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

DAIDS Document ID: 38655

A Study by the HIV Prevention Trials Network

Sponsored by:
Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases (NIAID), 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

DMPA	depot medroxyprogesterone acetate
DSMB	Data and Safety Monitoring Board
DTG	Dolutegravir
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
EE	Ethinyl estradiol
EFD	early fetal development
EFV	efavirenz
EQA	external quality assurance
FACTS	Follow-on African Consortium for Tenofovir Studies
FDA	(US) Food and Drug Administration
FEM-PrEP	Pre-exposure Prophylaxis Trial for HIV Prevention among African Women
FSH	Follicular stimulating hormone
FTC	emtricitabine
FTC-TP	emtricitabine triphosphate
GC	*Neisseria gonorrhoeae*
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
LH	luteinizing hormone
LNG	Levonorgestrel
LOC	(HPTN) Leadership and Operations Center
LLQ	Lower limit of quantification
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
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NI	non-inferiority
NIAID	(US) National Institute of Allergy and Infectious Diseases
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
PEP	Post-exposure prophylaxis
PI	package insert
Pgp	permeability glycoprotein
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
SAHPRA	South African Health Products Regulatory Authority
SC	Subcutaneous
SDMC	(HPTN) Statistics and Data Management Center
SHIV	simian human immunodeficiency virus
SMC	Study Monitoring Committee
SMS	Short message service
SOE	Schedule of Evaluations
SOC	standard of care
SOP	standard operating procedure
SSA	sub-Saharan Africa
SSP	Study Specific Procedures Manual
SRC	(HPTN) Scientific Review Committee
STI	sexually transmitted infection
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TCID	tissue culture infective dose
TDF	tenofovir disoproxil fumarate
TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®)	tenofovir/emtricitabine (trade name: TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®)®)
TFV	Tenofovir
TFV-DP	tenofovir diphosphate
TGW	transgender women
Tmax	time after drug administration when maximum drug concentration in serum is reached
TP	Triphosphate
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
YKP	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 female 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 34 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 TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®) for daily use for 48 weeks. Total study duration per participant will be approximately 21 months.

Study Sites:
Ward 21 CRS, Johannesburg, South Africa; Spilhaus CRS, Harare, Zimbabwe; MU-JHU Research Collaboration (MUJHU CARE LTD) CRS, Kampala, Uganda

Study Regimen:
Step 1 – oral cabotegravir (30mg tablet); Step 2 – injectable cabotegravir 3 mL (600 mg) intramuscular (IM) 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 female adolescents aged below 18 years.

Secondary Objectives:

- To examine adherence to and timeliness of injections over time among adolescent participants provided CAB LA and information regarding its safety and unknown efficacy.
- To examine patterns of sexual risk behavior over time among adolescent participants provided CAB LA and information regarding its safety and unknown efficacy.
- To evaluate the safety of CAB LA for up to 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. Youth are over-represented in the current HIV epidemic: in 2017, nearly 2000 of the 5000 new HIV infections which occur globally each day are in individuals aged 24 years or younger (one-third of these new HIV infections occur in youth 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]

Girls and young women between 15 and 30 years old have an extraordinarily high incidence, particularly in countries such as South Africa.[4-6] The most recent household survey confirms the feminization of the epidemic nationally in that country, with adolescent girls 15 to 19 years of age four times more likely to be infected than their male counterparts.[6] In recent HIV prevention trials, annual HIV incidence was 5-6% in South African young women, even in the context of counseling, condom provision and STI treatment.[7-9] HIV prevention and decreasing HIV-related deaths depend critically on reaching adolescents, engaging them in HIV prevention research, and ensuring access to HIV prevention products via regulatory approvals.

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

Tenofovir-based ARV 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.[10-13] Given the growing body of evidence about its effectiveness, including encouraging "real world" demonstration projects[14,15], 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[16,17].

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. In at least two clinical trials of women, oral PrEP did not show a decreased risk of HIV transmission and these results appeared to be related to poor adherence among study participants.[7,18] In the FEM-PrEP study, for example, only 12% of women had serum drug levels associated with good adherence throughout trial participation.[18] Similarly, the VOICE trial[7] failed to show efficacy of either oral PrEP or daily vaginal gel, largely attributable to very low rates of adherence among a cohort of young women. Trials of other short-acting prevention technologies have also been negatively impacted by low adherence among the youngest participants. The FACTS 001 licensure trial[18] for tenofovir gel that followed CAPRISA 004 recently reported no effect on HIV acquisition among a large sample of young

South African women, primarily because participants struggled to adhere to the prescribed regimen.[9] Furthermore, results from two recent randomized trials of the dapivirine vaginal ring, which showed modest efficacy overall, demonstrated consistently low adherence among women under the age of 21, which attenuated the overall protective effect of the intervention.[8,19]

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/caregivers, 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.[20,21] 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.[22,23] Just as increased choice in type and method of delivery of contraceptive methods has increased acceptability and effectiveness for contraception[24,25], we believe that expanded choices for HIV prevention will similarly increase utilization, satisfaction, and effectiveness.

A recent discrete choice experiment conducted in Kenya and South Africa[26], which was designed to assess preferences for prevention technologies among young women ages 18 to 30 years, found that an injection every 2 to 3 months was preferred over daily oral pills, and that there was desire for multi-purpose prevention technologies combining contraception with prevention of HIV. 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[27].

Adult safety data on long-acting cabotegravir (CAB LA) will need to be expanded to adolescents in order to license the product for adolescents 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 4500 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.

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.[28] 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.[29,30] 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 unblended, single arm trial is most developmentally-appropriate for youth, 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. The team feels it is unreasonable to request this type of commitment and burden from vulnerable youth (and their parents/caregivers), 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.[31,32,33]

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) V8.0, Effective Dated 17 December 2018, 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 bimonthly parenteral dosing using a nanosuspension 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 of 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.[34] 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 ($PA\text{-}IC_{90}$) value. None of 59 challenges resulted in infection when plasma levels were greater than 3 times the $PA\text{-}IC_{90}$, compared with 1 out of 22 challenges resulting in infection when plasma levels were between one to three times the $PA\text{-}IC_{90}$, and 11 out of 43 challenges resulting in infection when plasma levels were less than 1 times the $PA\text{-}IC_{90}$. Twelve out of 26 challenges resulted in infection in control animals; rectal tissue levels of CAB were approximately 20% of plasma levels.[35]

1.2.2 Non-human Primate Studies Relevant to Vaginal Exposure

CAB prevented SHIV infection in two non- human primate models. In one study which used medroxyprogesterone acetate (Depo-Provera) to increase the risk of infection,[35] CAB LA 50 mg/kg offered 90% protection from high-dose exposure to SHIV162P3. In a second study using the same SHIV with a low-dose challenge model, animals were provided complete protection by CAB.[34,35] To evaluate concentrations at the site of virus entry, CAB concentrations were measured in vaginal and rectal secretions. CAB was consistently detected in both vaginal and rectal secretions throughout the 4 weeks of the study. At first dose, peak CAB concentrations in vaginal secretions (median, 911 ng/mL; range, 427 to 1,877) were similar to those seen in rectal secretions (median, 2,215 ng/mL; range, 647 to 2,680) (P = 0.240), albeit at concentrations significantly lower than in plasma (P = 0.002) (Figure 1. CAB LA PK Profiles following Q8W Dosing in Males and Females (HPTN077, Cohort 2)) The area under the curve values over 28 days ($AUC_{0–28d}$) in vaginal secretions were compared to the values with those seen in plasma or rectal secretions. The $AUC_{0–28d}$ values in vaginal secretions (median, 11,511 ng × day/mL; range, 3,956 to 14,011) were lower than those in rectal secretions (median, 26,717 ng × day/mL; range, 10,120 to 39,989), although the difference was not statistically significant. In contrast, $AUC_{0–28d}$ values in vaginal secretions were lower than those in plasma (median, 70,333 ng × day/mL; range, 40,265 to 169,341) (P = 0.002) (Figure 1). Despite the lower CAB concentrations in vaginal secretions, concentrations remained above the PA-IC90 throughout the entire 4-week period after each dose (Figure 1). In summary, CAB partitioning in vaginal, cervical, and rectal tissues is within the range seen in humans. It should be noted that similar doses of CAB appeared to result in higher concentrations of drug in male animals than females.[34,35] In addition, the concentration of SHIV in rectal tissues was greater than in cervical tissue.[34,35] In summary, these preclinical non-human primate studies suggest that CAB can be expected to protect women from HIV. However, because of differences in men and women and human and macaques, careful consideration of the most appropriate dose and frequency of dosing is essential (see below).

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 $AUC_{0\text{-}24}$ 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 C_{max} 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.[36,37] In LATTE, the Phase 2b study in HIV-infected, ART-naïve adult participants,[38] 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 4.2 μg/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 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

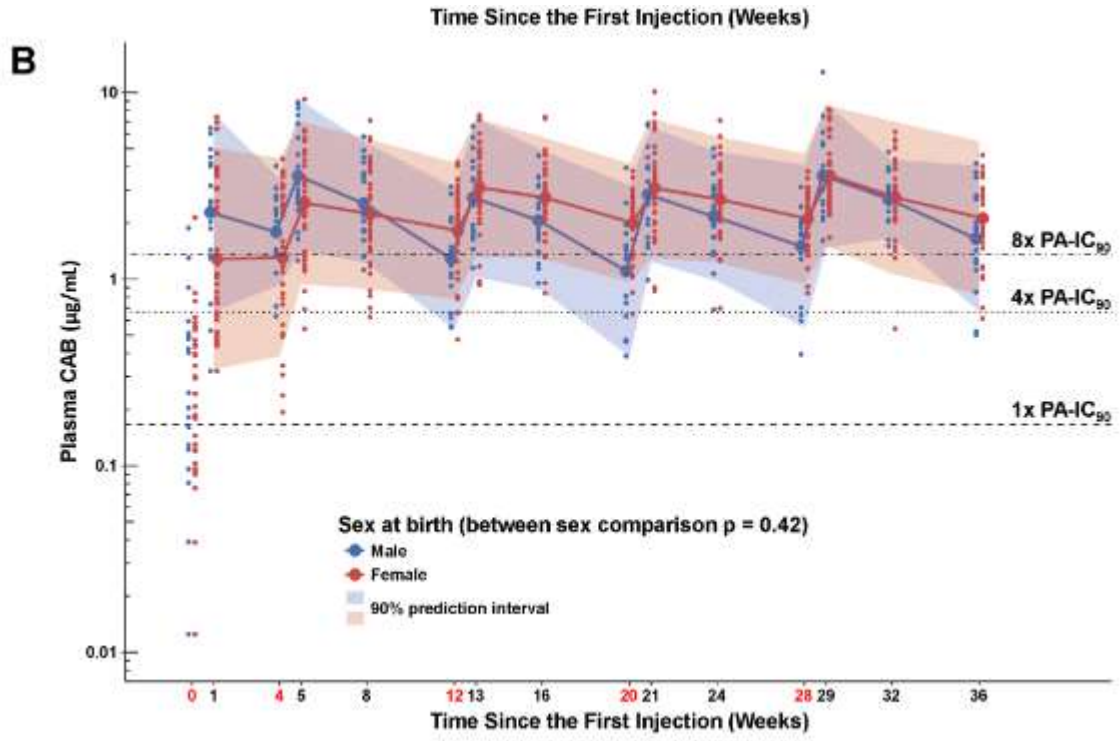
Through October 2018, approximately 4236 adult participants have been exposed to at least one dose of CAB (oral and/or LA) across 18 completed or ongoing Phase 1, 2 & 3 clinical trials (see Table 1).

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 (W), followed by CAB (or PBO) 800mg IM at W5, 17, and 29 (Cohort 1) or 600 mg IM at W5, 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. Pharmacokinetics supported the development of CAB for HIV prevention using 600 mg IM every 8 weeks with a 4-week loading dose for all sexes.

In HPTN 077, overall 65% of the study participants were female. Median BMI was 28 kg/m^2 in female participants and 25 kg/m^2 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 C_{max} after the first injection, but significantly lower trough concentrations than female participants after all three injections. Trough CAB concentrations were below 4X PA-IC90 in 72%, 35%, and 32% of male participants at weeks 17, 29, and 41, respectively. In contrast, trough CAB concentrations in female participants were largely at goal throughout the trial, with 24%, 5% and 0% of female participants having trough concentrations below 4X PA-IC90 at weeks 17, 29, and 41. In Cohort 2 (CAB LA 600mg IM q 8 weeks), male participants achieved significantly higher CAB C_{max}, $AUC_{0\text{-}tau}$, and C_{trough} 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 concentrations < 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 concentrations below 4X PA-IC90 after injections 1, 2, 3, 4, and 5, respectively.

Figure 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[39], differences were observed in the median time to undetectable cabotegravir levels 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 detected in plasma in 22% of men and 63% of women at 60 weeks and 13% of men and 44% of women at 76 weeks post the last injection).

The observed pharmacokinetics 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.[40] Although the medium waning PK tail for women participating in HTPN 077 was 66.3 weeks, the HPTN 084-01 team has determined that participants in this trial should receive TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®) for 48 weeks, in order to mimic the parent trial, HPTN 084.

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

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

A population PK model (n=1647) that included data from HPTN 077 (n=134, 89 females, 45 males) and 15 other studies was used to predict exposures following the proposed CAB LA Q8W regimen in adolescents. Gender and BMI are significant covariates affecting the absorption rate following IM administration and were retained in the model to extrapolate to smaller adolescent females expected to enroll in HPTN 084-01. Model predicted concentrations in adolescent females (simulated with median weight and BMI of 59 kg and 22 kg/m2, respectively) to enroll in HPTN 084-01 are similar to adult females in HPTN 077 and below oral dosing, and therefore are expected to be safe in this population (Table 1). Greater than >95% are expected to achieve trough concentrations > 4x PA-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. Predicted CAB Parameters following Injection 5 of the CAB LA 600mg IM Q8W Regimen in Female Adolescents compared with Predicted and Observed Data in Female Adults in HPTN 077

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

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

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

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

Dose adjustments are not anticipated for this protocol. However, a pre-specified weight-based analysis from Cohort 1 of IMPAACT 2017 is scheduled to compare dosing safety above and below 50kg (110 lbs.). The HPTN 084-01 protocol team will review these findings when data is available to determine whether the dose of the oral and injectable CAB study products must be revised. In that case, the new doses will be specified in a letter of amendment.

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

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

1.8 Pregnancy and Pregnancy Prevention with CAB Use

There is no requirement to exclude women of reproductive potential from clinical trials of CAB based on reproductive toxicity findings available to date. Given the limitations of the data and because animal studies are not always predictive of the human situation, women of reproductive potential are required to adopt highly reliable means of contraception during participation and throughout long term follow up phases of studies following exposure to CAB LA.

In vitro and clinical data suggest that CAB is unlikely to cause or be subject to clinically significant drug interactions with the components of hormonal contraceptives. In a clinical drug-drug interaction study in healthy female volunteers, oral CAB had no significant impact on the pharmacokinetics of either levonorgestrel (LNG) or ethinyl estradiol (EE) containing combination oral contraceptive.[42] There were no apparent differences in pharmacodynamic assessments of follicular stimulating hormone (FSH), luteinizing hormone (LH) or progesterone and concomitant administration of CAB and LNG/EE was well-tolerated in the study. Because the pathways of metabolism and excretion are comparable between the oral and injectable formulation of CAB, it is expected that the results of this drug interaction study can be extrapolated to long-acting CAB. In clinical studies, combination estrogen and progestin or progestin-only hormonal contraceptives available in oral, injectable or implant formulations may be used concurrently with CAB. However, clinical data are limited evaluating the use of injectable or

implantable forms of hormonal contraceptives and CAB to date. Progestin-only products, such as injectable NET-EN and DMPA, and etonogestrel implants are commonly prescribed, specifically in SSA. Although the metabolic pathways for such products are complex and vary somewhat from ethinyl estradiol and levonorgestrel, no pharmacokinetic drug-drug interaction between CAB and progestin-only contraceptives is anticipated.[43] HPTN 077 did not find any evidence that use of hormonal contraceptives altered the CAB LA concentration profile during or after injections in either univariate or multivariate analysis.[43]

1.8.1 Dolutegravir and Pregnancy

Dolutegravir (DTG) is an integrase inhibitor in the same class of pharmaceuticals as CAB. Thus far, limited safety or efficacy data for DTG in pregnancy in humans have been published or presented. In May 2018, WHO and several other regulatory agencies released advisories regarding the safety of dolutegravir in early pregnancy.[44]

This was based on information received from the Botswana NICHD-funded Tsepamo Birth Outcomes Surveillance Study, the largest body of data related to birth outcomes following the use of DTG in pregnancy. This study was designed to evaluate adverse birth outcomes by maternal HIV status and ART regimen, and to determine whether there is an increased risk of neural tube defects (NTDs) among infants exposed to efavirenz (EFV) from conception. Botswana's HIV program moved to universal ART with DTG/TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®) as first line treatment for patients starting ART (including pregnant women) in May of 2016 (women already on other regimens were not switched to DTG). The previous first-line regimen was EFV/TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®). Almost all women on DTG-based and EFV-based ART took these drugs in combination with TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®). More than 95% of women in Botswana deliver in a hospital, and obstetric records were available for >99% of women. The Tsepamo surveillance study is conducted at 8 of the largest public maternity wards across Botswana (representing ~45% of the total births in the country). Research assistants abstract ART data from the maternity card for all consecutive in-hospital deliveries (both HIV-infected and HIV-uninfected women). Each newborn, whether stillborn or live-born, undergoes a systematic infant surface examination that is completed by trained nurse midwives. Reports and photographs (where available) of major abnormalities are reviewed by an experienced medical geneticist who is blinded to exposure information. During a preliminary unscheduled analysis of the Tsepamo data collected between August 15, 2014 and May 1, 2018, which was undertaken at the request of colleagues who were preparing for a WHO meeting, the investigators found 4 cases of neural tube defects in babies of 426 women who became pregnant while taking DTG (prevalence 0.9%). This rate compares to a 0.1% risk of neural tube defects in infants born to women taking other antiretroviral medicines at the time of conception. Data is expected on the pregnancy outcomes of an additional 600 women in the Tsepamo study who were taking DTG around the time of conception. A follow-up analysis of 1729 pregnant women in the same observational cohort in Botswana found that there was no difference in the risk for any adverse birth outcome among children born to women on dolutegravir as compared to those on efavirenz (33.2% vs 35% for DTG and EFV, respectively; aRR 0.95, 95% CI 0.88-1.03). There was also no difference in the occurrence of any severe birth outcome (10.7% for women on DTG versus 11.3% for women on EFV; aRR 0.94, 95% CI 0.81-1.11).[45] More data are also expected to be forthcoming from other studies of DTG in pregnancy. These data will provide more information on the safety of DTG for women of childbearing age.

Cabotegravir is not dolutegravir. While these medications share a common molecular backbone, and have a similar mechanism of activity, they are separate chemical compounds and have differences in antiviral activity, pharmacokinetics, metabolism and drug-drug interactions. It is not known if the safety signal identified with dolutegravir will be observed with cabotegravir, in keeping with a class effect. Cabotegravir was evaluated in a complete package of reproductive toxicology studies, including embryo-fetal development studies, and no safety findings suggestive of teratogenesis or neural tube defects were identified in the December 2017 version of the Investigator's Brochure. Nevertheless, given limited experience with use of cabotegravir in pregnancy, women of reproductive potential are required to adopt highly reliable means of contraception during participation and throughout long-term follow-up phases of studies using CAB LA.

1.9 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.

1.10 Weight gain

There is emerging evidence from randomized trials that the use of integrate inhibitors could lead to significant increases in body weight.[46] 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).[47]

1.11 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 female adolescents aged below 18 years.

2.2 Secondary Objectives

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

2.3 To evaluate the pharmacokinetics of CAB LA. Study Design and Overview

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

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. 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 TDF-FTC 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 sites) to explore issues of acceptability and preference for oral tablets and/or injections. Additionally, up to 10 parents/guardians of participants 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 adolescents.

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 87 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, through community-based venues by 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 adolescents.

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

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

3.1.1 Assigned female at birth;

3.1.2 At enrollment, below 18 years of age;*

3.1.3 At enrollment, body weight ≥ 50 kg (110 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, local laws and regulations, 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, local laws and regulations, 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 (oral, anal or vaginal) 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/mm^3,
- Hemoglobin ≥ 11g/dL,
- Calculated creatinine clearance ≥ 60 mL/minute using the modified Schwartz equation,
- Alanine aminotransferase (ALT) < 2.0 times the upper limit of normal (ULN) (≤ grade 1) 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 Must have a negative beta human chorionic gonadotropin (βHCG) pregnancy test (sensitivity of ≤ 25 mIU/mL) performed (and results known) on the same day as Enrollment and before initiating study product;

3.1.9 Must agree to use a reliable form of long acting contraception, during the trial and for 48 weeks after stopping the long acting injectable, or 30 days after stopping oral study product, from the list below:

- Intrauterine device (IUD) or intrauterine system (IUS) that meets <1% failure rate as stated in the product label
- Hormone-based contraceptive that meets <1% failure rate when used consistently and correctly as stated in the product label (implants or injectables only; this excludes combined oral contraception).

*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

Female 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 Currently receiving PrEP from a non-study source;

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

3.2.4 Exclusively had sex with biological females in lifetime;

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

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

3.2.6 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;

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

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

3.2.9 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);

3.2.10 Known history of clinically significant bleeding;

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 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;

3.2.14 Pregnant or currently breastfeeding at the time of screening or intends to become pregnant and/or breastfeed while on study.

3.3 Recruitment Process

The study will be targeted towards at-risk, sexually active adolescent populations of female adolescents in SSA. 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 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.
- 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 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, US government or regulatory authorities (including Office for Human Research Protections [OHRP] and the FDA), site IRBs/ECs and other regulatory bodies, 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 loading dose)
- 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, the +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 (TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®)) for daily use for 48 weeks.

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 (TDF) 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 30ºC (86ºF), 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 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.

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 site. Contraceptive products will be provided 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 destroyed 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 VI.

4.4 Concomitant, Prohibited, and Precautionary Medications

In order to avoid AEs caused by drug interactions, whenever a concomitant medication is taken, site staff must 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 precautionary or prohibited drug listed in the Truvada PI or cabotegravir IB, it is required that the HPTN 084 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 (as of the time this section of the SSP was written) pare listed below.

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.
    - Immunomodulators
    - 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, Descory).
  - lamivudine (e.g. Combivir, Dutrebis, Epivir, Epivir-HBV, Epivir A/F, Epzicom, Triumeq, or Trizivir)
  - adefovir (e.g. HEPSERA®)
  - tenofovir alafenamide (e.g. Vemlidy)
  - didanosine (e.g. Videx EC)
  - atazanavir (e.g. Reyataz, Evotaz (atazanari/cobicistat))
  - ledipasvir/sofosbuvir (e.g. HARVONI®)
  - darunavir (e.g. Prezista)
  - lopinavir/ritonavir (e.g. Kaletra)
  - orlistat (e.g. Alli, Xenical)

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

  - 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.

  - 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, including rifampin, 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, II, III and Appendix IV (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/or assent (as appropriate) will be obtained before any study procedures are initiated. Both clinical and laboratory evaluations will occur at this visit (see Appendix 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 referred for appropriate care, as necessary.

Contraception counselling and provision must be initiated before or at the week 2 visit in Step 1 so that the method is in place prior to transition to Step 2.

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 may be permitted with prior 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 (see Appendix 1).

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, second instrumented HIV test, 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 form.

Participants will meet with study staff to receive education and information about the 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. Measures have been previously used either in adolescent biomedical prevention trials or in the Phase III adult trials of cabotegravir.

A pregnancy test must be conducted on the same day that study product is dispensed, and the test must be confirmed to be negative prior to dispensing.

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 1). Adherence counseling will be provided at both Weeks 2 and 4 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 084-01cmc@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

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 VI, Toxicity Management for detailed instruction on participant management. All AEs are to be followed until the 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;
- Not on effective long-term contraception at the Week 4 visit;
- Any suspected or confirmed pregnancy (see SSP and Section 5.16);
- Specific AEs per Table 5.1**Error! Reference source not found.**;
- At substantial risk of HIV infection and/or qualifies for oral PrEP by local guidelines;
- Any HIV reactive/positive test (see SSP and Section 5.12).

If any of the above conditions occur, investigators should notify the HPTN 084-01 CMC at 084-01cmc@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. Participants should continue contraception for at least 30 days following the last dose of oral CAB.

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 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 VI, 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 both the injection visits and the safety visits as well as CASI administration for either behavioral or acceptability assessments (see Appendix II. Schedule of Evaluations for Injection– 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.

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

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

5.8 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.

Increase in Risk for HIV Infection

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

Post-exposure Prophylaxis (PEP)

At any time during study participation, any participant who express 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 084-01 CMC at 084-01cmc@hptn.org.

5.8.2 Adherence Counseling and Monitoring

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

5.9 Injection Visit Windows

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

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

5.10 Procedures for Injectable Dosing

Refer to Appendix VI, 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 / 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 outlined in the SSP Manual.

5.11.2 After Study Enrollment

Frequent testing for HIV acquisition during the study period (at all study visits in Step 1 and 3, and at all injection visits in Step 2) 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 II. 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 instructions 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 Appendices II and III quarterly for 48 weeks. 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.

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 III quarterly through study exit. 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 offered HBV vaccination, ideally starting 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 scheduled visits while on Step 2 (see Appendix II). Incident HCV infection during follow-up will not mandate discontinuation of study product absent other requirements per Appendix VI - Toxicity Management.

5.14 Contraception

Contraception Requirements

Because oral CAB and CAB LA are investigational agents, women may not enroll if they are pregnant or desire to become pregnant. Receipt of study product by participants requires use of a reliable form of long acting contraception during the trial and for 48 weeks after stopping the long acting injectable, or 30 days after stopping oral study product. Study approved methods of contraception are outlined in Section 3.1 and are as follows:

- Intrauterine device (IUD) or intrauterine system (IUS) that meets <1% failure rate as stated in the product label
- Hormone-based contraceptive that meets <1% failure rate when used consistently and correctly as stated in the product label (implants or injectables only; this excludes combined oral contraception).

All participants will be actively encouraged to also use condoms for prevention of HIV and other STIs.

Contraceptive Service Provision

Study staff will provide contraceptive services to enrolled participants throughout the duration of study participation. Participants must be using one of the study-approved contraceptive methods by the Week 2 visit in Step 1 to transition to Step 2.

Verification of Contraceptive Use

Study staff should confirm adequate contraception at each visit. Where adequate contraception cannot be confirmed, and in the opinion of the investigator, early pregnancy cannot be excluded, then the investigator should contact the HPTN 084-01 CMC at 084-01cmc@hptn.org for further guidance.

All participants who are not currently pregnant and decide to discontinue long acting contraception for any reason will immediately discontinue study product (oral CAB or CAB LA injections). In all such cases, contact the HPTN 084-01 CMC at 084-01cmc@hptn.org for further guidance.

5.15 Pregnancy

Participants are assessed for pregnancy throughout Steps 1, 2 and 3 as specified in the schedules of evaluation. Participants with a positive pregnancy test during a study visit or as reported by the

participant between study visits must be reported to the CMC within seven days of site awareness. Administration of study product (oral CAB or CAB LA injections) will be held immediately and open label TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®) offered. Confirmation of pregnancy at a subsequent visit at least 4 weeks after the initial pregnancy test is required.

All participants who are confirmed pregnant must be referred for an Ultrasound and evaluation by an obstetric specialist at about 12-14 weeks gestational age, for other testing, counseling, and management. Further biochemical blood tests may be done as indicated. The preceding services will be covered by the study. All findings and pregnancy outcomes will be collected and reported. The site IoR or designee will refer pregnant participants to all applicable pregnancy-related services **and will provide a letter to obstetric services detailing participation in the trial**; however, sites will not be responsible for paying for pregnancy-related care. The site IoR or designee will counsel any participants who become pregnant regarding possible risks to the fetus according to site-specific SOPs.

Confirmed Pregnancies in Step 1

These participants will permanently discontinue oral CAB and will not transition to Step 2. They will skip to Step 3, be provided open label TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®) as PrEP and be reviewed every 12 weeks until delivery. If pregnancy is not confirmed on subsequent testing, Step 1 participants will exit the study. Site staff will refer to their SOP for detailed management.

Confirmed Pregnancies in Steps 2 and 3

Participants in Step 2 with confirmed pregnancy will permanently discontinue CAB LA injections and transition to Step 3 to be followed by the study every 12 weeks for 48 weeks after the last CAB LA injection or delivery whichever comes last. Open label TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®)will be provided for 48 weeks after the last CAB injection. Site staff will refer to their SOP for detailed management.

5.16 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.

5.17 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.

5.18 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. 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, other regulatory bodies or ViiV terminate the study prior to its planned end date. Study staff will record the reason(s) for all withdrawals in participants' study records.

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 injectable suspension 3 mL (600 mg) intramuscular (IM) injectable suspension. 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.

6.2.1 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).[34] 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.[34]

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.32 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 in the injection phase discontinued study participation 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, 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.

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

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

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 (<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) of 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 for 48 weeks.

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 endpoints: 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 48 weeks following final injection
- Proportion of injection visits that occurred "on-time"
- Change from enrollment of self-reported sexual behavior (number of sexual partners, increased episodes of unprotected vaginal or anal intercourse) during the study period

7.3 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 2. Width of 95% confidence interval for estimated proportion as a function of the true proportion, assuming a sample size of 50. shows the precision (confidence interval width) that will be obtained for each endpoint with a sample size of 50.

Table 2. 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 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).

7.6.2 Primary Analyses

All participants who receive at least one injection will contribute to the primary analyses. The safety and tolerability will be analyzed in aggregate. 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).

7.6.3 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. Secondary safety analyses will include the same definition applied over the oral phase only (week 0 to week 4) and the aggregate oral+injectable+follow-up period.

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.

7.6.4 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.

7.6.5 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 separately from those that are treatment emergent during oral dosing and also for those that are treatment emergent across the entire treatment phase of the study (combining both LA and oral 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.

7.6.6 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.

7.6.7 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.

7.6.8 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.

7.7 Secondary Analyses

7.7.1 Sexual Risk Behaviors

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

7.7.2 Plasma Drug-Level Concentrations

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

In addition to concentration summaries, parameters may be derived by non-compartmental methods. Details of the analysis will be described in the study Reporting and Analysis Plan (RAP), separately.

7.8 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 IV— and any subsequent modifications — will be reviewed and approved by the HPTN Scientific Review Committee (SRC) and DAIDS Prevention Science Review Committee (PSRC) with respect to scientific content and compliance with applicable research and human subjects regulations.

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 other responsibilities. 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; the government or 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 local 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, government or regulatory authorities (including the OHRP and US FDA), site IRBs/ECs or if appropriate, the SAHPRA, or ViiV. This would be done primarily due to safety concerns for the participants 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 IV 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)
- Pregnancy testing (see below)
- HBV and HCV testing to include HBsAg, HBsAb, HBcAb (total), 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)
- Vaginal swabs OR urine for GC/CT nucleic acid amplification testing (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.

Pregnancy testing
All women will have a βHCG test for pregnancy (sensitivity of ≤ 25 mIU/mL) at the majority of visits. Pregnancy testing may be performed in the clinic or the laboratory at all visits where this testing is indicated. Testing may be performed using a urine, plasma, or serum sample. Continued pregnancy testing is not required following a confirmed (done in 4 weeks after initial positive) positive test result.

Each study site will adhere to standards of good laboratory practice, 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 after until discard approval is given by DIADS, the 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 retrospectively at the end of 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 pre-dose 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

HIV diagnostic tests will be listed on the site Protocol Analyte List (PAL) and will be subject to review and approval by DAIDS and the HPTN LC. 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. 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, and urinalysis testing as indicated in each relevant SOE. Non-US laboratories performing these tests will be monitored by Patient Safety Monitoring and International Laboratory Evaluation (pSMILE) and must demonstrate successful participation in the relevant EQA programs.

9.8 Quality Assurance for CD4 Cell Count Testing

Local laboratories may also perform CD4 cell count testing as indicated in Appendix II. Non-US laboratories performing these tests will be monitored by the DAIDS Immunology Quality Assurance (IQA) program and UKNEQAS program and must demonstrate successful participation in these programs.

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. Non-US sites may use local laboratories for this testing. Non-US laboratories performing these tests will be monitored by the DAIDS Virology Quality Assurance (VQA) program and must demonstrate successful participation in this program.

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). 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 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 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 HPTN SDMC 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; site IRBs/ECs; other local or international regulatory authorities (including the OHRP and US FDA); or, if appropriate, 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. 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.

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

1. World Health Organization. Department of Maternal Newborn Child and Adolescent Health. *Health for the world's adolescents: A second chance in the second decade. Summary.* Geneva, Switzerland: WHO, Department of Maternal, Newborn, Child and Adolescent Health;2014.
2. UNAIDS. *Global HIV & AIDS statistics — 2018 fact sheet.* 2018.
3. UNAIDS. *The Gap Report – July 2014* Geneva: Switzerland.2014.
4. Cowan F, Pettifor A. HIV in adolescents in sub-Saharan Africa. *Current Opinion in HIV and AIDS.* 2009;4(4):288-293.
5. Abdool Karim Q, Kharsany ABM, Leask K, et al. Prevalence of HIV, HSV-2 and pregnancy among high school students in rural KwaZulu-Natal, South Africa: a bio-behavioural cross-sectional survey. *Sexually Transmitted Infections.* 2014;90(8):620-626.
6. Shisana O, Rehle T, Simbayi LC, al. e. *South African National HIV Prevalence, Incidence and Behaviour Survey, 2012.* . Cape Town, South Africa. 2014.
7. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-Based Preexposure Prophylaxis for HIV Infection Among African Women. *Obstetrical & Gynecological Survey.* 2015;70(7):444-446.
8. Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women. *New England Journal of Medicine.* 2016;375(22):2121-2132.
9. Rees H, S. D-M, Baron D, et al. Facts 001 Phase III Trial of Pericoital Tenofovir 1% Gel for HIV Prevention in Women. . Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI). February 23-26 2015., 2015; Seattle, WA, USA. .
10. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med.* 2012;367(5):399-410.
11. Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *The Lancet.* 2013;381(9883):2083-2090.
12. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med.* 2010;363(27):2587-2599.
13. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana. *New England Journal of Medicine.* 2012;367(5):423-434.
14. Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *The Lancet Infectious Diseases.* 2014;14(9):820-829.
15. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *The Lancet.* 2016;387(10013):53-60.
16. WHO. *Guideline on when to start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV*. 2015.
17. U.S. Public Health Service. *Preexposure prophylaxis for the prevention of HIV infection in the United States - 2017 update. A clinical practice guideline.* . 2018.
18. Van Damme L, Corneli A, Ahmed K, et al. Preexposure Prophylaxis for HIV Infection among African Women. *New England Journal of Medicine.* 2012;367(5):411-422.
19. Nel A, Haazen W, Nuttall J, Romano J, Rosenberg Z, van Niekerk N. A safety and pharmacokinetic trial assessing delivery of dapivirine from a vaginal ring in healthy women. *AIDS.* 2014;28(10):1479-1487.

20. Murphy DA, Wilson CM, Durako SJ, Muenz LR, Belzer M. Antiretroviral medication adherence among the REACH HIV-infected adolescent cohort in the USA. *AIDS Care.* 2001;13(1):27-40.
21. LaGreca AM, Schuman W. Adherence to prescribed medical regimens. . In: Roberts MC, ed. *Handbook of Pediatric Psychology.* 2nd ed. New York, NY, USA.: Guilford Press.; 1995.
22. Rome E. Use of long-acting reversible contraceptives to reduce the rate of teen pregnancy. *Cleveland Clinic Journal of Medicine.* 2015;82(suppl 1):S8-S12.
23. Rosenberg MJ, Waugh MS, Meehan TE. Use and misuse of oral contraceptives: Risk indicators for poor pill taking and discontinuation. *Contraception.* 1995;51(5):283-288.
24. Bureau PR. *2019 Family Planning Data Sheet.* . Washington, DC, USA.2019.
25. Reece M, Herbenick D, Schick V, Sanders SA, Dodge B, Fortenberry JD. Condom Use Rates in a National Probability Sample of Males and Females Ages 14 to 94 in the United States. *The Journal of Sexual Medicine.* 2010;7:266-276.
26. Minnis AM, Browne EN, Boeri M, et al. Young Women's Stated Preferences for Biomedical HIV Prevention: Results of a Discrete Choice Experiment in Kenya and South Africa. *J Acquir Immune Defic Syndr.* 2019;80(4):394-403.
27. Spreen WR, Margolis DA, Pottage JC. Long-acting injectable antiretrovirals for HIV treatment and prevention. *Current Opinion in HIV and AIDS.* 2013;8(6):565-571.
28. Hume M, Lewis LL, Nelson RM. Meeting the goal of concurrent adolescent and adult licensure of HIV prevention and treatment strategies. *Journal of Medical Ethics.* 2017;43(12):857-860.
29. Bekker LG, Slack C, Lee S, Shah S, Kapogiannis B. Ethical issues in adolescent HIV research in resource-limited countries. *J Acquir Immune Defic Syndr.* 2014;65 Suppl 1:S24-28.
30. Shah SK, Allison SM, Kapogiannis BG, Black R, Dawson L, Erbelding E. Advancing independent adolescent consent for participation in HIV prevention research. *J Med Ethics.* 2018;44(7):431-433.
31. Glidden DV, Amico KR, Liu AY, et al. Symptoms, Side Effects and Adherence in the iPrEx Open-Label Extension. *Clin Infect Dis.* 2016;62(9):1172-1177.
32. Spinner CD, Boesecke C, Zink A, et al. HIV pre-exposure prophylaxis (PrEP): a review of current knowledge of oral systemic HIV PrEP in humans. *Infection.* 2016;44(2):151-158.
33. Mujugira A, Baeten J, Kidoguchi L, et al. High levels of viral suppression among East African HIV-infected women and men in serodiscordant partnerships initiating antiretroviral therapy with high CD4 counts and during pregnancy. *AIDS Res Hum Retroviruses.* 2018;34(2):140-147.
34. Radzio J, Spreen W, Yueh YL, et al. The long-acting integrase inhibitor GSK744 protects macaques from repeated intravaginal SHIV challenge. *Science Translational Medicine.* 2015;7(270):270ra275-270ra275.
35. Andrews CD, Spreen WR, Mohri H, et al. Long-Acting Integrase Inhibitor Protects Macaques from Intrarectal Simian/Human Immunodeficiency Virus. *Science.* 2014;343(6175):1151-1154.
36. Min S, DeJesus E, McCurdy L, et al. Pharmacokinetics (PK) and safety in healthy and HIV-infected subjects and short-term antiviral efficacy of S/GSK 1265744, a next generation once daily HIV integrase inhibitor [Abstract no. H-1228]. Paper presented at: 9th Interscience Conference on Antimicrobial Agents and Chemotherapy 2009; San Francisco, CA.
37. Spreen W, Min S, Ford SL, et al. Pharmacokinetics, safety, and monotherapy antiviral activity of GSK1265744, an HIV integrase strand transfer inhibitor. *HIV clinical trials.* 2013;14(5):192-203.
38. Margolis D, Brinson C, Eron J, et al. 744 and Rilpivirine as Two-Drug Oral Maintenance Therapy: LAI116482 (LATTE) Week 48 Results. Abstract 91LB. Paper presented at: 21st Conference on Retrovirus and Opportunistic Infections 2014; Boston, MA.
39. Landovitz RJ, Eron JJ, Grinsztein G, al. e. Tail-phase safety, tolerability and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected individuals: HPTN 077 final results. .

Paper presented at: HIV Research for Prevention (HIV R4P). October 21-25 2018., 2018; Madrid, Spain.
40. Landovitz RJ, Li S, Grinsztejn B, et al. Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial. *PLoS Med.* 2018;15(11):e1002690.
41. Spreen W, Ford SL, Chen S, et al. GSK1265744 pharmacokinetics in plasma and tissue after single-dose long-acting injectable administration in healthy subjects. *Journal of acquired immune deficiency syndromes (1999).* 2014;67(5):481-486.
42. Trezza C, Ford SL, Gould E, et al. Lack of effect of oral cabotegravir on the pharmacokinetics of a levonorgestrel/ethinyl oestradiol-containing oral contraceptive in healthy adult women. *British Journal of Clinical Pharmacology.* 2017;83(7):1499-1505.
43. Blair CS, Li S, Chau G, et al. Hormonal Contraceptives Do Not Alter Cabotegravir PK in HIV Uninfected Women: HPTN 077. Conference on Retroviruses and Opportunistic Infections (CROI); 2019; Seattle, WA, USA.
44. EMA. New study suggests risk of birth defects in babies born to women on HIV medicine dolutegravir. 2018.
45. Zash R, Jacobson DL, Diseko M, et al. Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study. *Lancet Glob Health.* 2018;6(7):e804-e810.
46. Hill A, Waters L, Pozniak A. Are new antiretroviral treatments increasing the risks of clinical obesity? *J Virus Erad.* 2019;5(1):41-43.
47. Landovitz RJ, Zangeneh SZ, Chau G, et al. Cabotegravir is Not Associated with Weight Gain in HIV-uninfected Individuals in HPTN 077. *Clin Infect Dis.* 2019.

12.0 APPENDICES I - X

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		X		
HIV prevention counseling	X	X	X	X
Offer condoms	X	X	X	X
Behavioral/Acceptability Assessment (CASI)		X		X
CLINICAL EVALUATIONS & PROCEDURES				
Dispense study product (enough for 5 weeks)		X		
Observe participant take oral study product[1]		X	X[1]	X[1]
Adherence counseling/pill count (pill count Weeks 2 and 4 only)		X	X	X
Contraception counselling and provision or verification of use	X	X	X	X
Medical history, con meds, targeted physical exam (with weight)[2]	X	X	X	X
Hep B vaccination (if needed)[3]			X	
Blood collection	X	X	X	X
Urine and/or vaginal swab collection	X	X	X	X
LOCAL LABORATORY EVALUATIONS & PROCEDURES				
HIV testing[4]	X	X	X	X
Pregnancy 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 or vaginal swab)	X			
Urinalysis (protein and glucose)		X		
Plasma storage[10]	X	X	X	X

FOOTNOTES FOR APPENDIX I:

[1] 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.

[2] 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.

[3] 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.

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

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

[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 hrs 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, HIV prevention/risk reduction counselling	X	X	X	X	X	X	X	X	X	X
Contraception counselling and provision or verification of use	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
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®) provision (3 months' worth)										X
LOCAL LABORATORY EVALUATIONS & PROCEDURES										
HIV testing[3]	X		X		X		X		X	
Pregnancy testing[4]	X		X		X		X		X	
CBC with differential	X	X	X	X	X	X	X	X	X	X
Chemistry testing[5]	X	X	X	X	X	X	X	X	X	X
Liver function testing[6]	X	X	X	X	X	X	X	X	X	X
Fasting lipid profile[7]	X	X	X	X	X	X	X	X	X	X
Syphilis testing									X	
GC/CT testing (urine or vaginal swab)					X				X	
Urinalysis (protein, glucose)	X	X	X	X	X	X	X	X	X	X
Plasma storage[8]	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 test must be available and reviewed the same day as sample collection and before product is administered.

[4] Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Confirmation of pregnancy at a subsequent visit at least 4 weeks after the initial pregnancy test is required. Participants with confirmed pregnancies will permanently discontinue oral CAB and will not complete Step 2. They will skip to Step 3, be provided open label TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®) as PrEP and be reviewed every 12 weeks until delivery. Site staff will refer to their SOP for detailed management.

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

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

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

[8] 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.

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 begin (approximately)		X				
Contraception counselling and provision or verification of use		X	X	X	X	
Medical history[1], concomitant medications, targeted physical exam		X	X	X	X	X
Hep B vaccination (if needed) [2]						
Blood collection	X		X	X	X	X
Urine collection		X	X	X	X	X
Provision of TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®) (3 months' worth)		X	X	X		
LOCAL LABORATORY EVALUATIONS & PROCEDURES						
HIV testing[3]		X	X	X	X	X
Pregnancy testing[4]		X	X	X	X	X
CBC with differential		X	X	X	X	X
Chemistry testing[5]		X	X	X	X	X
Liver function testing[6]		X	X	X	X	X
Fasting lipid profile[7]		X				
Syphilis testing				X		
GC/CT testing (urine or vaginal swab)		X	X	X	X	X
Urinalysis (protein, glucose)		X	X	X	X	
Plasma storage[8]	X	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 test must be available and reviewed the same day as sample collection and before product is administered.

[4] Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Confirmation of pregnancy at a subsequent visit at least 4 weeks after the initial pregnancy test is required. Participants with confirmed pregnancies in Step 3 will continue to be followed by the study every 12 weeks for 48 weeks after the last CAB LA injection or delivery, whichever comes last. Open label TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®) will be provided for 48 weeks after the last CAB injection. Site staff will refer to their SOP for detailed management.

[5] BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.
[6] AST, ALT, TBili, and alkaline phosphatase.
[7] Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants must have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. Do not collect or test if <8 hrs fasting.
[8] 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

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. They are completed in addition to the procedures included in Appendix II. 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, 26, and 48, and will be determined by the members of 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 Steps 2 and 3 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					
Targeted 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 will collect specimens for resistance testing at a local laboratory to assist with clinical management; results from resistance testing performed at local laboratories will not be reported to the SDMC. Stored plasma 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.

12.5 APPENDIX V: SCHEDULE OF EVALUATIONS FOR PREGNANT PARTICIPANTS

WEEKS in Study	4 weeks after first positive pregnancy test	Quarterly Visit 1 (12 weeks since first positive pregnancy test)	Quarterly Visit 2 (24 weeks since first positive pregnancy test)	Quarterly Visit 3 (36 weeks since first positive pregnancy test)	Quarterly Visit 4 (48 weeks since first positive pregnancy test)
ADMINISTRATIVE, BEHAVIORAL, REGULATORY					
Locator information	X	X	X	X	X
HIV prevention and risk reduction counseling	X	X	X	X	X
Offer Condoms per local SOC	X	X	X	X	X
Behavioral/Acceptability assessment (CASI)	X	X	X	X	X
CLINICAL EVALUATIONS & PROCEDURES					
Medical history, concomitant medications, targeted physical exam	X	X	X	X	X
Blood collection	X	X	X	X	X
Urine collection	X	X	X	X	X
Vaginal swab collection[1]		X		X	X
Provision of TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®)	X	X	X	X	
LOCAL LABORATORY EVALUATIONS & PROCEDURES					
HIV testing[2]	X	X	X	X	X
Pregnancy testing[3]	X				
Chemistry testing[4]	X	X	X	X	X
Liver function testing[5]	X	X	X	X	X
Urinalysis (protein, glucose)	X				
Plasma storage[6]	X	X	X	X	X

FOOTNOTES FOR APPENDIX V:

[1] GC/CT NAAT testing may be performed using urine or a vaginal swab.

[2] 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 test must be available the same day as sample collection and before product is administered.

[3] Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant. If the confirmatory pregnancy test is positive, the participant is referred for an Ultrasound and evaluation by an obstetric specialist at about 12-14 weeks gestational age, for other testing, counseling, and management. Further biochemical blood testing may be done as indicated. All findings and outcomes will be collected and reported.

[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 Section 9.0.

12.6 APPENDIX VI: 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 she 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, 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. 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 will be followed for 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.

12.7 APPENDIX VII: SAMPLE INFORMED CONSENT with PARENT/GUARDIAN PERMISSION

INFORMED CONSENT STATEMENT FOR RESEARCH

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

FINAL, Version 1.0
14 October 2019
DAIDS Document ID: 38655

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), US National Institutes of Health (NIH)

Study product provided by: ViiV Healthcare

PRINCIPAL INVESTIGATOR: *[Insert Name*]
PHONE: *[Insert Number]*

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 consent 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 [insert appropriate entity (e.g., hospital, clinic)].

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 medication called cabotegravir (CAB) that can treat people who have HIV infection. CAB is also being tested to see if it can protect people from getting HIV. In this study, we want to know if it is safe and acceptable for adolescent girls 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.
   - *Contraception and Pregnancy* – Even if you are not currently sexually active, you must agree to use a long-acting, reversible type of contraception. We will provide you with contraception and related counselling throughout this study and test you for pregnancy.
   - *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 and vaginal swabs to test for HIV, Hepatitis, liver and kidney health, cholesterol, and sexually transmitted infections.
   - *HIV Prevention* – We will offer you Truvada tablets as PrEP after you stops the CAB injections.

   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; however, there is no guarantee that it will help you. 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 What are the Potential Benefits of Taking Part in the Study* section below.

5. **Will taking part in this 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.

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

FINAL, Version 1.0
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Study product provided by: ViiV Healthcare

PRINCIPAL INVESTIGATOR: *[Insert Name*]
PHONE: *[Insert Number]*

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

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, or have it read to you, 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 or make your mark on 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 women 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 medicine that is still being studied. Other studies showed that CABcan treat people who have HIV infection, but we do not know if CAB could also be used as PrEP to protect people from getting HIV. First, we must study if CAB is safe for people who do not have HIV. CAB comes in the form of a pill and also as an injection *[sites may insert appropriate term commonly used e.g.* (shot)*]*. CAB pills and injections are not yet approved for the treatment or prevention of HIV infection by the US FDA or *[add local drug regulatory authority]*. CAB injections are not HIV vaccinations.

You are being invited to join this study because you live in sub-Saharan Africa, where young women are at high risk of getting infected with HIV – as many as five to ten out of 100 each year. This study will be

offered to about 50 women under 18 years old across several study sites in Africa. The person in charge of the study at *[insert site name]* is *[insert name of IoR]*. The United States National Institutes of Health is paying for the study.

Some of the questions that we want to answer with this study are:

- Is it safe for adolescent women to take CAB pills and CAB injections?
- Is it acceptable and practical for adolescent women to use CAB for HIV prevention?
- Are adolescent women able to make it to the clinic for injection appointments?
- What do parents/guardians think about their daughters using CAB for HIV prevention?

This study will ***not*** show us if CAB prevents new infections with HIV. There are other studies being done that will answer that question, but those studies only involve adults. Currently, the only known 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. If the CAB injections work, people could 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 adolescent women use CAB for HIV prevention and whether it is safe and acceptable.

A description of this study will be available on www.ClinicalTrials.gov. This website will not include information that can identify you. At most the website will include a summary of the results. You can search this website 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 about18 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 this consent 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). You will also come back to the study clinic for a blood draw 8 weeks after the last injection.
- 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 almost a 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, so we will be following you to see how well things are going on oral PrEP and doing bloodwork, as well as HIV and other STI testing.

You will be in the study for 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 takes. 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 talk to you about plans in the next year for becoming pregnant. We will discuss any challenges you have about taking the CAB pill or attending study visits.
- *Contraception and pregnancy* – We will provide you with contraception throughout this study free of charge because we do not know if CAB will harm a baby. Even if you are not currently sexually active, you must agree to use a long-acting, reversible type of contraception. These include implants, injectables, and intrauterine devices (IUD). You must agree to use one of these forms of contraception during the study and for 48 weeks (almost a year) after stopping CAB injections because CAB remains in the body for a long time. If you leave the study early (in Step 1), you must agree to use contraception for 30 days after stopping oral study product. Study staff will discuss with you and help choose a method of contraception that will work best for you. At the majority of visits, we will check your contraception, test you for pregnancy (urine test) *[site insert sample type]* and offer you condoms.
- *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 and a vaginal swab. 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 another country, 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.
    - Urine – To test if there is sugar or protein in your urine and for sexually transmitted infections and pregnancy. *[Sites to distinguish if prenancy testing is done via urine or plasma/serum.]*
    - Vaginal swab – To test 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* – We do not know for sure if CAB will protect you from getting HIV. Also, 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. 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 pills (5 weeks' worth)		√		
Pill count			√	√
Questions/CASI	√	√	√	√
Counselling	√	√	√	√
Physical exam	√	√	√	√
Blood	√	√	√	√
Urine	√	√		
Vaginal swab	√			
CAB pills		√	√	√

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	√	√	√	√	√	√	√	√	√	√
Vaginal swab					√				√	
CAB injection	√		√		√		√		√	

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		√	√	√	√
Vaginal swab		√	√	√	√
PrEP pills offered		√	√	√	

Permanently Stopping Study Medicine

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 IF I BECOME PREGNANT?

You should not fall pregnant while receiving CAB. During the study you will use contraception. If there is a reason you can't use contraception or if you wish to be pregnant in the next two years, you should not join the study. The reason for this is because the World Health Organization recommends that women should not fall pregnant when using a medicine similar to CAB, called Dolutegravir, until more information is available about using these drugs during pregnancy. If you become pregnant during this study, you will stop CAB injections and we will refer you to available maternity care. CAB will probably last in your body and the baby's body throughout the pregnancy up until delivery. If you are still pregnant after your last study visit, we will ask your doctor to provide updates on the progress of the pregnancy. The outcome of the pregnancy is important to the study, so we would like updates for the first year of your baby's life. The study doctor will share this information with the study sponsor for safety monitoring follow-up.

- If you become pregnant in Step 1:

- You will permanently discontinue oral CAB and will not transition to Step 2. You will skip to Step 3, be provided TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®) tablets as PrEP, and visit us every 12 weeks until delivery. If your pregnancy is not confirmed on subsequent testing, you will exit the study.

- If you become pregnant in Steps 2 and 3:

  - If you become pregnant in Step 2, you will permanently discontinue CAB LA injections and transition to Step 3 to be followed by the study every 12 weeks for 48 weeks after the last CAB LA injection or delivery, whichever comes last. You will be provided with TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®) tablets as PrEP for 48 weeks after the last CAB injection.

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 medications used in this study and other anti-HIV medications, or tests about your genes. There is a separate informed consent 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").

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 [*sites to modify*] 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 medications 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 medication 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 patient'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.

- 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 medicine 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 medicines, you may have symptoms or side effects while taking PrEP. These symptoms or sides 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 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, but happened in only about 10% or 1 in 10 people. Nausea and diarrhea mainly happened in the first month and then went away. A small number (<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 drug. Other side effects were very rare and have always gotten better when the 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

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

WHAT ARE THE BENEFITS OF TAKING PART IN THIS STUDY?
You may not get direct benefit from being in this study. You will get information about your health and the results of the tests, as well as treatment for sexually transmitted infections and free contraception. 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.

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. Because we do not know if CAB injections will protect you against HIV, if you prefer to take PrEP instead of joining the study, ask the clinic 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.

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:

- 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 staff 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?
You will receive [*sites to fill in*] for your time, effort, and travel to and from the clinic at each scheduled visit.

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 [*insert name of site here*] Institutional Review Board (IRB), Ethics Committee (EC), study staff, study monitors, the company that makes CAB, and [*insert applicable local authorities*].

Groups that oversee the study include:

- *[insert name of site IRB/EC]*
- *[insert name of site drug regulatory authority]*
- *[insert name of other site regulatory entities]*
- Representatives of the HPTN
- The United States National Institutes of Health and its study monitors
- 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. *[Sites add more specific detail here as needed; example follows:]* 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 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.

[Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.] 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 *[site name or]* the U.S. National Institutes of Health.

WHO DO I CONTACT IF I HAVE PROBLEMS OR QUESTIONS ABOUT THE STUDY?
If you ever have any questions about the study, or if you have a research-related injury, you should contact [*insert name of the investigator or other study staff*] at [*insert telephone number and/or physical address*].

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

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

SIGNATURE PAGE
HPTN 084-01:
Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV among Female Adolescents – A Sub-study of HPTN 084

FINAL, Version 1.0
14 October 2019
DAIDS Document ID: 38655

SCREENING AND ENROLLMENT CONSENT

WHAT DOES YOUR SIGNATURE ON THIS CONSENT FORM MEAN?

Your signature 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 your child's legal rights by signing 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 informed consent document to keep for my records. I agree to let my child take part in this study.

Write your initials or make your mark below.

_____	_____
Name of Participant (print)	Signature and Date

PARENT/GUARDIAN INFORMED CONSENT

_____	
Relationship to participant	
_____	_____
Name (print)	Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness Name (print) (As appropriate)	Witness Signature and Date

12.8 APPENDIX VIII: SAMPLE INFORMED CONSENT FOR SPECIMEN STORAGE AND FUTURE USE with PARENT/GUARDIAN PERMISSION

HPTN 084-01:
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FINAL, Version 1.0
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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), US National Institutes of Health (NIH)

Study product provided by: ViiV Healthcare

PRINCIPAL INVESTIGATOR: *[Insert Name*]
PHONE: *[Insert Number]*

INTRODUCTION
You have decided to let your child join the study named above. As part of the study, she will have blood, urine and vaginal swabs collected. After all the tests for this study have been done for her, there may be some of the samples left over. We call these left over samples. The HPTN 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, or have it read to you, 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 her participation in the study. If you say no, all left over samples will be destroyed.

2. If you agree, her leftover samples will be kept in a repository.
[Sites should insert one of the two options shown below. Choose/adapt the second option if local regulations do not permit storage of samples for future research use in the United States.]

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 *[sites may insert time limits or additional site-specific requirements here if required by local authorities]*.

A repository is a secure facility that is used to store samples. The HPTN has a repository in the United States. However, our local regulations require that left over samples be stored in our country. Therefore, we will keep the samples here at our laboratory. There is no limit on how long the samples will be kept

[sites may insert time limits or additional site-specific requirements here if required by local authorities].

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 left over samples could also be used for research that looks at your child's 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 child's samples would only be used to look at genes related to how the body responds to the medicines used in this study and the immune system. These tests would not include whole genome sequencing (WGS).

Any research done with the left over 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 child's health. Therefore, the results will not be given to the study staff or to you. The results also will not be placed in your child's study records.

4. There is little risk to your child.

When left over samples are used for research, they are labeled with a code number only. To protect your child's 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 child's genes. If others found out the results of these tests, they could treat your child 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 her 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.

By allowing your child's left over samples to be used for research, she will be part of the search for new information that may benefit people in the future. However, the research done with the extra samples is not expected to directly benefit your child in any way.

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

There is no cost to you for use of your child's left over 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 or your child.

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

These groups include:

- *[insert name of site IRB/EC]*
- *[insert name of site drug regulatory authority]*
- *[insert name of other site regulatory entities]*
- Representatives of the HPTN
- The United States National Institutes of Health and its study monitors
- 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 left over samples and the groups listed above are required to make efforts to keep information private and confidential.

The results of research done with the left over samples may be presented publicly or published. However, no presentation or publication will use your child's name or identify her personally.

8. If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about use of your child's left over samples:

[insert name and telephone number of investigator or other study staff].

- If you later change your mind about use of your child's left over samples:

[insert name and telephone number of investigator or other study staff].

- If you have questions about your child's rights as a research participant or concerns about how she is being treated in the study:

[insert name and telephone number of IRB/EC contact person or other appropriate person/organization].

PARENT/GUARDIAN SIGNATURE PAGE

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

FINAL, Version 1.0
14 October 2019
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SPECIMEN STORAGE AND FUTURE USE INFORMED CONSENT

Before deciding about storage of laboratory specimens, 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 your options and the possible risks and benefits before making your decision. You and your child do not give up any rights by signing this form.

For your child's leftover samples, write your initials or make your mark 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 medicines used in this study 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 or her genes.

_____ allow my child's leftover samples to 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. I do not allow my baby's samples to be used for tests of his or her genes.

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

_____
Participant Name (print)

PARENT/GUARDIAN INFORMED CONSENT

_____
Relationship to participant

_____ _____
Name (print) Signature or Mark and Date

Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
Witness Name (print) (As appropriate)	Witness Signature and Date

12.9 APPENDIX IX: SAMPLE INFORMED CONSENT FOR ADOLESCENT INTERVIEWS with PARENT/GUARDIAN PERMISSION

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

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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), US National Institutes of Health (NIH)

Study product provided by: ViiV Healthcare

PRINCIPAL INVESTIGATOR: *[Insert Name*]
PHONE: *[Insert Number]*

INTRODUCTION
You are being asked to take part in a sub-study of the HPTN 084-1 research study that involves completing an interview. Joining this sub-study is voluntary. You may refuse to join, or you may withdraw your consent to be in this sub-study for any reason. Before you decide whether to join this sub-study 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 sub-study. We will help you to understand the form and answer your questions before you sign this form. Once you understand the sub-study, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep. Because you are a child, your parent/guardian must also give their permission.

Note for parent/guardian – In this form, we use 'you' to refer to your child.

Participation is voluntary
Before you learn about the sub-study, it is important that you know the following:
Your participation is voluntary. You do not have to take part in this sub-study if you do not want to.
You may decide not to take part in the sub-study, or you may decide to leave this sub-study at any time without losing your regular medical care.
You are not not required to participate in these interviews in order to remain in the rest of the HPTN 084-1 study.

About the sub-study
The HPTN 084-1 study is being done to find out if it is safe and acceptable for adolescent women who do not have HIV to take a new HIV medicine called cabotegravir (CAB) as PrEP to prevent HIV. This sub-study will ask young women what they like and do not like about getting CAB injections. We will

also ask questions to find out what makes some young women 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 sub-study
In order to understand better what makes it easier or harder for young women in this study to get CAB injections as directed, we will be doing interviews with up to 10 young women 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 HPTN 084-1 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, and
- 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 sub-study
There may be no benefit from being in the sub-study. 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 sub-study
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 sub-study

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:

- [insert name of site IRB/EC]
- [insert name of site drug regulatory authority]
- [insert name of other site regulatory entities]
- Representatives of the HPTN
- The United States National Institutes of Health and its study monitors
- 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 sub-study interview.

There are no costs to you for being in the sub-study

There will be no cost to you for participating in the in-depth interview, and you will not receive payment for being interviewed. *[Insert information about compensation/reimbursement here, e.g.,* You will be reimbursed for the cost of transport to the clinic for the interview. You will be given (specify amount).

Whom to contact

If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about the sub-study:

[insert name and telephone number of investigator or other study staff]

- If you have questions about your rights as a research participant or concerns about how you are being treated in the sub-study:

[insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

- If you have any health or other problems that may be related to sub-study participation:

[insert name and telephone number of investigator or other study staff]

- If you want to leave the sub-study:

[insert name and telephone number of investigator or other study staff]

SIGNATURE PAGE
ADOLESCENT IN-DEPTH INTERVIEW INFORMED CONSENT FORM

HPTN 084-01:
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If you decide to join this sub-study, sign or make your mark below. Before deciding whether to join this study, 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 this form.

ADOLESCENT ASSENT

Write your initials or make your mark below.

_____ I agree to be interviewed for HPTN 084-01 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

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

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

12.10 APPENDIX X: SAMPLE INFORMED CONSENT FOR PARENT/GUARDIAN INTERVIEW

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

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Study product provided by: ViiV Healthcare

PRINCIPAL INVESTIGATOR: *[Insert Name*]
PHONE: *[Insert Number]*

INTRODUCTION
You are being asked to take part in a sub-study of the HPTN 084-1 research study that involves completing an interview. Joining this sub-study is voluntary. You may refuse to join, or you may withdraw your consent to be in this sub-study for any reason. Before you decide whether to join this sub-study 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 sub-study. We will help you to understand the form and answer your questions before you sign this form. Once you understand the sub-study, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep.

Participation is voluntary
Before you learn about the sub-study, it is important that you know the following:
Your participation is voluntary. You do not have to take part in this sub-study if you do not want to.
You may decide not to take part in the sub-study, or you may decide to leave this sub-study at any time without losing your regular medical care.
You are not not required to participate in these interviews in order for your child to to remain in the rest of the HPTN 084-1 study.

About the sub-study
The HPTN 084-1 study is being done to find out if it is safe and acceptable for adolescent women who do not have HIV to take a new HIV medicine called cabotegravir (CAB) as PrEP to prevent HIV. This sub-study will ask young women what they like and do not like about getting CAB injections. We will also ask their parents/guardians questions to find out what it is like to have a child getting CAB injections and things that made that easier, and that is why you have been chosen to take part.

Entering the sub-study
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 HPTN 084-1 study,
- Whether you feel that they personally are at risk of HIV,
- Whether you talked to your children about sexual activity or preventing HIV and pregnancy,
- If your child had any bad effects from being in the HPTN 084-1 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 sub-study
There may be no benefit from being in the sub-study. 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 sub-study
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 sub-study
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:
- [insert name of site IRB/EC]
- [insert name of site drug regulatory authority]
- [insert name of other site regulatory entities]
- Representatives of the HPTN
- The United States National Institutes of Health and its study monitors
- 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 sub-study interview.

There are no costs to you for being in the sub-study
There will be no cost to you for participating in the in-depth interview, and you will not receive payment for being interviewed. *[Insert information about compensation/reimbursement here, e.g.,* You will be reimbursed for the cost of transport to the clinic for the interview. You will be given (specify amount).*]*

Who to contact
If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about the sub-study:

[insert name and telephone number of investigator or other study staff]

- If you have questions about your rights as a research participant or concerns about how you are being treated in the sub-study:

[insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

- If you have any health or other problems that may be related to sub-study participation:

[insert name and telephone number of investigator or other study staff]

- If you want to leave the sub-study:

[insert name and telephone number of investigator or other study staff]

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

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

FINAL, Version 1.0
14 October 2019
DAIDS Document ID: 38655

If you decide to join this sub-study, sign or make your mark below. Before deciding whether to join this study, 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 this form.

Write your initials or make your mark below.

_____ I agree to be interviewed for HPTN 084-1 and to have the interview audiotaped

_____	_____
Name of Participant (print)	Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness Name (print) (As appropriate)	Witness Signature and Date