leadership and Operations Center
HPTN SDMC	(HPTN) Statistical and Data Management Center
HR	hazard ratio
IATA	International Air Transport Association
IB	Investigator Brochure
ICF	informed consent form
ID	Identification
IDI	In-depth interview
IM	Intramuscular
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IND	investigational new drug
INSTI	integrase strand transfer inhibitor
IoR	Investigator of Record
IP	Intraperitoneal
iPrEX OLE	iPrEx Open Label Extension
IQA	(DAIDS) Immunology Quality Assurance
IRB	Institutional Review Board
ISR	injection site reaction
IUD	intrauterine device
IUS	Intrauterine system
LA	long-acting (injectable)

LC	(HPTN) laboratory center
LATTE	Cabotegravir plus Rilpivirine, once a day, after Induction with Cabotegravir plus Nucleoside Reverse Transcriptase Inhibitors in Antiretroviral-naïve Adults with HIV-1 Infection
LATTE-2	Cabotegravir plus Rilpivirine as Long-Acting Maintenance Therapy
LDL	low-density lipoprotein
LDMS	(HPTN) Laboratory Data and Management System
LFTs	liver function tests
LLQ	Lower limit of quantification
LOC	(HPTN) Leadership and Operations Center
MedDRA	Medical Dictionary for Regulatory Activities
MO	Medical Officer
MOP	Manual of Operations
MRC	(HPTN) Manuscript Review Committee
MRI	Magnetic resonance imaging
MSM	men who have sex with men
NAAT	nucleic acid amplification test
NET-EN	Norethisterone enanthate
NI	non-inferiority
NIAID	(US) National Institute of Allergy and Infectious Diseases
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH	(US) National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NRTI	nucleotide reverse transcriptase inhibitor
OHRP	Office for Human Research Protections
Oral CAB	oral formulation of cabotegravir
PA-IC_{90}	protein-adjusted 90% inhibitory concentration
PAL	Protocol Analyte List
PBMC	Peripheral blood mononuclear cells
PEP	Post-exposure prophylaxis
Pgp	Permeability glycoprotein
PHQ-9	Patient Health Questionnaire-9
PI	package insert
PK	Pharmacokinetic
PO	by mouth/orally
PPN	pre- and postnatal development
PrEP	pre-exposure prophylaxis
PROUD	Pre-exposure Prophylaxis to Prevent Acquisition of HIV-1 Infection
pSMILE	Patient Safety Monitoring and International Laboratory Evaluation
PSRC	(DAIDS) Prevention Science Review Committee
PTCA	percutaneous transluminal coronary angioplasty
PY	person-years
QA	quality assurance
QC	quality control
QT	time between the start of the Q wave and the end of the T wave
RCT	randomized clinical trial
RE	regulatory entity
RNA	ribonucleic acid

RPV	Rilpivirine
RPV LA	rilpivirine long-acting (injectable)
SAE	serious adverse events
SC	Subcutaneous
SDMC	(HPTN) Statistics and Data Management Center
SHIV	simian human immunodeficiency virus
SMC	Study Monitoring Committee
SMS	Short message service
SOC	standard of care
SOE	Schedule of evaluations
SOP	standard operating procedure
SSA	sub-Saharan Africa
SSP	Study Specific Procedures Manual
SRC	(HPTN) Scientific Review Committee
STI	sexually transmitted infection
TBili	total bilirubin
TCID	tissue culture infective dose
TDF	tenofovir disoproxil fumarate
TDF/FTC	tenofovir/emtricitabine (trade name: TDF/FTC, Truvada®)
TFV	Tenofovir
TFV-DP	tenofovir diphosphate
TGW	transgender women
T_{max}	time after drug administration when maximum drug concentration in serum is reached
TP	Triphosphate
TV	*Trichomonis vaginalis*
UGT 1A1	Uridine diphosphate glucuronyltransferase type 1A1
UKNEQAS	United Kingdom National External Quality Assessment Service
ULN	upper limit of normal
US	United States of America
VOICE	Vaginal and Oral Interventions to Control the Epidemic
VQA	(DAIDS) Virology Quality Assurance
WHO	World Health Organization
YKPs	Youth key populations
YMSM	Young men who have sex with men

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Protocol Signature Page

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Support Provided by:
ViiV Healthcare

I will conduct the 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 U.S. 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.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

_____

Name of Investigator of Record (print name)

_____ _____

Signature of Investigator of Record | Date (DD/MM/YYYY)

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SCHEMA

Purpose:
To establish the minimum safety, tolerability and acceptability data needed to support the use of cabotegravir long-acting injection (CAB LA) in an adolescent population, potentially transforming the field of HIV prevention for young people.

Design:
A Phase IIB single arm, open label safety, tolerability, and acceptability study.

Population:
Sexually-active, healthy male (assigned at birth) adolescents aged below 18 years.

Study Size:
Approximately 50.

Study Duration:
Participant recruitment will take approximately 12 months. Oral study product will be administered for 5 weeks, followed by 29 weeks on injectable product, then quarterly visits for 48 weeks after final injection. All participants who have received at least one injection will be followed for 48 weeks after their last injection. Waning levels of cabotegravir (the PK tail) will be covered with locally sourced oral TDF/FTC for daily use for 48 weeks. Total study duration per participant will be approximately 21 months.

Study Sites:
Adolescent and Young Adult Research at The CORE Center (AYAR at CORE), Chicago, IL; St. Jude Children's Research Hospital CRS, Memphis, TN; Fenway Health CRS, Boston, MA

Study Regimen:
Step 1 – oral cabotegravir (30mg tablet); Step 2 – 3 mL (600 mg) intramuscular (IM) CAB LA injection; Step 3 – Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) (300mg/200mg tablet)

Primary Objectives:

- To evaluate the safety, tolerability and acceptability of CAB LA in healthy HIV-uninfected male adolescents aged below 18 years.

Secondary Objectives:

- To examine adherence to and timeliness of injections over time among adolescent participants who are provided CAB LA and information regarding its safety and unknown efficacy.
- To examine patterns of sexual risk behavior over time among adolescent participants who are provided CAB LA and information regarding its safety and unknown efficacy.

- To evaluate the safety of CAB LA for 48 weeks of follow-up after final injection.
- To characterize the pharmacokinetics of CAB LA

1.0 INTRODUCTION

1.1 Background and Rationale

The burden of HIV infection worldwide is disproportionately borne by youth.

Despite reductions in other age groups, the number of deaths attributable to HIV is rising in the adolescent age group, with AIDS being the leading cause of death among adolescents in Africa and the second leading cause for adolescents worldwide.[1] Between 2005 and 2012, the number of AIDS-related deaths decreased by 30% for all ages except adolescents, who experienced a 50% increase in that same period. Similarly, two-thirds of new HIV infections in 2012 occurred among adolescents and young adults aged 15 to 24.[2] Among youth, there are also key populations that bear disproportionate burdens of HIV and are the most vulnerable. These key populations (YKPs) include young men who have sex with men (YMSM) globally and adolescent/young adult women in Sub-Saharan Africa.[3]

Among YMSM, HIV incidence has been shown to be very high across multiple countries, and global reports estimate an HIV prevalence of 4.2% for young gay men under the age of 25.[3,4] In the United States (US), MSM account for most (72%) new HIV infections among youth aged 13 to 24, making them the only group that has shown a significant increase in estimated new infections.[5] Young MSM who engage in sex work are even more vulnerable to HIV and a study in Kenya found a baseline HIV prevalence of 40% among young MSM who sell sex in Nairobi.[6] Recent PrEP demonstration studies conducted by this investigative team (ATN 110/113) found an HIV incidence of 3.41/100 person-years among YMSM ages 18-22 and a staggering 6.41/100 person-years among 15-17 year old participants in the US.[7,8]

HIV prevention and decreasing HIV-related deaths depend critically on reaching adolescents, engaging them in HIV prevention research, and insuring access to HIV prevention products, such as CAB LA, via regulatory approvals. Therefore, participants in this trial may directly benefit from taking part in this study, HPTN 083-01.

Oral Pre-exposure Prophylaxis is highly efficacious against HIV, but poor adherence has limited its effectiveness for youth.

Tenofovir-based regimens have been shown to significantly reduce HIV acquisition among men who have sex with men (MSM), heterosexual men and women, injection drug users and HIV sero-discordant couples.[9-12] Given the growing body of evidence about its effectiveness, including encouraging "real world" demonstration projects[13,14] oral daily PrEP is now recommended for HIV prevention by the US Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO) and a growing number of countries worldwide.[15,16]

As with many daily medication regimens, the effectiveness of oral PrEP is highly dependent on adherence to the prescribed drugs. This appears to be particularly true for adolescents and young adults. Among MSM, young age has consistently correlated with lower adherence to PrEP. In the iPrEx

licensing randomized clinical trial[9], overall efficacy was 44% for Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) compared with placebo among 2499 MSM, with efficacy increasing to over 90% when drug in plasma or peripheral blood mononuclear cells (PBMC) was detectable, reflecting the importance of adequate adherence to medication. YMSM ages 18-24 in iPrEx demonstrated lower PrEP efficacy (28%) compared to older participants (56%) and were over 3 times less likely to have drug detected in plasma. The iPrEx Open Label Extension[14] reported no significant difference of PrEP uptake on the basis of age, however, the odds of having detectable drug in plasma significantly decreased as age decreased, with those 18 to 24 years of age differing substantially from those 30 and older. In the ATN 110 trial of young adult MSM, protective levels of adherence (defined by dried blood spot levels consistent with ≥ 4 pills/week) declined sharply over time from 56% at week 4 to 34% at week 48 [7]. In the ATN 113 trial of adolescent MSM, the declining adherence was even more striking, from 54% at week 4 to 22% at week 48[8]. Thus, while PrEP appears to be of interest to YMSM, barriers to adherence adversely impact effectiveness.

For youth, PrEP may only reach its full potential with drugs that do not depend on daily or near-daily pill-taking.

Challenges with adherence to medication are commonplace among adolescents, regardless of whether it is adherence to a treatment or prevention regimen. Non-adherence among youth is often a reflection of both the biological and behavioral transitions that occur during this developmental time, including increased autonomy from parents/guardians, increased importance of peers and corresponding vulnerability to peer influence and stigma, and undeveloped cognitive capacity for organization and planning. Rates of adherence among adolescents and young adults with chronic illnesses requiring daily medication, such as HIV, diabetes, and cancer are consistently low, with estimates often about 50% overall.[17,18] Similarly, rates of adherence to oral prevention strategies, such as contraception, demonstrate similar challenges to daily adherence. Many studies have found that continuation rates are lower and pregnancy rates are higher among adolescents using oral contraception versus long-acting contraceptives.[19,20] Just as increased choice in type and method of delivery of contraceptive methods has increased acceptability and effectiveness for contraception[21,22], we believe that expanded choices for HIV prevention will similarly increase utilization, satisfaction, and effectiveness.

A recently presented qualitative study investigating PrEP preferences among young MSM supports that prevention choice is important for young men. Participants, ages 16-29, reported that injections may be more manageable and better for those who have adherence difficulties as well as beneficial for those who engage in sex more frequently. However, concerns specific to injectable PrEP were expressed regarding severity/duration of side effects, pain, level of protection prior to next injection, distrust of medical system and injections, and cost – all issues that must be addressed with further research among young populations.[23,24] The development of alternative agents for PrEP, with more adherence-friendly schedules, could increase prevention choices and increase acceptability. Long-acting injectable agents have the potential to prevent HIV acquisition without relying on adherence to a daily oral regimen.[25]

Adult safety data on long-acting cabotegravir (CAB LA) will need to be expanded to adolescents in order to license the product for youth under the age of 18

Currently, two parent protocols (HPTN 083 and HPTN 084) are being conducted globally. HPTN 083 is a study being done to evaluate the efficacy of CAB LA for PrEP in HIV-uninfected MSM and TGW, ages 18 and older, and is enrolling approximately 4,500 MSM and TGW in the Americas, Asia and

South Africa. HPTN 084 is a study being done to evaluate the safety and efficacy of CAB LA, compared to daily oral Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®), for PrEP in approximately 3,200 HIV-uninfected women ages 18 to 45 years old in sub-Saharan Africa who are at risk for acquiring HIV. See Section 1.7.3 for results from the HPTN 083 study.

Historically, medical treatments applied to children were often based upon testing done only in adults, rendering evidence-based treatments less available to children due to their exclusion from studies. Since 1996, one goal of the National Institutes of Health as well as the US FDA has been to increase the participation of children in research so that adequate data can be developed to support treatment (and prevention) modalities for disorders and conditions that affect adults as well as children. In order for adolescents to access safe and effective new biomedical HIV prevention products at the same time that these products are approved and marketed for adults, the scientific development and testing of these products for adolescents must proceed concurrently.[26] Similarly, adolescents are often excluded from prevention intervention trials due to concerns from regulatory or ethics boards as well as investigator concerns around the complexity of recruitment/retention and/or fear that adolescent difficulties will adversely impact the primary outcomes of the trial.[27,28] This exclusion from large Phase 3 trials as well as hesitancy to launch youth-focused bridging trials only exacerbates the gaps in HIV prevention intervention availability and access, which continues to fuel the HIV epidemic among vulnerable young people.

This trial has been designed as an open label clinical trial. An unblinded, single arm trial is most developmentally-appropriate for adolescents, while also minimizing participant and staff burden. The design of the parent trials (HPTN 083 and HPTN 084) is quite complicated. They are double-blind, double dummy trials with a complex visit schedule and a lengthy commitment for participant completion. It is unreasonable and unnecessary to request this type of commitment and burden from vulnerable adolescents (and their parents/guardians), when efficacy data can be extrapolated from the parent studies. Furthermore, open label prevention studies have demonstrated that product adherence improves when participants know what they are taking and can be counseled about the unblinded product.[29-31]

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), unless otherwise noted.

CAB is an investigational HIV integrase strand transfer inhibitor (INSTI) that has attributes favorable for both HIV treatment and prevention indications. Currently in Phase 2 and Phase 3 clinical trials, it was initially selected for development based on its potential for a high genetic barrier to resistance and a PK profile that allows low-dose, once-daily oral dosing or monthly to every 2-month parenteral dosing using an aqueous suspension for injection formulation. An oral tablet version of CAB has also been developed as lead-in therapy to establish acute safety and tolerability in individual participants prior to switching to the long-acting formulation. CAB LA has an absorption half-life 21 to 50 days in adults.

1.2.1 Non-human Primate Studies Relevant to Rectal Exposures

CAB LA has demonstrated activity in preventing simian human immunodeficiency virus (SHIV) infection in non-human primate models.[32] In a preclinical study evaluating the potential of CAB LA for

PrEP, 2 weekly doses of CAB LA (50 mg/kg intramuscularly [IM]) were highly protective against weekly rectal challenges with SHIV162p3 (50% tissue culture infective dose [$TCID]_{50}$) for up to eight exposures. In these protected animals, the plasma concentrations of CAB LA throughout the period of virus challenges were comparable to clinically-relevant concentrations in humans. In follow-up studies, a single dose of CAB 50 mg/kg IM one week prior to the serial weekly viral challenges with SHIV162p3 (50 $TCID_{50}$) were evaluated. The percent of challenges resulting in infection was calculated relative to the plasma CAB protein-adjusted 90% inhibitory concentration (PA-IC_{90}) value. None of 59 challenges resulted in infection when plasma levels were greater than 3 times the PA-IC_{90}, compared with 1 out of 22 challenges resulting in infection when plasma levels were between one to three times the PA-IC_{90}, and 11 out of 43 challenges resulting in infection when plasma levels were less than 1 times the PA-IC_{90}. Twelve out of 26 challenges resulted in infection in control animals; rectal tissue levels of CAB were approximately 20% of plasma levels.[33]

1.3 Metabolism

CAB is highly protein bound in human plasma (>99%). It is a substrate for permeability glycoprotein (Pgp), but because of its high permeability, no alteration in absorption would be expected by co-administration of either Pgp or breast cancer resistance protein (BCRP) inhibitors. Elimination occurs predominantly in feces via biliary excretion. Renal excretion is minimal, with less than 1% of the dose eliminated in the urine. The primary route of biotransformation is conjugation with glucuronic acid (M1) via uridine diphosphate glucuronyltransferase type 1A1 (UGT 1A1).

1.4 Preclinical Studies

The CAB toxicology package supports the careful conduct of clinical studies with CAB up to the no observed adverse effect level (NOAEL) exposure in the 39-week monkey toxicity study (Week 39 gender mean AUC_{0-24} and C_{max} of 547 μg·h/mL and 34.6 μg x h/mL, respectively). The results of the multiple dose rat subcutaneous (SC) and IM toxicity study, along with data from the oral toxicity program, support the careful conduct of clinical studies with CAB LA up to the mean C_{max} plasma concentration observed at the NOAEL in the 39-week monkey oral CAB toxicity study (34.6 μg/mL) or the mean AUC1,440-2,160h following once monthly IM dosing at the NOAEL (75 mg/kg/dose) in the 3-month rat CAB LA toxicity study (92,566 μg x h/mL).

In a rat pre- and post-natal study, CAB exposure during pregnancy resulted in increased offspring mortality at the highest dose tested (1000mg/kg/day). This is in excess of the established safety limit (NOAEL) of 5mg/kg/day. The NOAEL is >20 fold the predicted clinical Cmax and AUC exposures in humans for both HIV treatment and prevention. The mechanism for the reduction in viable pups at this supratherapeutic dose up to 4 days post-partum is unknown. Clinical dosing in HPTN 077 (a safety, tolerability, and PK of CAB LA in HIV-uninfected, low-risk men and women) is approximately 7-fold below the NOAEL in 10-day-old rat offspring. Importantly, an early fetal development (EFD) study in rats was negative.

1.5 Dose Rationale

1.5.1 Oral CAB

CAB is readily absorbed following oral administration in healthy and HIV-infected participants with a median T_{max} of approximately two hours. The apparent terminal phase half-life following oral administration is approximately 40 hours.

In a short-term monotherapy study, seven HIV-infected participants received oral CAB 5 mg once daily for 10 days, which achieved a geometric mean Day 10 plasma trough concentration (Cτ) of 0.57 μg/mL, 3.4-fold above the PA-IC_{90} value, and was associated with a mean Day 11 HIV ribonucleic acid (RNA) change from a baseline of -2.2 $\log_{10}$ c/mL.[34,35] In LATTE, the Phase 2b study in HIV-infected, ART-naïve adult participants,[36] suppression of HIV replication was accomplished with oral CAB at doses of 10 mg to 60 mg once daily in combination with two nucleoside reverse transcriptase inhibitors (NRTIs), and HIV viral load was maintained below 50c/mL at similar rates across oral CAB 10 mg to 60 mg doses through >72 weeks when combined with oral rilpivirine (RPV) 25 mg once daily. The geometric mean individual average plasma Cτ following oral CAB 10 mg and 30 mg once daily were 1.35 μg/mL, eight-fold above PA-IC_{90}, and 4.2μg/mL, 25-fold above PA-IC_{90}, respectively.

An oral tablet version of CAB has been developed as lead-in therapy to establish acute safety and tolerability in individual participants prior to switching to the long-acting formulation. Oral CAB has been studied at doses between 5 mg and 150 mg in HIV-uninfected and HIV-infected adults. The oral formulation of CAB has been generally well-tolerated as single or repeated doses in clinical studies of HIV-uninfected adults. CAB 30 mg once daily has been used as the oral lead-in the ECLAIR (Phase IIa Safety and PK Study of Cabotegravir LA in HIV-uninfected Men), LATTE-2 (CAB + RPV as Long-Acting Maintenance Therapy), HPTN 077 (A Phase IIa Safety, Tolerability and Acceptability Study of an Investigational Injectable HIV Integrase Inhibitor for PrEP in HIV Uninfected Men and Women) studies, and 4 Phase III studies in adults - 2 PrEP studies, HPTN 083 and HPTN 084, and 2 treatment studies (201584 (FLAIR) and 201585 (ATLAS). Therefore, CAB 30mg once daily has been selected for the oral run-in regimen for this study.

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 1.1).

Table 1.1 Cumulative CAB Exposures from Phase 1 through Phase 3 Clinical Studies Through October 2018

Treatment Population/ Dose	Duration	Completed	Ongoing/ Concluded [a]	Total
Healthy Volunteers/HIV-Uninfected				
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 [g]	230 [b]	1377 [c]	1607
Any dose		**599**	**1694**	**2293**
HIV-infected patients				

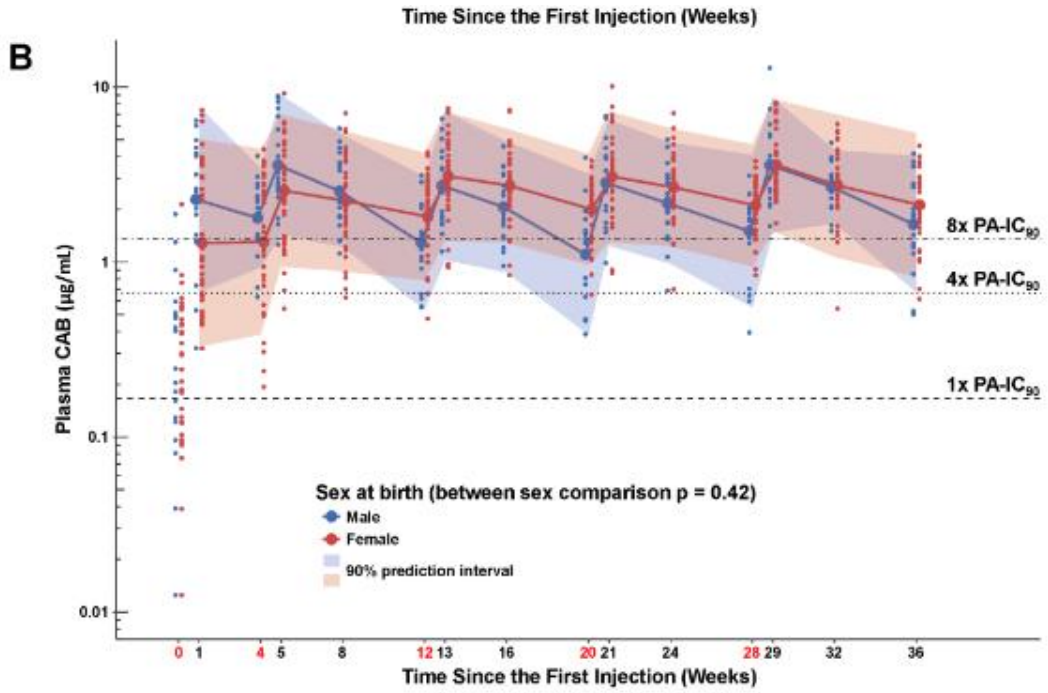
5 to 30 mg once daily oral (Ph 2a)	10 days	15	0	15
10 to 60 mg once daily oral (Ph 2b)	Max 2247 days [h]	0	181	181
30 mg once daily oral (Ph 2b)		0	1739	1739
Up to 800 mg IM LA [d]	Max 1477 days [g]	0	1745 [e]	1745
Any dose		**15**	**1928**	**1943**
All participants				
Single dose oral (5 to 150 mg)		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 [b]	3122 [f]	3352
Any dose		**614**	**3622**	**4236**

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

The regimen proposed for this study was evaluated in HPTN 077 Cohort 2. For the HPTN 077 study, participants were low-risk HIV-uninfected individuals at eight sites globally, randomized (3:1) to daily oral CAB 30mg (or placebo) for four weeks, followed by CAB (or PBO) 800mg IM at weeks 5, 17, and 29 (Cohort 1) or 600 mg IM at weeks 5, 9, 17, 25, and 33 (Cohort 2). One hundred ten participants enrolled in Cohort 1, 89 in Cohort 2. Ninety-four percent of participants completed the oral phase, 89% received at least one injection, and 75% completed all injections, which did not differ by arm, cohort or sex. Over 41 weeks, injection site pain and injection site reactions (ISR) were more common in CAB vs. placebo. No other differences were found in safety or tolerability. ISR led to injection discontinuation in 2/134 (1.5%). Cohort 2 dosing consistently achieved plasma trough targets whereas Cohort 1 dosing did not. Overall, CAB was well tolerated among low-risk HIV-uninfected men and women.

In HPTN 077, overall 65% of the study participants were female. Median BMI was 28 kg/m2 in female participants and 25 kg/m2 in male participants. Among participants in Cohort 1 (who received a split injection of CAB-LA 800mg IM q12 weeks), males had a higher geometric mean Cmax after the first injection, but significantly lower trough concentrations than female participants after all three injections. Trough CAB levels were below 4X PA-IC90 in 72%, 35%, and 32% of male participants at weeks 17, 29, and 41, respectively. In contrast, trough CAB levels in female participants were largely at goal throughout the trial, with 24%, 5% and 0% of female participants having trough levels below 4X PA-IC90 at weeks 17, 29, and 41. In Cohort 2 (Figure 1.1) (CAB LA 600mg IM q 8 weeks), male participants achieved significantly higher CAB Cmax, AUC0-tau, and Ctrough after the first injection than female participants (and overall, participants with lower BMI were observed to have significantly higher trough concentrations after the first injection). However, CAB trough levels < 4X PA-IC90 (between 1 and 4X the PA-IC90) were observed in 5%, 20%, 20%, 16%, and 11% of male participants after injections 1, 2, 3, 4, and 5, respectively. For female participants, 21%, 5%, 3%, 0%, and 3% had CAB trough levels below 4X PA-IC90 after injections 1, 2, 3, 4, and 5, respectively.

Figure 1.1 CAB LA PK Profiles following Q8W Dosing in Males and Females (HPTN077, Cohort 2)



During the 76-week follow-up phase of the HPTN 077 study[37], differences were observed in the median time to undetectable cabotegravir concentrations between men and women: 42.7 weeks (range 20.4-134) in men as compared to 66.3 weeks (range 17.7-182) in women. CAB was detectable in plasma in 22% of men and 63% of women at 60 weeks and in 13% of men and 44% of women at 76 weeks post the last injection). The observed PK in HPTN 077 supported the development of CAB for HIV prevention using 600mg IM every 8 weeks with a 4-week loading dose for all sexes.

1.6 Genital Tract (GT) Tissue Levels after Oral and Injectable Administration

Genital tissue concentrations have been measured after CAB LA 400 mg IM single dose administration in 24 healthy men and 15 healthy women. Median cervical and vaginal tissue concentrations ranged from 16-28% (overall range 0-70%) of plasma concentrations, roughly 1 x PA-IC90 (0.166 µg/mL). Median rectal tissue concentrations were ≤ 8% of plasma concentrations (range 0-20%).37 Further tissue studies using single and multiple doses of the 800 mg IM dose are currently ongoing.

1.7 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.

1.7.1 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

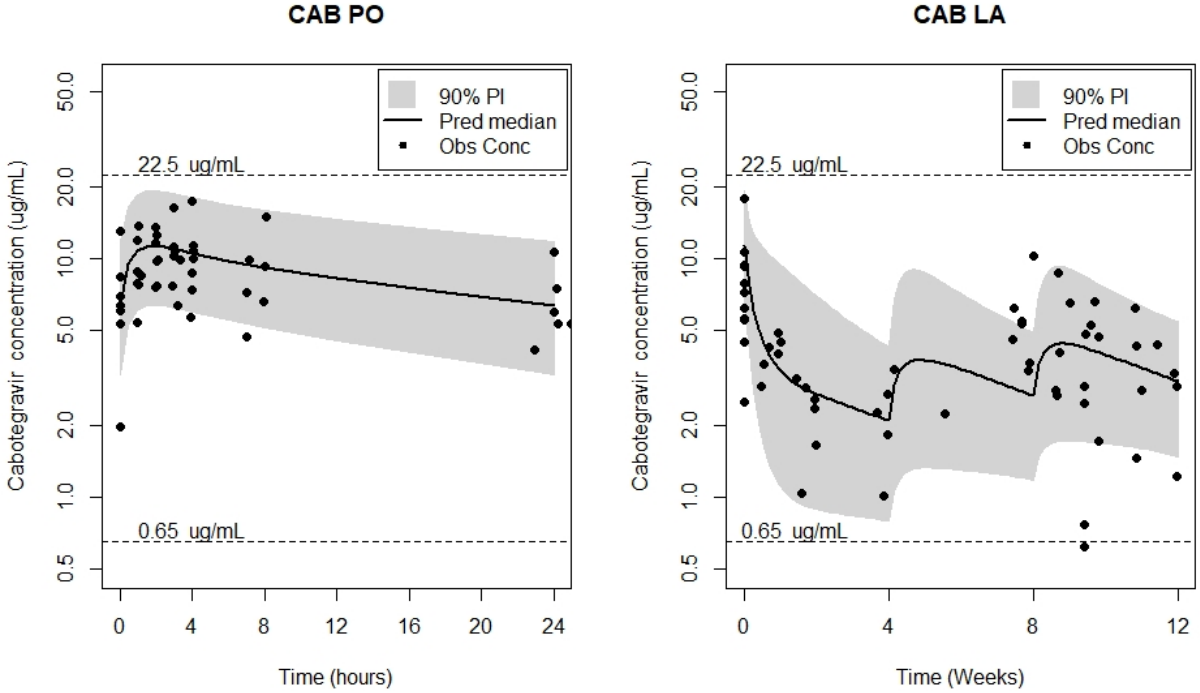
Dosing Phase	Dosage Regimen	Geometric Mean (5^{th}, 95^{th} Percentile)[a]	
		$AUC_{(0\text{-}tau)}$[b] (mcg•h/mL)	C_{tau}[b] (mcg/mL)
Oral Lead-In[c]	30 mg once daily	145 (93.5, 224)	4.6 (2.8, 7.5)
Initial Injection[d]	600 mg IM Initial Dose	1,591 (714, 3,245)	1.5 (0.65, 2.9)
Monthly Injection[e]	400 mg IM monthly	2,415 (1,494, 3,645)	2.8 (1.7, 4.6)

[a] All pharmacokinetic parameter values based on pooled FLAIR and ATLAS individual post-hoc estimates from cabotegravir population pharmacokinetic model (n = 581, 2018N384611_01).
[b] tau is dosing interval: 24 hours for oral administration; 1 month for IM injections of extended-release injectable suspension.
[c] Oral lead-in pharmacokinetic parameter values represent steady-state.
[d] Initial injection $AUC_{(0\text{-}tau)}$ value includes contribution following oral dosing because the initial injection was administered on the same day as the last oral dose; however, the C_{tau} value at Week 4 reflects the initial injection.
[e] 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 supratherapeutic 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 Cτ (μg/mL)[b]	
		Post First Injection	Post Second Injection[c]
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] [a]	1.61 [0.80, 2.99][d]

a. Geometric mean [5th and 95th percentile] - Week 8 pre-dose concentrations were obtained following a CAB 600 mg IM dose.)
b. Median [90% prediction Interval]
c. Cτ after second injection is 8 weeks post injection
d. Geometric mean [5th and 95th percentile] - Cτ at Week 48 with Q8W dosing regimen (ATLAS 2M, 207966)

1.7.2 Results from HPTN 077

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 males expected to enroll in HPTN 083-01. Model predicted concentrations in adolescent males (simulated with median weight and BMI of 63 kg and 21 kg/m2, respectively) to enroll in HPTN 083-01 are similar to adult males in HPTN 077 (median weight and BMI of 77kg and 24 kg/m2, respectively) receiving the same regimen and below oral dosing, and therefore are expected to be safe in this population (Table 1.4). Approximately 95% of male subjects are expected to achieve trough concentrations > 4x PA-IC90 following the 5th injection. This regimen is currently being evaluated in uninfected adult males and females in HTPN 083 and HPTN 084, respectively, and has maintained HIV suppression in infected adults when combined with RPV LA (LATTE-2).

Table 1.4 Predicted CAB Parameters following Injection 5 of the CAB LA 600mg IM Q8W Regimen in Male Adolescents compared with Predicted and Observed Data in Male Adults in HPTN 077

Plasma CAB Parameter ((μg/mL)	**Male Participants in HPTN 077 Median (range)**		**Predicted Exposures Male Adolescents ≥50kg (110 lbs.)**		
	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 Cmax or C,Wk 34 (1-week post Inj5)	7.6 (4.6 - 12.0)	3.4 (1.6 - 12.9)	**5.0 (2.7, 9.1)**	**0.7**	**1.5**
Oral Cτ or C,Wk 41 (8-weeks post Inj5)	4.5 (2.3 - 7.6)	1.78 (0.50 - 4.2)	**1.8 (0.5, 3.4)**	**0.4**	**1.0**

Plasma CAB will be evaluated during follow up period and but is not expected to be detectable in a majority of subjects one year after 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 the 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.

Seven uninfected participants in HPTN 077 weighing <50kg at baseline received CAB LA injections during the study. Individual W41 Ctau values following final injections in participants <50 kg ranged from 0.616 μg/mL to 4.17 μg/mL (

Table), which is within the range of W41 Ctau for the study population overall of 0.203 to 4.72 μg/mL for Cohort 1 (n=57) and 0.503 to 4.62 μg/mL for Cohort 2 (n=52) and are consistent with expected concentration targets. Individual t1/2 estimates ranged from 13.6 days to 90.4 days in participants <50 kg and from 19.8 to 183 days in Cohort 1 overall and from 13.6 to 241 days in Cohort 2 overall.

Table 1.5 Select PK Parameters in Participants with Baseline Weight <50kg

Cohort	Sex	Subject	Baseline Weight (kg)	Baseline BMI (kg/m^2)	Ctau (μg/mL)		T1/2 (day)
					Week 9 (Initial Injection)	Week 41 (Final Injection)	
Cohort 1	F	257000081	42.7	16.5	0.655	1.73	28.3
	F	264000146	41.4	18.2	1.36	3.13	50.3
Cohort 2	F	261000208	46.5	19.4	4.41	4.02	90.4
	M	261000299	49.7	17.0	2.22	4.17	60.8
	F	263000215	46.5	19.4	2.74	0.616	13.6
	F	263000350	47.5	20.3	2.27	2.67	21.9
	F	264000392	49.5	18.4	3.68	1.04	14.5

Source Data: Listings 6.4, 8.23, 8.24
Cohort 1: 800mg Q12W x 3 doses
Cohort 2: 600mg Q8W (Injections 2 administered 4 weeks following injection 1, Injections 3-5 administered 8 week following prior injections).

1.7.3 Results from HPTN 083

On 14 May 2020, the international DSMB met to review safety and efficacy data for the HPTN 083 and 084 study trials. In HPTN 083, a study among cisgender men and transgender women who have sex with men, they reviewed 50 overall HIV infections for an overall HIV incidence of 0.79%. Of those infections, 38 occurred in the TDF/FTC arm compared to 12 in the CAB LA arm. Based on this data, the DSMB agreed that CAB LA had crossed the prespecified non-inferiority margin and was highly effective in preventing HIV infections. The DSMB recommended unblinding of all study participants and providing them their choice of study product in HPTN 083. In addition, the DSMB reported no safety concerns for either the HPTN 083 or 084 trials.

On 7 July 2020, at the 23rd International AIDS Conference (AIDS 2020: Virtual), the HPTN 083 study team announced that the HPTN 083 clinical trial showed that CAB LA, injected once every 8 weeks, was superior to daily oral tenofovir/emtricitabine (TDF/FTC) for HIV prevention amongst the HPTN 083 study population. A total of 52 HIV infections occurred during follow-up, with 13 infections in the CAB arm (incidence rate 0.41%) and 39 infections in the TDF/FTC arm (incidence rate 1.22%). The

hazard ratio in the CAB versus TDF/FTC arms was 0.34 (95% CI 0.18-0.62), corresponding to a 66% reduction in incident HIV infections in study participants given CAB compared to TDF/FTC. These results meet the statistical criteria for superiority of the regimen containing CAB compared to TDF/FTC in the HPTN 083 study population.[37]

1.8 Hepatic and Central Nervous System Adverse Events

As part of the early phase development of CAB (HPTN 077, LATTE and LATTE-2), some participants developed transaminase elevations, which were clinically asymptomatic and resolved rapidly with cessation of study product.

In a single-dose study (LAI116815), a healthy male volunteer with a history of prior seizure activity (one episode 14 years prior), on no anti-epileptic medication, experienced an unwitnessed seizure event 270 days after a single injection of CAB LA 400 mg IM. Plasma levels of CAB were undetectable for 4 months prior to the seizure event. The event occurred in the context of consumption of approximately 10 cans of beer, and a magnetic resonance imaging (MRI) study was unrevealing for pathology. An electroencephalogram was consistent with benign juvenile epilepsy; the participant recovered without additional events.

A participant in the ongoing Phase 2b LATTE-2 trial of HIV-infected individuals received oral ABC/3TC with CAB 30 mg daily for 20 weeks, and received ABC/3TC, CAB and oral RPV for 4 weeks, all without incident or clinically significant AEs or laboratory abnormalities. He was randomized to continue CAB LA 400 mg IM + RPV LA 600 mg IM Q4W. On day 349 of overall CAB treatment (139 days of oral CAB + 210 days of CAB LA exposure), the participant was found in his apartment by emergency personnel unresponsive, unconscious, and having generalized tonic-clonic seizures. The participant was hospitalized in the intensive care unit, had recurrent seizures, and was found to have anoxic brain injury resulting in death. The participant had no prior history of seizures, and clinical history and toxicity screens suggested possible recreational substance use.

A participant in the healthy volunteer HPTN 077 study, with a prior history of seizures treated with Dilantin had been taken off Dilantin 2 years prior to study participation and had been seizure-free. A "spell" 1 month prior to study enrollment did not prompt re-initiation of anti-epileptics. Oral CAB 30 mg (or placebo) was administered for four weeks without incident, and Day 62 after administration of CAB LA 800 mg IM x 1 (or placebo), the participant had an unwitnessed seizure event; he was subsequently hospitalized for transient dizziness and hemiparesis, for which work-up was unrevealing, and resolved with meclizine treatment. The participant recovered without additional events and is not planned for additional intraperitoneal (IP) dosing.

A participant in HPTN 077 without known pre-existing liver disease, and without HIV-infection developed Grade 3 ALT elevation after 12 weeks of injectable placebo treatment; the participant was asymptomatic, and ALT returned to normal 15 weeks after withdrawal of study product. A serologic and ultrasonographic evaluation did not reveal alternative etiology for the ALT elevation; no biopsy was performed.

1.9 Weight gain

There is emerging evidence from randomized trials that the use of integrase inhibitors could lead to significant increases in body weight.[38] Two trials of raltegravir and three involving dolutegravir all observed greater weight gain increases in integrase containing regimens. These effects appear to vary by gender and race, with highest increases observed in women and those of black race. The mechanism for this needs to be fully elucidated. These data are from populations receiving treatment and more data is needed in healthy HIV uninfected populations using PrEP. HPTN 077 evaluated changes in weight and fasting metabolic parameters in 177 HIV-uninfected individuals randomized to cabotegravir or a placebo who had received at least one injection. No differences between study groups were found for change in weight or fasting metabolic parameters overall, or for subgroups. Among the 146 participants with paired weights, between W0 and W41 the median increase in weight for CAB treated participants was 1.1 (IQR -0.9, +3.0) kg compared to median 1.0 (IQR -1.2, +3.2) kg gained by PBO treated participants (=+0.1 kg, p=0.66). The distribution of weight changes across the 41 week treatment period did not differ between CAB and PBO-treated participants, nor when divided into the oral phase (=+0.3 kg, p=0.6) and the injection phase (=+0.2 kg, p=0.65). A 5% or greater increase in weight from W0 to W41 was seen in 24 (22%) CAB participants and 7 (18%) of PBO participants (p=0.62).[39]

1.10 Rationale for use of Oral Run-in Prior to Injectable Dosing

The CAB LA formulation has a PK decay rate that exposes the injected individual to detectable levels of CAB for a year or more after an injection (see Section 1.5.2 of the protocol). In order to maximally identify any acute toxicity prior to administration of a non-dialyzable, non-removable depot injection, a five-week lead-in period of daily oral (short acting) CAB will be employed. This lead-in period will be evaluated with serial safety assessments prior to injectable administration. The current plans for product labeling should FDA approval be granted include an oral lead-in strategy when adequate safety is established after four weeks of oral drug exposure. The 5-week exposure in this study is designed to provide un-interrupted study product coverage while awaiting return of the Week 4 safety laboratory assessments.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objectives

- To evaluate the safety, tolerability and acceptability of CAB LA in healthy, HIV-uninfected male adolescents aged below 18 years.

2.2 Secondary Objectives

- To examine adherence to and timeliness of injections over time among adolescent participants who are provided CAB LA and information regarding its safety and unknown efficacy.
- To examine patterns of sexual risk behavior over time among adolescent participants who are provided CAB LA and information regarding its safety and unknown efficacy.
- To evaluate the safety of CAB LA for 48 weeks of follow-up after final injection.

- To characterize the pharmacokinetics of CAB LA.

2.3 Study Design and Overview

We propose a single arm, open label, safety, tolerability, and acceptability study (n= approximately 50) in sexually-active, healthy adolescents assigned male sex at birth.

Study participation includes, Step 1: a 5-week oral CAB 30mg QD safety lead-in followed by a series of 5 intramuscular (IM) injections of 3 mL (600 mg), administered at 8-week intervals after a 4-week loading dose (injections at weeks 5, 9, 17, 25 & 33) in Step 2. Adherence support strategies (e.g., counseling, reminders, pill cases) will be included to support pill-taking during the first five weeks and to support retention during the injectable phase. A safety visit will follow each injection to ascertain pharmacokinetic-peak safety data, including injection site reactions. Step 3: a blood draw visit, the +8 Week Visit, will follow the last injection to monitor CAB drug levels. All participants who have received at least one injection will be followed for 48 weeks after their last injection. Waning levels of cabotegravir (the PK tail) will be covered with locally sourced oral Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) 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).

Participants who discontinue study product during Step 2 for any reason other than HIV infection or AE occurrence will be transitioned to open label Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) for 48 weeks.

Finally, in-depth qualitative interviews will be conducted at the end of the product exposure period (Week 34) with 10 participants (total, across all sites) to explore issues of acceptability and preference for oral tablets and/or injections. Additionally, up to 10 parents/guardians of participants (total, across all sites) will be asked to participate in in-depth interviews to explore facilitators and barriers to adolescent enrollment in biomedical clinical trials as well as parental acceptability of injectable prevention products for youth.

As previously mentioned, we have chosen an unblinded, single arm trial because it is most developmentally-appropriate for adolescents and minimizes participant and staff burden, while also offering a more streamlined visit schedule than the parent protocols and, hopefully, promoting study drug adherence.

2.3.1 Participating Sites/Institutions

Participating sites are listed in the Schema and in the SSP Manual.

2.3.2 Study Duration

The initial phase, Step 1, will be an oral lead-in phase of 5 weeks. After that, follow up on study product will be for 34 weeks, followed by quarterly visits for 48 weeks after the final injection. Total participant commitment for the entire study is approximately 82 weeks, or approximately 1.5 years. We anticipate recruitment for the study will take approximately 12 months.

3.0 STUDY POPULATION

We are using clinical sites that have proven ability to enroll and retain adolescent participants, astute awareness of the developmental and cultural issues experienced by adolescents, as well as outstanding productivity with previous bio-behavioral clinical trials. Participants will be recruited from the clinical sites' patient populations, as well as through community-based venues, including working with sites' community partners and community advisory boards, as well as through social media and/or other technology-based recruitment methods successfully used in our previous PrEP studies for youth.

Approximately 50 participants will be included in this study. Each site will be asked to work with its Community Advisory Board and outreach, education and recruitment teams to develop a recruitment plan appropriate for the local population. Participants will be selected for the study according to the criteria in Sections 3.1 and 3.2. Study participants will be recruited as described in Section 3.3. Requirements related to participant retention and withdrawal from the study are described in Sections 3.5 and 3.6, respectively. Individual sites will be given enrollment targets such that overall cross-site enrollment meets overall protocol goals.

3.1 Inclusion Criteria

Male adolescents who meet the following criteria are eligible for inclusion in this study:

3.1.1 Assigned male at birth (includes MSM, TGW, and gender non-conforming people)

3.1.2 At enrollment, aged below 18 years*

3.1.3 At enrollment, body weight ≥ 35 kg (77 lbs.)*

3.1.4 Willing to provide written informed assent/consent for the study and/or able to obtain written parental/guardian informed consent;

- *If not of legal age or otherwise not able to provide independent informed consent as determined by site SOPs and consistent with site IRB/EC policies and procedures: Parent or legal guardian is willing and able to provide written informed consent for study participation and potential participant is willing and able to provide written assent for study participation.*

- *If of legal age or otherwise able to provide independent informed consent as determined by site SOPs and consistent with site IRB/EC policies and procedures: Willing and able to provide written informed consent for study participation.*

3.1.5 Self-reported sexual activity with a male in the past 12 months;

3.1.6 In general, good health, as evidenced by the following laboratory values:

- Non-reactive / negative HIV test results**,
- Absolute neutrophil count > 799 cells/mm^3,

- Platelet count ≥ 100,000 cells/mm^3,
- Hemoglobin ≥ 11g/dL,
- Calculated creatinine clearance ≥ 60 mL/minute using modified Schwartz equation (≤ grade 2),
- Alanine aminotransferase (ALT) < 2.0 times the upper limit of normal (ULN) and total bilirubin (Tbili) ≤ 2.5 x ULN,
- Hepatitis B virus (HBV) surface antigen (HBsAg) negative and accepts vaccination,
- HCV Antibody negative.

3.1.7 Willing to undergo all required study procedures

3.1.8 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.

*Please see Section 1.7 for explanation.

**HIV-uninfected, based on HIV test results obtained at Screening and at the Enrollment visit. All HIV test results from the Screening visit must be obtained and must all be negative/non-reactive. This includes testing for acute HIV infection, which must be performed within 14 days of Enrollment. Individuals who have one or more reactive or positive HIV test result(s) will not be enrolled, even if subsequent confirmatory testing indicates that they are not HIV-infected (see SSP Manual).

3.2 Exclusion Criteria

Male adolescents with any of the following criteria will be excluded from the study:

3.2.1 Co-enrollment in any other HIV interventional research study or other concurrent studies which may interfere with this study (as provided by self-report or other available documentation);

3.2.2 Past or current participation in HIV vaccine trial with exception for participants who can provide documentation of receipt of placebo;

3.2.3 Exclusively had sex with biological females in lifetime;

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

- active or planned use of any substance which would, in the opinion of the site investigator, would hinder study participation (including herbal remedies), as described in the IB or listed in the SSP, and/ or Protocol Section 4.4,

3.2.5 Known history of clinically significant cardiovascular disease, as defined by history/evidence of symptomatic arrhythmia, angina/ischemia, coronary artery bypass grafting (CABG) surgery or percutaneous transluminal coronary angioplasty (PTCA) or any clinically significant cardiac disease;

3.2.6 Inflammatory skin conditions that compromise the safety of intramuscular (IM) injections;

3.2.7 Tattoo or other dermatological condition overlying the buttock region that may interfere with interpretation of injection site reactions;

3.2.8 Current or chronic history of liver disease (e.g., non-alcoholic or alcoholic steatohepatitis) or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome, asymptomatic gallstones, or cholecystectomy);

3.2.9 Known history of clinically significant bleeding;

3.2.10 Surgically-placed or injected buttock implants or fillers, per self-report. Contact the CMC for guidance regarding questions about individual cases;

3.2.11 A history of seizure disorder, per self-report;

3.2.12 Medical, social, or other condition that, in the opinion of the site investigator, would interfere with the conduct of the study or the safety of the participant (e.g., provided by self-report, or found upon medical history and examination or in available medical records);

3.2.13 Plans to move out of the geographic area within the next 18 months or otherwise unable to participate in study visits, according to the site investigator.

3.3 Recruitment Process

The study will be targeted towards at-risk, sexually active adolescent populations of MSM in the US. Enrollment will occur over approximately 12 months.

Sites will be responsible for developing appropriate recruitment processes that are geared toward their respective local communities. All advertising materials must undergo approval by each participating site's Institutional Review Board (IRB)/Ethics Committee (EC).

Sites will implement wide-reaching educational efforts, community engagement, and multimedia advertising including rapidly changing and adaptive social media strategies to reach young populations. Participant retention during prolonged follow-up will be accomplished using study-visit incentives as permitted by local IRBs at the maximum permissible level.

3.4 Co-Enrollment Guidelines

Participants in this study will not be allowed to take part in other concurrent interventional research studies during their participation in the study. This is due in part to concerns about: 1) participant study

burden, 2) limitations on per-unit-time phlebotomized blood volumes, and 3) to avoid confounding in the interpretation of the study data.

3.5 Participant Retention

Once a participant enrolls in this study, the study site will make every effort to retain the participant for the entire follow-up period. Study site staff are responsible for developing and implementing local standard operating procedures to target this goal. Components of such procedures may include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process with both participants and parents/guardians and re-emphasis at each study visit.
- Thorough explanation of the importance of adherence/retention to the overall success of the study.
- Collection of detailed locator information at the study Screening Visit, and active review and updating of this information at each subsequent visit, including where the participant lives and other locator venues, and parents/guardians or other family members.
- Use of appropriate and timely visit-reminder mechanisms, including SMS/WhatsApp/text messaging.
- Immediate and multifaceted follow-up on missed visits, including SMS/WhatsApp/text messaging.
- Mobilization of trained staff to complete in-person contact with participants at their homes and/or other community locations.
- Regular communication with the study community at large to increase awareness about HIV/AIDS and explain the purpose of HIV prevention research and the importance of completing research study visits.
- Incentives or reimbursements as permitted by local IRB/ECs.

3.6 Participant Withdrawal

Regardless of the participant retention methods described in Section 3.5, participants (or their parents/guardians if under legal age of consent) may voluntarily withdraw from the study for any reason at any time.

The IoR also may withdraw participants from study product dosing in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the Protocol Chair, DAIDS Medical Officer, Statistical and Data Management Center (SDMC) Protocol Statistician, representatives from the Laboratory Center (LC), the Leadership and Operations Center (LOC) Clinical Research Manager (CRM), and others.

Participants may be withdrawn from the study if the study sponsor, government or regulatory authorities (including Office for Human Research Protections [OHRP] and the FDA) or site IRBs/ECs, or ViiV terminate the study prior to its planned end date.

Every reasonable effort will be made to complete a final evaluation of participants who terminate study product prior to the final protocol-dictated study week, and study staff will record the reason(s) for all

withdrawals from the study product in participants' study records. In such cases, the IoR or designee must contact the CMC for guidance regarding final evaluation procedures.

4.0 STUDY PRODUCT CONSIDERATIONS

Site pharmacists should consult the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations. Refer to study schema on page 15 for an overview of steps and study design, and to the investigator's brochures (IBs) for further information about the study products.

4.1 Study Product Regimens/Administration/Formulation Content

Study Product Regimens

Step 1 – Oral Run-in Phase

- CAB 30 mg tablet, one tablet orally once daily for five weeks, with or without food

Step 2 – Injection Phase

- CAB LA 600 mg administered as one 3 mL (600 mg) IM injection in the gluteal muscle at weeks 5, 9, 17, 25, and 33 (5 injections, administered at 8-week intervals after a 4-week load)
- A safety visit will follow each injection to ascertain safety data, including injection site reactions

Step 3 – Follow-up Phase

All participants who have received at least one injection will be followed for 48 weeks after their last injection, beginning with a blood draw visit, +8 Week Visit, that will follow eight weeks after the last injection to monitor CAB drug levels. Waning levels of cabotegravir (the PK tail) will be covered with locally sourced oral Tenofovir/Emtricitabine (TRADE NAME: TDF/FTC, TRUVADA®) for daily use for 48 weeks. Participants may also be provided the opportunity to enroll in a local open label study of CAB, if available.

4.1.1 Oral Product

Step 1 – Oral CAB tablets 30 mg are formulated as white to almost white oval-shaped film-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 bottles should be stored up to 30ºC (86ºF) and protected from moisture.

Step 3 – Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) is a fixed dose combination tablet containing 200 mg of emtricitabine (FTC) and 300 mg of tenofovir disoproxil fumarate (Tenofovir/Emtricitabine [TRADE NAME: TDF/FTC, TRUVADA®]) in each tablet. The tablets must be stored as per the manufacturer's recommendation. Refer to the package insert for recommended storage conditions.

4.1.2 Injectable Suspension

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 treatment or prevention of HIV-1 infection. Further information on the study product is available in the IB, which will be provided by the DAIDS Regulatory Support Center (RSC).

CAB LA formulation

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 3 mL (600mg) vial. The total amount to be administered to each participant is 3 mL (600 mg) per intramuscular (IM) injection. The formulation does not require dilution prior to administration. CAB LA injectable suspension is to be stored up to 30°C (86°F), do not freeze.

The investigational pharmacist(s) must be proficient in the preparation of study products using aseptic technique under a pharmacy biological safety cabinet (BSC) Class II or better isolator. 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.

One syringe containing 3 mL (600 mg) of CAB LA study product must be prepared using aseptic technique under a pharmacy BSC/isolator.

Materials required for preparation and administration:

1. One CAB LA 600 mg/3 mL vial
2. Becton Dickinson (BD) 5-mL Syringe, Luer-Lok Tip, Product No.: 309646 or equivalent
3. Needle for aspiration: BD general use sterile hypodermic needle, 21G x 1½ inch (e.g. PrecisionGlide Needle, Product No.: 305165 or equivalent)
4. Needle for intramuscular injection: BD IM sterile hypodermic needle, 23G x 1½ inch (e.g. PrecisionGlide Needle, Product No.: 305194 or equivalent)

Preparation Steps:

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

2. Vigorously shake the vial for a full 10 seconds, by shaking the vial with long arm movements.
3. Invert the vial and inspect to ensure uniform suspension. If solid remains undispersed, repeat Steps 2-3 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.

4. 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 and allow to dry. Do not touch the rubber stopper at any time.

5. Remove a 5-mL syringe and a 21G x 1½ inch needle for aspiration. Attach the needle to the Luer connection of the syringe.
6. With the needle sheath on, pull the syringe plunger rod to allow approximately 1 mL of air into the syringe. Remove the needle sheath.
7. Push the needle through the vial stopper and inject approximately 1 mL of air into the vial.
8. Withdraw the entire contents of the vial into the syringe. Since the suspension can contain some air after having shaken the vial, withdraw all suspension from the vial in order to be able to de-aerate the syringe properly.
9. Record the time that the suspension was withdrawn from the vial into the syringe.
10. Remove the needle that was used to withdraw the suspension into the syringe and discard the needle.
11. Attach a 23G x 1½ inch needle for intramuscular injection to the Luer connection of the syringe. Remove the needle sheath from the needle.
12. De-aerate the syringe by first tapping a finger against the syringe and then by moving the plunger rod carefully forward with the needle in the 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 in order to avoid spilling.

After withdrawal of the 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 into a syringe (Step 8) and administration to the study participant.

The prepared CAB LA suspension in a syringe must be stored at controlled room temperature between 20°C to 25°C 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.

4.1.3 IM Dosing Considerations

IM injections are administered into the gluteus muscle (gluteus medius method preferred) using a needle of appropriate gauge and length (recommended 1.5” 23-gauge needle for CAB LA). The needle should be long enough to reach the muscle mass and prevent study drug from seeping into subcutaneous tissue, but not so long as to involve underlying nerves, blood vessels, or bone. Variable needle lengths and/or needles with different gauge (21 to 25 gauge) are permitted if needed to accommodate individual body type. Longer needle lengths may be required for participants with higher body mass indexes (BMIs, example ≥ 30), to ensure that injections are administered intramuscularly as opposed to subcutaneously.

4.2 Study Product Acquisition and Accountability

The CAB study products (oral and LA injectable) for Steps 1 and 2 are being provided by ViiV Healthcare. For Step 3, the sites will provide locally sourced Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) for 48 weeks after the participants' last CAB LA injection.

4.2.1 Study Product Acquisition

The CAB study products (oral and LA injectable) will be supplied through 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.

Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) will be obtained locally by the sites.

4.2.2 Study Product Accountability

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. 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.*

4.3 Toxicity Management

Toxicity management guidelines can be found in Appendix V.

4.4 Concomitant, Prohibited, and Precautionary Medications

In order to avoid adverse events caused by drug interactions, whenever a concomitant medication is taken, site staff should review the concomitant medication's and study product's most recent package insert (PI - for Truvada®) and investigator's brochure (IB - for cabotegravir) to obtain the most current information on drug interactions and contraindications. Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study.

After Enrollment, for any drug listed in the Truvada® PI or cabotegravir IB, it is required that the HPTN 083-01 CMC be notified for recommendations for continuing or stopping (or holding) study product.

Experimental agents not otherwise specified in the SSP Manual may not be administered. Precautionary and prohibited medications include:

Cabotegravir:

- Not to be administered concurrently:
  - Cytotoxic chemotherapy or radiation therapy
  - Systemically administered immunomodulators

    - *NOTE: Stable physiologic glucocorticoid doses (defined as prednisone ≤15 mg/day or equivalent as a stable or tapering dose) are not prohibited. Use of corticosteroids for an acute condition such as asthma exacerbation or receiving a short course (defined as ≤2 weeks of pharmacologic glucocorticoid therapy) is also not prohibited.*
  - barbiturates
  - carbamazepine
  - oxcarbazepine
  - phenytoin
  - pheonobarbital
  - rifabutin
  - rifampin
  - rifapentine
  - St. John's wort

- 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)

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

- Co-administration of the following drugs should be clinically monitored by site clinician, as per considerations below:

    - o Drugs that are eliminated by active tubular secretion (e.g. drug, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDS), as these may increase concentrations of emtricitabine, tenofovir, and/or the co-administered drug.

    - o Drugs that decrease renal function (e.g., cause nephrotoxicity) as these may increase concentrations of emtricitabine and/or tenofovir.

- *NOTE: Please report to the CMC if a participant takes a total daily dose of NSAIDS that meets or exceeds high dose for MORE than 72 consecutive hours.*

- *NOTE: Acyclovir and valacyclovir may be used when indicated. If needed for treatment – sites do NOT need CMC permission for the use of these products, but sites should counsel the participant to increase hydration to avoid additive nephrotoxicity; no additional laboratory monitoring is required per protocol.*

Further information regarding prohibited and precautionary concomitant medications can be found in the SSP Manual and IB. The SSP Manual will be revised (as a whole or as a Memorandum of Changes) and re-issued when changes are made.

All concomitant medications/preparations (prescription and non-prescription) including alternative/complementary medications/preparations (e.g., herbs, vitamins, etc.) taken within 30 days prior to enrollment and anytime thereafter during study participation will be collected in the study participant's chart and on study case report forms (CRFs).

5.0 STUDY PROCEDURES

Overviews of the study visit and procedures schedules are presented in Appendices I and II, and Appendix III (for suspected and/or confirmed HIV infection). Presented below is additional information for visit-specific study procedures. Detailed instructions to guide and standardize all study procedures across sites are included in the SSP Manual.

5.1 Screening

It is the responsibility of the local site to determine the best approach to screening. Written informed consent and assent (as appropriate) will be obtained before any study procedures are initiated. Both clinical and laboratory evaluations will occur at this visit (see Appendix I, Schedule of Evaluations for

Oral Phase – Step 1). Screening procedures may occur over one or more visits. The SSP Manual provides additional information regarding the procedures outlined below, including clinical and laboratory procedures and requirements. Enrollment must occur within 30 days of specimen collection at Screening for the clinical and laboratory evaluation and procedures (except for HIV RNA testing samples, which must be collected and results obtained within 14 days before enrollment).

Sites will follow the HIV testing algorithm for Screening included in the SSP Manual. If a reactive/positive/indeterminate result is obtained for any HIV test, the person is not eligible for the study. Additional testing to confirm suspected HIV infection during Screening will be performed in accordance with local guidelines. If HIV infection is confirmed, participants will receive counseling and be immediately linked to care either at the study site or other qualified adolescent competent clinic, as necessary.

Individuals deemed not eligible will be informed that they do not meet the elibility criteria for the study and will be referred for appropriate medical care, if necessary.

Potential participants may be rescreened once at the discretion of the IoR or their designee. Further re-screening for administrative reasons may be permitted with the approval of the CMC. However, potential participants with clinically-significant cardiovascular disease as outlined in the exclusion criteria in Section 3.2, or any reactive HIV test, may not be re-screened. Participants with symptoms concerning for acute HIV infection (per IoR or designee) may be re-screened in consultation with the CMC, once appropriate testing has ruled out acute HIV infection.

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 HIV test results including testing for acute HIV from Screening, which must be performed within 14 days of Enrollment, and at least one HIV test result from Enrollment must be available and confirmed to be negative/non-reactive PRIOR to provision of study product. Results from the chemistry testing, liver function tests (LFTs), lipid profile, hematology testing, and urinalysis from this visit are NOT required prior to enrollment.

Eligible participants will be reminded that the use of anticoagulant and/or antiplatelet medications as outlined in the SSP Manual are prohibited within seven days before and seven days after injections. Reminders will be built in to the concomitant medication history.

Participants will meet with study staff to receive education and information about adherence during the oral phase, identify potential barriers to adherence for the participant, and decide on adherence support strategies that will facilitate adherence. During counseling, participants will be offered supportive tools such as discrete pill containers, mobile reminder tools including text messaging and/or mobile app alerts, and weekly telephone check-ins from study teams.

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).

At the end of this visit, participants will be dispensed oral cabotegravir, with first dose directly observed by study staff. Study product must be dispensed with instruction to participants.

5.3 Step 1, Oral Run-in Phase: Safety Visits

Oral Run-in Safety Visits at Weeks 2 and 4

There will be 2 brief follow-up visits during the oral phase of cabotegravir for the purpose of safety and adherence checks. Both clinical and laboratory evaluations will occur at these visits (see Appendix I Schedule of Evaluations for Oral Phase – Step 1). Adherence counseling will be provided at both Weeks 2 and 4 to visit to address barriers to daily pill taking, as well as remind participants of adherence support options available to them. Pill counts will occur at these visits and participants will take a dose directly observed by study staff at each of these visits.

Participants with pill counts resulting in less than 50% adherence at the Week 4 visit will not be allowed to transition to Step 2. Anyone not moving to Step 2 will be terminated from the study.

Investigators should contact the CMC at 083-01cmc@hptn.org if a participant has missed or delayed week 4 visit or has not had sufficient oral drug exposure during the four-week oral run-in period to transition to step 2.

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

The oral run-in (Step 1) is included to reduce risk to participants. Participants with significant, negative side effects to oral study product will not continue on to Step 2, the Injection Phase. See Table 5.1 for brief instruction and Appendix V, Toxicity Management, for detailed instruction on participant management. All AEs are to be followed until they return to ≤ Grade 2.

Table 5.1. Management of Participants with AEs in Step 1

Grade of AE	Brief Instruction
Grade 1 AE	Proceed with SOE and to Step 2
Grade 2 AE, excluding ALT	Proceed with SOE and to Step 2
Grade 2 ALT	At Enrollment or Week 2 → continue oral product, repeat ALT labs in 1 week
	At Week 4→ continue oral CAB, repeat ALT labs in 1 week If result is ≤ Grade 1, participant may move to Step 2 if otherwise qualifies;

	If result is ≥ Grade 2, permanently discontinue oral CAB, do not move to Step 2 and repeat ALT weekly until ≤ Grade 1, then terminate from study
Grade 3 AE, excluding ALT & CPK	Report to CMC and if determined to be: • Related AE→ permanently stop oral product, follow until stabilizes and then terminate from study • NOT related AE→ follow CMC guidance
Grade 3 ALT	Report to CMC Permanently discontinue oral CAB, do not move to Step 2 and repeat ALT weekly until ≤ Grade 1, then terminate from study
Grade 3 CPK + < Grade 3 ALT	Report to CMC for adjudication
Grade 4 AE, excluding ALT & CPK	Report to CMC Permanently stop oral product, follow until stabilizes and then terminate from study
Grade 4 ALT	Report to CMC Regardless of CPK permanently stop oral product, repeat ALT labs weekly until ≤ Grade 1, then terminate from study
Grade 4 CPK + < Grade 3 ALT	Report to CMC for adjudication

5.4 Transitioning from Step 1 to Step 2

Conditions in Step 1 that could disqualify a participant from transitioning to Step 2 are as follows:

- Pill count suggestive of less than 50% adherence at the Week 4 visit;
- Missed or delayed Week 4 visit;
- Specific AEs per Table 5.1;
- At substantial risk of HIV infection and/or qualifies for oral PrEP by local guidelines;
- Any HIV reactive/positive test (see SSP).

If any of the above conditions occur, investigators should notify the HPTN 083-01 CMC at 083-01cmc@hptn.org within one week of awareness for final determination of fitness to enter Step 2.

5.4.1 Early Discontinuation in Step 1

Participants who do not enter Step 2 will discontinue study follow-up. Prior to termination, study staff will complete study evaluations due at the Week 4 visit in Appendix I, if possible. All appropriate referrals will be made to primary care service providers for sexual reproductive health and HIV prevention.

5.5 Step 2, Injection Phase: Injection Visits

Injection Phase Injection Visits at Weeks 5, 9, 17, 25, and 33

All HIV test results from previous visits and at least one HIV test result from the current visit (from blood drawn that same day) must be available and confirmed to be negative/non-reactive PRIOR to injection of study product. The injection may NOT be given if any HIV test is reactive/positive. For management of participants with an HIV-positive test, see Section 5.10.

Results from the other clinical and laboratory evaluations (e.g., chemistry, LFTs, hematology) from previous visits must be available and be reviewed by the IoR or their designee prior to provision of study product. Results from STI tests do not need to be reviewed prior to provision of study product. For management of participants with AEs, see Appendix V, Toxicity Management.

During Step 2, the injection phase of the study, all participants will have brief safety visits one week after each injection. Both clinical and laboratory evaluations will occur at the injection visits as well as CASI administration for either behavioral or acceptability assessments (see Appendix II. Schedule of Evaluations for Injection Phase – Step 2).

5.6 Step 2, Injection Phase: Safety Visits

Injection Phase Safety Visits at Week 6, 10, 18, 26, and 34

During the injection phase of the study, all participants will have brief safety visits one week after each injection. Blood will also be collected at these visits to monitor drug levels of CAB. A three-month supply of Tenofovir/Emtricitabine [TRADE NAME: TDF/FTC, TRUVADA®]) will be provided at Week 34.

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®]). Participants may also join a local open label CAB study, if available.

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).

5.8 Standard of Care (SOC) Counseling for all Participants

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.

Post-exposure Prophylaxis (PEP)

At any time during study participation, any participant who expresses concern about a potential HIV exposure will be referred for PEP services. Any participant receiving PEP will temporarily hold study product. Participants may qualify to resume study product dosing and remain in follow-up, after consultation with the HPTN 083-01 CMC at 083-01cmc@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.

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 all injection visits is +/- 3 days.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 Procedures for Injectable Dosing

Refer to Appendix V, Toxicity Management, for general toxicity management, as well as specific clinical and laboratory toxicity management guidelines, including directions regarding temporary and permanent study product holds.

5.11 Participants with Suspected or Confirmed HIV Infection at Screening, Enrollment, or Follow-Up

All participants with preliminary positive HIV test results at screening or throughout the study will be actively linked with care and treatment from their choice of primary HIV service provider. Each of the clinical study sites have adolescent-friendly HIV care clinics available.

5.11.1 Screening and Enrollment

HIV testing will be performed to identify participants with HIV infection. Individuals who have one or more reactive or positive HIV tests at Screening or Enrollment are not eligible to participate in this study. Furthermore, at Screening and Enrollment individuals with any signs or symptoms consistent with acute (pre-seroconversion) HIV infection will not be enrolled, unless acute HIV infection is ruled out with appropriate laboratory testing, in consultation with the CMC. Signs and symptoms consistent with acute HIV infection are included in the SSP Manual.

5.11.2 After Study Enrollment

Frequent testing for HIV acquisition during the study period (at all study visits specified in the schedules of evaluation) will help prevent dosing with the study product in a participant who may have acquired HIV infection, minimizing the risk that resistant virus will emerge. In addition, if a participant has signs or symptoms consistent with acute HIV infection (see SSP Manual), or expresses a concern about recent HIV acquisition, HIV testing will be performed using an RNA test that, in the opinion of the IoR or designee, is able to detect early HIV infection. Whenever possible, an assay that is US FDA-cleared for early HIV diagnosis, such as the Aptima HIV-1 RNA Qualitative Assay, should be used.

Regardless of whether HIV RNA testing is used for diagnostic purposes, HIV acquisition after study enrollment must be confirmed in all cases using two independent samples collected on different days.

Participants who have any reactive or positive HIV test result during follow-up visits will have further testing to confirm infection, as described in the SSP Manual and Appendix IV. Study product will be withheld while this further testing is performed.

Additional samples from participants with confirmed HIV infection may be sent to a local laboratory for resistance testing to assist with clinical management (results from resistance testing performed in local laboratories should not be reported to the HPTN SDMC or the HPTN LC). If a participant has a reactive or positive HIV test, the participant will not receive additional doses of study products pending further direction regarding testing and continued participation in the study from designated study team members, including the HPTN LC and the CMC. Refer to the SSP Manual for further information.

Step 1 – Oral Phase
Participants with confirmed HIV infection prior to receipt of their first injection will have oral study product permanently discontinued and will be transitioned to local HIV-related care and terminated from the study.

Step 2 – Injection Phase
Participants with confirmed HIV infection during Step 2 will not receive additional injections and will be followed per the SOE in Appendix IV quarterly for approximately 48 weeks. In addition, sites will

have a standard operating procedure (SOP) that outlines a plan in the event that a participant becomes HIV-infected during any Step of the study, and in particular during Step 2 of the study, which must include the participant's facilitation into locally-available ART to be started immediately, to prevent emergence of drug resistance. Participants who seroconvert will be referred for care; sites will not be responsible for the actual provision/payment of ART. Neither ART nor funds for provision of ART will be provided by the study.

Step 3 – Follow-up Phase

Participants with confirmed HIV infection during Step 3 will not receive oral Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) and will be followed per the SOE in Appendix IV quarterly through study exit (following an initial +8 Week Visit). In addition, sites will have a standard operating procedure (SOP) that outlines a plan to facilitate immediate initiation of non-study ART and link with appropriate HIV services in the event that a participant becomes HIV-infected during any Step of the study, and in particular during Step 2 of the study, to prevent emergence of drug resistance. Participants who seroconvert will be referred for care; sites will not be responsible for the actual provision/payment of ART. Neither ART nor funds for provision of ART will be provided by the study.

5.12 STIs

Testing for *Neisseria gonorrhoeae* (GC)/*Chlamydia trachomatis* (CT), and syphilis will occur throughout the study. Testing will be performed at local laboratories. Symptomatic screening for STIs beyond what is required by the protocol will be at a site's discretion. Participants will be referred for treatment of STIs as per local standard of care.

5.13 HBV and HCV

Testing for HBV and HCV will be performed at Screening (HBsAg and HCAb). Persons positive for these tests will not be enrolled in the study and will be referred to their primary provider for management. Participants will be tested for Hepatitis B surface antibody (HBsAb), and Hepatitis B core antibody (HBcAb, total) at Screening or Enrollment. Participants who do not have evidence of immunity to HBV (e.g., negative HBsAb) will be provided HBV vaccination, starting ideally at week 2. For participants who do not have evidence of HBV immunity at Enrollment, HBV testing should be repeated at the discretion of the IoR or designee during the study if clinically indicated, if the participant has elevated AST/ALT results (elevated level at discretion of IoR or designee), or if the participant expresses a concern about having acquired HBV infection after enrollment. Refer to the SSP Manual for persons who have a positive result for HBcAb (total) only.

For enrolled individuals, HCV antibody testing will be performed at Screening (see Appendix I). Incident HCV infection during follow-up will not mandate discontinuation of study product absent other requirements per Appendix V - Toxicity Management.

5.14 Behavioral and Acceptability Assessments

Behavioral assessment questions have been previously used either in adolescent biomedical prevention trials or in the Phase III adult trials of cabotegravir. Behavioral assessment areas include sexual risk behavior, substance use, study product adherence and stigma associated with HIV and prevention technologies.

Acceptability assessments of CAB LA will be administered via brief behavioral surveys. The surveys will include, but not be limited to, questions about participants' attitudes/beliefs towards CAB LA as well as product and study-related motivations. All measures will be programmed into CASI.

5.15 Interim Contacts and Visits

Interim contacts and visits (those between regularly scheduled follow up visits) may be performed at participant request or as deemed necessary by the investigator or designee at any time during the study.

Some interim visits may occur for administrative reasons. For example, the participant may have questions for study staff. Interim visits at which no data are collected are not documented on CRFs. Other interim contacts and visits may occur in response to AEs experienced by study participants. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically, record the event on the CRF, and provide or refer the participant to appropriate medical care.

5.16 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.

Site IoRs may, with the agreement of the CMC, Protocol Chairs, DAIDS MO, and study statistician, withdraw participants before their scheduled termination visit to protect their safety, the safety of the staff, and/or if participants are unable or unwilling to comply with study procedures. Participants also may be withdrawn if the study sponsors, government or regulatory authorities (including the OHRP and US FDA), or site IRBs/ECs or ViiV terminate the study prior to its planned end date.

6.0 SAFETY MONITORING AND AE REPORTING

6.1 AE Definition and Reporting

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

Study participants will be provided a 24-hour telephone number and contact information and instructed to contact the study clinician to report any AEs they may experience. For life-threatening events, they will also be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where the study clinician is based, and to request that

the clinician be contacted upon their arrival. With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to AEs will be obtained and required data elements will be recorded on study CRFs. All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline) or stabilizes.

Study site staff will document in source documents and the appropriate CRF all AEs [Grade 1 and higher, and any AE that leads to a study product hold (temporary or permanent) will be captured on CRFs] reported by or observed in enrolled 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, Corrected Version 2.1, July 2017. This version will be used for the entire duration of the study.

The AE reporting period for this study is from Enrollment (Week 0) until follow-up in the study ends.

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 AEs to study product will be assessed as specified in Version 2.0, January 2010 of the DAIDS EAE Reporting Manual.

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 the entire duration of the study for determining and reporting the severity of AEs. 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.

6.2 EAE Reporting

After the protocol-defined AE reporting period, unless otherwise noted, only SUSARs as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

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

The study agents for the purposes of EAE reporting are: Oral CAB 30 mg oral tablet; CAB LA 3 mL (600 mg) intramuscular (IM) injectable suspension.

6.2.1 Reporting to 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. For questions about DAERS, please contact CRMSSupport@niaid.nih.gov. Site queries may also be sent with the DAERS application itself.

If the DAERS website or site internet is non-functional, sites will submit expedited AEs by documenting the information on the current DAIDS EAE form. This form is available on the DAIDS RSC website: https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting. For questions about EAE reporting, please contact the DAIDS RSC at DAIDSRSCSafetyOffice@tech-res.com.

6.2.2 Reporting Requirements for This Study

The 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 for each study participant from Enrollment (Week 0) until follow-up in the study ends. After this time, sites must report serious, unexpected, clinical suspected adverse drug reactions 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 (200 mg/mL).

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.

6.3 Safety Monitoring

Two hundred and thirty (n=230) healthy participants from completed studies have received single or repeat doses of CAB LA in Phase 1 studies at doses ranging from 100-800 mg administered as single or split IM or SC injections. In the Phase 1 program, to date there have been no drug-related Grade 3 or Grade 4 clinical AEs and only one participant has been withdrawn from dosing due to mild and transient rash. Injection site reactions (ISR) occurred in the majority of participants following IM (77% with any ISR) dosing, however, the reactions were mild and moderate (overall ISR Grade 2: 14% in IM without any Grade 3 or 4 ISRs).[32] ISRs related to CAB LA injection were common but generally mild (IM: 86%, SC: 99%) with no Grade 3 ISR AEs in Phase 1 studies. The most frequent ISRs for IM dosing were pain (71%), erythema (9%) and nodules (7%). Median IM ISR durations were approximately 5 days for pain and erythema, and approximately 22 days for nodules.[32]

AEs were reported at all studied doses. The most frequent (>5%) non-ISR AEs were headache (overall rate of 16%: 10% in oral and 27% in LA) which occurred more frequently than in placebo subjects (11%) and upper respiratory tract infection (overall rate of 6%: 2% in oral and 12% in LA) versus none in placebo subjects. CAB was well tolerated across all studies with an overall incidence of 13% of any drug-related AEs and few drug related withdrawals.

The ECLAIR study, conducted at 10 US sites, screened 205 individuals in order to enroll and randomize 127 HIV-uninfected low-risk men. Participants received daily oral CAB 30 mg or daily oral placebo in a randomized 5:1 ratio during the 4-week oral lead-in phase.35 One participant randomized to active study

product (oral CAB and CAB LA) withdrew prior to the oral lead-in due to being incarcerated. During the oral lead-in, 11 participants withdrew prior to their first injection, all of whom were randomized to CAB LA, seven for AEs and four for other reasons. Ninety-four (94) participants received at least one injection of CAB LA 800 mg and 21 participants received at least one injection of placebo. Of those that started injections 95% (20 of 21) of those randomized to placebo and 93% (87 of 94) of those randomized to CAB LA completed all three injections. The participant in the placebo arm who did not complete all three injections reached a protocol-defined stopping criteria (he acquired HIV infection after his second injection). Four participants on the CAB LA arm withdrew after their second injection, citing injection tolerability as a primary reason. Three other participants discontinued study participation after receiving injections for non-AE and non-injection-related reasons.

Fifteen participants experienced a Grade 1 or higher ALT and 14 experienced a Grade 1 or higher AST. There were no Grade 3 or 4 ALT elevations. AE events leading to withdrawal included transient neutropenia (three participants), transiently elevated CPK (three participants), and fatigue (one participant). Two SAEs were reported, one deep vein thrombosis on placebo that was considered possibly drug-related and one appendicitis on CAB LA that was not considered drug related. Eighteen participants reported Grade 3 ISR pain.

Grade 4 treatment emergent CPK elevations with concomitant AST and/or ALT elevations were noted in four participants at the Week 4 visit, leading to early withdrawal in three participants. One of the four participants described a new rigorous exercise regimen prior to the Week 4 study visit; a second of these events resolved despite ongoing exposure to study product. All four Grade 4 abnormalities were resolving at one-week follow-up visits and have subsequently returned to normal off study product.

Close cooperation between the Protocol Chair, study site Investigator(s), DAIDS Medical Officer, LOC Clinical Research Manager, SDMC Biostatistician, SDMC Clinical Affairs Staff, HPTN LC, and other study team members will be necessary in order to monitor participant safety and to respond to occurrences of toxicity in a timely manner.

The study site Investigators are responsible for continuous close monitoring and management of AEs. Sites are required to have detailed SOPs describing methods for AE reporting and toxicity management to ensure that AEs are reported and managed in accordance with the protocol and for alerting the CMC (outlined below) if unexpected concerns arise.

A sub-group of the Protocol Team, including the Protocol Chair and Co-Chair, DAIDS Medical Officer, and other site investigators will serve as members of the CMC. The CMC provides support to sites regarding individual participant clinical management (e.g., questions related to eligibility, toxicity management, clinical holds of study drug, etc.).

6.4 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.

This study 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.

6.5 Social Harms and Social Benefits Reporting

It is possible that participants' involvement in the study could become known to others, and that a social harm may result (i.e., because participants could be perceived as being HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities. These are social harm events. Social harms events are those negative events that a participant reports as affecting them as a result of being involved in a research study, not the researcher's opinion of how they perceive an event has affected a participant. A social harm 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 harms and benefits will be collected and reported on CRFs during regular visits. In the event that a participant reports a social harm, 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 Community Advisory Board in exploring the social context surrounding instances of social harms, to minimize the potential occurrence of such an impact. In addition to social harms, any benefits of study participation, which are outcomes reported by the participant as a benefit to them as a result of being in the study (e.g., improvement in relationships), will also be collected and reported into the database.

6.6 Critical Events Reporting

Per the DAIDS policy on Identification and Classification of Critical Events, a critical event is defined as an unanticipated study-related incident that is likely to cause harm or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity. All such events must be reported following procedures specified in the DAIDS Critical Events Manual, available at: https://www.niaid.nih.gov/sites/default/files/criticaleventsmanual.pdf.

7.0 STATISTICAL CONSIDERATIONS

7.1 Review of Study Design

This is a single arm, open label, safety, tolerability, and acceptability study of CAB LA for prevention of HIV-acquisition in sexually-active, HIV-uninfected adolescents (below aged 18 years old at time of enrollment).

The study includes a 5-week oral CAB 30mg QD safety lead-in followed by a series of 5 intramuscular (IM) injections of 3 mL (600 mg) CAB LA administered at 8-week intervals after a 4-week loading dose

(injections at weeks 5, 9, 17, 25 & 33). Follow up on study product (oral and injectable) will occur for 34 weeks. All participants who have received at least one injection will be followed for 48 weeks after their last injection. Waning levels of cabotegravir (the PK tail) will be covered with locally sourced oral Tenofovir/Emtricitabine (TRADE NAME: TDF/FTC, TRUVADA®) for daily use or participation in an open-label CAB study (if available) for 48 weeks. ~~for daily use for 48 weeks or offered enrollment into local open label CAB study."~~

The sample size for this study will be set to enroll approximately 50 participants. The sample size for this protocol (n=50) is the number of participants agreed upon by the industry sponsor and regulators in order to provide supplementary safety and behavioral data on adolescents in collaboration with the HPTN 083 and HPTN 084 adult trials. The primary aims of the study are focused on safety, tolerability, and acceptability of this long-acting product.

Finally, in-depth qualitative interviews will be conducted with 10 participants (total, across all sites) after Week 34 to explore issues of acceptability and preference for oral tablets and/or injections. Additionally, up to 10 parents/guardians of participants (total, across all sites) will be asked to participate in in-depth interviews to explore facilitators and barriers to adolescent enrollment in biomedical clinical trials.

7.2 Endpoints

7.2.1 Primary Endpoints

- Safety endpoint: Proportion of participants experiencing any Grade 2 or higher clinical adverse events (AEs) and laboratory abnormalities among participants who receive at least one injection of CAB LA
- Tolerability endpoint: Proportion of participants who receive at least 1 injection and who discontinue receiving injections prior to the full course of injections due to intolerability of injection, frequency of injections or burden of study procedures
- Acceptability endpoint: Proportion of participants who complete all scheduled injections and proportion of participants who receive at least one injection whom would consider using CAB LA for HIV prevention in the future

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
- Proportion of injection visits that occurred "on-time"
- Change from enrollment of self-reported sexual behavior (number of sexual partners, increased episodes of unprotected anal intercourse) during the study period

7.3 Sample Size

The sample size for this protocol (n=50) is the number of participants agreed upon by the industry sponsor and regulators in order to provide supplementary safety and behavioral data on adolescents in collaboration with the HPTN 083 and HPTN 084 adult trials. The goal of the safety evaluation for this study is to identify safety concerns associated with CAB LA.

Since each of the primary endpoints is a proportion, table S1 shows the precision (confidence interval width) that will be obtained for each endpoint with a sample size of 50.

Table S1. Width of 95% confidence interval for estimated proportion as a function of the true proportion, assuming a sample size of 50.

True proportion	Width of 95% CI
0.1	± 0.083
0.2	± 0.11
0.3	± 0.13
0.4	± 0.14
0.5	± 0.14

The study will recruit sufficient participants to ensure that at least 50 participants progress to the injection phase.

7.4 Randomization

There is no treatment randomization due to this study being a single arm, open label trial.

7.5 Blinding

Participants and site staff will be unblinded throughout the trial.

7.6 Data and Safety Monitoring Analysis

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).

7.7 Primary Analyses

All participants who receive at least one injection will contribute to the primary analyses. When the use of descriptive statistics to assess group characteristics or differences is required, the following methods will be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum).

7.7.1 Safety Endpoints

The primary safety analysis will include Grade 2 or higher clinical and laboratory events that occur from the initial injection to 48 weeks after the last injection among participants who receive at least one injection.

To assess safety, the number and the percent of participants experiencing each safety endpoint will be tabulated. Each participant will contribute once in each category (for example, only for the highest severity AE for each participant) for the calculation of event rates. Exact binomial confidence intervals will be calculated for each safety endpoint.

7.7.2 Injection Site Reaction (ISR)

The number and percentage of participants experiencing each type of injection site reaction sign or symptom will be tabulated by severity. For a given sign or symptom, each participant's ISR will be counted once under the maximum severity for all injection visits as well as by each successive injection.

In addition, we will report the proportion of injections (over all participants) that resulted in an ISR. A 95% CI (using a robust variance) will be computed.

7.7.3 AEs and Serious Adverse Events (SAEs)

AEs will be tabulated using MedDRA preferred terms. The number and percentage of participants experiencing each specific AE (All AEs, Grade 2 or higher, and SAEs) will be tabulated by severity and by relationship to study product. For the calculations in these tables, each participant's AEs will be counted once as the maximum severity and relationship to study product. AEs leading to temporarily or permanently stopping drug will also be summarized. AEs will be summarized for those that are treatment emergent during LA dosing.

A listing of EAEs reported to the DAIDS RSC Safety Office will provide details of the events including severity, relationship to study product, time between onset and last injection, number of injections received, and a summary of the event.

7.7.4 Tolerability

To assess tolerability, the number and the percent of participants who receive at least one injection and discontinue receiving injections prior to the full course due to intolerability of injection (including but not limited to ISR), frequency of injections, or burden of procedures or any AE will be tabulated.

7.7.5 Acceptability

To assess acceptability, the number and percentage of participants who complete all scheduled injections will be described. Additionally, the number and the percent of participants who receive at least one injection that would consider using CAB LA for HIV prevention in the future will be tabulated. Acceptability will be assessed by age and in aggregate.

Acceptability of CAB LA will also be assessed through administration of brief behavioral surveys and qualitative interviews. The surveys will include, but not be limited to, questions about participants' attitudes/beliefs towards CAB LA; product and study-related motivations. In addition, a subset of participants will be invited to take part in qualitative assessments of acceptability in order to provide more holistic and contextualized information on motivations, attitudes and experiences using injectable PrEP, reasons for and circumstances related to product and/or study discontinuation, and future intentions related to PrEP use.

A subset of 10 willing participants will complete an in-depth interview (IDI) to be scheduled after the Week 34 visit. In addition, up to 10 parents of participants will be invited to participate in in-depth interviews that will explore facilitators and barriers to adolescent participation in biomedical HIV prevention trials. When conducting a qualitative exploration, the sampling method should be designed to include a range of possible perspectives on the phenomenon under study, thus ideal qualitative samples are purposive in nature. For this study, we will utilize a purposive sampling strategy, which will allow for consideration of the concepts of range, saturation/redundancy, and stratification in the sampling frame. We will ask sites to identify potential participants as well as parents/caregivers who would be interested in and comfortable with sharing their experiences with the study product as well as study procedures. Data on acceptability and factors affecting adherence will be collected during the IDI, including questions that explore the use and the acceptability of both the oral and injectable CAB, along with examination of preference for pills or injections. Additional interview topics will include challenges to study participation as well as product use. We will also discuss with participants the acceptability of parental involvement in the consent process.

These interviews will be conducted by a trained study interviewer and will follow a semi-structured questionnaire guide. They will be approximately 30-60 minutes in duration and will be conducted in an area that maximizes participant privacy and confidentiality. Participants may be compensated for the completion of the in-depth interview. These interviews will be recorded for analysis and transcribed.

7.7.6 Local Laboratory Values

Box plots of local laboratory values will be generated for baseline values and for values measured during the course of the study by visit. Each box plot will show the first quartile, the median, and the third quartile. Outliers will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

The number (percentage) of participants with local laboratory values recorded as meeting Grade 2 AE criteria or above as specified in the DAIDS AE Grading Table will be tabulated for follow-up time points. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will also be included in the tabulation of AEs described above.

7.8 Secondary Analyses

7.8.1 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.

7.8.2 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.

7.8.3 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.

7.8.4 Injection adherence

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

7.8.5 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.

7.9 Qualitative Analysis

All qualitative interviews will be conducted by trained interviewers, digitally-recorded, transcribed and translated into English (as needed), and then uploaded into a qualitative software analysis program (such as NVivo 12.) The protocol chair and her team will follow a process of reading, coding, data display and data reduction in order to explore in greater depth participants' attitudes towards and experiences with the product. Data coding and analysis will be both iterative and interactive processes. The team will first read all interview transcripts in order to increase familiarity with the data. Next, the team will assign *a priori* codes and create emergent codes. Transcripts will then be re-read to create pattern codes that connect subsequent concepts under larger headings. Consistent patterns in meaning, concepts, and themes across all interviews will be identified, and detailed memos/data matrices will be developed to examine how participants' perceptions related to product use (i.e., ease of use, perceived efficacy, side effects) and to trial participation (i.e., motivations for participation, interactions with trial staff, impact

on partner, parent or other social relationships) influence acceptability and interest in future use of an injectable PrEP product. Comparative analyses will be conducted to clarify differences that may exist for any subgroups of adolescents. Coding and analytic activities will be discussed during qualitative data analysis meetings, and discrepancies in coding and interpretation will be resolved through consensus. A similar analytic approach will be followed for parent/guardian interviews.

8.0 HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

This protocol and the template informed consent form contained in Appendix V 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.

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

Subsequent to initial review and approval, the responsible IRBs/ECs will review the protocol at least annually. The Investigator will make safety and progress reports to the IRBs/ECs at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. Study sites are responsible for the submission of continuing review to the DAIDS Protocol Registration Office (PRO), in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual.

8.2 Informed Consent

This section provides details regarding informed consent and assent requirements and procedures for adolescents. Site investigators and their designees will be required to determine participant age and ability to provide independent informed consent for study participation consistent with IRB/EC policies and procedures. Each site must establish SOPs, roles, and responsibilities for completing these determinations, and study staff involved in completing these determinations must have documented training in the relevant policies and procedures prior to initiating study activity.

Written informed consent and written assent will be obtained for study participation as follows:

- *If the potential participant is of legal age or otherwise able to provide independent informed consent as determined by site SOPs, local laws and regulations, and consistent with site IRB/EC policies and procedures:* The potential participant must provide written informed consent for study participation.
- *If the potential participant is not of legal age to provide independent informed consent as determined by site SOPs and local laws and regulations:* Parent, legal guardian, or other legally authorized representative must provide written informed permission for study participation and the potential participant must provide written assent for study participation.

Note: IRB/EC risk determinations will guide whether the consent of one or both parents may be required for this study. All IRB/EC requirements must be followed.

- *During study follow-up, if such a participant reaches the legal age and is able to provide independent informed consent as determined by site SOPs:* The participant must then provide written informed consent to continue study participation.

Written informed consent and assent (as applicable) for participation will be obtained before any study-specific procedures are performed. The informed consent process will include information exchange, detailed discussion, and formal assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. The process will describe what is known about the safety and tolerability of the study products and participants and parents/guardians will be extensively counseled on the importance of adherence to the study product regimen and study visit schedule. The approach adopted by the site will be tailored to adolescents, utilizing a variety of supporting materials, and may be spread over multiple sessions to foster sufficient understanding of the study prior to making the decision to take part.

Appendix VI provides sample informed consent/assent forms for obtaining parent or legal guardian permission and adolescent assent for study participation. Appendices VII, VIII and IX provide sample informed permission and assent forms for specimen storage and future use, adolescent qualitative interviews and parent/legal guardian interviews. All sample informed consent and assent forms may be modified by sites to meet IRB/EC requirements. If the participant, parent, or guardian (as applicable) is unable to read, the process for consenting illiterate participants, as defined or approved by the local IRB/EC, should be followed.

As indicated above, parental consenting requirements at each site will depend on the IRB/EC risk determination and all IRB/EC requirements will be followed. Participants enrolling in the study as minors will generally require permission from a parent or guardian.

In general, each participant is expected to take part in the informed consent process with his or her parent or legal guardian, and both the assent of the participant and the permission of the parent or legal guardian will be required for all consent decisions. For example, if the participant does not provide assent, or the parent or legal guardian does not provide permission, the participant will not be enrolled in the study.

Should the consenting parent (or guardian) of a participant no longer be available for any reason, sites should follow the guidelines and procedures described by their IRBs/ECs. Study sites may continue to provide care for the participant as needed and appropriate (outside of the study), consistent with local standard of care.

Participants may also reach the legal age of consent during follow-up. In this case, written informed consent for continued participation will be obtained from participants once they reach legal age at their next study visit. If participants do not consent for continued study participation, they should be discontinued from the study.

Each study site is responsible for developing study informed consent forms for local use that describes the purpose of the study, 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 and assent by signing their informed consent forms. All participants will be offered a copy of their informed consent form.

8.3 Incentives

Pending IRB approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. This includes the time and effort of parents or legal guardians who bring their child to the study visits. Site-specific reimbursement amounts will be specified in the study informed consent forms.

8.4 Confidentiality

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; representatives of the HPTN LOC, HPTN SDMC, and/or HPTN LC; site IRBs/ECs; other local, US, or international regulatory authorities; (including the OHRP and US FDA); or ViiV.

8.5 Communicable Disease and Statutory Rape Reporting Requirements

Study staff will comply with all applicable local requirements to report communicable diseases identified among study participants to local health authorities and will comply with applicable state laws regarding the reporting requirements of sexual activity of minors that can be considered statutory rape. Participants will be made aware of all reporting requirements during the study informed consent process.

8.6 Study Discontinuation

The study also may be discontinued at any time by NIAID, the HPTN, the study sponsors, government or regulatory authorities (including the OHRP and US FDA), site IRBs/ECs or if appropriate, or ViiV. This would be done primarily due to safety concerns for the patients or due to an earlier-than-expected indication of product efficacy or study futility.

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

Laboratory procedures are described below and in Appendices I and II. Refer to Appendix III for any participant who has a reactive or positive HIV test after Enrollment.

9.1 Local Laboratory Specimens

The following types of tests will be performed at the local laboratory:

- HIV testing (see SSP Manual)
- HBV and HCV testing to include HBsAg, HBsAb, HBcAb, HCV antibody tests
- Complete blood count (CBC) with differential
- Chemistry testing (blood-urea nitrogen (BUN) or urea, creatinine, CPK, glucose, calcium, phosphorous, amylase, lipase)
- LFTs (AST, ALT, TBili, alkaline phosphatase)
- Fasting lipid profile (total cholesterol, high-density lipoprotein (HDL), triglycerides, low-density lipoprotein (LDL)) – calculated or measured
- Syphilis serologic testing
- Urine (protein and glucose)
- Urine for GC/CT NAAT testing
- Rectal swabs for GC/CT NAAT testing;
- Oral pharyngeal swabs for GC/CT NAAT testing;
- Plasma storage
- DBS storage
- HIV viral load (if HIV-infected)
- CD4 cell count (if HIV-infected)
- Real-time resistance testing for clinical management, if indicated and available (if HIV-infected)

If the HIV testing algorithm includes HIV rapid testing, that testing may be performed in the clinic or laboratory.

Each study site should adhere to standards of Good Clinical Laboratory Practice (GCLP), the HPTN Manual of Operations (MOP), the SSP Manual and local SOPs for proper collection, processing, labeling, transport, and storage of specimens to the local laboratory. Specimen collection, testing, and storage at the local laboratory will be documented using the HPTN Laboratory Data Management System (LDMS) as described in the SSP Manual.

All specimens will be shipped in accordance with International Air Transport Association (IATA) specimen shipping regulations. All shipments will be documented using the HPTN LDMS as described in the SSP Manual.

9.2 Stored Specimens

Plasma will be stored at the local site throughout the study and afterwards, until discard approval is given by DIADS, the Principal Investigator (PI), and the HPTN LC. A subset of the stored samples will be shipped to the HPTN LC (located in the US) for Quality Assurance (QA) and other assessments. As indicated below, testing on stored samples will be performed by the HPTN LC or another laboratory designated by the HPTN LC.

9.3 Virology

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 diagnostic 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 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.

9.4 Pharmacology

Blood samples will be collected throughout the study from all participants and assayed for plasma CAB concentrations. PK sample times include predose trough samples at W5, W9, W17, W25, and W33, (final concentration in injection phase) and 1-week post injection samples at W6, W10, W18, W26, W34. In addition, follow-up samples will be collected at +8, +24. +36 and +48-weeks following the final injection (Appendix II and Appendix III) and at HIV confirmatory visit (Appendix IV).

Plasma samples will be processed and frozen locally for subsequent shipment to the HPTN LC following procedures outlined in the SSP Manual. Pharmacology testing will be performed at the HPTN LC or at an outside laboratory designated by the HPTN LC. The primary pharmacologic assessments will be performed using assays that have been validated and approved by the Clinical Pharmacology Quality Assurance (CPQA) Committee (reference assay validation report). Results will not be returned to the study participants or study sites.

Plasma and DBS samples will be processed and frozen locally for subsequent shipment to the HPTN LC following procedures outlined in the SSP Manual. Pharmacology testing will be performed at the HPTN LC or at an outside laboratory designated by the HPTN LC. The primary pharmacologic assessments will be performed using assays that have been validated and approved by the Clinical Pharmacology Quality Assurance (CPQA) Committee (reference assay validation report). Results will not be returned to the study participants or study sites. Plasma and DBS will be collected in Step 3 and if a study participant seroconverts for potential pharmacologic analysis of plasma TFV and DBS TFV-DP concentrations, respectively, to assess PrEP adherence.

Stored plasma may also be tested for the presence of other ARV drugs or other concomitant medications.

9.5 Quality Control and Quality Assurance Procedures

Study sites will document that their laboratories are certified under the Clinical Laboratory Improvement Amendments Act of 1988 (CLIA-certified) and/or participate in DAIDS-sponsored External Quality Assurance (EQA) programs. HPTN LC staff will conduct periodic visits to each site to assess the

implementation of on-site laboratory quality control (QC) procedures, including proper maintenance of laboratory testing equipment and use of appropriate reagents. HPTN LC staff will follow up directly with site staff to resolve any QC or QA problems identified through proficiency testing and/or on-site assessments.

9.6 QC for HIV Diagnostic Testing

Local laboratories will perform testing for HIV diagnosis at Screening, Enrollment, and follow-up visits. Algorithms for HIV diagnostic testing are provided in the SSP Manual.

Throughout the course of the study, the sites will ship an aliquot per visit per participant quarterly, per the SSP schedule. The HPTN LC with guidance from the SDMC will select a random sample of stored specimens to test for QA purposes. The total number of specimens undergoing QA testing will follow the QA processes as described in the HPTN MOP and at the discretion of the HPTN LC.

The HPTN LC will test the specimens for evidence of HIV infection and compare the results of their tests with the results obtained by the local labs. HPTN LC staff will follow-up directly with site staff to resolve any QA problems identified through this process.

9.7 Quality Assurance for General Laboratory Testing

Local laboratories will perform hematology, chemistry, liver function, lipids, hepatitis, STI, CD4, RNA and urinalysis testing as indicated in each relevant SOE.

9.8 Quality Assurance for CD4 Cell Count Testing

Local laboratories may also perform CD4 cell count testing as indicated in Appendix II.

9.9 Quality Assurance for HIV RNA Testing

Local laboratories may also perform HIV RNA/viral load testing (platform and test kit approved by the HPTN LC) as indicated in Appendix II or for evaluation of possible acute HIV infection.

9.10 Specimen Storage and Possible Future Research Testing

Study sites will store specimens collected in this study at least through the end of the study (completion of all study-related testing, including testing at the HPTN LC, which is typically one year post main paper publication). In addition, study participants will be asked to provide written informed consent for the collected samples to be stored after the end of the study, for possible future non-protocol listed testing. The specimens of participants who do not consent to long-term storage and additional testing will be collected and remain stored as planned, and then be destroyed after all of the protocol specified testing (including assessments at the HPTN LC) has been completed and approval from the protocol team and network leadership is provided.

Samples from participants who did not successfully enroll in the study may be discarded once sample lists are provided by the HPTN LC in consultation with the HPTN SDMC.

9.11 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the US CDC. All infectious specimens will be transported in accordance with United States regulations (42 CFR 72) and in accordance with IATA.

10.0 ADMINISTRATIVE PROCEDURES

10.1 Protocol Registration

Initial Registration of the protocol by the DAIDS PRO is required prior to implementation of this protocol. As part of this process, each site must have the protocol and protocol informed consent form(s) (ICFs) approved, as appropriate, by their IRB/EC and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the DAIDS RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received. In the case of Initial Registration, site-specific ICFs *WILL* be reviewed and approved by the DAIDS PRO. Sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Following Initial Registration, any full protocol amendments require submission of a protocol registration packet to the DAIDS PRO as described above; however, the DAIDS PRO *WILL NOT* review and approve site-specific ICFs. Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites will receive a Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site’s regulatory files.

There may be cases where a site submits as their Initial Registration a protocol amendment (Version 2.0 or higher of a protocol); in such cases, the instructions for Initial Registration will be followed.

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/daids-protocol-registration-policy-and-procedures-manual.

10.2 Study Activation

Pending successful protocol registration and submission of all required documents, the HPTN LOC staff will “activate” a site. Study implementation may not be initiated until a study activation notice is provided to the site by the HPTN LOC. In addition, if study “activation” is determined to be necessary for any subsequent amendments, study implementation may not be initiated until a study activation notice is provided to the site by the HPTN LOC.

10.3 Study Coordination

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 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 between DAIDS and ViiV Healthcare.

Study implementation will be directed by this protocol as well as the SSP Manual. The SSP Manual, which will include links to the DAIDS SOPs for Source Documentation and Essential Documents, as well as links to the Manual for Expedited Reporting of AEs to DAIDS and the DAIDS Toxicity Tables, will outline procedures for conducting study visits; data and forms processing; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations.

Study CRFs will be developed by the study team and HPTN SDMC. Data will be transferred to the HPTN SDMC, entered, and cleaned using the MediData Rave electronic data management system. Queries routinely will be generated and distributed to the study sites for verification and resolution.

Close coordination between protocol team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the team as well as the HPTN SMC. The protocol team's CMC will address issues related to study eligibility and AE management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites.

10.4 Study Monitoring

On-site study monitoring will be performed in accordance with DAIDS policies. Study monitors will visit the site to:

- 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, CRFs), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN LOC, HPTN SDMC, HPTN LC, NIAID and/or its contractors; NICHD and/or its contractors (including Westat); site IRBs/ECs; other local, US, or international regulatory authorities (including the OHRP and US FDA); or, if appropriate, the HPTN's sIRB, Advarra, or ViiV. A site visit log will be maintained at each study site to document all visits.

10.5 Protocol Compliance

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 RSC prior to implementing the amendment.

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.

10.7 Use of Information and Publications

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 (MRC), DAIDS, and ViiV Healthcare for review prior to submission.

11.0 REFERENCES

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12.0 APPENDICES I – XII

12.1 APPENDIX I. SCHEDULE OF EVALUATIONS – ORAL PHASE (STEP 1)

WEEKS in Study (Shaded column = dispense oral product)	**Screening**	**WEEK 0 Enrollment**	**WEEK 2**	**WEEK 4**
ADMINISTRATIVE, BEHAVIORAL, REGULATORY				
Informed consent	X			
Locator information	X	X	X	X
Demographic information[1]	X	X		
HIV prevention counseling	X	X	X	X
Offer condoms	X	X	X	X
Patient Health Questionnaire-9 (PHQ-9)		X		
Behavioral/Acceptability Assessment (CASI)		X		X
CLINICAL EVALUATIONS & PROCEDURES				
Dispense study product (enough for 5 weeks)		X		
Observe participant take oral study product[2]		X	X	X
Adherence counseling/pill count (pill count Weeks 2 and 4 only)		X	X	X
Medical history, con meds, targeted physical exam[3]	X	X	X	X
Hep B vaccination (if needed)[4]			X	
Blood collection	X	X	X	X
Urine collection	X	X		
Rectal swab collection	X			
LOCAL LABORATORY EVALUATIONS & PROCEDURES				
HIV testing[5]	X	X	X	X
HBV and HCV testing[6]	X	X		
CBC with differential	X	X	X	X
Chemistry testing[7]	X	X	X	X
Liver function tests[8]	X	X		X
Fasting lipid profile[9]		X		
Syphilis testing	X			
GC/CT testing (urine, rectal, and oral pharyngeal swabs)	X			
Urinalysis (protein and glucose; this test can be done at either the clinic or in the local laboratory)		X		
Plasma storage[10]	X	X	X	X

FOOTNOTES FOR APPENDIX I:

[1] Demographics may be collected and reported at either Screening or Enrollment.

[2] 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.

[3] 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 must be calculated.
[4] 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.
[5] The HIV testing algorithm is provided in the SSP Manual. Testing for acute HIV must be negative and must be performed within the 14 days prior to enrollment of the participant. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory. At least one HIV assay result must be available and reviewed the same day as sample collection and before product is administered.
[6] 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.
[7] At Screening: Creatinine. At and after enrollment: BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.
[8] At Screening: ALT and TBili. At and after Enrollment: AST, ALT, total bilirubin, and alkaline phosphatase.
[9] 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 hours fasting.
[10] 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.

12.2 APPENDIX II. SCHEDULE OF EVALUATIONS – INJECTION PHASE (STEP 2)

WEEKS in Study (shaded column = injection visit)	**Wk 5**	**Wk 6**	**Wk 9**	**Wk 10**	**Wk 17**	**Wk 18**	**Wk 25**	**Wk 26**	**Wk 33**	**Wk 34**
ADMINISTRATIVE, BEHAVIORAL, REGULATORY										
Locator information	X	X	X	X	X	X	X	X	X	X
HIV prevention counseling	X	X	X	X	X	X	X	X	X	X
Condoms per local SOC	X	X	X	X	X	X	X	X	X	X
Behavioral/Acceptability assessment (CASI)	X		X		X		X		X	
Qualitative interviews begin (approximately)										X
CLINICAL EVALUATIONS & PROCEDURES										
Adherence, risk reduction counseling	X	X	X	X	X	X	X	X	X	X
Medical history[1], concomitant medications, targeted physical exam	X	X	X	X	X	X	X	X	X	X
Hep B vaccination (if needed)[2]		X							X	
Blood collection	X	X	X	X	X	X	X	X	X	X
Urine collection	X	X	X	X	X	X	X	X	X	X
Rectal swab collection					X				X	
Injections for all participants	X		X		X		X		X	
ISR evaluation		X		X		X		X		X
Provision of Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) (3 months' worth)										X
LOCAL LABORATORY EVALUATIONS & PROCEDURES										
HIV testing[3]	X		X		X		X		X	
CBC with differential	X	X	X	X	X	X	X	X	X	X
Chemistry testing[4]	X	X	X	X	X	X	X	X	X	X
Liver function testing[5]	X	X	X	X	X	X	X	X	X	X
Fasting lipid profile[6]										X
Syphilis testing									X	
GC/CT testing (urine, rectal, and oral pharyngeal swabs)					X				X	
Urinalysis (protein, glucose; at the clinic or local lab)	X	X	X	X	X	X	X	X	X	X
Plasma storage[7]	X	X	X	X	X	X	X	X	X	X

FOOTNOTES FOR APPENDIX II:

[1] Medical history must include pulse, blood pressure, weight and Body Mass Index (BMI) calculated at each visit

[2] The initial dose of the HBV vaccination is ideally 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.

[3] The HIV testing algorithm is provided in the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory. At least one HIV assay result must be available and reviewed the same day as sample collection and before product is administered.

[4] BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.

[5] AST, ALT, TBili, and alkaline phosphatase.

[6] 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 hours 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.

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

12.3 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
CLINICAL EVALUATIONS & PROCEDURES						
Qualitative interviews continue (approximately)		X	X			
Medical history[1], concomitant medications, targeted physical exam		X	X	X	X	
Hep B vaccination (if needed)[2]						X
Blood collection	X	X	X	X	X	
Urine collection		X	X	X	X	X
Rectal swab collection		X	X	X	X	
Provision of Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) (3 months' worth)		X	X	X		X
LOCAL LABORATORY EVALUATIONS & PROCEDURES						
HIV testing[3]		X	X	X	X	
CBC with differential		X	X	X	X	X
Chemistry testing[4]		X	X	X	X	X
Liver function testing[5]		X	X	X	X	X
Syphilis testing				X		X
GC/CT testing (urine, rectal, and oral pharyngeal swabs)		X	X	X	X	
Urinalysis (protein, glucose; at the clinic or local lab)		X	X	X	X	X
Plasma storage[6]	X	X	X	X	X	
DBS storage		X	X		X	

FOOTNOTES FOR APPENDIX III:

[1] Medical history must include pulse, blood pressure, weight and Body Mass Index (BMI) calculated at each visit

[2] The initial dose of the HBV vaccination is ideally 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.

[3] The HIV testing algorithm is provided in the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory. At least one HIV assay result must be available and reviewed the same day as sample collection and before product is administered.

[4] BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.

[5] AST, ALT, TBili, and alkaline phosphatase.

[6] Stored plasma will be used for Quality Assurance testing and other assessments at the HPTN LC (see Section 9) including potential assay for plasma CAB concentrations. 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.

12.4 APPENDIX IV: SCHEDULE OF ADDITIONAL PROCEDURES FOR REACTIVE/POSITIVE HIV TESTS

(For enrolled participants)

Note 1: The procedures listed for the HIV Confirmation Visit apply to participants who acquire HIV infection at any time during the study. The procedures listed for Weeks 12, 24, 36, and 48 apply to participants who acquire HIV infection after having one or more injections. Participants who acquire HIV in Step 3 may undergo similar procedures as listed in Weeks 12, 24, 36, and 48, and will be determined by the members of the protocol team. Note that participants who acquire HIV-infection during Step 1 will permanently discontinue study product, will be terminated from the study, and be referred for HIV-related care.

Participants who acquire HIV infection in Injection and Follow-up Phase only					
	HIV Confirmation Visit	Week 12	Week 24	Week 36	Week 48
ADMININISTRATIVE, BEHAVIORAL, REGULATORY					
Locator information	X	X	X	X	X
Offer condoms	X	X	X	X	X
HIV counseling	X				
CLINICAL EVALUATIONS AND PROCEDURES					
History, con meds, targeted 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	X	X
Liver function testing[4]		X	X	X	X
Plasma storage[5]	X	X	X	X	X
DBS storage	X				

FOOTNOTES FOR APPENDIX IV:

[1] The HIV confirmatory visit must be held on a different day from the visit where the participant had their initial reactive/positive HIV test. The testing algorithm for the HIV Confirmation Visit is 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 may 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 may not be used real-time/local resistance testing; additional samples must be collected for this testing.
[3] Required chemistry testing: BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.
[4] Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.
[5] Stored plasma will be used for Quality Assurance testing and other assessments at the HPTN LC (see Section 9), including potential assay for plasma CAB concentrations. Assessments will be performed retrospectively; results will not be returned to study sites or participants, except as noted in Section 9.0. Samples cannot be used by site or other lab for local purposes without specific instructions from the LC w/ CMC consult.

12.5 APPENDIX V: TOXICITY MANAGEMENT

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. In addition, a CMC has been established for this study. The CMC's responsibilities will include consultation and decision-making regarding management of toxicities and study product administration, including product resumption following the occurrence of certain types of toxicities and/or permanent discontinuation. 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. IoRs 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. Refer to the table below for specific guidance for ALT.

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 elsewhere in the protocol or in the Tables below may continue use of the study product per protocol.

Grade 3

For participants who develop a Grade 3 AE or toxicity that is not specifically addressed elsewhere in the protocol or in the Tables below and is judged to be related to study product by the IoR, study product use should be temporarily discontinued in consultation with the CMC. In general, and unless otherwise decided in consultation with the CMC, the IoR should re-evaluate the participant until resolution of the toxicity.

Related:
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 and the same Grade 3 AE recurs at any time, the IoR must consult the CMC for further guidance on holding of study product, frequency of reevaluation or progression to permanent discontinuation of the study product.

Unrelated:
For Grade 3 AEs deemed unrelated to study product, the CMC should be consulted for further management recommendations.

Grade 4

Participants who develop a Grade 4 AE or toxicity that is not specifically addressed elsewhere in the protocol or in the Tables below (regardless of relationship to study product) must have the study product temporarily discontinued. The IoR must consult the CMC and continue the temporary study product hold until a recommendation is obtained from the CMC.

In general, study product use will not be resumed if the Grade 4 AE is considered related to study

product use. If, in consultation with the CMC, 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.

General Criteria for Discontinuation of Study Product

Participants may voluntarily discontinue the study product for any reason at any time. IoRs 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. IoRs 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 or HBV infection

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 Protocol Section 4.4. Study product use may resume upon consultation with the CMC and when the participant reports that he is no longer taking the prohibited medication, provided other reasons for temporary study product hold/permanent discontinuation do not apply. The CMC should be consulted in all cases where a participant reports taking a prohibited product during the course of the study.
- 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 IoR must consult the CMC on all temporary study product holds instituted for this reason for further guidance on resuming study product use, continuing the temporary hold, or progressing to permanent discontinuation.
- 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.

Oral Phase:
Participants who temporarily or permanently discontinue study product during the Step 1, Oral Run-in Phase, will be instructed to return all study products as soon as possible.

Injection Phase:
Participants who have received at least one injection and refuse further injections or discontinue due to an AE will be transitioned to quarterly follow-up.

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	Treat symptomatically with hydration, oral antiemetic therapies or antiemetic suppositories at the discretion of the IoR. The IoR should order any clinically relevant laboratory analyses (per judgment of the IoR).
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 IoR 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

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 provided HBV vaccination. Therefore, pre-existing HBV infection is not likely to be a cause of AST/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.

Note the following for cases of exercise-induced CPK abnormalities:
Note the following for cases of exercise-induced CPK abnormalities: Cases of CPK abnormality $\geq$ Grade 3 or higher, presumed to be exercise induced, accompanied by < Grade 3 ALT must be brought to the attention of the CMC for adjudication of further management and further administration of study product. Grades 3 and 4 elevations in ALT, regardless of CK elevation will prompt permanent discontinuation of study product and the participant will be followed annually for HIV testing only until the conclusion of Step 2 of the study. All such cases must be reported to the CMC.

GUIDANCE ON TOXICITY MANAGEMENT FOR SPECIFIED TOXICITIES:

CONDITION AND SEVERITY	FOLLOW-UP AND MANAGEMENT
ELEVATIONS in ALT	
Grade 2 and higher	**Oral phase:** A Grade 2 ALT abnormality reported at Week 2 or Week 4, regardless of relatedness to the study product, should be confirmed within one week. Oral study drug may continue until the confirmatory results are available; no injections should be administered until confirmatory results are available during consideration of the Week 4 ALT value. If the repeat value is ≤ Grade 2 at Week 3, study drug may continue to Week 4. If the repeat value is < Grade 2 at Week 4, the participant may proceed to the injection phase. If the repeat value is Grade 2 or higher at Week 4, study product should be stopped, and the participant will be discontinued from the study. All such cases must be reported to the CMC. In addition, participants will be followed with weekly ALT assessments until they return to ≤ Grade 1. • A Grade 3 or higher ALT abnormality, regardless of relatedness to the study product, will result in permanent study product discontinuation and will prohibit a participant from entering the injection phase of the study. All such cases must be reported to the CMC. In addition, participants will be followed with weekly ALT assessments until they return to ≤ Grade 1.
Grade 2 and higher	**Injection phase**: The CMC should be notified as soon as possible. • For a Grade 2 ALT, the CMC will determine whether further injections may be given in cases where levels are ≤ Grade 2 prior to the next scheduled injection. Unless otherwise specified by the CMC, for Grade 2 ALT, repeat testing should be performed weekly until levels are ≤ Grade 1. • For Grade 3 and higher ALT, study product will be permanently discontinued. For Grade 3 and 4 ALT, repeat testing should be performed as soon as possible, and participants should be followed weekly until levels are ≤ Grade 1. Participants who are permanently discontinued from study product should continue to be followed 48 weeks post-last injection.

GUIDANCE ON TOXICITY MANAGEMENT FOR SPECIFIED TOXICITIES:

Creatinine Clearance

CONDITION AND SEVERITY	IMMEDIATE ACTION	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.
Confirmed CrCl< 60 mL/min	Permanently discontinue study product	If the calculated creatinine clearance is confirmed to be <60 mL/min, the CMC must be notified and the study product must be discontinued. 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 IoR must consult the CMC for further guidance on resuming study product use, continuing the hold temporarily, or progressing to permanent discontinuation. If the IoR, 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:

Creatine Phosphokinase (CPK)

Note the following for cases of exercise-induced CPK abnormalities:
Note the following for cases of exercise-induced CPK abnormalities: Cases of CPK abnormality ≥ Grade 3 or higher, presumed to be exercise induced, accompanied by < Grade 3 ALT must be brought to the attention of the CMC for adjudication of further management and further administration of study product. Grades 3 and 4 elevations in ALT, regardless of CK elevation will prompt permanent discontinuation of study product and the participant will be followed for 48 weeks post-last injection. All such cases must be reported to the CMC.

CONDITION AND SEVERITY	IMMEDIATE ACTION	FOLLOW-UP AND MANAGEMENT
Creatine Phosphokinase		
Grade 3	Continue study product until repeat test results are available	A Grade 3 or higher elevation in CPK should result in a repeat assessment within 2-4 weeks to ensure the result is transient or due to exercise and will not require a change in study treatment. A history regarding use of products known to cause increase of CPK (such as statins), physical activity, or exercise preceding the CPK evaluation should be obtained.
Grade 4	Continue study product until repeat test results are available if the elevation is thought to be possibly or probably related to study product.	Grade 4 elevations in CPK should have a repeat assessment after the subject has abstained from exercise for >24 hours. For persistent Grade 4 CPK elevations that are considered possibly or probably related to the study product, study product should be discontinued and the participant should be followed on study/off study product.

GUIDANCE ON TOXICITY MANAGEMENT FOR SPECIFIED TOXICITIES:

Guidance for Injection Site Reactions (ISRs)

The CMC must be informed of all Grade 3 or 4 ISRs to determine etiology and assess appropriate continued study participation. 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.

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 to be related to study product should permanently discontinue study product and continue to be followed quarterly. Participants should be treated as clinically appropriate and followed until resolution of the AE.

12.6 APPENDIX VI: INFORMED CONSENT FOR PARENTS/LEGAL GUARDIANS AND PARTICIPANTS WHO REACH THE AGE OF MAJORITY AND ASSENT FOR ADOLESCENT PARTICIPANTS AGES 14 – AGE OF MAJORITY

Sponsor / Study Title:	**Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases (NIAID), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), US National Institutes of Health (NIH) / "HPTN 083-01: Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV among Adolescent Males – A sub-study of HPTN 083"**
Protocol Number:	**HPTN 083-01**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

If you are a parent or legal guardian of a child participating on this study, throughout this document "you(r)" = "your child."

Key Information:

The first two pages of this document include summary information about this study that will help you decide whether or not you should participate. More detailed information is provided after this summary section.

About this research

You are being asked to join a research study. Scientists do research to answer important questions which might help change or improve the way we do things in the future. This form explains the research study and your part in the study. Please read it carefully and take as much time as you need. Ask your study doctor or the study team to explain any words or information that you do not understand. You may take this description home and discuss it with your family or friends to help you decide.

Taking part in this research study is voluntary

You may choose not to take part in the study or may choose to leave the study at any time. Deciding not to participate, or deciding to leave the study later, will not result in any penalty or loss of benefits to which you are entitled and will not affect your relationship with the study site.

Important Information

This information gives you an overview of the research. More information about these topics may be found in the pages that follow.

1. **Why is this research being done?**
   There is a new drug called cabotegravir (CAB) that can treat people who have human immunodeficiency virus (HIV) infection. CAB is also being tested to see if it can protect people from getting HIV and has been found to be effective at preventing HIV among adult men and transgender womenIn this study, we want to know if it is safe and acceptable for adolescent boys who do not have HIV to take CAB. For more information, please see the *What is this Study About* section below.

2. **What will happen to me during the study?**
   You will move through the study in 3 steps:
   - Step 1: You will take one CAB pill every day for five weeks
   - Step 2: You will receive a total of 5 CAB injections over 6 months
   - Step 3: You will come to the clinic for study visits quarterly for up to one year.

   Different procedures are done at different study visits. The procedures include:
   - *Physical examinations* – We will examine you to check on your health by measuring height, weight, temperature and blood pressure.
   - *Questions* – We will ask general questions about your age, living situation, medical health, and as well as beliefs about HIV, opinions about taking pills and getting injections, sexual behavior, and any alcohol or drug use.
   - *Counselling* – We will discuss ways to protect you from getting HIV and offer condoms. We will discuss any challenges you have taking the CAB pill or attending study visits.
   - *CAB pills or injection* – During Step 1, we will explain how to take the study pills, watch you take a study pill, and explain any side effects the pills may cause. In Step 2, the CAB injection will be given into your buttock.
   - *Laboratory tests* – We will collect blood, urine, rectal swabs, and oral pharyngeal swabs to test for HIV, Hepatitis, liver and kidney health, cholesterol, and sexually transmitted infections (STIs).
   - *HIV Prevention* – We will offer you Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) tablets as pre-exposure prophylaxis (PrEP) after you stop the CAB injections. You may, instead, have the opportunity to join an open label CAB study, if available.

   For more information on each procedure and when it happens, please see the *What Will I have to Do in the Study* section below.

3. **How long will I participate in the study?**
   If you decide to join the study, participation will last about 1.5 years and include a maximum of 18 study visits at this clinic.

4. **Will I benefit from the study?**
   It is possible that you may benefit from taking part in this study.. The study medication being used has been shown to prevent HIV infections among some adults. You will get information about your health and the results of the tests, as well as treatment for sexually transmitted infections. The counseling you get during this study may help you avoid HIV and other sexually transmitted infections. For more information, please see the *What are the Potential Benefits of Taking Part in the Study* section below.

5. **Will taking part in the study expose me to risks?**
   Taking part in this research may expose you to risks. We may not know or understand all the risks at this time. Some people may experience side effects or discomfort, some of which may be serious. It is very important that you understand the risks in this research study before you decide whether you will participate. For details and a list of risks you should know about, please see the *What Are the Risks of Taking Part in the Study* section below.

6. **Will I be paid to participate?**
   Payment for your time or travel is available if you decide that you will take part in this study. For more information, please see the *What Will I Get for Taking Part in this Study* section below.

7. **Will it cost me anything to participate?**
   There is no cost to you for taking part in this study.

Please review the rest of this document for details about these topics and additional things you should know before making a decision about whether you will participate in this research.

INTRODUCTION

We invite you to take part in a research study about PrEP for Human Immunodeficiency Virus (HIV). PrEP is short for Pre-Exposure Prophylaxis. Pre-exposure means before being exposed to HIV. Prophylaxis is the way people prevent a disease from infecting them. With PrEP for HIV, medications are being developed to prevent people from getting infected if they are exposed to HIV.

This form gives information about what it means to join the study. Please read it and ask any questions that you may have. You can take as much time as you need to fully understand the study. We will ask questions to see if we have explained the study clearly. After you understand the study, if you decide that you will take part, we will ask you to sign and date this form. You will be offered a copy to keep. Because you are still a minor, we must have permission from a parent or guardian for you to take part. This process is called "informed consent."

WHAT IS THIS STUDY ABOUT?

In this study, we want to know if it is safe and acceptable for adolescent men who do not have HIV to take an anti-HIV drug called cabotegravir (CAB). We would also like to look at the tolerability, or side effects, of CAB. CAB is a new drug that is still being studied and is not yet approved by the FDA, or U.S. Food and Drug Administration. Other studies showed that CAB can treat people who have HIV infection and it has recently been shown as a way to prevent HIV infection from sex is to use condoms and/or take the PrEP pill called Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) every day. But some people have a hard time remembering to take a pill every day, so it is a good idea to have

other HIV prevention options. With CAB, people would get injections every 8 weeks and would not have to remember to take a pill every day. It is important that we learn what happens when adolescents use CAB for HIV prevention and whether it is safe and acceptable.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

DO I HAVE TO JOIN THIS STUDY?

You do not have to be in this study. The study staff can tell you about other places where you can get the care you need even if you do not join the study. If you join the study today, you can still change your mind later and leave the study at any time for any reason without penalty. If you decide not to take part in this study, you can join another study at a later time if one is available and you qualify for it.

You can't join this study if you are taking part in another study of drugs, HIV vaccines, or medical devices. You must tell the study staff about any other studies you are taking part in or thinking of taking part in. ***This is very important for your safety.*** *[Some sites may have biometric fingerprint screening and, if so, sites should add information regarding that here.]*

HOW LONG WILL THE STUDY LAST?

If you decide to join the study, participation will last about 1.5 years and include about 18 study visits at this clinic. You will move through the study in 3 steps:

- Step 1: You will take one CAB pill every day for five weeks
- Step 2: You will receive a total of 5 CAB injections over 6 months
- Step 3: You will come to the clinic for study visits quarterly for up to one year

WHAT WILL I HAVE TO DO IN THE STUDY?

If you want to be in this study, you will sign and date this form before you begin the study.

Study Visit Schedule

- Screening (1 visit) – First, we will find out if you qualify to be in the study.
- Step 1 (3 visits) – If you qualify and decide to join the study, you will swallow 1 CAB tablet every day for 5 weeks starting at the Entry, or Enrollment, Visit. Step 1 is done to make sure your body is tolerating the CAB well, so you should take the tablets every day. You will come back for a medical check-up at weeks 2 and 4. If Step 1 goes well for you, then you will move to Step 2.
- Step 2 (10 visits) – If you qualify, you will get the first CAB injection at week 5, then again at weeks 9, 17, 25 and 33 (5 injection visits). You will come back to the study clinic for a brief check-up 1 week after each injection at weeks 6, 10, 18, 26 and 34 (5 safety visits).
- Step 3 (5 visits) – After a blood draw 8 weeks after your last injection, you will come to the clinic quarterly (every 3 months) for 1 year to check how you are doing and to see how long CAB remains in your body after your last injection (+8, +12, +24, +36, +48 weeks). In most people, CAB disappears from the body slowly over 6 months, but it may last for a year or so. During this Step, you will be provided with Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) to take daily or be offered the opportunity to join an open label CAB study if

available, so we will be following you to see how well things are going on oral PrEP, doing bloodwork, as well as HIV and other STI testing.

You will be in the study for the about 1.5 years. Your parent/guardian does not need to come with you to the study visits. The study visits will take from 1 to 4 hours each *[sites to modify accordingly]*. It is important that you attend all of these study visits. If you do not come for a scheduled visit or if a test result comes back abnormal, study staff will contact you or visit you. We will ask for your address and contact information so that we will be able to get in touch with you. You should not join the study if it's not okay for study staff to contact you and visit you where you stay. If at any time you feel sick, you should let the study staff know right away and we may ask you to come back for a check-up.

Study Visit Procedures

Different procedures are done at different study visits. We will now explain each of the procedures and then show you which ones are done at which visits.

- *Physical examinations* – We will examine you to check on your health by measuring height, weight, temperature and blood pressure. At each study visit, we will check on whether CAB may be causing side effects. We will also tell you what to do if you have side effects.
- *Questions* – We will ask general questions about your age, living situation, medical health, and any medications or vitamins that you take. At some visits, you will also answer questions on a computer about your beliefs about HIV, opinions about taking pills and getting injections, sexual behavior, and any alcohol or drug use (we call these questions "CASI" for computer-assisted self-interview).
- *Counselling* – We will discuss ways to protect you from getting HIV and offer condoms. We will discuss any challenges you have about taking the CAB pill or attending study visits.
- *CAB pills or injection* – During Step 1, we will explain how to take the study pills, watch you take a study pill, and explain any side effects the pills may cause. In Step 2, the CAB injection will be given into your buttock.
- *Laboratory tests* – We will collect blood and urine. Some of these tests are done right away and we will tell you the results when they are available. The HIV results will be available before you are given CAB each time. Other tests are stored and then done later in a batch. More details are shown in the table below this section. Some tests are done in laboratories in other states, so your samples may be shipped there for testing. The laboratory tests are done for the following reasons:
    - Blood – To check for infections (HIV, hepatitis B and C, Syphilis), your general health, the health of the liver and kidneys, the amount of cholesterol (a fatty substance in your blood) and the amount of the study drug that is in your blood. How much blood is taken depends on which tests are due at each visit and is between 1 and 4 teaspoons each time (5-20mL). Study staff will tell you more about fasting before the cholesterol test. The study staff may be required by law to report the result of the HIV and Hepatitis tests to the local health authority.
    - Urine – To test if there is sugar or protein in your urine and for sexually transmitted infections.
- *Hepatitis B vaccination* – At Week 2 or soon thereafter, you will be given the hepatitis B vaccination if testing shows you are not already immune. Additional vaccination (boosters) will be given at approximately Weeks 6 and 33).
- *HIV Prevention* –The amount of CAB remaining in the body disappears slowly after you stops the CAB injections – it can last in the body for about one year, so you must use other ways of

preventing HIV if you are at risk of infection. For this reason, we will offer you Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) tablets as PrEP after you stop the CAB injections or offer you the opportunity to join an open label CAB study, if available. Before you leave the study, we will help you find a place where you can continue getting HIV prevention care *[sites to add information here or elsewhere in the consent form]*.

Tables of Study Visit Procedures

Step 1 – to see if your body is tolerating the CAB well

	screening	entry	Week 2	Week 4
Receive CAB pills (5 weeks' worth)		√		
Pill count			√	√
Questions/CASI	√	√	√	√
Counselling	√	√	√	√
Physical exam	√	√	√	√
Blood	√	√	√	√
Urine	√	√		
Rectal and oral pharyngeal swabs	√			

Step 2 – to give you the CAB injections and check your health (grey columns mean injection weeks)

	Week 5	Week 6	Week 9	Week 10	Week 17	Week 18	Week 25	Week 26	Week 33	Week 34
Questions/CASI	√		√		√		√		√	
Counselling	√	√	√	√	√	√	√	√	√	√
Brief physical exam	√	√	√	√	√	√	√	√	√	√
Blood	√	√	√	√	√	√	√	√	√	√
Urine	√	√	√	√	√	√	√	√	√	√
Rectal and oral pharyngeal swabs					√				√	
CAB injection	√		√		√		√		√	
PrEP pills offered										√

Step 3 Follow-Up Visits – to see how long the CAB remains in your body

	+8 Weeks	+12 Weeks	+24 Weeks	+36 Weeks	+48 Weeks
Questions/CASI		√	√	√	√
Counselling	√	√	√	√	√
Brief physical exam		√	√	√	√
Blood	√	√	√	√	√
Urine		√	√	√	√
Rectal and oral pharyngeal swabs		√	√	√	√
PrEP pills offered		√	√	√	

Permanently Stopping Study Drug

CAB pills are only given in Step 1, and then stopped permanently. If you need to leave the study before you receive any CAB injections, we'd still like to do a final study visit, which will include the same activities as the Step 3 Follow-Up Visits. If you permanently stop taking CAB after you had at least 1 CAB injection, then you will move straight to Step 3 follow-up visits, if you agree to stay in the study.

WHAT IF I BECOME INFECTED WITH HIV?

Being in this study will not cause HIV infection, but you could become infected with HIV through sex or other activities while in this study. If you get HIV infection, you will stop using CAB, but you should still come for the study visits to make sure that you are doing okay. The study staff will counsel you and refer you for HIV treatment and other available services, but the study will not pay for this treatment. We will share any test results that will help you get the treatment you need. Testing, which will take an additional 1-3 mL of blood, will be done to see if your HIV is resistant to any drugs that are used to treat HIV infection. This testing will help select the best drugs to treat your HIV infection.

Tables of Study Visit Procedures if you become infected with HIV during Step 2 or Step 3

If you become infected with HIV infection before your first injection, you will have the oral CAB stopped permanently and will be referred to local HIV-related care and exit from the study.

	HIV Confirmation Visit	**+12 weeks**	**+24 weeks**	**+36 weeks**	**+48 weeks**
Questions/CASI	√	√	√	√	√
Counselling	√				
Brief physical exam	√	√	√	√	√
Blood	√	√	√	√	√

WHAT OTHER TESTS WILL BE DONE?

After all the laboratory tests mentioned above for this study have been done, there may be some of your samples left over. We want to keep these in storage for future tests related to HIV and other infections, including testing for the drugs used in this study and other anti-HIV medications, or tests about your genes. There is a separate form with more information about this. We will not use DNA from your stored samples to study your whole genetic sequence (also called your "genome"). If you agree to this future research, identifiers might be removed from your identifiable private information or identifiable biospecimens collected during this study. That information could then be used for future research studies or distributed to another investigator for future research studies without additional informed consent.

WHAT ARE THE RISKS OF TAKING PART IN THIS STUDY?

Taking part in this study may involve some risks and discomfort.

Risk from Blood Draws – The needle can cause pain, swelling, bruising, or bleeding from the needle site. Drawing blood can cause fainting or infection, but this is very rare.

Risk from Receiving CAB Injections – People who got CAB injections in other studies had pain, skin irritation, skin redness, bumps, swelling, itching, or bruising at the spot where they got the shot. Most reactions go away in a week or less but sometimes they can last a long time. The injection could be given too deeply or not deeply enough, missing the muscle and entering your skin, blood, or a nerve. Everything possible will be done to decrease this risk, including watching you for problems during the study. If we think that the injection was not given the right way, you might be asked to stay in the clinic up to 2 hours after the injection to watch how you are doing. Receiving injections can cause some people to feel lightheaded or feel like they might pass out, or 'faint'. This is called a 'vasovagal reaction' and it can occur with many medical procedures but usually resolves quickly.

Risk of CAB Side Effects – All drugs can cause side effects. Some side effects are minor; others can be severe. Some side effects are common; others are rare. Some people who take the study drug have some of the side effects. Other people have different side effects, or no side effects. The most common side effects for CAB are listed below. It is not known if CAB, other drugs or the participant's other health problems caused these side effects. There may be other side effects that we do not know about now. This may be especially true for adolescents, because this is the first study of CAB in adolescents.

Very Common Side Effects of CAB	**Common Side Effects of CAB**
• Nausea (feeling sick to the stomach) • Diarrhea or loose stools • Runny nose, sore throat/Upper respiratory tract infection • Headache • Fever • Lack of energy	• Rash • Itching • Vomiting (being sick) • Stomach pain and discomfort • Problems sleeping • Abnormal dreams/nightmares • Feeling light headed • Depression • Passing gas or wind • Joint or muscle pain • Increase in the level of enzymes made in the muscles (creatine phosphokinase)

Some of the people who received CAB in other studies also had abnormal liver tests. In most people, this was explained by other things such as a new virus infection with Hepatitis. Very few people did not have another possible reason, so it is possible that a mild form of liver damage happened from taking CAB. In those people, the liver tests got better after stopping CAB, showing that any damage was temporary. Seizures have been seen (rarely) in people who had CAB. They are not thought to be caused by CAB, but the study staff will ask you about them. We have an information sheet about CAB and its side effects for you to keep.

Allergic Reaction Risks – As with taking any drug, there is a risk of allergic reaction. If you have a very serious allergic reaction, you may be at risk of death. Some symptoms of allergic reactions are:

- Rash
- Wheezing and difficulty breathing
- Dizziness and fainting
- Swelling around the mouth, throat or eyes
- A fast pulse

- Sweating

Please seek treatment immediately and tell the study doctor and study staff if you have any of these symptoms.

Risk of HIV Resistance to CAB – We do not know if using CAB for PrEP will mean that CAB will not work to treat the HIV if you get infected with HIV during the study or in the future (this is called drug resistance). Drug resistance usually occurs when the amount of a drug in the body is too low to kill the virus. You will have low levels of CAB in the body for about one year after the last injection, or if you don't get the injections when they are due. This is why it is very important that you use other methods to protect against HIV infection whenever you are at risk, like using condoms and Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) PrEP pills.

Risks potentially related to Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) for PrEP - Like all other drugs, you may have symptoms or side effects while taking PrEP. These symptoms or side effects may be due to participation in the study or due to illnesses that have no relation to the study, like a cold or flu. You should tell the study staff at the study clinic about any symptoms that you feel while you are participating in the study. In past PrEP research studies, nausea and diarrhea were the most common side effects, and happened in about 10% or 1 in 10 people. Nausea and diarrhea mainly happened in the first month and then went away. A small number (less than 1% or 1 out of 100 people) in PrEP studies showed a small decrease in how their kidneys work, but this stopped when the people stopped taking the study drug. Other side effects were very rare and usually resolved when the study drug was stopped.

Risks of Asking Sensitive Questions – You may feel uncomfortable when we ask personal questions. You do not have to answer any question that you do not want to and you can stop answering the questions at any time.

Risk of Disclosure of Private Information – We will make every effort to keep your information private and confidential. It is possible that others may learn that you are part of this study and they may think that you are infected with HIV or are at high risk for HIV. Because of this you may feel stigma, stress or embarrassment. We will not share any information about you or your health with anyone, even your parent/guardian, without talking to you first, except when *[sites to insert relevant information about any legal obligations for disclosure, for example…*your life is thought to be in danger*]*.

Risks of Rectal Swabs – You may have mild discomfort when the swab is performed, particularly if you have hemorrhoids. In some cases, a very small amount of bleeding may occur. If you are already having pain in the rectal area, be sure to let the study staff know.

Risks of Oral Pharyngeal Swabs – There are no risks or complications associated with this collection procedure. The procedure may cause momentary gagging because the back of the throat is a sensitive area, but it shouldn't be painful.

Other Risks – There may be uncommon or previously unknown risks that might occur. You should report any problems to the study staff immediately.

WHAT ARE THE BENEFITS OF TAKING PART IN THIS STUDY?
You may get direct benefit from being in this study. CAB LA has been shown to prevent HIV infections among adult men and transgender women. You will get information about your health and the results of the tests, as well as treatment for sexually transmitted infections. The counseling you get during this study may help you avoid HIV and other sexually transmitted infections. You or others in your community may benefit from this study later. The information gathered during this study may help to prevent the spread of HIV. This may be beneficial to you and your community.

ARE THERE ANY COSTS TO ME FOR TAKING PART IN THIS STUDY?
You will pay no money to be in the study. The study drug CAB will be provided and study procedures will be performed at no additional cost to you and/or your insurance company.

WHAT OTHER CHOICES DO I HAVE?
It is possible that Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) PrEP is available in your local area for HIV prevention. If you prefer to take PrEP instead of joining the study, ask the study staff to refer you for HIV prevention medical services.

[Sites to include/amend the following if applicable: There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about. There also may be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.]

WILL I BE TOLD IF THERE IS NEW INFORMATION?
You will be told about any new information learned during the course of the study that might cause you to change your mind about being in the study. At the end of the study, you will be told when study results may be available and how we will let you know about the results.

COMMERCIAL PROFIT
Your biospecimens collected during this study will **not** be used for commercial profit.

CLINICALLY RELEVANT RESULTS
Research results that are clinically relevant, including individual research results, **will be disclosed to you** under these conditions:

- HIV diagnostic testing results
- Any results that affect the treatment of HIV

ARE THERE ANY REASONS WHY I MAY BE ASKED TO STOP TAKING PART IN THIS STUDY?
You may be withdrawn from the study if any of the following occur:

- Your parent/guardian decides that they do not want you to participate anymore (if still under the legal age of consent).
- You are unable or unwilling to attend clinic visits and/or follow all of the study procedures or instructions.
- You could be harmed by continuing to take the pills or getting an injection.
- The study is stopped or canceled.
- The study doctor feels that staying in the study would be harmful to you.

- Other reasons, as decided by the study staff.

WHAT WILL I GET FOR TAKING PART IN THIS STUDY?
«Compensation»

You will be paid up to a total of $xx.xx if you complete this study. You will be paid for the visits you complete according to the following schedule:

- $xx.xx for Visits xxx.
- $xx.xx for Visits xxx.
- $xx.xx for Visits xxx.

If you do not complete the study, for any reason, you will be paid for each study visit you do complete.

You will be paid _____ ***[“after each visit,” “annually,” “bi-weekly,” etc.]***

If you have any questions regarding your compensation for participation, please contact the study staff.

HOW WILL MY PRIVACY BE PROTECTED?
To keep your information private, your samples will be labeled with a code that can only be traced back to the study clinic. Your name, where you live, and other personal information will be protected by the study clinic. The results of any tests done will not be included in your health records without your permission. Every effort will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. Your records may be reviewed, under guidelines of the United States Federal Privacy Act, by the United States Food and Drug Administration (FDA); the sponsor of the study (United States National Institutes of Health [NIH]), other US, local and international regulatory entities may also review your study records, as well as the Advarra Institutional Review Board (IRB), Ethics Committees (EC), study staff, study monitors, the company that makes CAB, and other local authorities. Groups that oversee the study include:

- Advarra IRB
- *[insert name of other site regulatory entities]*
- Representatives of the HPTN
- The United States National Institutes of Health and its study monitors (including NICHD and its monitor, Westat)
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- ViiV Healthcare (the company that makes CAB)

The study staff and these groups are required to keep study records private and confidential. The results of the study may be presented publicly or published. However, no presentation or publication will use your name or identify you personally. Your study information may be given to other authorities if required by law, including diagnoses of sexually transmitted infections. For example, we are required to follow state laws and report any risk of harm to you or others. This would include sexual activity with an adult while you are a minor.

In addition to the efforts made by the study staff to help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This Certificate protects researchers from being forced to tell people who are not connected with this study about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

WHAT HAPPENS IF I AM INJURED DURING THE STUDY?

Your health is important to us. We will make every effort to protect your well-being and minimize risks. It is possible, however, that you could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of the study procedures or the study drug.

If a study-related illness or injury occurs, we will treat you or tell you where you can get treatment. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation either through the study site or the U.S. National Institutes of Health.

By signing and dating this document, you will not lose any of your legal rights or release anyone involved in the research from responsibility for mistakes.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the study doctor at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact**:**

- By mail:
  Study Subject Adviser
  Advarra IRB
  6940 Columbia Gateway Drive, Suite 110
  Columbia, MD 21046
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00040790.

SCREENING AND ENROLLMENT CONSENT

Your signature and date on this form means that:

- You understand the information given to you in this form,
- You accept the provisions in the form, on behalf of your child, and
- You agree to permit your child to join the study

You will not give up any of you or your child's legal rights by signing and dating this consent form.

CONSENT FOR MINOR TO TAKE PART IN THIS STUDY

In consideration of all of the above, I give my consent for my child to participate in this research study. I will be given a copy of this document to keep for my records. I agree to let my child take part in this study.

_____

Name of Participant (print)

PARENT/GUARDIAN INFORMED CONSENT

_____

Relationship to participant

_____ _____

Name (print) Signature and Date

ASSENT TO TAKE PART IN THIS STUDY FOR ADOLESCENT PARTICIPANTS AGES 14 YEARS – AGE OF MAJORITY

I have read this form. I know that this is a research study. I have been told about the risks and potential benefits of taking part in the study. I have asked all the questions I have about the study and have gotten answers to my questions. I know that I am free to quit the study at any time without any penalties or loss of benefits. I will tell the study doctor, the study staff or my parent(s)/guardian(s), if I choose to stop the study so that I can stop in the best way to not harm my health. I will be given a signed and dated copy of this form to keep.

I agree to take part in this research study.

_____ _____

Participant's Name (print) Signature and Date

CONSENT TO TAKE PART IN THIS STUDY FOR ADOLESCENT PARTICIPANTS WHO HAVE REACHED THE AGE OF MAJORITY

I have read this form. I know that this is a research study. I have been told about the risks and potential benefits of taking part in the study. I have asked all the questions I have about the study and have gotten answers to my questions. I know that I am free to quit the study at any time without any penalties or loss of benefits. I will tell the study doctor or the study staff if I choose to stop the study so that I can stop in the best way to not harm my health. I will be given a signed and dated copy of this form to keep.

I agree to take part in this research study.

Participant's Name (print)	Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date

12.7 APPENDIX VII: INFORMATION SHEET AND ASSENT FOR ADOLESCENT PARTICIPANTS AGES 10-13

Sponsor / Study Title:	**Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases (NIAID), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), US National Institutes of Health (NIH) / "HPTN 083-01: Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV among Adolescent Males – A sub-study of HPTN 083"**
Protocol Number:	**HPTN 083-01**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

About this research

We are scientists doing a research study that we'd like you to join. This form explains what the study is about and what will happen if you decide to join. Please read it carefully. You can take as much time as you need to decide. Take the form home if you like. Ask the study team to explain any words or information that you do not understand. We will ask questions to see if we have explained the study clearly. After you understand the study, if you decide that you will take part, we will ask you to sign and date this form. You will be offered a copy to keep.

Because you are still a minor, we must have permission from a parent or guardian for you to take part. This process is called "informed consent." You don't have to join the study, even if your parent or guardian says you should. You can also quit the study at any time, and it won't change how you are treated here at the clinic.

This study is about PrEP for HIV (Human Immunodeficiency Virus).

- PrEP is short for Pre-Exposure Prophylaxis.
- Pre-exposure means before being exposed to HIV.
- Prophylaxis is the way people prevent a disease from infecting them.
- With PrEP for HIV, medications are being developed to prevent people from getting HIV if they are exposed to it.
- The usual PrEP medication is a pill called Truvada® that works well if taken every day.
- Some people have a hard time remembering to take a pill every day, so it is a good idea to have choices.

We're testing a new drug called cabotegravir (CAB) to see if it can be used as PrEP to **protect people from getting HIV.**

- CAB comes in the form of a pill and also as an injection (or 'shot') that's given every 8 weeks.
- In this study, about 50 men under 18 who do not have HIV will take CAB. We want to know:
  - Is it safe for adolescents to take CAB pills and CAB injections?
  - Is it acceptable and tolerable for adolescents to use CAB for HIV prevention?
  - Are adolescents able to make it to the clinic for injection appointments?
  - What do parents/guardians think about their sons using CAB for HIV prevention?
- You can't join this study if you are taking part in another study of drugs, HIV vaccines, or medical devices. You must tell the study staff about any other studies you are taking part in or thinking of taking part in. ***This is very important for your safety.***

If you join, you will complete about 18 study visits over the next 1½ years. You will move through the study in 3 steps:

- Step 1: You will take one CAB pill every day for five weeks.
- Step 2: You will receive a total of 5 CAB injections in your butt over 6 months.
- Step 3: You will come to the clinic for study visits every 3 months for up to one year. You will take the Truvada® PrEP pill every day while your body clears out the CAB or be offered an opportunity to join another CAB study.

Different procedures are done at different study visits. The procedures include:

- *Physical examinations* – We will examine you to check on your health by measuring height, weight, temperature and blood pressure.
- *Questions* – We will ask general questions about your age, living situation, medical health, and as well as beliefs about HIV, opinions about taking pills and getting injections, sexual behavior, and any alcohol or drug use.
- *Counselling* – We will discuss ways to protect you from getting HIV and offer condoms. We will discuss any challenges you have taking the CAB pill or attending study visits.
- *CAB pills or injection* – During Step 1, we will explain how to take the study pills, watch you take a study pill, and explain any side effects the pills may cause. In Step 2, the CAB injection will be given into your butt using a needle and syringe – this will probably be painful, just like any other shot.
- *Laboratory tests* – We will collect blood, urine, rectal swabs, and oral pharyngeal (throat) swabs to test for HIV, Hepatitis, liver and kidney health, cholesterol, and sexually transmitted infections (STIs). The needle stick can cause pain where it enters the skin and the swabs can be uncomfortable when they're collected. The study staff may be required by law to report the result of the HIV and Hepatitis tests to the local health authority.
- *HIV Prevention* – We will offer you Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) tablets as pre-exposure prophylaxis (PrEP) after you stop the CAB injections or you may be able to join another CAB study.

Your parent or guardian does not need to come with you to the study visits. The study visits will take from 1 to 4 hours each. It is important that you attend all of these study visits. If you do not come for a scheduled visit or if a test result comes back abnormal, study staff will contact you or visit you. We will ask for your address and contact information so that we will be able to get in touch with you. You should not join the study if it's not okay for study staff to contact you and visit you where you stay. If at

any time you feel sick, you should let the study staff know right away and we may ask you to come back for a check-up.

You may benefit from taking part in this study, but there is no guarantee that it will help you. Being in this study may expose you to risks.

- We may not know all the risks of CAB.
- Some people may have bad effects or discomfort, some may be serious.
- The most common bad effects include nausea, diarrhea, headaches and flu-like symptoms. You should tell the study staff whenever you don't feel well.
- We'll discuss in more detail about these risks with your parent or guardian through the informed consent session before you decide whether you will join the study.
- You may feel uncomfortable when we ask personal questions. You do not have to answer any question that you do not want to and you can stop answering the questions at any time.
- If others find out that you are on this study, they may think you have HIV and you may feel bad.

It doesn't cost you anything to be in the study. We will cover your transport costs to come to the study clinic.

«Compensation»

You will be given $XX each time you complete a study visit.

If you get HIV while you are in this study, you will stop using CAB and will be referred to start HIV treatment. You should still come for the study visits to make sure that you are doing okay.

You might be able to get Truvada® PrEP in your local area for HIV prevention. If you prefer to take PrEP instead of joining the study, ask the study staff to refer you for HIV prevention medical services.

We won't tell anyone else that you are in the study.

- We won't share anything we find out about you with anyone, even your parent or guardian, without talking to you first.
- We use a code number instead of your name on all the study forms.

Have I explained the study clearly to you? Now you should ask the study staff any questions you have.

If you have more questions later, or have any problems or complaints about the study, please contact the study doctor. If you are seen at another clinic for anything, let them know that you're in this study and we can call them to share details.

ASSENT TO TAKE PART IN THIS STUDY FOR ADOLESCENT PARTICIPANTS AGES 10-13

I have read this form. I know that this is a research study. I have been told about the risks and potential benefits of taking part in the study. I have asked all the questions I have about the study and have gotten answers to my questions. I know that I am free to quit the study at any time without any penalties or loss of benefits. I will tell the study doctor, the study staff or my parent(s)/guardian(s) if I choose to stop the

study so that I can stop in the best way to not harm my health. I will be given a signed and dated copy of this form to keep.

I agree to take part in this research study.

Participant's Name (print)	Signature and Date
Study Staff Conducting Assent Discussion (print)	Study Staff Signature and Date

12.8 APPENDIX VIII: INFORMED CONSENT FOR ADOLESCENT INTERVIEW FOR PARENTS/LEGAL GUARDIANS AND PARTICIPANTS WHO REACH THE AGE OF MAJORITY AND ASSENT FOR ADOLESCENT PARTICIPANTS AGES 14 – AGE OF MAJORITY

Sponsor / Study Title:	**Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases (NIAID), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), US National Institutes of Health (NIH) / "HPTN 083-01: Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV among Adolescent Males – A sub-study of HPTN 083"**
Protocol Number:	**HPTN 083-01**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

If you are a parent or legal guardian of a child participating on this study, throughout this document "you(r)" = "your child."

INTRODUCTION

You are being asked to take part in an interview as part of the research study listed above. Participating in this interview is voluntary. You may refuse to join, or you may withdraw your consent to be interviewed for any reason. Before you decide whether to take part in the interview, we would like to explain the purpose of the interview, the risks and benefits to you and what is expected of you.

This consent form gives information about taking part in the interview. We will help you to understand the form and answer your questions before you sign and date this form. Once you understand the details about taking part in the interview, and if you agree to take part, you will be asked to sign your name and date this form. You will be offered a copy of this form to keep. If you are a child, your parent/guardian must also give their permission.

Participation is voluntary

Before you learn about the interview, it is important that you know the following:

Your participation is voluntary. You do not have to take part in this interview if you do not want to. You may decide not to take part in the interview, or you may decide to leave the interview at any time without losing your regular medical care.

You are not required to participate in this interview in order to remain in the rest of the main study.

About the interview
The main study is being done to find out if it is safe and acceptable for adolescent men who do not have HIV to take an experimental HIV drug called cabotegravir (CAB) as PrEP to prevent HIV. The interview portion will ask young men what they like and do not like about getting CAB injections. We will also ask questions to find out what makes some young men more or less interested in starting PrEP. Finally, we will ask about difficulties you had getting CAB injections and things that made that easier.

Entering the interview
In order to understand better what makes it easier or harder for young men in this study to get CAB injections as directed, we will be doing interviews with up to 10 young men at participating sites. You have been selected to take part in one interview sometime after your last CAB injection.

What will happen during the interview
The interview will be led by a member of the research team that you do not work with during the study. It should take about 1 hour and your parent/guardian will not be there. [*To be modified to reflect site practices: The interview will take place in a location that the study staff have determined will provide you with privacy and confidentiality such as the clinic, or another appropriate place. The study team will talk with you about this so you know where to go for the interview*].

During the interview we will ask you questions about:

- How and when you decided to join the study
- Whether you feel that you personally are at risk of HIV
- How you made daily pill-taking part of your routine in Step 1
- Where you kept your CAB pills
- Whether you talked to your family members, peers, or partner(s) about being in this study or getting CAB injections in Step 2
- If you had any bad effects from the CAB injections, and if this influenced your decision to keep getting the injections
- If you are taking daily Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) pills, how you feel about being on PrEP
- Other related topics

If any of the questions make you upset, either you or the interviewer may stop the interview at any time. You will also be provided with contact and referral information if any of the questions raise issues that you would like to talk about later.

Benefits of taking part in the interview
There may be no benefit from being interviewed. You may not receive any other direct benefit from being in this part of the study; however, you or others in your community may benefit from this study later.

Risk of taking part in the interview
There is little risk from the interview. To minimize any discomfort and to protect your privacy, the interview will be conducted in a private area that will allow you to speak comfortably without being overheard. Although we hope that you will be comfortable answering all of the questions openly and

honestly, please keep in mind that you may refuse to answer any of the questions, or stop the interview completely, at any time. The greatest risk may involve your privacy and confidentiality. The steps that the study team have taken to protect your privacy are described below.

Other information about the interview

Privacy – Every effort will be made to keep your personal information confidential. Your personal information (name, address, phone number) will be protected by the research clinic. Your name, or anything else that might identify you personally, will not be used in any publication of information about this study.

To help assure that we get the best understanding possible from your answers during the interview, the entire interview **will be audio-recorded**. After the interview is finished, the recording will be typed (called a transcript) by people who know how to do this. All identifying information will be removed from the transcript. Your name will not be included on the transcript. These recordings will be destroyed after all analysis is completed.

Your records may be reviewed by the following groups, involved with the study:

- Advarra Institutional Review Board
- [insert name of other site regulatory entities]
- Representatives of the HPTN
- The United States National Institutes of Health and its study monitors (including NICHD and its monitor, Westat)
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- ViiV Healthcare (the company that makes CAB)

If the study staff learns that you are at risk of harm, we will tell the proper authorities as we are required to do by the law. We are also required to follow state laws regarding reporting of sexual activity of minors with adults.

New Information – You will be told any new information learned during this study that might affect your willingness to stay in the study. You will also be told when the results of the study may be available, and how to learn about them.

Alternatives to participating

You can talk to the study staff at any time about your experiences in the study, without taking part in the interview.

There are no costs to you for being interviewed

There will be no cost to you for participating in the in-depth interview.

«Compensation»

You will receive $XX for being interviewed. You will be paid _____ ***[“after each visit,” “annually,” “bi-weekly,” etc.]***

If you have any questions regarding your compensation for participation, please contact the study staff.

Whom to contact
If you have questions about the interview, please contact the study staff listed on page 1 of this document.

If you have a research-related injury, please contact: *[insert name of site contact]*

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact**:**

- By mail:
  Study Subject Adviser
  Advarra IRB
  6940 Columbia Gateway Drive, Suite 110
  Columbia, MD 21046
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00040790.

SIGNATURE PAGE
ADOLESCENT IN-DEPTH INTERVIEW INFORMED CONSENT FORM

If you decide to join this interview portion of the main study, sign and date below. Before deciding whether to be interviewed, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you if you decide to join. You can ask questions or request more information at any time. You do not give up any rights by signing and dating this form.

ADOLESCENT ASSENT FOR PARTICIPANTS AGES 14 – AGE OF MAJORITY

Write your initials and sign and date below.

_____ I agree to be interviewed for the study and to have the interview audiotaped.

_____ _____
Name of Participant (print) Signature and Date

PARENT/GUARDIAN INFORMED CONSENT

_____
Relationship to participant

_____ _____
Name (print) Signature and Date

CONSENT FOR PARTICIPANTS WHO REACH THE AGE OF MAJORITY

Write your initials and sign and date below.

_____ I agree to be interviewed for the study and to have the interview audiotaped.

_____ _____
Name of Participant (print) Signature and Date

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

12.9 APPENDIX IX: INFORMATION SHEET AND ASSENT FOR ADOLESCENT INTERVIEWS FOR PARTICIPANTS AGES 10-13

Sponsor / Study Title:	**Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases (NIAID), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), US National Institutes of Health (NIH) / "HPTN 083-01: Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV among Adolescent Males – A sub-study of HPTN 083"**
Protocol Number:	**HPTN 083-01**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

About this form

You have decided to join the study named above, with permission from your parent or guardian. We also invite you to be interviewed for this study. This interview part will ask young men what they like and do not like about getting CAB injections. We will also ask questions to find out what makes some young men more or less interested in starting PrEP. Finally, we will ask about difficulties you had getting CAB injections and things that made that easier. Joining this interview part is voluntary.

- You can take as much time as you need to decide. Take the form home if you like.
- Ask the study team to explain any words or information that you do not understand. We will ask questions to see if we have explained it clearly.
- After you understand the interview part, we will ask you to sign and date this form.
- You will be offered a signed and dated copy to keep.
- It is your decision whether or not to be interviewed. You are free to say yes or no, and to change your mind at any time.
- If you say no, you can still be in the main study.

What will happen if you agree to be interviewed

One of the study staff that you do not work with during the study will interview you at [*Site to insert location]*. It will be for about 1 hour. Your parent or guardian will not be there. We will ask you questions about joining the main study and who you talked to about the study. We will also ask about your experiences with taking the study pills and having the injections. We will ask what you feel about your risk of getting HIV and such topics.

If any of the questions make you upset, either you or the interviewer may stop the interview at any time. You will also be provided with contact and referral information if any of the questions raise issues that you would like to talk about later.

Being interviewed won't benefit you in any way, but the information we get from the interviews may benefit your community later.

«Compensation»

You will be given $XX for the cost of transport to the clinic for the interview.

Have I explained the interview part of this study clearly to you? Now you should ask the study staff any questions you have.

If you have more questions later, or have any problems or complaints about the study, please contact the study doctor. If you are seen at another clinic for anything, let them know that you're in this study and we can call them to share details.

ASSENT TO TAKE PART IN THIS STUDY FOR ADOLESCENT PARTICIPANTS AGES 10-13

I agree to be interviewed for the study and to have the interview audiotaped.

Participant's Name (print)	Signature and Date
Study Staff Conducting Assent Discussion (print)	Study Staff Signature and Date

12.10 APPENDIX X: INFORMED CONSENT PARENT/GUARDIAN INTERVIEW FOR PARENTS/LEGAL GUARDIANS

Sponsor / Study Title:	**Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases (NIAID), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), US National Institutes of Health (NIH) / "HPTN 083-01: Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV among Adolescent Males – A sub-study of HPTN 083"**
Protocol Number:	**HPTN 083-01**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

INTRODUCTION

You are being asked to take part in an interview for the research study listed above. Joining this interview is voluntary. You may refuse to join, or you may withdraw your consent to be interviewed for any reason. Before you decide whether to join the interview, we would like to explain the purpose of the interview, the risks and benefits to you and what is expected of you.

This consent form gives information about being in the interview. We will help you to understand the form and answer your questions before you sign and date this form. Once you understand the interview, and if you agree to take part, you will be asked to sign your name and date this form. You will be offered a copy of this form to keep.

Participation is voluntary

Before you learn about the interview, it is important that you know the following:

Your participation is voluntary. You do not have to take part in the interview if you do not want to. You may decide not to take part in the interview, or you may decide to leave the interview at any time without losing your regular medical care.

You are not required to participate in these interviews in order for your child to remain in the rest of the study.

About the interview

The main study is being done to find out if it is safe and acceptable for adolescent men who do not have HIV to take an experimental HIV drug called cabotegravir (CAB) as PrEP to prevent HIV. This interview will ask parents/guardians questions to find out what it is like to have a child getting CAB injections and things that made that easier. We will also ask young men what they like and do not like about getting CAB injections.

Entering the interview

We will be doing interviews with up to 10 parents/guardians at participating sites (total, across sites). You have been selected to take part in one interview sometime after your child's last CAB injection.

What will happen during the interview

The interview will be led by a member of the research team that you do not work with during the study. It should take about 1 hour and your child will not be there. [*To be modified to reflect site practices: The interview will take place in a location that the study staff have determined will provide you with privacy and confidentiality such as the clinic, or another appropriate place. The study team will talk with you about this so you know where to go for the interview*].

During the interview we will ask you questions about:

- How and when you decided to allow your child to join the study
- Whether you feel that they personally are at risk of HIV
- Whether you talked to your children about sexual activity or preventing HIV
- If your child had any bad effects from being in the study, and if this influenced your decision to keep coming for the study visits
- Other related topics

If any of the questions make you upset, either you or the interviewer may stop the interview at any time. You will also be provided with contact and referral information if any of the questions raise issues that you would like to talk about later.

Benefits of the interview

There may be no benefit from being interviewed. You may not receive any other direct benefit from being in this part of the study; however, you or others in your community may benefit from this study later.

Risk of the interview

There is little risk from the interview. To minimize any discomfort and to protect your privacy, the interview will be conducted in a private area that will allow you to speak comfortably without being overheard. Although we hope that you will be comfortable answering all of the questions openly and honestly, please keep in mind that you may refuse to answer any of the questions, or stop the interview completely, at any time. The greatest risk may involve your privacy and confidentiality. The steps that the study team have taken to protect your privacy are described below.

Other information about the interview

Privacy – Every effort will be made to keep your personal information confidential. Your personal information (name, address, phone number) will be protected by the research clinic. Your name, or anything else that might identify you personally, will not be used in any publication of information about this study.

To help assure that we get the best understanding possible from your answers during the interview, the entire interview **will be audio-recorded**. After the interview is finished, the recording will be typed (called a transcript) by people who know how to do this. All identifying information will be removed from the transcript. Your name will not be included on the transcript. These recordings will be destroyed after all analysis is completed.

Your records may be reviewed by the following groups, involved with the study:

- Advarra Institutional Review Board
- [insert name of other site regulatory entities]
- Representatives of the HPTN
- The United States National Institutes of Health and its study monitors (including NICHD and its monitor, Westat)
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- ViiV Healthcare (the company that makes CAB)

If the study staff learns that you are at risk of harm, we will tell the proper authorities as we are required to do by the law.

New Information – You will be told any new information learned during this study that might affect your willingness to stay in the study. You will also be told when the results of the study may be available, and how to learn about them.

Alternatives to participating

You can talk to the study staff at any time about your child's experiences in the study, without taking part in the interview.

There are no costs to you for being interviewed

There will be no cost to you for participating in the in-depth interview.

«Compensation»

You will receive $XX for being interviewed. You will be paid _____ ***["after each visit," "annually," "bi-weekly," etc.]***

If you have any questions regarding your compensation for participation, please contact the study staff.

Whom to contact

If you have questions about the interview, please contact the study staff listed on page 1 of this document.

If you have a research-related injury, please contact: *[insert name of site contact]*

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact**:**

- By mail:
  Study Subject Adviser
  Advarra IRB
  6940 Columbia Gateway Drive, Suite 110
  Columbia, MD 21046
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00040790.

SIGNATURE PAGE
PARENT/GUARDIAN IN-DEPTH INTERVIEW INFORMED CONSENT FORM

If you decide to be interviewed, sign and date below. Before deciding whether to join this study, make sure you have read this form and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you if you decide to join. You can ask questions or request more information at any time. You do not give up any rights by signing and dating this form.

_____	_____
Name of Parent/Guardian (print)	Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date

12.11 APPENDIX XI: INFORMED CONSENT FOR SPECIMEN STORAGE AND FUTURE USE FOR PARENTS/LEGAL GUARDIANS AND PARTICIPANTS WHO REACH THE AGE OF MAJORITY AND ASSENT FOR ADOLESCENT PARTICIPANTS AGES 14 – AGE OF MAJORITY

Sponsor / Study Title:	**Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases (NIAID), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), US National Institutes of Health (NIH) / "HPTN 083-01: Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV among Adolescent Males – A sub-study of HPTN 083"**
Protocol Number:	**HPTN 083-01**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

If you are a parent or legal guardian of a child participating on this study, throughout this document "you(r)" = "your child."

INTRODUCTION
You have decided to join the study named above. As part of the study, you will have blood, urine, rectal swab, and oral pharyngeal swabs collected. After all the tests for this study have been done, there may be some samples left over. We call these left over samples. The study doctor would like to keep these left over samples and use them for other research in the future. This form gives information about use of left over samples. Please read it and ask any questions you may have. After we discuss the information with you, you will record your decisions on use of extra samples at the end of the form.

1. It is your decision whether or not to allow the left over samples to be used.
You are free to say yes or no, and to change your mind at any time. Your decision will not affect your participation in the study. If you say no, all left over samples will be destroyed.

2. **If you agree, his left over samples will be kept in a repository.**
A repository is a secure facility that is used to store samples. The HPTN repository is in the United States. If you agree to have left over samples stored, the samples will be kept in this repository. There is no limit on how long the samples will be kept.

3. Left over samples could be used for different types of research.
Left over samples may be used for research on HIV and other infections, including testing for the medicines used in this study and other anti-HIV medicines, the immune system, and other diseases. The

research may be done in the United States or in other locations. If you agree, the leftover samples could also be used for research that looks at your genes. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people get a disease while others do not. Your samples would only be used to look at genes related to how the body responds to the study drugs and the immune system. These tests would not include whole genome sequencing (WGS).

Any research done with the leftover samples must be reviewed and approved by the HPTN. The research must also be approved by an ethics committee. The role of an ethics committee is to review the research plan and protect the rights and well-being of the people whose samples will be used.

The research done with left over samples is not expected to give any information relevant to your health. Therefore, the results will not be given to the study staff or to you. The results also will not be placed in your study records.

4. There is little risk to you.

When left over samples are used for research, they are labeled with a code number only. To protect your privacy, no names are used. However, information such as age, gender, HIV status, and other health information may be linked to the samples. There may be some risks from tests of your genes. If others found out the results of these tests, they could treat you badly or unfairly. However, this is almost impossible because the results will not be given to the study staff or to you and will not be in his study records.

Any identifiers will be removed from the identifiable private information or biospecimens and, after removal, the information or biospecimens can be used for future research studies or distributed to another investigator for future research studies without additional informed consent.

5. There may be no benefit to you or your child.

You will not get direct benefit from storage of the samples. You or others in your community may benefit from this study later. The information gathered during this study may help to prevent the spread of HIV. This may be beneficial to you and your community.

6. You will not be paid for use of your child's samples.

There is no cost to you for use of your leftover samples. The samples will not be sold, and you will not be paid for use of the samples. It is possible that research done with the samples could lead to a new discovery or a new product. If this happens, there is no plan to share any money with you.

7. Information from research using extra samples may be reviewed by groups that oversee the research.

These groups include:

- Advarra Institutional Review Board
- [insert name of other site regulatory entities]
- Representatives of the HPTN
- The United States National Institutes of Health and its study monitors (including NICHD and its monitor, Westat)
- The United States Food and Drug Administration

- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- ViiV Healthcare (the company that makes CAB)

The people who do research with the leftover samples and the groups listed above are required to make efforts to keep information private and confidential.

The results of research done with the leftover samples may be presented publicly or published. However, no presentation or publication will use your name or identify you personally.

8. Whom to contact about this sub-study

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the study doctor at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact**:**

- By mail:
  Study Subject Adviser
  Advarra IRB
  6940 Columbia Gateway Drive, Suite 110
  Columbia, MD 21046
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00040790.

SPECIMEN STORAGE AND FUTURE USE INFORMED CONSENT

Before deciding about storage of laboratory specimens, make sure you have read this form and that all of your questions have been answered. You should feel that you understand your options and the possible risks and benefits before making your decision. You and your child do not give up any rights by signing and dating this form.

For your child's leftover samples, write your initials next to your choice *(choose only one).*

_____ I allow my child's leftover samples to be used for research on HIV and other infections, including testing for the study drugs and other anti-HIV medicines, the immune system, and other diseases. I also allow my child's samples to be used for tests of his genes.

_____ I allow my child's leftover samples to be used for research on HIV and other infections, including testing for the study drugs and other anti-HIV medicines, the immune system, and other diseases. I do **not** allow my child's samples to be used for tests of his genes.

_____ I do not allow my child's leftover samples to be used for any research.

_____
Participant's Name (print)

PARENT/GUARDIAN INFORMED CONSENT

_____
Relationship to participant

_____ _____
Name (print) Signature and Date

ASSENT FOR ADOLESCENT PARTICIPANTS AGES 14 YEARS – AGE OF MAJORITY
I have read this form. I have asked all the questions I have about the study and have gotten answers to my questions. I will be given a signed and dated copy of this form to keep.

For your leftover samples, write your initials next to your choice *(choose only one).*

_____ I allow my leftover samples to be used for research on HIV and other infections, including testing for the study drugs and other anti-HIV medicines, the immune system, and other diseases. I also allow my samples to be used for tests of my genes.

_____ I allow my leftover samples to be used for research on HIV and other infections, including testing for the study drugs and other anti-HIV medicines, the immune system, and other diseases. I do **not** allow my samples to be used for tests of my genes.

_____ I do not allow my leftover samples to be used for any research.

Participant's Name (print) Signature and Date

CONSENT FOR ADOLESCENT PARTICIPANTS WHO REACH THE AGE OF MAJORITY

I have read this form. I have asked all the questions I have about the study and have gotten answers to my questions. I will be given a signed and dated copy of this form to keep.

For your leftover samples, write your initials next to your choice *(choose only one)*.

_____ I allow my leftover samples to be used for research on HIV and other infections, including testing for the study drugs and other anti-HIV medicines, the immune system, and other diseases. I also allow my samples to be used for tests of my genes.

_____ I allow my leftover samples to be used for research on HIV and other infections, including testing for the study drugs and other anti-HIV medicines, the immune system, and other diseases. I do **not** allow my samples to be used for tests of my genes.

_____ I do not allow my leftover samples to be used for any research.

Participant's Name (print) Signature and Date

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

12.12 APPENDIX XII: INFORMATION SHEET AND ASSENT FOR SPECIMEN STORAGE AND FUTURE USE FOR PARTICIPANTS AGES 10-13

Sponsor / Study Title:	**Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases (NIAID), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), US National Institutes of Health (NIH) / "HPTN 083-01: Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV among Adolescent Males – A sub-study of HPTN 083"**
Protocol Number:	**HPTN 083-01**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

About this form

You have decided to join the study named above, with permission from your parent or guardian. As part of the study, we will collect lab samples for the study tests. After all the tests for this study have been done, there may be some of the samples left over. We call these leftover samples. The study doctor would like to keep these leftover samples and use them for other research in the future, if you and your parent or guardian agree.

- You can take as much time as you need to decide. Take the form home if you like.
- Ask the study team to explain any words or information that you do not understand. We will ask questions to see if we have explained it clearly.
- After you understand specimen storage, we will ask you to enter your decision and then sign and date this form.
- You will be offered a signed and dated copy to keep.
- It is your decision whether or not to allow the leftover samples to be used. You are free to say yes or no, and to change your mind at any time.
- If you say no, you can still join the main study and all your leftover samples will be destroyed at the end.

What will happen if you agree to store your leftover samples

If you agree, your leftover samples will be kept in a secure storage lab called a repository in [*Sites should insert the location*]. There is no limit on how long the samples will be kept. Leftover samples could be used for different types of research, mostly related to HIV, testing for anti-HIV medicines, the immune system, and other diseases. If you agree, the leftover samples could also be used for research that looks at your genes.

This research may be done in the United States or other countries. Any research done with the leftover samples must be reviewed and approved by the HPTN and an ethics committee to protect your rights and well-being. We won't give you the results of any tests done on your leftover samples because they won't be relevant to your health. Leftover samples are labeled with a code number only, not your name. Only your age, gender, HIV status, and other health information may be linked to the samples.

Storing your samples won't benefit you in any way, but the information we get from these future studies may benefit your community later. The samples will not be sold, and you will not be paid for use of the samples.

Have I explained the specimen storage clearly to you? Now you should ask the study staff any questions you have.

If you have more questions later, or have any problems or complaints about the study, please contact the study doctor. If you are seen at another clinic for anything, let them know that you're in this study and we can call them to share details.

ASSENT TO TAKE PART IN THIS STUDY FOR ADOLESCENT PARTICIPANTS AGES 10-13

For your leftover samples, write your initials next to your choice (choose only one).

_____ I allow my leftover samples to be used for research on HIV and other infections, including testing for the study drugs and other anti-HIV medicines, the immune system, and other diseases. I also allow my samples to be used for tests of my genes.

_____ I allow my leftover samples to be used for research on HIV and other infections, including testing for the study drugs and other anti-HIV medicines, the immune system, and other diseases. I do **not** allow my samples to be used for tests of my genes.

_____ I do not allow my leftover samples to be used for any research.

_____	_____
Participant's Name (print)	Signature and Date
_____	_____
Study Staff Conducting Assent Discussion (print)	Study Staff Signature and Date