HPTN 084:
A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women

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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
BSC	biological safety cabinet
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
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
CPK	creatine phosphokinase
CRF	case report form
CRM	Clinical Research Manager
CRPMC	Clinical Research Products Management Center
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 Contract
DBS	dried blood spot
DMPA	depot medroxyprogesterone acetate
DSMB	Data and Safety Monitoring Board
EAE	expedited adverse event

EC	Ethics Committee
ÉCLAIR	Phase IIa Safety and PK Study of Cabotegravir LA in HIV-Uninfected Men
EE	ethinyl estradiol
EFD	early fetal development
EFV	efavirenz
EQA	external quality assurance
FDA	(US) Food and Drug Administration
FEM-PrEP	Pre-exposure Prophylaxis Trial for HIV Prevention among African Women
FSH	follicle stimulating hormone
FTC	emtricitabine
FTC-TP	emtricitabine triphosphate
GC	*Neisseria gonorrheae*
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
HSV-2	herpes simplex virus type 2
IATA	International Air Transport Association
IB	Investigator Brochure
ICF	informed consent form
ID	identification
IM	intramuscular
IND	investigational new drug
INSTI	integrase strand transfer inhibitor
IoR	Investigator of Record
IP	intraperitoneal
iPrEX OLE	iPrEx Open Label Extension
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
LOC	(HPTN) Leadership and Operations Center
MOP	Manual of Operations
MRC	(HPTN) Manuscript Review Committee
MSM	men who have sex with men
NAAT	nucleic acid amplification test
NET-EN	Norethisterone enanthate
NI	non-inferiority
NIAID	(US) National Institute of Allergy and Infectious Diseases
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
PI	package insert
Pgp	permeability glycoprotein
PK	pharmacokinetic
PO	by mouth/orally
PPN	pre- and postnatal development
PrEP	pre-exposure prophylaxis
PRO	(DAIDS) Protocol Registration Office
PROUD	Pre-exposure Prophylaxis to Prevent Acquisition of HIV-1 Infection
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)
RSC	(DAIDS) Regulatory Support Center

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
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
TBili	total bilirubin
TCID	tissue culture infective dose
TDF	tenofovir disoproxil fumarate
TDF/FTC	tenofovir/emtricitabine (trade name: Truvada®)
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TGW	transgender women
TP	triphosphate
TV	*Trichomonis vaginalis*
ULN	upper limit of normal
US	United States
VOICE	Vaginal and Oral Interventions to Control the Epidemic
WHO	World Health Organization

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PROTOCOL SIGNATURE PAGE

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A Study of the HIV Prevention Trials Network (HPTN)

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Division of AIDS, US National Institute of Allergy and Infectious Diseases
National Institutes of Health
Support Provided by:
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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 (MM/DD/YYYY)

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TERMINOLOGY FOR CABOTEGRAVIR AND TDF/FTC FORMULATIONS

Compound Name or Abbreviation	Comments
Cabotegravir or CAB	When written as shown, this is the ViiV Healthcare compound under study and refers to the parent compound, irrespective of formulation, usually in the context of PK measurement.
Oral CAB	When written as shown, this refers to the oral tablet formulation of cabotegravir. **NOTE:** HPTN 084 will use the 30 mg tablets.
CAB LA	When written as shown, this refers to the long-acting injectable formulation of cabotegravir. **NOTE:** HPTN 084 will use the 200 mg/mL intramuscular (IM) formulation.
TDF/FTC (tenofovir disoproxil fumarate/emtricitabine)	When written as shown, this refers to the antiretroviral drug tenofovir/emtricitabine (trade name: Truvada®), manufactured by Gilead Sciences, Inc. **NOTE:** HPTN 084 will use the 300 mg/200mg fixed-dose combination tablets.
TFV (tenofovir)	When written as shown, this is the inactive, de-esterified form of TDF. This form of the drug is measured in plasma and other body fluids.
TFV-DP (tenofovir diphosphate)	When written as shown, this is the active, phosphorylated form of tenofovir that is generated in cells. This is the form of the drug that is measured in cells (including PBMCs and RBCs). It is rapidly dephosphorylated to the inactive form outside of cells, and has a very short half-life outside of cells in tissue
FTC (emtricitabine)	When written as shown, this is the inactive form of FTC. This form of the drug is measured in plasma and other body fluids.
FTC-TP (emtricitabine triphosphate)	When written as shown, this is the active form of FTC that is generated in cells. This is the form measured in cells (including PBMCs and RBCs).

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SCHEMA

Purpose: To evaluate the safety and efficacy of the injectable agent, cabotegravir (CAB LA) compared to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), for pre-exposure prophylaxis (PrEP) in HIV-uninfected women.

Design: Multi-site, double blind, two-arm, randomized (1:1), controlled superiority trial of the safety and efficacy of CAB LA compared to daily oral TDF/FTC for HIV prevention.

Population: HIV-uninfected women at risk for acquiring HIV, 18 to 45 years old.

Study Size: Approximately 3,350 women will be enrolled.

Study Duration: Approximately 4.6 years total, with individual participants being followed on randomized study product between 1.6 years (for the last enrolling participants) to approximately 3.6 years (for the earliest enrolling participants), and on oral TDF/ FTC for an additional 48 weeks. Accrual will require approximately 2 years.

Study Sites: Study sites will be in sub-Saharan Africa (SSA).

Study Regimen: Once randomized to one of two arms, participants will move through the following steps (active study products are shown in bold text):

Step 1, Oral Run-in Phase:
Arm A – **Daily oral cabotegravir (CAB)** and oral TDF/FTC placebo for five weeks plus an HIV prevention package including behavioral risk reduction and adherence counseling, and offer of condoms.

Arm B – Daily TDF/FTC and oral CAB placebo for five weeks plus an HIV prevention package including behavioral risk reduction and adherence counseling, and offer of condoms.

Step 2, Injection Phase:
Arm A – CAB LA as a single intramuscular [IM] injection at two time points four weeks apart and every eight weeks thereafter and daily oral TDF/FTC placebo plus an HIV prevention package including behavioral risk reduction and adherence counseling, and offer of condoms.

Arm B – Daily TDF/FTC and IM placebo (matching vehicle, identical volume as active injectable product in Arm A) at two time points four weeks apart and every eight weeks thereafter plus an HIV prevention package including behavioral risk reduction and adherence counseling, and offer of condoms.

SCHEMA (continued)

Study Regimen Continued:

Step 2 will continue until the required number of endpoints (114) is reached, estimated to be 81 weeks after enrolling the last participant.

Step 3, Follow-up Phase:
Arms A and B – Open-label daily TDF/FTC (in order to cover the pharmacokinetic [PK] tail for Arm A participants) will be provided no later than eight weeks after the last injection visit, for up to 48 weeks plus an HIV prevention package including behavioral risk reduction and adherence counseling, and offer of condoms. Participants will then transition to locally available HIV prevention services, including services for PrEP, if available.

Primary Objectives:

- Efficacy: To evaluate the relative efficacy of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) vs. daily oral TDF/FTC for HIV prevention (Steps 1 and 2).
- Safety: To evaluate the relative safety of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) vs. daily oral TDF/FTC for HIV prevention (Steps 1 and 2).

Secondary Objectives:

- To compare HIV incidence among participants receiving oral CAB/CAB LA vs. daily oral TDF/FTC (Steps 1, 2 and 3).
- To evaluate relative efficacy of oral CAB/CAB LA vs. oral TDF/FTC in subgroups defined by the baseline factors of: age, herpes simplex virus-2 (HSV-2) serostatus, contraceptive method, and body mass index (BMI).
- To describe and model the relationship between HIV incidence and drug concentration, within each arm.
- To describe the distribution and correlates of drug concentration, within each arm.
- To compare the acceptability of and preferences for CAB LA vs. oral TDF/FTC.

SCHEMA (continued)

Tertiary Objectives:

- To estimate sexual risk behaviors, as measured by self-report and rates of incident sexually transmitted infections (STIs).
- To compare Grade $\geq$2 adverse event (AE) rates in women with baseline BMI $</\geq$ 25 kg/m^2, within each study arm.
- To compare differences in weight gain and BMI, by arm.
- To compare pregnancy incidence and outcomes between arms.
- To evaluate rates of HIV drug resistance among participants who acquire HIV infection during the study among participants receiving oral CAB/CAB LA vs. oral TDF/FTC.
- To determine plasma concentrations of depot medroxyprogesterone (DMPA) or norethisterone (NET-EN) or etonogestrel when co-administered for contraception with study products (TDF/FTC or CAB LA).

Exploratory Objectives:

- To compare the estimated programmatic cost, cost-effectiveness and disease impact indicators of CAB LA vs. daily oral TDF/FTC vs. no PrEP for HIV-uninfected women in the study sites locations.
- To perform secondary laboratory assessments that may include evaluation of factors related to HIV infection, hepatitis infection, and other infections; antiretroviral (ARV) drug use; pharmacogenomics; characterization of HIV in infected participants; and evaluation of laboratory assays related to the study objectives.

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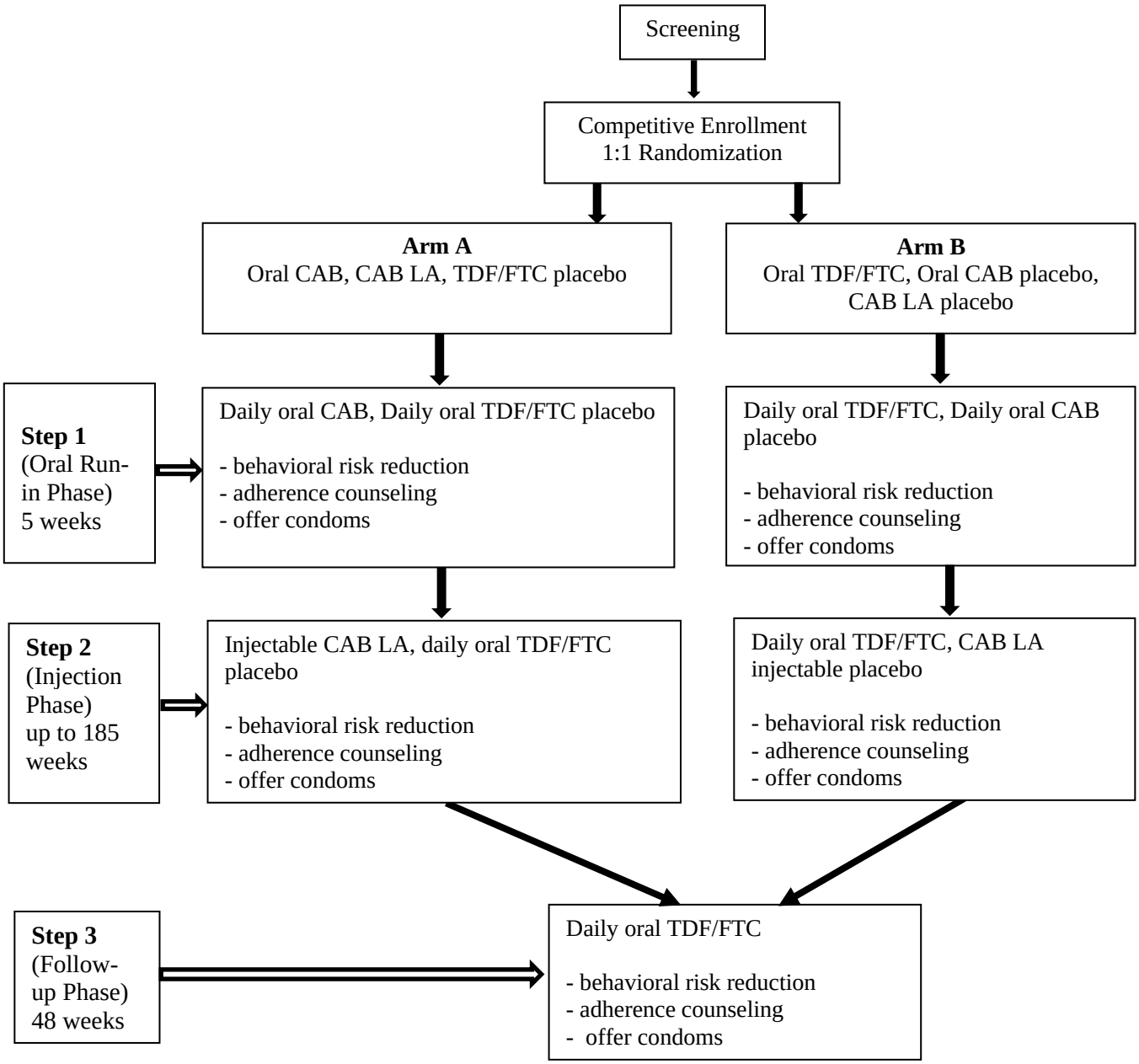
OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME



1.0 INTRODUCTION

1.1 Background and Rationale

This study is a Phase 3 double-blind study designed to evaluate the efficacy of the long-acting injectable integrase inhibitor, cabotegravir (CAB LA), for HIV prevention when compared to oral tenofovir dispoproxil fumarate/emtricitabine (TDF/FTC) in a population of sexually-active HIV-uninfected women at risk for HIV and interested in using pre-exposure prophylaxis (PrEP) (oral or injectable). This study has a similar design to an efficacy study in HIV-uninfected men who have sex with men (MSM) and transgender women (TGW) (HPTN 083) and will provide complementary information on uptake, usage and efficacy of CAB LA vs. daily oral TDF/FTC in HIV-uninfected women to be submitted as a single package for licensure of CAB LA for HIV prevention. Small single-dose and multiple-dose studies and Phase 2a safety/tolerability studies have been performed for CAB LA. A parallel development program for use of cabotegravir (CAB) (oral and injectable) for treatment of HIV-infected individuals is currently in Phase 2b studies with a salutary safety and efficacy profile to date.

The study of systemic antiretroviral (ARV) drug use for both HIV treatment and prevention has provided consistent and compelling evidence of efficacy.[1-9] The United States (US) Food and Drug Administration (FDA) approved oral TDF/FTC for PrEP and the US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have offered guidance for its use.[10,11] Most recently, the WHO recommended that TFV-based PrEP be offered to individuals at substantial risk for HIV infection as part of a comprehensive package of HIV prevention. This recommendation was based on a systematic review of 15 randomized controlled trials of oral PrEP across a range of populations and settings and found that TFV-based oral PrEP was effective in reducing HIV risk across gender, PrEP regimen, dosing, and mode of acquisition subgroups.[12] Several African countries have already licensed Truvada® (oral TDF/FTC) for PrEP, while others have started the guideline development process.

A challenge in the use of current oral ARV formulations for HIV prevention is the requirement for adherence to daily or near-daily dosing strategies.[13,14] In the same systematic review cited above, increased adherence was associated with a demonstrable increase in PrEP effectiveness. Among trials with adherence ≥80%, PrEP reduced risk of infection by 70% compared to placebo (relative risk [RR]=0.30, 95% confidence interval (CI): 0.21-0.45, p=0.001).[12] In healthy HIV-uninfected individuals, sustaining adherence becomes increasingly challenging over time.[15]

In women, pharmacokinetic (PK) studies have indicated significantly lower concentrations of TFV-diphosphate (TFV-DP) in vaginal than rectal tissues,[16,17] suggesting that adherence for women will need to be more consistent than for MSM. Low levels of adherence were observed in two blinded, placebo-controlled trials conducted in women from sub-Saharan Africa (SSA). Both the VOICE (Vaginal and Oral Interventions to Control the Epidemic) and FEM-PrEP (PrEP Trial for HIV Prevention among African Women) trials observed <30% had evidence of recent dose-taking based on plasma TFV concentrations. Subsequent analyses and qualitative research have revealed several reasons for low uptake and failure to sustain use of oral PrEP in these populations including concerns about randomization to placebo or a product of uncertain efficacy. Trial participants were reminded on a monthly basis that they may be in a placebo arm

and not receiving active product, and that the active product had not been determined to be effective—factors that may have influenced adherence behaviour.

Oral PrEP uptake and adherence among participants in randomized clinical trials (RCTs) conducted prior to knowledge of product efficacy may not predict PrEP uptake and adherence after efficacy is known. In the PROUD (PrEP to Prevent Acquisition of HIV-1 Infection) trial conducted in MSM attending sexual health clinics in the United Kingdom (UK) randomised to immediate or deferred oral PrEP, HIV incidence was reduced by 86%, a much greater level of protection than observed in placebo-controlled trials in similar populations.[18] There are fewer data on uptake and adherence to oral PrEP in women in SSA. In HPTN 067, a randomized trial of open-label oral TDF/FTC in 179 young women in South Africa, 79% of the 60 women randomized to the daily dosing arm had detectable drug in plasma at Week 30.[19]

In addition to adherence challenges inherent to daily oral tablet regimens, concerns related to drug resistance and the safety of TFV-based PrEP have propelled the evaluation of additional agents (and delivery systems) for PrEP. TDF/FTC is used commonly in ARV regimens for treatment of HIV-infected individuals, and viral strains that are resistant to TDF and/or FTC exist and are transmitted in the community. The most recent review of drug resistance following PrEP use across six randomized trials and one demonstration project found that the absolute risk of excess drug resistance during TDF/FTC PrEP was 0.05%.[20] It is possible that an HIV variant resistant to one or more ARVs will be acquired in either arm of the study. Acquired drug resistance is a risk if ARV(s) received in either arm of the study provides incomplete suppression of viral replication. The primary objective of CAB LA PrEP is to prevent HIV transmission and subsequent chronic infection. Preclinical NHP data indicates CAB monotherapy is capable of providing high-level protection from SIV/SHIV challenge (see protocol Section 1.2.1 and 1.2.2). In NHP studies where animals were repeatedly challenged intravaginally or intrarectally with virus under declining drug concentrations until infected, CAB drug resistance was not observed. The dosage schedule and dose of CAB selected are designed to mitigate against subtherapeutic concentration. In an analogous manner to the appropriate use of TDF/FTC for HIV PrEP but not for stand-alone treatment of chronic HIV infection, we believe current data support evaluation of CAB LA monotherapy for HIV PrEP but not for treatment of established HIV infection.

Concerns about the longer-term side effects of TDF/FTC include renal, hepatic and bone toxicity. Renal toxicity, including acute renal failure and Fanconi's syndrome, can occur with prolonged TDF use.[21,22] Across Phase 3 randomized studies, the rate of Grade 2-4 confirmed creatinine elevations was approximately 0.2%, with no documented cases of renal dysfunction requiring dialysis or permanent renal dysfunction.[1,9,23-25] Several studies have reported small but significant decreases in renal function while taking TDF/FTC as PrEP, although renal function returns to normal following discontinuation of PrEP.[25,26] There have also been reports of small decreases in liver function,[24,27] and bone mineral density (0.5-1.5%) when taking TDF/FTC as PrEP.[28,29,30]

PrEP may only reach its full potential for HIV prevention with agents that do not depend on daily or near-daily pill-taking. The development of alternative agents for PrEP, and/or more adherence-friendly schedules for currently available agents, 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.[31] Long-acting injectable

contraceptives provide a useful prevention parallel: injectable contraceptives are used widely by women in southern and eastern Africa, and are highly acceptable. The popularity of injectable contraception has raised total contraceptive use in many settings, although discontinuation and method-switching are frequent; most discontinue because of lack of access to renew the prescription, or fear of side effects.[32] However, it is clear that increased choice in type and method of delivery of contraceptive methods has increased acceptability and reduced the unmet need for contraception.[33] Our hypothesis is that expanded choices for HIV prevention will similarly increase utilization, satisfaction, and effectiveness.

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 Date 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 quarterly 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 subjects prior to switching to the long-acting formulation. CAB LA has a plasma half-life of 21 to 50 days in healthy HIV-uninfected 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-IC_{90}) value. None of 59 challenges resulted in infection when plasma levels were greater than 3 times the PA-IC_{90}, compared with 1 out of 22 challenges resulting in infection when plasma levels were between one to three times the PA-IC_{90}, and 11 out of 43 challenges resulting in infection when plasma levels were less than 1 times the PA-IC_{90}. Twelve out of 26 challenges resulted in infection in control animals; rectal tissue levels of CAB were approximately 20% of plasma levels.[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 using 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 1.1. The area under the curve values over 28 days (AUC0–28d) in vaginal secretions were compared to the values with those seen in plasma or rectal secretions. The AUC0–28d 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, AUC0–28d 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 1.1.). Despite the lower CAB concentrations in vaginal secretions, concentrations remained above the PA-IC90 throughout the entire 4-week period after each dose (Figure 1.1.). 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 postnatal development (PPN) study, female pregnant rats were administered 0.5, 5 or 1000 mg/kg of oral CAB daily from gestation day 6 to post-natal day 21 (without dosing to the offspring directly). In the high-dose (1000 mg/kg/day) group, there was an increased number

of rat offspring dead at birth (2.9% stillborn vs. 0.7% in control) and offspring that died during the early post-natal period (10.2% dead or missing on post-natal day 2-4 vs. 0.7% in control). This resulted in a decrease in rat offspring viability during post-natal day 1-4 (87.4% vs. 98.9%) and a corresponding decrease in live litter size on post-natal day four (10 offspring/litter vs. 11.5 in control on post-natal day four). There were no treatment-related findings in the 0.5 or 5 mg/kg/day groups. 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 ($C\tau$) 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 $C\tau$ following oral CAB 10 mg and 30 mg once daily were 1.35 μg/mL, eight-fold above PA-IC_{90}, and 4.2μg/mL, 25-fold above PA-IC_{90}, respectively.

CAB 30 mg once daily has been used as the oral lead-in in both ÉCLAIR (Phase IIa Safety and PK Study of Cabotegravir LA in HIV-uninfected Men) and LATTE-2 (CAB + RPV as Long-Acting Maintenance Therapy), where it achieved a similar pre-dose CAB concentration at baseline as observed in LATTE. The geometric mean (CVb%) C_{max} following CAB 30mg once daily is 7.5μg/mL (28%), which provides adequate safety coverage for the predicted median (90% IB [V8.0, Effective Date 17 December 2018] peak concentrations following CAB LA of 4.0μg/mL (1.8, 8.9μg/mL). Therefore, CAB 30mg once daily has been selected for the oral run-in regimen for this study.

Relevant PK parameters following oral administration are listed in Table 1.1.

1.5.2 CAB LA

CAB LA exhibits absorption-limited (flip-flop) kinetics, compressing plasma exposure to a narrow range of concentrations over extended periods of time. The CAB LA PrEP dose has been selected to deliver adequate drug concentrations to prevent sexual transmission of HIV. The proposed dosing schedule for evaluation in humans is based on maintaining CAB LA plasma concentrations well above the PA-IC_{90} value of 0.166 μg/mL, a concentration range shown to

have significant antiviral activity.

The ÉCLAIR study was undertaken to evaluate PK and safety following three injections of CAB LA 800mg IM Q12W in healthy male participants. This regimen was selected based in part on results of a small cohort (n=9) of healthy participants receiving two quarterly doses of CAB LA 800 mg IM that achieved a geometric mean (CVb%) C_τ of 1.11 μg/mL (139%), approximately 6.7-fold above the PA-IC_{90} and between the 5 mg and 10 mg oral doses (Table 1.1). These data were included in a population PK model with other PK data following CAB LA single or repeat doses ranging from 100mg to 800mg IM. Simulations with this model showed that CAB LA 800 mg IM given every 12 weeks (Q12W) was predicted to achieve a median concentration above the 1.35 μg/mL target based on 10 mg daily oral dosing with the lower bound of the 90% CI at ~four-fold PA-IC_{90}. The overall range of predicted CAB C_τ values following CAB LA 800 mg IM was similar to that following once daily dosing of oral CAB 10 mg.

Results from ÉCLAIR, however, showed that only 30 to 37% of CAB LA C_τ values were ≥4-fold PA-IC_{90} following each of the three quarterly injections, while 15 to 31% were below the PA-IC_{90}. Graphical evaluation of the CAB plasma concentration-time profiles suggests that absorption was more rapid among participants in the ÉCLAIR study than that observed in prior studies, resulting in higher peak and lower trough concentrations (Figure 1.1.). Of note, the CAB LA nanosuspension formulation has remained essentially unchanged throughout the clinical development program, indicating that other factors are contributing to the observed PK differences. Given this information, a regimen of CAB LA 800 mg Q12W may not maintain sufficient exposures in all participants, particularly in males.

During the Follow-up Phase of ÉCLAIR, CAB was detectable in plasma at 52 weeks post last injection for some individuals (14 out of 83, 17%).[39] The CAB concentrations in these study participants ranged from 0.029-0.105 μg/ml, falling between the lower limit of quantitation (LOQ) of 0.025 μg/ml and 1 x PA-IC_{90} (0.166 μg/ml).

Two regimens of CAB LA have been evaluated in HIV infected subjects – one 400mg IM Q4W and the other 600mg IM Q8W. Both regimens were initiated with an 800mg IM loading dose, and 600mg IM was administered 4 weeks following the loading dose of the second regimen prior to commencing with dosing at Q8W intervals. The Q8W regimen achieved a geometric mean CAB Cτ of 1.49μg/mL at Week 48 (Figure 1.2), above the geometric mean Cτ value for the 10 mg oral dose in LATTE. At Week 48, the proportion of participants maintaining suppression of HIV in the Q8W arm was 91%.

HPTN 077 is Phase 2a study that was initiated to evaluate safety, tolerability, acceptability, and PK of the ÉCLAIR regimen (800mg IM Q12W) in low-risk HIV-uninfected men and women at eight sites globally. Based on the ÉCLAIR and LATTE-2 results, this study was amended to enroll a second cohort with dosing of CAB LA 600 mg IM at two time points 4 weeks apart and every eight weeks (Q8W) thereafter for five injection visits. Both cohorts were randomized 3:1 active to placebo and included a 4-week lead in of daily oral CAB 30 mg orally (or matching placebo) to assess initial safety and tolerability. After completing the oral lead-in, Cohort 1 participants (n=110, fully enrolled) received three IM injections of CAB LA 800mg at QW12 (or matching placebo injection), and were followed for 52 weeks after the final injection to observe PK washout. Cohort 2 participants (n=90, fully enrolled) receive five IM injections of CAB LA

600mg at weeks 5, 9, and at 8 week intervals thereafter; these participants are also followed for 52 weeks after the final injection. The 800mg dose of CAB LA is administered as a split two x 2cc injection administered as one injection to each buttock in sequence; the 600 mg dose is administered as a single 3cc injection to one buttock. Given the persistent CAB concentrations detectable in 17% of ÉCLAIR participants at 52 weeks post Injection 3, HPTN077 was amended to extend the follow-up period from 52 to 76 weeks post final injection (24 weeks longer than the current follow-up of 52-weeks post last injection). In HPTN 077, the median time to undetectable cabotegravir concentrations was 43.7 weeks for males and 67.3 weeks for females. At 76 weeks after the final injection, 13% of males and 42% of females had detectable cabotegravir; among women 11% still had cabotegravir levels >1x PA-IC90 which has been shown in NHP models with be consistent with 97% protection. $T_{1/2}$app was significantly associated with female sex at birth and BMI. HPTN 084 will help define further the clinical implications of these prolonged exposures, both in terms of ongoing HIV protection as well as the theoretical risk of seroconversion with resistant virus. [40]

The CAB population PK model has been updated with PK data from ÉCLAIR (an additional 94 males) and LATTE-2 (an additional 230 participants; 216 males and 14 females), significantly increasing the data in the population PK dataset. The absorption rate constant following CAB LA was increased approximately 2-fold (4.54×10^{-4} hr^{-1} to 9.19×10^{-4} hr^{-1}; i.e., more rapid absorption) and resulted in higher peak to trough ratios than previously observed. Preliminary data for males and females in each cohort of HPTN 077 have been compared to simulations based on the updated population PK model. Good correspondence between model predictions and HPTN 077 data (currently not in the model) supports use of the simulations to select CAB LA doses for Phase 3 (Figure 1.3, female plot). Both HPTN 083, the Phase 3 study of CAB LA in MSM and transgender women, and HPTN 084, the Phase 3 study of CAB LA in women, are employing the HPTN 077 Cohort 2 regimen supported by the updated population PK modeling and simulation results. Therefore, the proposed regimen for this study is CAB LA 600 mg IM as a single injection at two time intervals four weeks apart and every eight weeks thereafter. This dosing regimen is predicted to yield a median steady-state $C\tau$ in females of approximately 2.5 μg/mL, which is approximately 15-fold above PA-IC_{90}, with $C\tau$ above 4x PA-IC_{90} in > 95% of participants. Simulated delays in dosing of Injection 2, 3, and 4 showed that little forgiveness occurs prior to Injection 2 (Table 1.2), and it is recommended that subjects receive their second injection 1 week early to on time. However, more forgiveness is evident prior to subsequent injections, and a one-week delay is permitted per the protocol. Percentage of participants predicted to achieve targets are shown in Figure 1.4.

Relevant PK parameters following CAB LA in healthy and HIV-infected participants and following simulations based on the initial and updated population PK models are listed in Table 1.1.

Table 1.1. Summary of CAB PK Parameters Following Oral and LA (IM) Administration and PK Simulations in Healthy and HIV-Infected Participants

Route Study Population N	CAB Regimen	CAB PK Parameter			
		C_τ or C_0 (μg/mL)	C_{max} (μg/mL)	AUC(0-τ) (μg•h/mL)	Geomean IQ C_0 or C_τ/PA-IC-90[b]
Oral Data					
Ph2a - ITZ112929 HIV-infected N=7 Women = 2	5 mg oral once daily x10 d monotherapy	0.57 [33%]	1.02 [25%]	17.7 [31%]	3.4
Ph2b - LATTE HIV-infected N=14 Women= 0	10 mg oral once daily with 2NRTIs	1.35 [45%] (n=57)	2.77 [33%]	45.7 [32%]	8.1
Ph2b - LATTE HIV-infected N=12 Women= 1	30 mg oral once daily with 2 NRTIs	4.20 [40%] (n=53)	7.49 [28%]	134 [32%]	25
LA Data					
Ph1 - LAI115428 Healthy Volunteers N=9 Women = 4	800 mg IM every 12weeks x 2 (2nd dose interval)	1.11 [139%]	3.35 [56%]	4417 [53%]	6.7
Ph2a - 201120 (ÉCLAIR) Healthy Volunteers (N=85) Women = 0	800 mg IM every 12 weeks x 3 (third dose)	0.387 [150%] (n=66)	4.91 [67%]	4021 [36%]	2.3
Ph2b – Q4WLATTE-2[a] HIV-infected (N=115) Women = 6	800 mg IM Day 1, 400 mg IM W4, then Q4W following 30 mg PO QD with 2 NRTIs lead-in	2.30 (0.85 – 5.0) (W32, n=85)	3.40 (1.64- 9.05) (W25, n=86)	ND[c]	13.9
Ph2b – Q8W LATTE-2[a] HIV-infected(N=115) Women = 8	800 mg IM LD, 600 mg IM W4, W8, then Q8W following 30 mg PO QD with 2 NRTIs lead-in	1.45 (0.21 – 3. 9) (W32, n=84)	3.36 (0.75- 12.4) (W25, n=87)	ND[c]	8.7
Modeling and Simulation					
PopPK simulation (Initial PopPK model) (N=1000)	800 mg IM every 12 weeks x 5 (last dose)	1.57 [56%]	ND[c]	ND[c]	9.5
PopPK simulation[a] (Current PopPK model) (N=10000)	600 mg IM Day1, 600 mg IM W4, then Q8W	1.3 (0.18, 2.84)	4.0 (1.8, 8.9)	ND[c]	8.0

a. Data presented as geometric mean, [CVb%], LATTE-2 data presented as median (range), current population PK model predictions presented as median (90% prediction interval (PI))
b. PA-IC_{90}=0.166 μg/mL
c. Not determined

Figure 1.1. Mean (SD) Plasma CAB Concentration-Time Profile following CAB LA 800 mg IM Q12W in ÉCLAIR and Original Simulated Phase 2 Dose Rationale Model Predictions (Sparse Time Points)

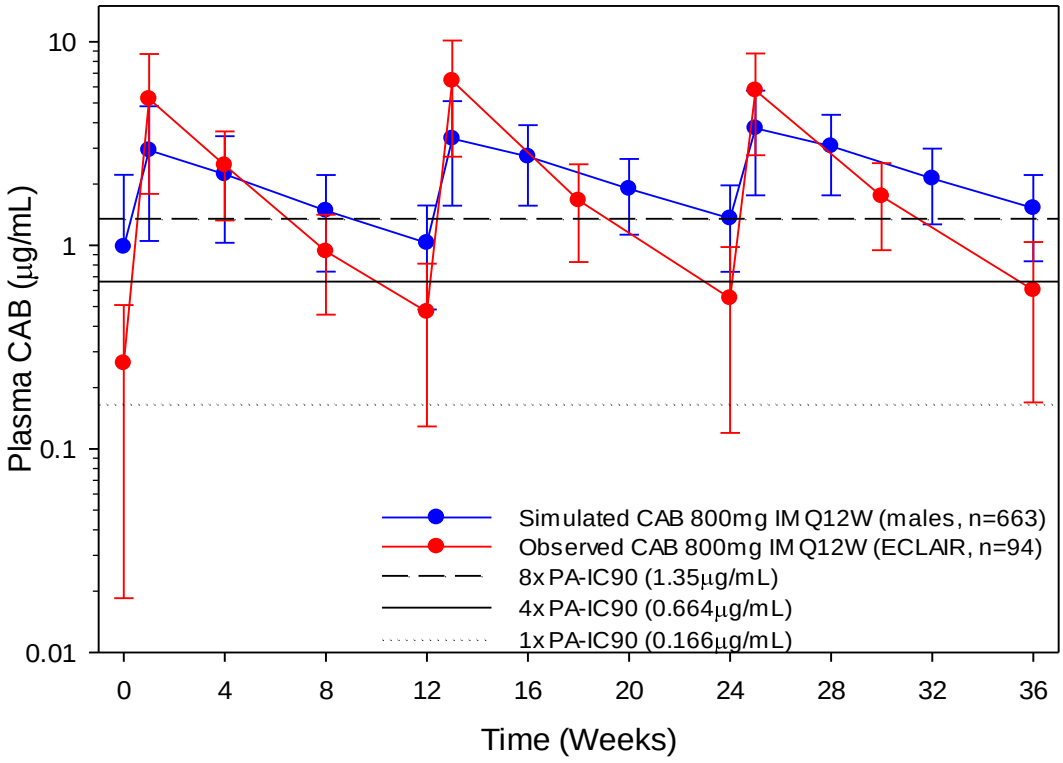


Figure 1.2. Mean (SD) Plasma CAB Concentration-Time Profile following CAB LA Q8W Regimen (800 mg IM Loading Dose, 600 mg IM Week 4, Week 8, then Q8W) in LATTE-2

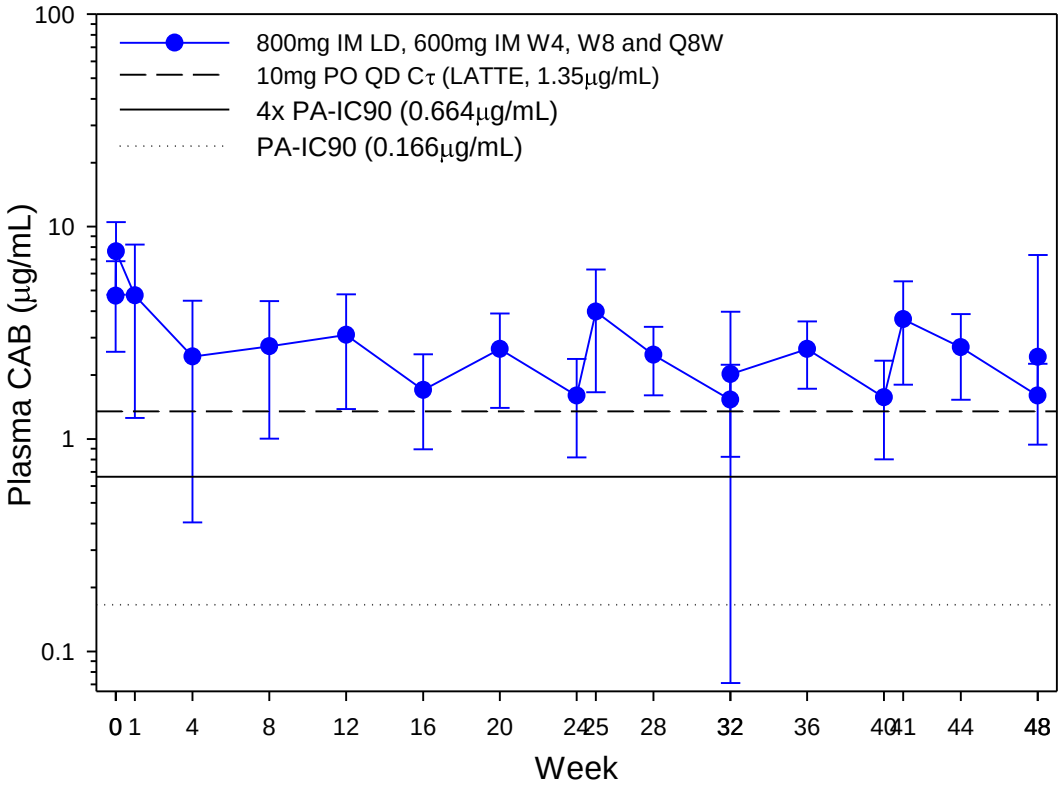


Figure 1.3. Simulated Plasma CAB Concentration-Time Profile for the Proposed Regimen (600 mg IM Day 1, Week 4 and Q8W) in Females based on Updated Population PK Model and Overlayed with Preliminary HPTN077 C2 Data in Females (semilog scale)

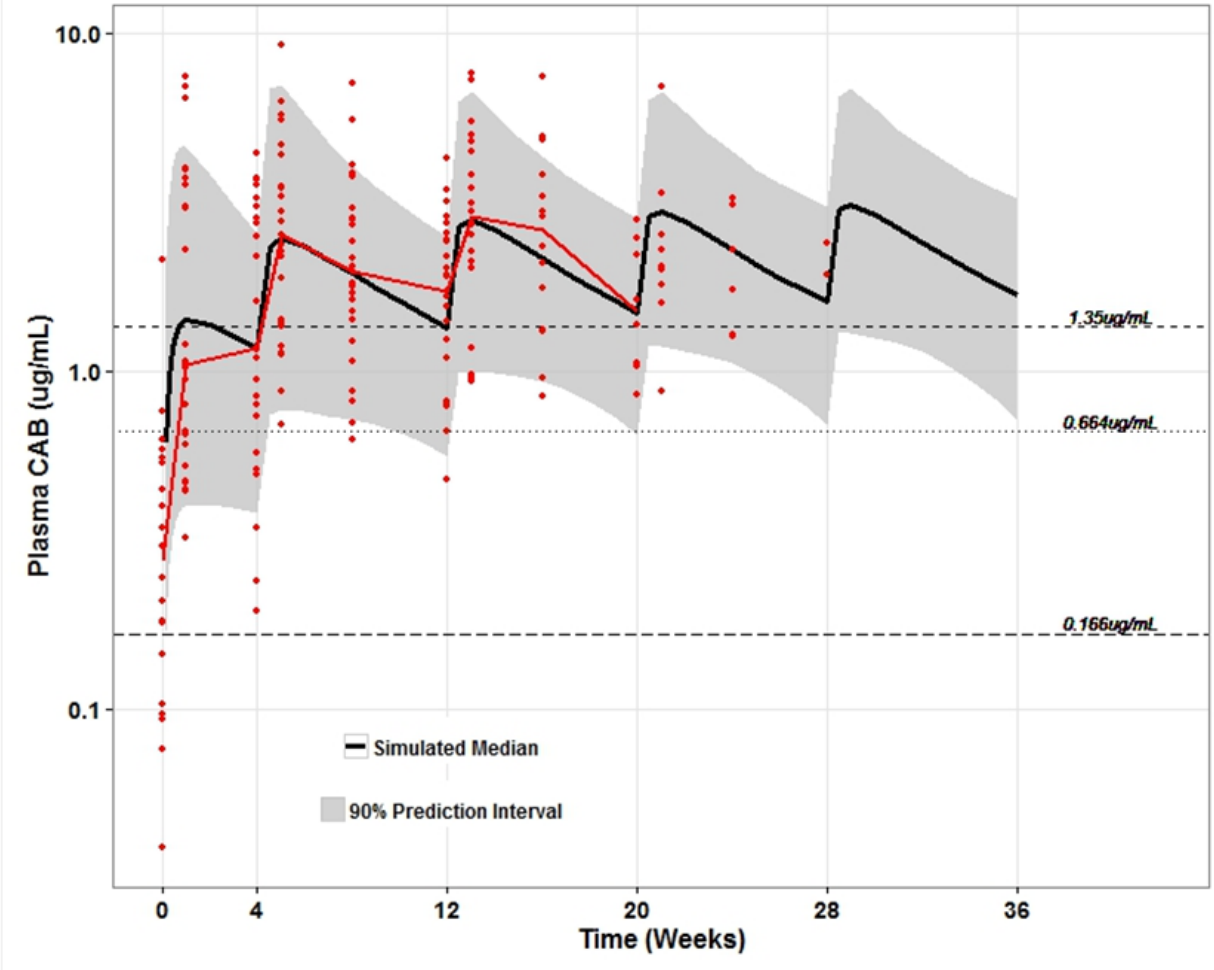
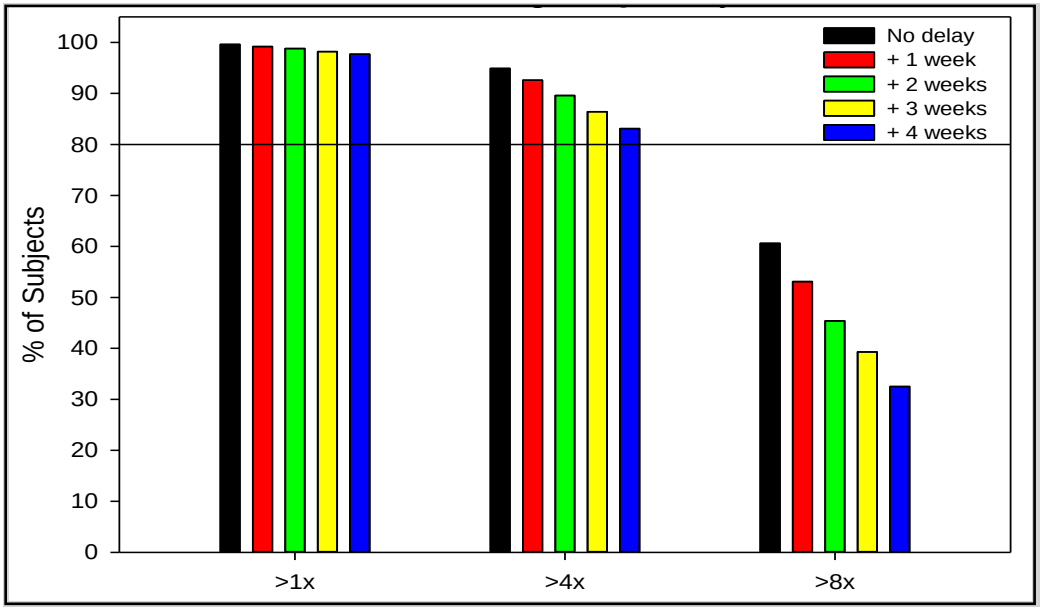


Table 1.2. Predicted Percent Above Targets for Delayed Dosing in Females

	% >PA-IC90					% > 4x PA-IC90					% > 8x PA-IC90				
Delayed Injection	0	+1 wk	+2 wk	+3 wk	+4 wk	0	+1 wk	+2 wk	+3 wk	+4 wk	0	+1 wk	+2 wk	+3 wk	+4 wk
Injection 2 (W4)	99.6	99.6	99.5	99.5	99.2	80.4	79.4	75.7	71.5	65.4	39.6	32.6	23.2	15.1	8.7
Injection 3 (W12)	99.7	99.4	98.9	98.5	98.1	92.1	90.0	86.8	83.7	79.1	50.8	42.9	34.0	26.7	20.0
Injection 4 (W20)	99.6	99.2	98.8	98.2	97.7	94.9	92.6	89.6	86.4	83.1	60.6	53.1	45.4	39.3	32.5

Figure 1.4. Percent Females Predicted to Achieve targets with Delayed Administration of Injection Four for the Proposed Regimen (600mg IM D1, W4, then Q8W)



>1x above $PAIC_{90}$ >4x above $PAIC_{90}$ >8x above $PAIC_{90}$

Updated models confirmed the selection of CAB LA 600 mg (3 mL unsplit) on day 1, week 4 and q8weekly thereafter for phase III PrEP studies in women to achieve steady state concentrations throughout the dosing interval above a threshold where CAB has demonstrated pre-clinical efficacy. [41]

1.5.3 Genital Tract (GT) Tissue Concentrations 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-IC_{90} (0.166 µg/mL). Median rectal tissue concentrations were ≤ 8% of plasma concentrations (range 0-20%).[42] Further tissue studies using single and multiple doses of the 800 mg IM dose are ongoing.

1.6 Clinical Experience to Date: Oral CAB and CAB LA

Through October, 2018, approximately 4,236 adult participants have been exposed to at least one dose of CAB (oral and/or LA) across 18 completed or ongoing Phase 1, 2 and 3 clinical trials (see Table 1.3).

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).[43] Thirty one 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.[43]

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.

Table 1.3 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

In the ÉCLAIR study, conducted in 10 US sites, 205 individuals were screened 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. One participant randomized to active study product (oral CAB and CAB LA) withdrew prior to the oral lead-in due to being incarcerated. During the oral lead-in, 11 participants withdrew prior to their first injection, all of whom were randomized to CAB LA, seven for AEs and four for other reasons. Ninety-four (94) participants received at least one injection of CAB LA 800 mg and 21 participants received at least one injection of placebo. Of those that started injections 95% (20 of 21) of those randomized to placebo and 93% (87 of 94) of those randomized to CAB LA completed all three injections. The participant in the placebo arm who did not complete all three injections reached a protocol-defined stopping criteria (he acquired HIV infection after his second injection). Four participants on the CAB LA arm withdrew after their second injection, citing injection tolerability as a primary reason. Three other participants discontinued study participation after receiving injections for non-AE and non-injection-related reasons.

Fifteen participants experienced a Grade 1 or higher ALT and 14 experienced a Grade 1 or higher AST. There were no Grade 3 or 4 ALT elevations. AE events leading to withdrawal included transient neutropenia (three participants), transiently elevated CPK (three participants), and fatigue (one participant). Two SAEs were reported, one deep vein thrombosis on placebo that was considered possibly drug-related and one appendicitis on CAB LA that was not considered drug related. Eighteen participants reported Grade 3 ISR pain. Grade 4 treatment emergent CPK elevations with concomitant AST and/or ALT elevations were noted in four participants at the Week 4 visit, leading to early withdrawal in three participants. One of the four participants described a new rigorous exercise regimen prior to the Week 4 study visit; a second of these events resolved despite ongoing exposure to study product. All four Grade 4 abnormalities were resolving at one-week follow-up visits and have subsequently returned to normal off study product.

In the LATTE study 181 HIV infected participants were randomized to receive oral CAB (10, 30, or 60 mg once-daily, blinded doses) in combination with either TDF/FTC or abacavir-lamivudine (ABC/3TC).[47] An additional 62 participants were randomized to a control arm of open-label efavirenz (EFV) 600 mg once daily in combination with one of the two NRTIs. A Week 24 interim analysis demonstrated good initial efficacy and safety of CAB in combination with NRTIs. The overall response rate across the three dosing arms of oral CAB were 87% <50 c/mL (FDA snapshot analysis) with minimal differences between oral CAB doses; the control arm response rate was 74% <50 c/mL. In the "maintenance" phase, participants randomized to any of the CAB doses who had viral loads < 50 copies/mL prior to Week 24 were transitioned to a regimen maintaining their CAB dosing but substituting oral RPV 25 mg daily for the NRTIs. EFV-treated participants were kept on their "induction" regimen of dual NRTIs with EFV. 96-week data (representing 72 weeks of maintenance dosing)) showed virologic suppression (<50 c/mL) rates via snapshot analysis to be 79%, 85% and 93% for oral CAB 10 mg, 30 mg, and 60 mg daily, and 83% for the EFV control participants. One participant randomized to oral CAB 10 mg who successfully transitioned to RPV plus oral CAB 10 mg daily experienced virologic failure at Week 48 in the context of subtherapeutic (<50% expected) CAB and RPV plasma levels (partially confounded by an extreme calorie-restricted diet during Weeks 40-48), and developed treatment-emergent high-level integrase (Q148R) and non-nucleoside reverse transcriptase inhibitor (NNRTI) (E138Q) resistance.[36]

Safety results through Week 96 support continuation of all three oral CAB dosing arms. There have been no deaths, oral CAB-related SAEs or clinically significant AE trends identified to date in LATTE. The most common clinical drug related AEs to date have been headache (15%), nausea (17%) and diarrhea (10%) with few oral CAB AEs leading to withdrawal from the study (744 - 4% vs EFV - 15%). Two HIV-infected participants receiving oral CAB 60 mg + ABC/3TC with pre-existing steatohepatitis developed an ALT >10x upper limit of normal (ULN) 4 weeks and 8 weeks after study initiation. Both participants remained asymptomatic with normal bilirubin levels and hepatic function, and ALT levels normalized after drug discontinuation. No other participants have required dose adjustment or discontinuation due to a change in transaminases through week 96. One participant receiving oral CAB and RPV 25 mg developed ALT values >10x ULN at Week 96 likely due to acute hepatitis C virus (HCV) infection.

Plasma drug concentrations after administration of CAB LA are expected to remain between the oral CAB 10 mg and 30 mg exposures. At this stage of development, a lead-in of oral CAB is being employed to determine safety and tolerability in individual participants, prior to the transition to CAB LA. The accumulated efficacy and safety data with oral CAB and CAB LA in HIV-infected and HIV-uninfected participants supports continued clinical development for HIV treatment and PrEP.

The LATTE-2 study evaluated a 20-week induction of HIV-1 RNA suppression with a three drug oral antiretroviral regimen consisting of CAB + ABC / 3TC Fixed Dose Combination (FDC) followed by randomization to a two-drug regimen consisting of intramuscular (IM) long-acting (LA) CAB LA + RPV LA compared to continuation of oral CAB + ABC / 3TC for the maintenance of HIV-1 RNA suppression[44]. A total of 309 participants were enrolled and treated. During the Induction Period there was a rapid and sustained decline in HIV-1 RNA, with 91% of participants (282/309) achieving HIV-1 RNA <50 c/mL through 20 weeks of therapy. There was a single participant (with known compliance issues) with confirmed virologic failure during the Induction Period. Virologic testing revealed no treatment emergent phenotypic or genotypic resistance in this participant.

Through 32 weeks (primary endpoint) of two-drug maintenance therapy, 95% (Q8W) and 94% (Q4W) of participants on injectable dosing were virologic successes, compared to 91% of participants continuing three drug oral CAB + NRTIs, meeting pre-specified criteria for comparability between the dosing arms. Week 48 data was a secondary endpoint for study 200056, and permitted the evaluation of the two-drug long-acting combinations' ability to maintain the virologic suppression demonstrated at Week 32. At Week 48, 92% (Q8W) and 91% (Q4W) of participants receiving injectable dosing had a sustained virologic response (HIV-1 RNA <50 c/mL) compared to 89% of participants continuing oral CAB + 2 NRTIs. Although the proportion of participants with virologic success was similar for Q8W and Q4W dosing, the reason for Snapshot failure was different between the arms. There were more Snapshot failures for virologic reasons on the Q8W arm (n=8, 7%) than in the Q4W arm (n=1, <1%), and more participants with no virologic data (discontinued due to AE or other reasons) on the Q4W arm (n=9, 8%) compared to the Q8W arm (n=1, <1%). Between Week 32 and Week 48, one additional participant (Q8W) had confirmed virologic failure, with treatment emergent NNRTI resistance (K103N, E138G, and E238T), and integrase resistance mutation Q148R.

Overall, AEs and clinical chemistries were similar to those observed in prior studies with CAB, without discernible trends between Q8W, Q4W, and oral. Injections were well tolerated with two participants discontinuing due to injection tolerability through 48 weeks (both on Q8W dosing). The vast majority of injection site reactions were due to pain/discomfort with nearly all injection site reactions classified as mild (82%) or moderate (17%), with <1% of reactions classified as severe. There was no discernible tolerability difference between Q4W (2 mL) dosing and Q8W (3 mL dosing). The most common non-ISR AEs during the Maintenance Phase were nasopharyngitis (24%), headache (16%), and diarrhea (13%) on IM arms and nasopharyngitis (30%), headache (11%), and diarrhea (5%) on oral CAB. Through Week 48, SAEs during the Maintenance Period occurred in 7% of participants randomized to CAB LA + RPV LA and 5% of participants randomized to remain on oral treatment, none were drug related. Based on the data from the Week 48 endpoint, Q4W dosing was chosen to progress for further clinical development.

Plasma drug concentrations after administration of CAB LA are expected to remain between the oral CAB 10 mg and 30 mg exposures. At this stage of development, a lead-in of oral CAB is being employed to determine safety and tolerability in individual participants, prior to the transition to CAB LA. The accumulated efficacy and safety data with oral CAB and CAB LA in HIV-infected and HIV-uninfected participants supports continued clinical development for HIV treatment and PrEP.

In May 2020 at a pre-planned interim review the DSMB recommended that the blinded portion of HPTN 083, a companion phase III trial of CAB LA for HIV prevention in MSM and transgender women (TGW), be stopped for evidence of efficacy. Subsequent analysis confirmed that CAB was superior to TDF/FTC (HR 0.35; 95% CI 0.18-0.62) in preventing HIV infection. Overall incidence was 0.81% (95% CI 0.61- 1.07). CAB and TDF/FTC were both well tolerated; most adverse events were mild/moderate and balanced between arms. Injection site reactions were more common in the cabotegravir arm but were generally grade 1-2 and decreased with time on study. Injection intolerance led to discontinuation in 46 (2.2%) active CAB-LA recipients and was associated with the severity of the reaction. Grade 2+ events observed with significant higher frequency in the CAB LA arm included nasopharyngitis, increased blood glucose and pyrexia. These differences were not observed when compared grade 3+ events. There were no significant differences in serious adverse events between the two groups.[45]

1.7 Pregnancy and Pregnancy Prevention with CAB Use

There is no requirement to exclude women of reproductive potential from clinical trials of CAB based on reprotoxicity 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 levonorgesterol (LNG) or ethinyl estradiol (EE) containing combination oral contraceptive.[46] There were no apparent differences in pharmacodynamic

assessments of follicle stimulating hormone (FSH), lutenizing 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,DMPA and etonogestrel are commonly prescribed, specifically in SSA. Although the metabolic pathways for such products are complex and vary somewhat from ethinyl estradiol and levonorgesterol, no pharmacokinetic drug-drug interaction between CAB and progestin-only contraceptives is anticipated. HPTN 077 initially 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, using contraceptive status at baseline [40]. However, a recent updated analysis using time-varying contraceptive status showed a statistically significant decrease in Cmax in women on hormonal contraception. The magnitude of the change is small and the clinical significance of this remains unclear (Landovitz, personal communication). Data from HPTN 084 will provide further insight into the clinical implications of this finding

1.7.1 Dolutegravir and Pregnancy

Dolutegravir (DTG) is an integrase inhibitor in the same class of pharmaceuticals as CAB. Thus far, limited safety or efficacy data for DTG in pregnancy in humans have been published or presented.

In May 2018, WHO and several other regulatory agencies released advisories regarding the safety of dolutegravir in early pregnancy based on an interim review of data from the Botswana NICHD-funded Tsepamo Birth Outcomes Surveillance Study, in Botswana. [47] This study was designed to evaluate adverse birth outcomes by maternal HIV status and ART regimen, and to determine whether there is an increased risk of neural tube defects (NTDs) among infants exposed to efavirenz (EFV) from conception. Botswana's HIV program moved to universal ART with DTG/TDF/FTC in first line for patients starting ART (including pregnant women) in May of 2016 (women already on other regimens were not switched to DTG). The previous first-line regimen was EFV/TDF/FTC. Almost all women on DTG-based and EFV-based ART took these drugs in combination with TDF/FTC.

Since August 2014, the Tsepamo study collected information on 153,899 deliveries. An updated analysis including births since March 2019 reported seven neural tube defects among 3,591 women exposed to dolutegravir at conception (0.19, 95% CI 0.09%, 0.40%). In comparison, neural tube defects occurred in 21/19,361 (0.11%; 95%CI 0.07%, 0.17%) women on any non-dolutegravir regimen at conception. The prevalence of neural tube defects did not differ significantly between dolutegravir and any non-dolutegravir antiretrovirals from conception (0.09% difference; 95%CI -0.03%, 0.30%). After a period of decline since the original safety signal, the prevalence of neural tube defects in infants born to women on dolutegravir around the time of conception appears to have stabilized at 2 per 1000.[48]

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. Cabotegravir was evaluated in a complete package of reproductive toxicology studies, including embryofetal 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 (IB). 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 following exposure to CAB LA.

1.8 Hepatic and Central Nervous System Adverse Events

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

In a single-dose study, 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 CAB LA or placebo treatment; the participant was asymptomatic, and ALT returned to normal 15 weeks after withdrawal of study product. A serologic and ultrasonographic evaluation did not reveal alternative etiology for the ALT elevation; no biopsy was performed.

1.9 Weight gain

There is emerging evidence from randomized trials that the use of INSTIs may lead to significant increases in body weight [49]. Two trials of raltegravir and three involving dolutegravir all observed greater weight gain increases in INSTI-containing regimens. These effects appear to vary by gender and race, with highest increases observed in women and those of black race. The recently published ADVANCE trial conducted in South Africa in a predominantly black and female population found that there was significantly more weight gain (both lean and fat mass) with dolutegravir-containing regimens, especially in combination with TAF, compared to the standard of care regimen (TDF/FTC/Efavirenz) [50]. The mechanism for this needs to be fully elucidated. These data are from populations receiving treatment and more data are 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). HPTN 084 provides an opportunity to collect additional data to address this question[51].

1.10 Rationale for Study Design

Based on its antiviral activity and biological plausibility of the dosage schedule provided above, it is anticipated that CAB LA will be effective in preventing acquisition of HIV. Based on studies in MSM and heterosexual couples, TDF/FTC was approved as an agent for PrEP. Therefore, it is considered to be the ethically appropriate active comparator for CAB LA, an experimental PrEP agent. While provision of oral TDF/FTC to all participants could offer a further possibility of HIV prevention, concomitant use of TDF/FTC is not a development pathway for a new agent and the development of a combination of CAB LA/TDF/FTC (requiring both oral and injectable PrEP) would not be a desirable outcome for prevention of HIV in women.

A non-inferiority design is often used to compare a new drug to an active control that has proven efficacy. However, as discussed in Section 7.8.4.1, multiple placebo-controlled trials of TDF/FTC in women in SSA have yielded mixed results, with some trials (primarily those done in young, unmarried women) showing no efficacy and some (primarily those done in HIV discordant

couples) showing high efficacy. This finding has largely been ascribed to low adherence resulting in suboptimal levels of TFV in vaginal tissues.

In the setting of HIV PrEP trials in women, the ability to construct a non-inferiority margin is not possible given the variable efficacy results from these trials (e.g., VOICE, FEM-PrEP vs TDF2 and Partners PrEP). Therefore, the proposed HPTN 084 trial can only be designed as a superiority trial. Thus, our primary analysis is designed to show superiority of CAB/LA to TDF/FTC. If, contrary to expectations, adherence to TDF/FTC is substantially higher than expected, we will provide a supportive non-inferiority analysis with an adherence-dependent margin (Section 7.8.4).

The increase in protection likely to occur with CAB LA results from the anticipated higher adherence to the long-acting injectable compared to daily oral TDF/FTC. Use of an injectable product should address the suboptimal adherence to an oral pill. This study is therefore primarily designed to answer the question whether CAB LA is superior to oral TDF/FTC in preventing new HIV infections in women in SSA. Thus, our primary analysis is designed to show superiority of CAB/LA to TDF/FTC. If, contrary to expectations, adherence to TDF/FTC is substantially higher than expected, we will provide a supportive non-inferiority analysis with an adherence-dependent margin (Section 7.8.4).

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

- Efficacy: To evaluate the relative efficacy of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) vs. daily oral TDF/FTC for HIV prevention (Steps 1 and 2).

- Safety: To evaluate the relative safety of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) vs. daily oral TDF/FTC for HIV prevention (Steps 1 and 2).

2.2 Secondary Objectives

- To compare HIV incidence among participants receiving oral CAB/CAB LA vs. daily oral TDF/FTC (Steps 1, 2 and 3).

- To evaluate relative efficacy of oral CAB/CAB LA vs. oral TDF/FTC in subgroups defined by the baseline factors of: age, herpes simplex virus-2 (HSV-2) serostatus, contraceptive method, and body mass index (BMI).

- To describe and model the relationship between HIV incidence and drug concentration, within each arm.

- To describe the distribution and correlates of drug concentration, within each arm.

- To compare the acceptability of and preferences for CAB LA vs. oral TDF/FTC.

2.3 Tertiary Objectives

- To estimate sexual risk behaviors, as measured by self-report and rates of incident sexually transmitted infections (STIs).

- To compare Grade $\geq$2 AE rates in women with baseline BMI $</\geq$ 25 kg/m^2, within each study arm.

- To compare differences in weight gain and BMI, by arm.

- To compare pregnancy incidence and outcomes between arms.

- To evaluate rates of HIV drug resistance among participants who acquire HIV infection during the study among participants receiving oral CAB/CAB LA vs. oral TDF/FTC.

- To determine plasma concentrations of DMPA, NET-EN or etonogestrel when co-administered for contraception with study products (TDF/FTC or CAB LA).

2.4 Exploratory Objectives

- To compare the estimated programmatic cost, cost-effectiveness and disease impact indicators of CAB LA vs. daily oral TDF/FTC vs. no PrEP for HIV-uninfected women in the study sites locations.

- To perform secondary laboratory assessments that may include evaluation of factors related to HIV infection, hepatitis infection, and other infections; ARV drug use; pharmacogenomics; characterization of HIV in infected participants; and evaluation of laboratory assays related to the study objectives.

2.5 Study Design and Overview

This is a Phase 3, randomized, multi-site, two-arm, double-blind study of CAB LA compared to daily oral TDF/FTC for HIV prevention. Approximately 3,350 participants will be enrolled and randomized 1:1 to Arm A (CAB LA and placebo TDF/FTC) and Arm B (TDF/FTC and CAB LA placebo) through the three Steps listed below. When the study reaches the required number of incident HIV endpoints (114), all participants will begin open-label daily oral TDF/FTC for approximately 48 weeks (to "cover the tail"), starting no later than 8 weeks after the last injection.

Step 1, Oral Run-in Phase:

Arm A – Daily oral CAB and oral TDF/FTC placebo for five weeks plus an HIV prevention package including behavioral risk reduction and adherence counseling, and offer of condoms.

Arm B – Daily TDF/FTC and oral CAB placebo for five weeks plus an HIV prevention package including behavioral risk reduction and adherence counseling, and offer of condoms.

Any participant who becomes HIV-infected during Step 1 will permanently discontinue study product, will be terminated from the study, and referred for HIV-related care.

Step 2, Injection Phase:

Arm A – Injections of CAB LA at two time points four weeks apart and every eight weeks thereafter and daily oral TDF/FTC placebo beginning at Week 5 plus an HIV prevention package including behavioral risk reduction and adherence counseling, and offer of condoms. Injections will consist of 600 mg of CAB LA administered as one 3 mL IM injection.

Arm B – Daily TDF/FTC and IM placebo (matching vehicle, identical volume as active injectable product in Arm A) beginning at Week 5 plus an HIV prevention package including behavioral risk reduction and adherence counseling, and offer of condoms.

This Step will continue until the required number of incident HIV endpoints (114) is reached, estimated to be when the last enrolled participant reaches approximately 76 weeks on Step 2 (Week 81 for the last enrolled participant).

Participants who prematurely 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 during Step 2 follow-up and then retained in annual testing for the duration of Steps 2 and 3.

Any participant who becomes HIV-infected during Step 2 will permanently discontinue study product, be referred for care, and will be followed at quarterly intervals for approximately 48 weeks.

Step 3, Follow-up Phase:

Arms A and B – Open-label daily TDF/FTC up to 48 weeks (to "cover the tail"), starting no later than 8 weeks after the last injection plus an HIV prevention package including behavioral risk reduction and adherence counseling, and offer of condoms.

All participants will be transitioned to locally-available HIV prevention services including services for PrEP, if available when participation in Step 3 ends.

Any participant who becomes HIV-infected during Step 3 will permanently discontinue product, continue to be followed for the duration of Step 3 visits (with possible additional assessments and follow-up determined by the Clinical Management Committee [CMC]), and referred for HIV-related care.

All participants will receive HIV testing with pre- and post-test counseling, risk-reduction counseling, and be offered condoms. All participants will be followed according to the Schedule of Evaluations (SOE) provided in Appendices I a-c, and in the event of possible HIV infection, according to Appendix II.

Injectable Contraceptive Sub-study:

Up to 180 evaluable participants will be invited to enroll in a sub-study after screening to evaluate the effect of CAB LA on the concentration and effectiveness of long acting contraceptive drugs: DMPA, NET-EN, and etonogestrel implant as compared to oral TDF/FTC. This sub-study will be implemented at selected sites where all these methods are used. Participants who are using injectable contraceptives (DMPA, NET-EN) or implants (etonogestrel) at enrollment will qualify for enrollment at these sites and will be asked their consent for this sub-study.

Participants will be selected so that approximately equal numbers of women using DMPA, NET-EN and etonogestrel implant are enrolled. These participants will go through the same study procedures as all other participants. In addition, blood samples will be collected at enrollment (time 0) and at the regularly scheduled study visits at week 25, 49 and 73 for the determination of CAB, TFV/FTC (and/or intracellular metabolites), DMPA, NET-EN and etonogestrel plasma concentrations. These visits are chosen because they should be at an approximately similar point in the injection cycle for DMPA and NET-EN as the enrollment visit, assuming an 8 or 12 week cycle.

Qualitative Sub-study:

A prospective, qualitative sub-study will be conducted at four sites to collect more in-depth information on women's preferences for and experiences with CAB LA versus other potential

HIV prevention methods, and to better understand circumstances related to special cases such as pregnancy, product disruption due to COVID- 19, early product termination or HIV seroconversion. The sub-study will include two sets of data collection activities: 1) a series of in-depth interviews with a total of approximately 104 participants (approximately 26 participants per site) who are each interviewed at a maximum of 3 timepoints; and 2) quarterly semi-structured observations conducted in waiting rooms or other public clinic venues where participants are gathered.

1) Repeated in-depth interviews: At each of the four sites, a subset of approximately 10-16 women will be invited to participate in a maximum of three in-depth interviews. Women will be sampled to reflect early (2018), middle (2019) and more recent enrollment (2020) into the trial, facilitating exploration of major events such as the dolutegravir and COVID-19 issues that affected trial implementation. In addition, up to 10 women per site who, over the course of the trial, become pregnant, experience product or visit disruptions due to COVID-19 measures, request to discontinue the study or terminate product use, or who seroconvert will be invited to participate in up two interviews to explore women's reproductive choices or other circumstances affecting continued trial participation.
2) Waiting room observations: Approximately once a quarter, as feasible, a qualitative team member will conduct a 45-minute semi-structured observation in the waiting room(s) of the study clinic. The team will use a qualitative data extraction sheet to make notes about the overall demeanor of participants, topics of discussion and any information participants wish to share about their overall experiences, concerns, or recommendation related to the trial.

2.5.1 Participating Sites/Institutions

Participating sites are listed in the SSP Manual and are located in SSA.

Sub-studies for HPTN 084 will not necessarily be conducted at all sites. Sites selected for sub-studies will be notified in writing by the study Chairs.

2.5.1.1 Study Duration

Study duration is approximately 4.6 years total, with individual participants being followed on randomized product between 1.6 years (for the last enrolling participants) to approximately 3.6 years (for the earliest enrolling participants), and on open-label oral TDF/TDF for an additional 48 weeks (starting no later than 8 weeks after the last injection for participants randomized to CAB LA). Accrual will be competitive and require approximately 2 years.

3.0 STUDY POPULATION

Approximately 3,350 HIV-uninfected women from SSA 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

Participants who meet all of the following criteria are eligible for inclusion in this study:

- Born female
- 18-45 years at the time of screening
- Willing and able to provide informed consent
- Willing and able to undergo all required study procedures
- Non-reactive HIV test results at Screening and Enrollment*
- Sexually active (i.e., vaginal intercourse on a minimum of two separate days in the 30 days prior to Screening)
- Score of ≥5 using a modified VOICE risk score[52]
- No plans to re-locate or travel away from the site for ≥8 consecutive weeks during study participation
- Creatinine clearance ≥60 mL/min (using Cockcroft-Gault equation) (use sex at birth for calculation)
    - Although not protocol exclusionary, sites should carefully consider the advisability of enrolling participants with calculated creatinine clearance between 60-70 mL/min, as limited changes in creatinine clearance during study conduct will lead to protocol-mandated product holds and may alter the risk-benefit considerations of study participation
- Hepatitis B virus (HBV) surface antigen (HBsAg) negative and accepts vaccination
- Alanine aminotransferase (ALT) < 2x upper limit of normal (ULN) and total bilirubin (Tbili) ≤ 2.5 x ULN
- HCV antibody negative
- If of reproductive potential (defined as pre-menopausal women who have not had a sterilization procedure per self-report, such as hysterectomy, bilateral oophorectomy, tubal ligation or salpingectomy), **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 and before initiating the protocol-specified study product(s) at Enrollment.

- Have documented evidence of surgical sterilization, OR documented evidence of no uterus (e.g. hysterectomy), OR must agree to use a reliable form of long acting contraception, during the trial and for 52 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)
- No medical condition that, in the opinion of the study investigator, would interfere with the conduct of the study (e.g., provided by self-report, or found upon medical history and examination or in available medical records)
- No alcohol or substance use that, in the opinion of the study investigator, would interfere with the conduct of the study (e.g., provided by self-report, or found upon medical history and examination or in available medical records)

*HIV-uninfected, based on HIV test results obtained at Screening and just prior to randomization 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. In addition, at least one HIV test result using blood drawn at the Enrollment visit must be obtained prior to randomization into the study and must be negative/non-reactive. 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). Those with any enrollment HIV test result positive will proceed through the HIV algorithm per the SSP but will not be able to receive study product regardless of subsequent test results.

3.2 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from this study:

- One or more reactive HIV test results at Screening or Enrollment, even if HIV infection is not confirmed
- Pregnant or currently breastfeeding, or intends to become pregnant and/or breastfeed during the study
- Co-enrollment in any other HIV interventional research study (provided by self-report or other available documentation), with one exception: IMPAACT 2026 (co-enrollment in IMPAACT 2026 is permitted for participants who become pregnant)
- Current or past enrollment in an HIV vaccine or broadly neutralizing antibody trial
- 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)

- History of seizure disorder, per self-report
- 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
- Inflammatory skin conditions that compromise the safety of IM injections, per the discretion of the Investigator of Record (IoR). Mild skin conditions may not be exclusionary at the discretion of the IoR or designee
- Has a tattoo or other dermatological condition overlying the buttock region which in the opinion of the IoR or designee may interfere with interpretation of ISRs
- Coagulopathy (primary or iatrogenic) which would contraindicate IM injection
- Active or planned use of prohibited medications as described in the IB or listed in the SSP Manual (provided by self-report, or obtained from medical history or medical records)
- Known or suspected allergy to study product components (active or placebo), including egg or soy products (egg and soy products are contained in Intralipid)
- If potentially able to conceive, unwilling to adhere to long acting contraception (IUD/IUS, injection, or implant) with a <1% failure rate when used consistently and correctly as stated in the product package insert/ manufacturer's guidelines

3.3 Recruitment Process

The study will be targeted towards most at-risk populations of women in each geographic setting (i.e., those with highest HIV incidence) in SSA. Enrollment will be competitive over approximately a two-year period, meaning that sites with a lengthy start-up period may end up with fewer enrolled participants versus those sites starting earlier.

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 most at-risk 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

In general, 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) American Red Cross-mandated limitations on per-unit-time phlebotomized blood volumes, 3) to avoid potential unblinding of studies, and 4) to avoid confounding in the interpretation of the study data. The CMC should be consulted for any possible exceptions, including for observational studies.

The one exception for co-enrollment is IMPAACT 2026. An HPTN 084 participant who becomes pregnant following randomization and is enrolled at a site also participating in IMPAACT 2026 may co-enroll in that study.

3.5 Participant Retention

Once a participant enrolls in this study, the study site will make every effort to retain her for the entire follow-up period. Optimally, participant retention procedures will be established such that loss rates do not exceed the range that would allow the incidence rate of the primary study outcome to be reliably estimated (i.e., a maximum of 5% per year as assumed in the sample size calculation). 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 both arms and adherence 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 text messaging.
- Immediate and multifaceted follow-up on missed visits, including SMS 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, government or regulatory authorities (including Office for Human Research Protections [OHRP] and the FDA) or site

IRBs/ECs or if appropriate, the South African Health Products Regulatory Authority (SAHPRA), ViiV/Gilead terminate the study prior to its planned end date.

Participants who decline to continue study product in Steps 1 or 3 should be offered the option of continued follow-up and at least annual HIV testing until study end. Participants who decline to continue study product in Step 2 and who have received study injections should be counselled about the long pharmacokinetic tail and offered transition to 48 weeks of open-label TDF/FTC followed by annual testing. Participants who decline follow up should be counselled regarding methods to reduce their HIV risk. (see section 5.10)

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 randomized 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

4.1 Study Product Regimens/Administration/Formulation Content

Study Product Regimens

Step 1 – **Oral Run-in Phase (Blinded daily oral tablet)**
Participants will be randomized 1:1 to one of two study arms:

- **Arm A:** Oral CAB tablets, 30 mg, one tablet orally daily for five weeks, with or without food **AND** placebo for TDF/FTC tablets, one tablet orally daily for five weeks, with or without food
- **Arm B:** TDF/FTC 300 mg/200 mg fixed dose combination tablet, one tablet orally daily for five weeks, with or without food **AND** placebo for oral CAB tablet, one tablet orally daily for five weeks, with or without food

Step 2 – **Injection Phase (Blinded injections and blinded daily oral tablet)**

- **Arm A:** CAB LA 600 mg administered as one 3 mL (600 mg) IM injection in the gluteal muscle at two time points four weeks apart and every eight weeks thereafter, **AND** placebo for TDF/FTC tablet, one tablet orally daily, with or without food
- **Arm B:** TDF/FTC 300 mg/200 mg fixed dose combination tablet, one tablet orally daily, with or without food **AND** placebo for CAB LA (Intralipid 20% fat emulsion infusion) administered as one 3mL IM injection in the gluteal muscle at two time points four weeks apart and every eight weeks thereafter

Step 3 – **Follow-up Phase**
All participants, including those who permanently discontinue receiving injections before their Step 2 participation in the study ends, will receive open-label TDF/FTC 300 mg/200 mg fixed dose combination tablets, one tablet orally daily for up to 48 weeks.

4.1.1 Oral Product

Oral CAB and placebo for oral CAB
CAB 30 mg tablets (blinded) are formulated as white to almost white oval-shaped coated tablets for oral administration. The tablets are packaged in high density polyethylene (HDPE) bottles with child-resistant closure that include an induction seal. The bottles contain 30 tablets and a desiccant. The tablets must be stored in the original container. The bottles are to be stored up to 30 degrees Celsius (30° C, 86 ° Fahrenheit [F]) and protected from moisture.

Placebo for CAB 30 mg tablets (blinded) are formulated as white to almost white oval-shaped coated tablets to visually match the CAB tablets. The tablets are packaged in HDPE bottles with child-resistant closure that include an induction seal. The bottles contain 30 tablets and a desiccant. The tablets must be stored in the original container. The bottles are to be stored up to 30°C (86 ° F) and protected from moisture.

Oral TDF/FTC and placebo for oral TDF/FTC

TDF 300 mg/FTC 200mg tablets (blinded) are capsule-shaped, film-coated blue tablets that must be stored in the original container. Each bottle contains a silica gel desiccant canister to protect the product from humidity. The bottles are to be stored up to 25°C (77°F). Excursions are permitted between 15° to 30°C (59°F to 86°F).

Placebo for TDF 300 mg/FTC 200 mg tablets (blinded) are capsule-shaped, film-coated blue tablets that visually match the TDF/FTC tablets. The tablets must be stored in the original container. Each bottle contains a silica gel desiccant to protect the product from humidity. The bottles are to be stored up to 25° C (77°F). Excursions are permitted between 15°C to 30°C (59°F to 86°F).

TDF 300 mg/FTC 200 mg tablets (open-label) are capsule-shaped, film-coated blue tablets that must be stored in the original container. Each bottle contains a silica gel desiccant canister to protect the product from humidity. The bottles are to be stored at 25°C (77°F). Excursions are permitted between 15° to 30°C (59°F to 86°F). The TDF/FTC fixed dose combination tablet containing 300 mg of TDF and 200 mg of FTC is available as Truvada®, and is approved by the U.S. FDA for treatment and prevention of HIV-1 infection. Further information on Truvada® is available in the current package insert (PI).[53]

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 2mL or 3 mL glass vial. Each vial is for single use containing 2mL (400 mg), or 3mL (600mg), and does not require dilution prior to administration. CAB LA injectable suspension is to be stored up to 30° C (86°F), do not freeze.

Placebo for CAB LA formulation

Placebo for CAB LA injectable suspension will be Intralipid 20% fat emulsion infusion which is packaged in 100 mL IV bags. Intralipid 20% fat emulsion infusion IV bags are to be stored below 25° C (77°F), do not freeze.

4.2 Study Product Preparation

4.2.1 Preparation of the Oral Study Product

The oral products for this study will be provided with customary two-part structure which includes a tear-off portion containing the un-blinded-product identification (i.e., active or placebo).

Prior to dispensing, the un-blinded portion of the tear-off label must be removed and attached to the participant specific pharmacy record such as participant prescription or participant specific study product accountability record. The permanently affixed section of the label will remain on the original container.

The site pharmacist will label the bottle with a participant specific label prior to dispensing. The participant specific label must be in accordance with the local regulations and the DAIDS Pharmacy Guidelines manual.

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

4.2.2 Preparation of Injectable Study Product

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

Preparation of Active Injectable Study Product (CAB LA 600 mg/3 mL)

The designated pharmacy personnel will follow the steps below for preparation of active injectable study product, CAB LA injectable suspension. In Step 2 of the study, for the participants in Arm A, one syringe containing 3 mL (600 mg) of CAB-LA must be prepared using aseptic technique under a pharmacy BSC/Isolator.

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

1. One CAB LA 600 mg/3 mL vial or two CAB LA 400 mg/2 mL vials
2. Becton Dickenson (BD) 3-mL syringe, Luer-Lok Tip, Product No.: 309657 or equivalent
3. Becton Dickinson (BD) 5-mL Syringe, Luer-Lok Tip, Product No.: 309646 or equivalent
4. Needle for aspiration: BD general use sterile hypodermic needle, 21G x 1½ inch (e.g. Precision Glide Needle, Product No.: 305165 or equivalent)
5. Needle for intramuscular injection: BD IM sterile hypodermic needle, 23G x 1½ inch (e.g. Precision Glide Needle, Product No.: 305194 or equivalent). Refer to the HPTN 084 SSP for further details on appropriate needle gauge size and length to use for IM administration.

Preparation Steps:

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

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

3. Invert the vial(s) 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 (isopropyl alcohol 70% or similar) and allow to dry. Do not touch the rubber stopper at any time.

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

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

8. While keeping the syringe with the needle in the upright position, withdraw needed volume of CAB LA suspension from the vial(s) into the syringe
   - Withdraw total of 3 mL (600 mg) of CAB LA suspension from the vial(s) into a syringe.
     - If using two CAB LA 400 mg/2 mL vials to prepare the dose, a second new aspiration needle should be used to withdraw suspension from the second vial. Remove the first needle that was used to withdraw the suspension out of the first vial and discard properly. Attached the new 21G x 1½ inch needle to the syringe already containing suspension per instructions in Step 5 and repeat Steps 6 and 7 to withdraw the remaining needed volume from the second vial.

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

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

10. Place an overlay around the prepared syringe to maintain the blind.

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

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

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

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

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

    After withdrawal of the CAB-LA suspension from the vial into a syringe, it is recommended to inject the suspension immediately. Do not exceed 2 hours between withdrawing the contents of the vial(s) into a syringe (Step 8) and administration to the study participant.

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

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

Preparation of Placebo Injectable Study Product (Intralipid 20%/ 3 mL syringe)

The designated pharmacy personnel will follow the steps below for preparation of placebo injectable study product. Placebo for CAB LA injectable suspension is Intralipid 20% fat emulsion infusion. In Step 2 of the study, for the participants in Arm B, one syringe containing 3mL of intralipid 20% fat emulsion infusion will be prepared using aseptic technique under a pharmacy BSC/Isolator.

Materials required for preparation and administration Placebo for CAB LA (Intralipid 20%) 3 mL dose:

1. One 100 mL IV bag of intralipid 20% fat emulsion
2. Becton Dickenson (BD) 3-mL syringe, Leur-Lok Tip, Product No.: 309657 or equivalent
3. Becton Dickinson (BD) 5-mL Syringe, Luer-Lok Tip, Product No.: 309646 or equivalent

4. Needle for aspiration: BD general use sterile hypodermic needle, 21G x 1½ inch (e.g. Precision Glide Needle, Product No.: 305165 or equivalent)
6. Needle for intramuscular injection: BD IM sterile hypodermic needle, 23G x 1½ inch (e.g. Precision Glide Needle, Product No.: 305194 or equivalent). Refer to the HPTN 084 SSP for further details on appropriate needle gauge size and length to use for IM administration.

Preparation Steps:

1. Remove one 100 mL IV bag of Intralipid 20% from storage. If the bags are stored in the refrigerator (2°C to 8°C), remove bag from the refrigerator and wait at least 15 minutes to equilibrate to room temperature.

2. Using aseptic technique under a pharmacy BSC/ Isolator, wipe the additive port of the infusion bag with an alcohol pad (isopropyl alcohol 70% or similar) and allow to dry.

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

4. Remove the needle sheath.

5. Push the needle through the additive port of the infusion bag and withdraw 3mL of Intralipid 20% into the syringe.

6. Since the suspension can still contain some air, withdraw enough suspension from the Intralipid 20% IV bag in order to be able to de-aerate the syringe properly.

7. Remove the needle that was used to withdraw the suspension out of the Intralipid IV bag and discard the needle properly.

8. Place an overlay around the dosing syringe to maintain the blind.

9. Attach a 23G x 1½ inch (or equivalent) needle to the Luer connection of the prepared Intralipid 20% (placebo) syringe for IM injection for the participant. Alternatively, the site pharmacist can attach a syringe cap to the prepared syringe. The study staff can then attach the appropriate needle for administration to the prepared syringe in the clinic before administration.

   NOTE: The participant-specific prepared Intralipid 20% syringe is to be de-aerated by administrator prior to injection so that the correct volume can be administered.

   De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in an upright position until the first drop of suspension appears. Remove the excess suspension in order

to administer the correct volume (3 mL). If needed, collect the excess suspension in a beaker to avoid spilling.

10. Record the time the suspension was withdrawn from the Intralipid 20% IV bag into the syringe in the participant's pharmacy log. This is the time of preparation.

11. Label the prepared syringe containing 3 mL of Intralipid 20% suspension in a blinded fashion as "CAB LA 600 mg or Placebo for CAB LA", including the volume (3 mL), route (IM), participant's PTID, date and time of preparation, and date and time of expiration. Follow the DAIDS Pharmacy guidelines and local regulations for preparing the participant specific label.

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

    After withdrawal of the Intralipid 20% suspension from the IV bag into a syringe, it is recommended to inject the suspension immediately. Do not exceed 2 hours between withdrawing from the IV bag into a syringe (Step 5) and administration to the study participant.

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

4.3 Study Product Acquisition and Accountability

CAB 30 mg tablets, Placebo for CAB tablets, and CAB LA injectables are manufactured and provided by ViiV Healthcare. Intralipid 20% IV bags are manufactured by Fresenius Kabi and provided by ViiV Healthcare. TDF 300 mg/FTC 200 mg tablets and Placebo for TDF/FTC tablets are manufactured and provided by Gilead Sciences, Inc.

4.3.1 Study Product Acquisition

All study products (active and placebo) 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.

DMPA,NET-EN and/or etonogestrel implants, which will be evaluated as part of the Contraceptive sub-study, will not be provided by the Study Sponsor.

4.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the CRPMC and subsequently dispensed to study participants. All study products must be stored in the pharmacy. All unused study products must be returned to the CRPMC after the study is

completed, terminated or otherwise instructed by the study sponsor. The procedures to be followed are provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.* The site pharmacist at non-US clinical research sites must follow the instructions in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks DAIDS Pharmaceutical Affairs for the destruction of unused study products.

4.4 Other Study Product Dispensing Considerations

While it is not required, it is recommended that sites dispense two bottles of each study product (TDF/FTC or placebo and CAB or placebo) at Week 0, two bottles of oral TDF/FTC or placebo at Week 5, and three bottles at each dispensation visit throughout Step 2 to ensure an extra month supply between visits. Participants should be advised to bring open bottles to appointments, finish an open bottle before opening a new one, and should not combine or transfer pills between open bottles. A formal pill count is not required in Step 2 (or Step 3), but an open bottle can be used to assist with determining refill quantity (that is, whether there is sufficient remaining oral study product supply in the participant's possession that only two bottles need be dispensed and still maintain a three-month supply in the participant's possession).

It is important to dispense all study products at each visit at which study product dispensation is scheduled per protocol. For example, if during Step 2 a participant reports for an injection visit but refuses the injection or does not receive the injection for any other reason, oral study product should not be dispensed. Participants should either receive all study products at each visit where study product is scheduled to be dispensed, or no study products.

4.5 Toxicity Management

Toxicity management guidelines can be found in Appendix III.

4.6 Concomitant, Prohibited, and Precautionary Medications

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).

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 PI for TDF/FTC and the 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 TDF/FTC 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 was written) are 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

TDF/FTC:

- 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 (please refer to the table below) 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, as designated in the table below, 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.*

5.0 STUDY PROCEDURES

Overviews of the study visit and procedures schedules are presented in Appendices I a-c, and Appendix II (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. For each participant, independent written informed consent will be obtained before any study procedures are initiated. 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 45 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 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.

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

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

5.2 Step 1, Oral Run-in Phase: Enrollment

Enrollment/Week 0 Visit

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 randomization and provision of study product. Randomization is the point at which the participant is enrolled in the study. 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 randomization.

Up to 180 evaluable participants enrolling at sites selected for the contraceptive sub-study who consent to participate in the sub-study should have blood for pharmacological analysis, including

hormonal contraceptive agents, (DMPA, NET-EN and etonogestrel) drawn prior to initiating study product.

If of reproductive potential, a pregnancy test must be conducted on the same day that study product is dispensed and the pregnancy test result from the same day must be confirmed to be negative prior to randomization. Study product must be dispensed with instruction to participants. Participants will take the first dose of the assigned study product in the presence of site staff.

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.

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

Oral Run-in Safety Visits at Weeks 2 and 4

All HIV test results from previous visits and at least one HIV test result from the current visit must be available and reviewed. If any of these tests is reactive/positive, study drug must be discontinued and procedures in Section 5.11 will be followed.

If of reproductive potential, study approved contraception should be confirmed and a pregnancy test must be conducted and the result from the current visit (same day) must be viewed. If the participant is not pregnant, the site will follow the SOE for the visit. If a participant tests positive for pregnancy, see Section 5.14.

All participants must receive adequate product exposure during step 1, in order to assess tolerability prior to transition to step 2.

Investigators should contact the CMC at 084cmc@hptn.org if a participant has missed her contraception, has a 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 in Arm A. 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 III, 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 Week 4→ continue oral product, repeat ALT labs in 1 week If ≤ Grade 1 at Week 5, move participant to Step 2 If ≥ Grade 2 at Week 5, follow annually for HIV testing until study end of Step 3
Grade 3 AE, excluding ALT & CPK	Report to CMC and if determined to be: • Related AE→ permanently stop oral product, follow annually for HIV testing until study end of Step 3 • NOT related AE→ see Toxicity Management Section and follow CMC guidance
Grade 3 ALT	Report to CMC Permanently stop oral product, repeat ALT labs weekly until ≤ Grade 1, follow annually for HIV testing until study end of Step 3
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 annually for HIV testing until study end of Step 3
Grade 4 ALT	Report to CMC Regardless of CPK permanently stop oral product, repeat ALT labs weekly until ≤ Grade 1, follow annually for HIV testing until study end of Step 3
Grade 4 CPK + < Grade 3 ALT	Report to CMC for adjudication

5.4 Step 2, Injection Phase: Injection Visits

Visits at Week 5, 9, and every 8 weeks thereafter (until end of Step 2)

The first study product injection is given at the Week 5 visit. 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. Neither the injection/placebo nor TDF/FTC/placebo may be given if any HIV test is reactive/positive. For management of participants with an HIV-positive test, see Section 5.11.

If of reproductive potential, a pregnancy test must be conducted on the same day that study product is injected or dispensed and the pregnancy test result from the same visit day must be confirmed to be negative PRIOR to injection/dispensing of study product. If the pregnancy test is positive, see Section 5.14.

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. For management of participants with AEs, see Appendix III, Toxicity Management.

If participants miss injections, contact the CMC.

In select circumstances e.g. "unconfirmed" pregnancy, use of prohibited concomitant drugs, or refusal to use long acting contraception it may be necessary to temporarily hold administration of blinded study product. If blinded study product cannot be administered for safety reasons, in consultation with the CMC, participants may be transitioned to open-label TDF/FTC temporarily. Such participants remain in Step 2 follow-up and attend regularly scheduled Step 2 visits. Should the reason(s) for temporary blinded study product later resolve and it becomes safe again for study product administration, participants may be transitioned back to blinded study product. The CMC must be contacted and its guidance must be followed in all cases of temporary blinded study product hold during Step 2.

Contraceptive Sub-study

Up to 180 evaluable participants enrolled at sites selected for the contraceptive sub-study who consented to participate in the sub-study should have blood for pharmacological analysis, including hormonal contraceptive agents, (DMPA, NET-EN and etonogestrel) drawn prior to study product administration. Subjects participating in the contraceptive sub-study should have blood samples drawn at Weeks 25, 49 and 73. These visits are chosen because they should be at an approximately similar point in the injection cycle for DMPA and NET-EN as the enrollment visit, assuming an 8 or 12 week cycle. Dosing date for all injectable contraceptives should be recorded throughout the study.

5.5 Step 2, Injection Phase: Safety Visits

Injection Phase Safety Visits at Week 6, 13, 21 and 42

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 for the participant to continue with study product. For management of participants with an HIV-positive test, see Section 5.11.

If of reproductive potential, a pregnancy test must be conducted on the same visit day and must be confirmed to be negative for the participant to continue with study product. If the pregnancy test is positive, see Section 5.14.

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. For management of participants with AEs, see Appendix III, Toxicity Management.

5.6 Step 3, Follow-up Phase

Follow-up Phase of Step 3 at Day 0 and Weeks 12, 24, 36, 48

For each study participant, Day 0 of Step 3 must occur within 8 weeks following completion of Step 2. 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 provision of study pills. For management of participants with an HIV-positive test, see Section 5.11.

If of reproductive potential, a pregnancy test must be conducted on the same day that study product is dispensed and the pregnancy test result from the current visit must be confirmed to be negative. If the pregnancy test is positive, see Section 5.14.

Results from the clinical and laboratory evaluations (e.g., chemistry, LFTs, hematology) must be available and be reviewed by the IoR or their designee prior to provision of study pills. For management of participants with AEs, see Appendix III, Toxicity Management.

5.7 Standard of Care (SOC) Counseling for all Participants

5.7.1 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. In addition, counseling will emphasize the double-blind nature of the study.

5.7.2 Adherence Counseling and Monitoring

It is clear that the effectiveness of daily oral TDF/FTC is tightly correlated with adherence.

The study will provide adherence support/counseling at baseline and at all follow-up visits for all participants. Counseling will be provided in accordance with recommendations from PrEP clinical guidance documents and in-country implementation strategies.[54 55] Using a participant-centered approach to frame discussions, standard adherence counseling will include education around the importance of daily pill adherence and supporting strategies that link pill taking to the participant's daily routine. Counseling will also focus on the importance of returning for injection visits on or as close to the scheduled date as practical.

Participants will receive oral adherence counseling during Steps 1, 2 and 3, and will also be regularly reminded during Step 2 of the importance of returning for injections. Oral adherence counseling for which will include an emphasis on the known relationship between adherence and TDF/FTC efficacy.

NOTE: While adherence to oral study product is important for the duration of the study; there are no minimal oral study product adherence requirements for Steps 2 or 3.

5.8 Injection Visit Windows

The visit windows for all visits, including injection visits, are outlined in the SSP Manual.

There are two types of visit windows: 1) narrower target visit windows, and 2) wider allowable visit windows. Allowable visit windows are contiguous. In general, the target visit window for injection visits is +/- 3 days. Sites must attempt to schedule participants as close to a given visit target date as possible.

Refer to SSP for instruction on managing participants who report to clinic outside of injection window.

5.9 Procedures for Continued Oral and Injectable Dosing

Refer to Appendix III, 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. Also consult Section 5.4 above for temporary study product hold instruction.

5.10 Procedures for Participants in Step 2 Who Do Not Complete the Full Course of Study Product

Participants who have received at least one injection and refuse further injections or discontinue due to an AE will be managed as follows:

- Participants will be transitioned to open-label TDF/FTC no later than eight weeks after the last injection (if it is safe to do so) for up to 48 weeks
- Participants will be followed on TDF/FTC according to the Step 3 SOE until the end of the participant's Step 3 schedule

Participants who refuse further TDF/FTC or discontinue due to an AE will be managed as follows:

- Participants will be followed off study product according to the SOE until the end of each participant's Step 3 schedule.

All participants will be followed up thereafter at least annually for HIV testing until Step 2 and 3 follow up is completed

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

5.11.1 Screening and Enrollment

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

5.11.2 After Study Enrollment/Randomization

Frequent testing for HIV acquisition during the study period (at all scheduled study visits) 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. If 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 (see SSP Manual for email alias regarding suspected HIV infection), including the HPTN LC. Refer to the SSP Manual for instructions regarding HIV testing.

Step 1
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
Participants with confirmed HIV infection during Step 2 will not receive additional injections or

oral study product, and will be followed per the SOE in Appendix II quarterly for approximately 48 weeks. In addition, sites will have a standard operating procedure (SOP) that outlines a plan in the event that a participant becomes HIV-infected during any Step of the study, and in particular during Step 2 of the study, which must include the participant's facilitation into locally-available ART to be started immediately, to prevent emergence of drug resistance; ART should be continued for a minimum of 52 weeks after the final injection. 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

Participants with confirmed HIV infection during Step 3 will have their TDF/FTC stopped and be followed quarterly at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by guidance from members of the HIV alias. Study product will be discontinued and participants will be referred for care.

5.12 STIs

Testing for *Neisseria gonorrhoeae* (GC)/*Chlamydia trachomatis* (CT), *Trichomonas vaginalis* (TV) and syphilis will occur throughout the study. Testing will be performed at local laboratories.

Participants will be referred for treatment of STIs as per local guidelines. Symptomatic screening for STIs beyond what is required by the protocol will be at a site's discretion and cost.

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. Persons with a positive HCV Ab test at Screening will be excluded from the study. Participants will be tested for Hepatitis B surface antibody (HBsAb), and Hepatitis B core antibody (HBcAb, total). Participants who do not have evidence of immunity to HBV (e.g., negative HBsAb) will be provided HBV vaccination. 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 Ib). Incident HCV infection during follow-up will not mandate discontinuation of study product absent other requirements per Appendix III - Toxicity Management.

5.14 Pregnancy

Because 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 an effective method of contraception as outlined in Section 3.1. Participants should be encouraged to delay pregnancy for at least 52 weeks following discontinuation of IM dosing. All participants must also use male or female condoms for prevention of HIV and other STIs. Study staff will provide contraceptive counseling to enrolled participants throughout the duration of

study participation and will facilitate access to contraceptive services through direct service delivery and/or active referrals to local service providers for methods that cannot be provided on-site.

Study staff should confirm adequate contraception with one of the study approved contraceptive methods (see section 3.1) at each visit. In situations 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 CMC at 084cmc@hptn.org for further guidance regarding the administration of study injections.

In the event of a first positive pregnancy test or where pregnancy cannot be excluded, a four-week supply of open label TDF/FTC should be given. No study product injections should be given if there is a positive pregnancy test. Participants who have a first positive pregnancy test during Step 1 (Week 2 or Week 4) may transition to Step 2 if subsequent pregnancy testing done 4 weeks after the initial positive pregnancy test determines that the participant is not pregnant and all other safety requirements for transition to Step 2 are met.

All participants who are 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 test may be done as indicated. All findings and outcomes will be collected and reported.

Refer to procedures in Appendix Id.

Study staff will also offer participants with male and/or female condoms and counseling on use of condoms.

Participants of reproductive potential will have pregnancy testing as outlined in the SOE. Participants will be encouraged to report all signs or symptoms of pregnancy to study staff.

Confirmed Pregnancies

Participants with a positive pregnancy test will require confirmation of pregnancy at a subsequent visit at least four weeks later. All pregnancies that occur during the course of the study must be reported to the CMC within seven days of site awareness (either upon confirmation by urine or blood pregnancy testing during a study visit or as reported by the participant between study visits). Site staff will refer to their SOP for detailed management.

All pregnant participants with a confirmed positive pregnancy test (four weeks after the initial pregnancy test) will be unblinded and followed by the study every 12 weeks. Regardless of the randomization assignment or point in the study, all pregnant participants will be placed on open-label TDF/FTC for the duration of the pregnancy. No participant with a positive pregnancy test will be administered CAB, CAB LA, or CAB LA placebo. The site IoR or designee will refer pregnant participants to all applicable pregnancy-related services and will be provided 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.

Once pregnancy outcome is reached, if the participant is not breastfeeding, she may resume study product and visits according to the SOE. Should a participant who delivers a child during the study elect to breastfeed, she will stay on open-label TDF/FTC and will be followed per the SOE. Once a participant has finished breastfeeding, she may resume study product and visits according to the SOE. To most closely reflect eventual real-world practice, unblinded participants will have the option to return to open-label study product in their original randomization arm (either CAB LA or oral TDF/FTC). Participants who are pregnant at their last study visit will continue to be followed until the pregnancy outcome is ascertained or it is determined that the pregnancy outcome cannot be ascertained through all reasonable means. All pregnancy outcomes will be reported on relevant CRFs. Outcomes meeting criteria for expedited AE (EAE) reporting also will be reported. Infants will be followed up for one year post-natally to ascertain final pregnancy outcomes in respect to congenital anomalies.

5.15 Participants who decline to use long acting contraception

All participants who are not currently pregnant and potentially able to conceive and decide to discontinue long acting contraception for any reason will be immediately placed onto open label TDF/FTC and follow procedures detailed in Appendix Ic.

> ***Please note that if a participant transitioned to open-label TDF/FTC during Step 2, either because she wanted to become pregnant or declined to continue using long-acting contraception, and subsequently changes her mind she may continue in the study on blinded study product (per original randomization) once she has documentation of a negative pregnancy test and of resuming long-acting contraception; she must also meet all other standard visit criteria.

Participants who continue to desire children and complete 48 weeks of TDF/FTC (initiated no later than eight weeks after her last injection) while study follow-up is ongoing will be required to be followed up at least annually for HIV testing.

If the participant conceives, she should follow procedures for pregnant participants (see section 5.14).

Participants who complete pregnancy and cease breastfeeding may resume open-label study product in their original randomization arm (either CAB LA or oral TDF/FTC) and visits according to Appendix Ib, provided they agree to use an approved contraceptive method (either injection, implant or IUD/IUS). If participants decline to use an approved contraceptive method, they will be given open-label TDF/FTC for 48 weeks starting no later than eight weeks after her last CAB LA/placebo injection. If study follow-up is ongoing she will be required to be followed up at least annually for HIV testing thereafter.

In all cases contact the HPTN 084 CMC at 084cmc@hptn.org

5.16 Acceptability Assessments

Acceptability of CAB LA and daily use of TDF/FTC will be assessed through administration of brief behavioral surveys conducted at Enrollment and every six months. The surveys will include, but not be limited to, questions about participants' attitudes/beliefs towards CAB LA and TDF/FTC; product and study-related motivations. In addition, four sites will participate in a qualitative sub-study.

Qualitative Sub-study
The qualitative sub-study includes two separate sets of activities: repeated in-depth interviews with a subsample of current trial participants and special cases; and semi-structured observations in waiting rooms.

In-Depth Interviews (IDIs)
The four sites participating in the qualitative sub-study will work with SCHARP to randomly select and short-list from 8-10 participants who are currently enrolled and on study product across several years of trial implementation (e.g., Jan-Dec 2018; Jan-Dec 2019; Jan 2020 to present). Sites will enroll from 4-6 participants in each of these time periods to participate in the sub-study. If a site is still enrolling, it may choose to enroll fewer (e.g., 4-5) participants each from 2018 or 2019, and more participants (6-8) from 2020.

They IDIs may be conducted remotely (by cell phone or video chat) or be conducted in another private and mutually agreed upon location in sites that are limiting non-essential clinic visits. Sub-study participants who participate in IDIs will be consented separately and must agree to being interviewed up to three times over the course of their trial participation. If an interview takes place virtually, informed consent will be documented in a manner that is consistent with local ethics committee or IRB guidelines. Several options may be considered including administering and recording the informed consent document, as well as the participant's verbal consent over the phone and documenting consent in a separate document.

Topics for the recently enrolled participants (within 1st or second injection):

- Household, relationship context, including any impact of COVID-19;
- Current and future goals, including perspectives on delaying fertility during trial;
- Perceived HIV risk;
- Current/previous experience with prevention products – contraception, condoms, other HIV prevention methods, including how local response to COVID-19 affected product use;
- Motivation for trial participation, including knowledge of and decisions related to joining HPTN 084 versus other HIV prevention trials;
- Disclosure to partner(s), family, friends about trial;
- Understanding of trial context – randomization, blood draws and other criteria;
- Beliefs about trial products;
- Understanding of and concerns about pregnancy restrictions;
- Experience with oral pill use and with first injection.

Topics experienced participants (in Step 2, but have received five or more injections):

- Household/relationship context, or any changes if previously interviewed;
- Any significant life events, including how local response to COVID-19 affected household/daily routine and trial participation;
- Partner/other support or lack for trial participation;
- Attitudes towards aspects of trial participation, including interactions with trial staff;
- Adherence to oral pills – focused on reasons for missing pills;
- Adherence to injections – focused on getting to clinic, acceptability of injection;
- Any impact of service disruption due to COVID-19 on product adherence;
- Acceptability of oral pills versus injectable prevention;
- Perceived HIV risk;
- Reproductive desires, contraceptive experiences and thoughts about pregnancy restrictions;
- Early preferences for prevention modalities and any other suggestions or concerns about the trial.

The final in-depth interview will be conducted while participants are still in active follow-up but have been unblinded to the product they are using (e.g., if an individual or the trial moves to an open-label TDF/FTC). Topics for this interview include:

- Any significant life events, including how local response to COVID-19 affected household/ daily routine and trial participation;
- Participant thoughts about which arm she was in, Participant thoughts about level of adherence;
- Perceptions about pregnancy restrictions for CAB LA;
- Perceptions of, questions about the open-label arm;
- Presentation of results (if available) and any discussion about discordance – explore barriers and facilitators of adherence, including any impact of COVID-19 on product adherence;
- Recommendations about how to better support access and adherence to prevention methods beyond trial;
- and Preferences for prevention beyond trial setting.

Additional topics for participants recruited as “special cases” include:

- Feelings toward and circumstances related to pregnancy, product discontinuation or seroconversion;
- Partner and family member attitudes towards pregnancy and/or product use;
- Impact of COVID-19 related clinic, community or household disruptions on trial participation, product use or general well-being
- Attitudes towards product unblinding as related to pregnancy or seroconversion;
- Attitudes towards using CAB LA and/or TDF/FTC during pregnancy;
- Prevention preferences beyond trial and any recommendations;
- treatment or care plans, if related to seroconversion.

Waiting room observations

Approximately once a quarter, a qualitative team member will conduct a 45-minute semi-structured observation in the waiting room(s) of the study clinic until data saturation. (This activity may take place less frequently if COVID-related policies suspend use of waiting rooms for study participants.) Because information about potential waiting room observations was included in the main study consent, no additional consent procedures are required for this activity. The qualitative team will use a data extraction sheet to note:

- Date/time; Approximate # of participants in waiting room, including gender and any babies, children;
- Materials, videos or other activities organized by site;
- Overall activity within waiting room;
- Focus on a nearby cluster of participants – overall demeanor of individuals (animated, calm, happy, bored, irritated) and topics of discussion if overheard;
- If any brief intercepts with participant, information about wait time in clinic, overall experience in trial, concerns, recommendations or other thoughts shared with observer.

Several measures will be taken to protect the confidentiality of trial participants who take part in semi-structured interviews. Single or repeated in-depth interviews aimed at understanding acceptability of an injectable PrEP product will be conducted in a private space. During interviews, the moderator will address participants by a unique number or pseudonym chosen by the participant after consenting to participation. This will ensure that no names are recorded on audio-recordings or appear in transcripts. When data collectors conduct observations or engage in brief conversations in clinic waiting rooms or more public spaces, they will not record any names or identifying information related to the trial participants they observe or talk with. Field notes will be labeled by the date, time and location of the observation/informal discussion only. Prior to engaging in a discussion with individuals or groups within waiting rooms, participants will be reminded that their identities will not be recorded in any notes and that they can choose whether or not to participate in these discussions.

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.

Note: HIV testing is only required at interim visits if study product is administered, if HIV infection is suspected or is required as part of an AE investigation.

5.18 Planned Unblinding of Study Participants

When the required number of incident HIV endpoints has been reached, or when the last participant completes scheduled Step 2 follow-up (meaning all participants will move to Step 3), and when all corresponding procedures at the HPTN SDMC, LC, and LOC have been completed, including final confirmation from the HPTN SDMC, the study will be unblinded.

Participants with a confirmed pregnancy (see section 5.14) will be unblinded. Procedures for unblinding pregnant participants will be detailed in the SSP.

5.19 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 if appropriate, the SAHPRA, ViiV/Gilead 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 AEs 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 expedited AE reporting period for this study is from Enrollment (Week 0) until follow-up in the study ends.

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).

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.

6.2 EAE Reporting

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.

6.2.1 Reporting to DAIDS

The DAIDS Adverse Event Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical

difficulties, EAEs may be submitted via the DAIDS EAE form. For questions about DAERS, please contact CRMSSupport@niaid.nih.gov. Site queries may also be sent with the DAERS application itself.

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

6.2.2 Reporting Requirements for This Study

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

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

- 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); TDF/FTC fixed dose combination tablet containing 200 mg of FTC and 300 mg of TDF (also outlined in Section 4.0).

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.

6.2.3 Grading Severity of Events

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.

6.3 Safety Monitoring

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.). Sites will be instructed to not solicit guidance from the CMC regarding HIV seroconversions in order to ensure to the extent possible that the team is blinded to the number of infections occurring in the study. The HPTN LC will be available for questions regarding HIV confirmation testing.

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 Study Monitoring Committee (SMC), which will meet by conference call approximately every 6 months. More frequent or *ad hoc* reviews may be conducted by the SMC as needed.

This study also will be monitored by a NIAID Data and Safety Monitoring Board (DSMB), 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 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 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 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/documents/criticaleventsmanual.pdf

7.0 STATISTICAL CONSIDERATIONS

7.1 Review of Study Design

This is a Phase 3 randomized, multi-site, two-arm, double-blind study of the safety and efficacy of CAB LA vs. TDF/FTC for prevention of HIV-acquisition in HIV-uninfected women. All participants will receive a placebo product. Eligible participants will be randomized 1:1 to receive either oral CAB/CAB LA + placebo TDF/FTC (Arm A) or daily oral TDF/FTC + placebo CAB/CAB LA (Arm B), and move through 3 Steps. In Step 1, study participants will receive both active and placebo oral tablets (appropriate for their arm) for five weeks. In Step 2, participants will receive either i) an injection of CAB LA (at two time points four weeks apart and every eight weeks thereafter) and placebo TDF/FTC pills (Arm A) or ii) daily oral TDF/FTC and placebo injections (at two time points four weeks apart and every eight weeks thereafter) (Arm B) until the required number of incident HIV endpoints (114) is accrued, estimated to be when the final participant reaches 76 weeks on Step 2 (Week 81 in study). In Step 3, all participants will receive open-label daily oral TDF/FTC for up to 48 weeks (starting 8 weeks after their last injection). Participants will therefore be followed between approximately 137 weeks to 241 weeks (between 81 and 185 weeks on study product during Steps 1 and 2 and up to 48 weeks on open-label daily oral TDF/FTC). All participants will transition to local HIV prevention services after completion of Step 3.

7.2 Endpoints

7.2.1 Primary Efficacy Endpoint

- Number of documented incident HIV infections in Steps 1 and 2

7.2.2 Primary Safety Endpoint

- Grade 2 or higher clinical and laboratory AEs

7.2.3 Secondary Endpoints

- Number of documented incident HIV infections in Steps 1, 2 and 3
- Number of documented incident HIV infections in participants in subgroups broken down by baseline age, HSV-2 status, contraceptive use method and BMI </≥ 25 kg/m^2
- Plasma concentrations of CAB in participants randomized to CAB/CAB LA
- Plasma and DBS concentrations of TFV/TFV-DP in a subset of participants randomized to TDF/FTC
- Survey of attitudes and willingness to use CAB LA and TDF/FTC

7.2.4 Tertiary Endpoints

- Sexual risk (number of partners, number of unprotected sex acts)
- Incident STIs (GC/CT, trichomonas, syphilis)

- Grade 2 or higher clinical and laboratory AEs broken down by BMI </≥ 25kg/m^2
- Weight
- Number of incident pregnancies
- Pregnancy outcomes
- Resistance mutations to study products (including but not limited to K65R, M184V/I, Q148R) among seroconverters
- Plasma concentrations of DMPA, or NET-EN, and etonogestrel when co-administered with study product (TDF/FTC or CAB LA)

7.3 Sample Size and Interim Monitoring

The primary analysis will be based on HIV incidence during Steps 1 and 2. As described previously, we assume that participants will be followed between 81 (latest enrollees) and 185 (earliest enrollees) weeks in Steps 1 and 2 (1.6 – 3.6 years), with a uniform distribution of enrollments over a two-year period. Thus, average time in Steps 1 and 2 will be 133 weeks (2.6 years). Sample size calculations are based on the following assumptions:

- Background HIV incidence, in the absence of any PrEP, is 3.5% per year
- Both CAB LA and TDF/FTC are 85% effective when used with 100% adherence
- 2.5% one-sided type I error rate and 90% power at the indicated alternative
- Average follow-up duration of 2.6 years (range: 1.6 – 3.6 years)
- Maximum 5% lost-to-follow-up per year

Table 7.1 presents five scenarios and associated total sample sizes. All are superiority designs. The first scenario assumes that adherence to TDF/FTC and CAB/CAB LA will be 50% and 85%, respectively, averaged over the entire Step 1 and 2 follow-up period. The second and third scenarios assume a higher adherence to TDF/FTC (second line) and lower adherence to CAB LA (80%) (third line) (these scenarios are considered unlikely).

The last two scenarios retain the conservative assumption of 80% adherence to CAB LA and assume lower adherence to TDF/FTC of 45% and 48%. The largest blinded trials of TDF/FTC among women in a similar setting have shown even lower adherence than assumed in Table 7.1 (see section 7.8.4.1). Given this history we believe that a sample size of at least 3,128 (111 events for a fixed sample size trial; we will target 114 events to allow for interim monitoring) provides an adequate degree of robustness against uncertainties in adherence rates to the two drug regimens.

The trial will continue until we reach 114 events or a stopping boundary is crossed (see below).

Table 7.1. Five Case Scenarios

Adherence		HIV Incidence (%/year)[1]				
TDF/FTC	CAB LA	TDF/FTC	CAB LA	RR	Number Events	Sample Size
.50	.85	2.01	0.97	.48	78	2352
.55	.85	1.86	0.97	.52	98	3112
.50	.80	2.01	1.12	.56	125	3590
.48	.80	2.07	1.12	.54	111	3128
.45	.80	2.16	1.12	.52	98	2686

[1]Background incidence is reduced by a weighted average of fully adherent and non-adherent individuals e.g. 2.01 = 3.5*((1-.85)*.5 + 1*(1-.5))

This study will be monitored by a NIAID DSMB, which will meet at least annually to review safety and efficacy data, as well as data quality. The DSMB will use an O'Brien-Fleming boundary to consider stopping the trial early for efficacy. Further details will be provided in a Statistical Analysis Plan prior to the first interim analysis.

Table 7.2. 95% CI for the estimated proportion of women below the contraceptive threshold in the CAB LA arm by contraceptive subgroup (assuming one observation per woman)

		Total number of women CAB LA arm for each contraceptive subgroup				
		10	15	20	30	50
Number below threshold	0	0 - .26	0 - .18	0 - .14	0 - .095	0 - .058
	1	.002 - .44	.002 - .32	.001 - .25	.001 - .17	.000 - .11
	2	.025 - .56	.016 - .40	.012 - .32	.01 - .22	.005 - .14
	3	.07 - .65	.04 - .48	.03 - .38	.02 - .26	.012 - .16

In a subset of women we will evaluate contraceptive drug levels for three groups of women defined by their contraceptive choice: i) DMPA, ii) NET-EN; iii) etonogestrel. Analyses will 1) estimate, for each contraceptive subgroup, the proportion of women in the CAB LA arm who have contraceptive drug concentrations (DMPA, NET-EN, and etonogestrel for the three contraceptive types, respectively) below the contraceptive threshold and 2) compare, for each contraceptive subgroup, mean contraceptive drug concentrations between the CAB LA and TDF/FTC arms. Table 7.2 shows the expected 95% CI for the estimated proportion of women below the contraceptive threshold, tabulated by the total sample size and the number of women

below threshold. Table 7.3 shows the minimum detectable difference in mean DMPA levels between the CAB LA and TDF/FTC arms. Both Table 7.2 and Table 7.3 assume one observation per woman. In fact, we expect to have up to three observations per woman so the realized confidence intervals and minimum detectable differences will be smaller than shown in these tables. Based on these tables we will target approximately 30 women in each arm in each contraceptive subgroup.

Table 7.3. Minimum detectable difference (ng/mL) in mean MPA levels (80% power) between CAB LA and TDF/FTC arms, assuming σ = .3 mg/mL and α = .05, two-tailed, assuming one observation per woman.

Total number of women in each arm for each contraceptive subgroup				
10	15	20	30	50
.37	.31	.26	.22	.17

7.4 Accrual and Retention

Approximately 3,350 participants will be enrolled in approximately 24 months and followed through Steps 1 and 2 for 1.6 to 3.6 years and on oral TDF/ FTC for an additional 48 weeks. An average annual retention rate of at least 95% percent will be targeted (87 - 88% for the entire Step 1 and 2 follow-up period).

7.5 Random Assignment

Participants will be randomized to one of two study arms in a 1:1 ratio. Randomization will be stratified by study site, and a permuted blocks design will be used to ensure balanced treatment assignments within study site. The randomization scheme will be generated, operationalized and maintained by the HPTN SDMC. Additional details regarding the process of randomization will be included in the SSP Manual. All endpoints will be analyzed according to a participant's original blinded randomization assignment, regardless of timing of endpoint occurrence.

7.6 Blinding

Study site staff, with the exception of the site Pharmacist of Record or their designee, and participants will be blinded to the random assignments. Blinding will be maintained until the trial is completed or stopped, i.e., the trial is stopped early, or the required number of endpoints (114) has been met. At a specified time directed by the HPTN SDMC, participants will be notified of their treatment assignment.

In addition, as described in sections 5.14 and 5.18, participants with a confirmed pregnancy will be unblinded. Participants who are unblinded due to pregnancy may restart open-label study product in their original randomization arm (open label CAB LA or TDF/FTC) following delivery and cessation of breastfeeding.

7.7 Data and Safety Monitoring Board Oversight and Study Monitoring Committee Oversight

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).

7.8 Statistical Analysis

This section briefly describes the final study analyses, unblinded as to treatment arm assignment. All analyses will be modified intent to treat (participants determined to be HIV-infected prior to randomization will be omitted from the analysis), unless otherwise specified. Detailed technical specifications of the statistical analyses will be described in a separate Statistical Analysis Plan.

7.8.1 Analyses of Primary Efficacy Objective

- To evaluate the relative efficacy of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) vs. daily oral TDF/FTC for HIV prevention (Steps 1 and 2)

To preserve the integrity of randomization, person-time and HIV events will be included in this analysis based on each individual's scheduled duration of participation in steps 1 and 2, as determined at randomization. Specifically, individuals who refuse injections, pills or both, or who receive open-label study product (e.g. due to pregnancy) will be included in this analysis in their original randomization arm for the duration of their originally scheduled participation in Steps 1 and 2..

The Hazard Ratio (HR) comparing CAB LA vs TDF/FTC and a 95% confidence intervals will be estimated using a Cox proportional hazards model with treatment arm as the only covariate, stratified by site using data from steps 1 and 2 only. As outlined in greater detail in the Statistical Analysis Plan, version 2.0, dated June 9, 2020, and the HPTN 084 COVID Disruption document, prespecified intervals of COVID-19 disruption may be administratively censored from the analysis using the Anderson-Gill counting process formulation of the Cox model. We will test the hypothesis Ho: HR = 1.0 versus Ha: HR $\neq$ 1.0 using $\alpha = 0.05$. If the number of events is small (<40) then the p-value will be confirmed using a permutation test based on 100,000 random permutations of the treatment assignments; if there is a meaningful difference between the permutation and asymptotic procedures, the permutation p-value will be used. Treatment efficacy will be estimated as TE = 1 - HR.

7.8.2 Analyses of Primary Safety Objective

- To evaluate the relative safety of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) vs. daily oral TDF/FTC for HIV prevention (Steps 1 and 2)

Local reactions
The number and percentage of participants experiencing local reactions to the injections will be tabulated by severity and treatment arm. For a given local reaction type, each participant's

reaction will be counted once under the maximum severity for all injection visits. In addition to the individual reaction types, the maximum severity of local pain or tenderness, induration or erythema, and of systemic symptoms will be calculated. Wilcoxon rank sum tests will be used to test for differences in severity between arms.

AEs and Serious Adverse Events (SAEs)
AEs will be summarized using MedDRA System Organ Class and preferred terms. Tables will show by treatment arm the number and percentage of participants experiencing an AE within a System Organ Class or within preferred term category by severity. For the calculations in these tables, a participant with multiple AEs within a category will be counted once under the maximum severity.

A listing of SAEs reported to the DAIDS Regulatory Support Center (RSC) Safety Office will provide details of the events including severity, time between onset and last dosing, and cumulative number of doses received. Formal statistical testing comparing arms is not planned since interpretation of differences must rely heavily upon clinical judgment.

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 treatment arm and 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 by treatment arm for follow-up time points. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will also be included in the tabulation of AEs described above.

7.8.3 Descriptive Analyses of Primary Efficacy Endpoint

HIV incidence

The HIV incidence rate will be calculated as the total number of participants with confirmed incident HIV infection during study follow-up of Step 1 and Step 2 divided by the person-years accumulated in each arm. 95% CIs will be calculated.

Cumulative incidence over follow-up for each arm will be computed using product limit estimates and plotted with 95% CIs.

7.8.4 Considerations for a Supportive Analysis if Adherence to TDF/FTC is Higher than Expected

The primary analysis for this protocol is the superiority analysis described in Section 7.8.1. However, there is substantial evidence that the efficacy of TDF/FTC (relative to placebo) is highly dependent on adherence to daily pill-taking and modestly dependent on sex. Specifically, if adherence to daily oral TDF/FTC is 50% or greater, there is credible evidence that TDF/FTC is superior to placebo (see section 7.8.4.1, below). The current HPTN 084 trial design has high power to show that CAB LA is superior to TDF/FTC for TDF/FTC adherence rates up to 48%, assuming adherence to CAB LA is 80% or higher. This design is appropriate if adherence in

young, unmarried women in South Africa is consistent with the low rates seen in previous placebo controlled trials in that population. However, if adherence to TDF/FTC is high, as in some recent open-label trials, then the power to demonstrate CAB LA superiority declines and a non-inferiority (NI) comparison of injectable CAB LA to daily oral TDF/FTC would be more appropriate.

In the following sections we outline the rationale and develop the methods for a supportive adherence-dependent NI comparison of injectable CAB LA to daily oral TDF/FTC. Specifically, we review the evidence showing that efficacy of TDF/FTC (relative to placebo) is adherence dependent, indicate how adherence to TDF/FTC could be measured in HPTN 084, describe how an NI margin could be chosen and provide results from analytic calculations and simulations showing that this procedure preserves the nominal type I error rate for the analysis. Since the primary superiority analysis is well-powered for TDF/FTC adherence up to 50%, the supportive NI analysis described here would only be triggered if TDF/FTC adherence is greater than 50%. Of course, if the primary analysis shows superiority, there is no need for an NI analysis. However, we note that Noninferiority and Superiority designs form a continuum where a superiority design can be thought of as a "Noninferiority" design with a margin equal to 1.0 (see section 7.8.4.2 for a discussion of margins). From that point of view, the adherence-dependent NI comparison described here encompasses the superiority analysis that has been designated as the primary analysis for the trial.

7.8.4.1 Evidence Showing that Efficacy of TDF/FTC is Adherence Dependent

Meta-analysis is a statistical technique for combining the results of studies to provide more information than any one study can on its own. We are fortunate to have comparable biomarker-based measures of adherence in seven large, high-quality, randomized controlled trials (iPrEX, TDF2, Partners-PrEP, VOICE, FEM-PrEP, Bangkok, IPERGAY) (Table 7.4), that can be incorporated into a meta-analytic model to provide a robust model of the relationship between TDF/FTC efficacy and adherence.

Table 7.4. Summary of Plasma-based Adherence Measurements from Previous RCTs of Daily Oral TDF or TDF/FTC.

All trials used daily oral dosing except IPergay, which used event-driven dosing.						
Trial	Year	Gender	How measured	Detection limit (TFV)	% TFV detectable	RR – placebo vs active
FEM-PREP	2012	Female	Nested case-control	0.25 ng/ml	24	1.05
VOICE - TDF/FTC	2015	Female	Quarterly sampling	0.31 ng/ml	29	0.97
VOICE - TDF	2015	Female	Quarterly sampling	0.31 ng/ml	30	0.67
iPrex	2010	Male	Nested case-control	10 ng/ml	51	1.79
Bangkok	2013	Male/ Female	Nested case-control	0.3 ng/ml	66	1.59/4.56

Partners-TDF/FTC	2012	Female	Nested case-cohort	0.3 ng/ml	77	2.84
Partners-TDF	2012	Female	Nested case-cohort	0.3 ng/ml	80	3.36
Partners-TDF/FTC	2012	Male	Nested case-cohort	0.3 ng/ml	82	6.32
Partners-TDF	2012	Male	Nested case-cohort	0.3 ng/ml	85	2.74
TDF2	2012	Male/ Female	Nested case-control	0.3 ng/ml	80	5.0/2.02
IPERGAY	2015	Male	Every 2 months in first 113 participants	0.1 ng/ml	86	6.93

Using the data from Table 7.4 we conducted a "random effects meta-analysis" (by fitting a mixed-effects regression model) with log (RR: placebo vs. active) as the outcome and adherence and gender as covariates. Each trial is weighted based on the inverse of the variance of the estimated log(RR) (primarily a function of the number of HIV infections). The random effects meta-analysis can account for heterogeneity between study populations (random effects component), and explicitly estimate the relationship between adherence and efficacy (fixed effects component). A broad range of adherence levels is represented in these trials, and this makes it possible to estimate efficacy at moderate (e.g., 55%) or moderately high (e.g., 75%) levels of adherence without extrapolating beyond the range of observed data[1]. A limitation, however, is that, for women, most data are available for very low (≤ 30%) and very high adherence levels (> 75%) with little in the middle range of interest to HPTN 084.

The fitted regression model is

$$\log(RR) = -0.752 + 0.105 * male + 2.276 * adh \qquad (1)$$

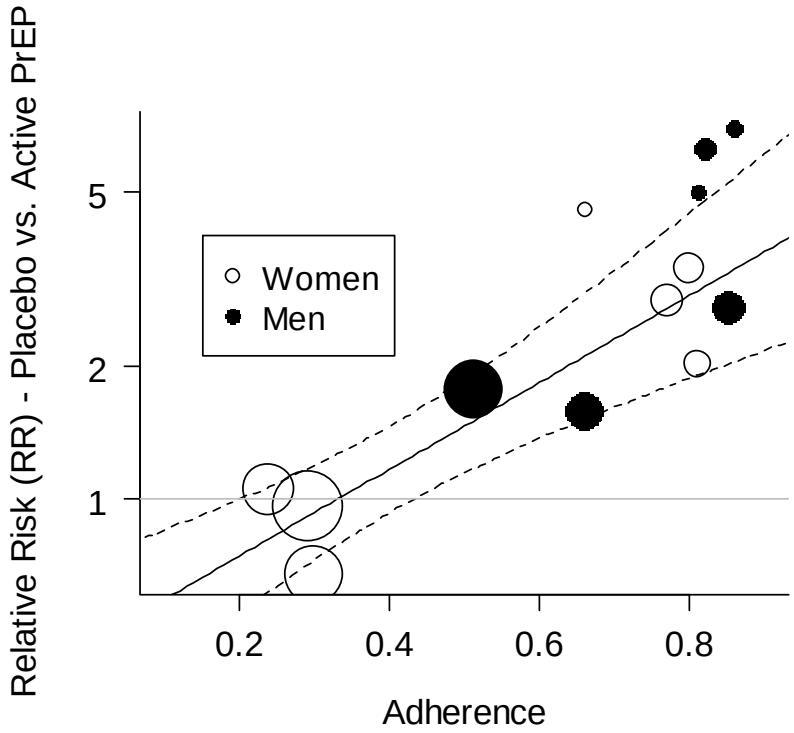
Figure 7.1 shows the meta-regression relating adherence to the RR (placebo vs PrEP) in women along with 95% confidence intervals. Note that in Figure 7.1 a RR greater than 1 implies efficacy because the RR compares placebo versus PrEP, not the reverse. Note also that the y-axis uses a log scale.

This model indicates that, in women, TDF/FTC is superior to placebo (RR > 1.0) with high confidence for adherence rates greater than 44%. The ability to estimate efficacy of TDF/FTC relative to placebo (along with a 95% CI) as a function of adherence can be used to select an NI margin when TDF/FTC adherence is high (see section 7.8.4.3).

[1] Adherence measures for the published trials are based on proportion of samples with detectable drug concentrations measured in a randomly selected subset of HIV-infected controls randomized to Truvada. The lower limit of 0.31 ng/mL generally corresponds to evidence of TDF/FTC taken within 14 days of the visit.

Figure 7.1. Meta-regression Analysis of Previous Trials - RR (Placebo vs Active Drug) Versus Adherence to Daily Oral PrEP.

Regression line (solid line) and 95% confidence intervals (dashed line) are specific to women.



7.8.4.2 Measurement of Adherence

As shown in Table 7.4 previous trials have generally measured adherence in longitudinal samples from randomly selected participants, or in randomly selected controls of a nested case-control study. These assessments have used plasma TFV concentrations, which provide information on dosing in the last 1-2 weeks. For consistency with these previous studies, therefore, measurement of adherence to determine an NI margin using model (1) should be based on detectability of TFV in plasma.

In HPTN 084, adherence will be measured at a subset of study visits in a random sample of 400 participants enrolled into Arm B (active TDF/FTC). A participant will be defined as adherent at a given visit if her plasma TFV level is greater than 0.31 ng/ml. Given the average of 2.6 years of follow-up, this sampling plan should yield up to 1,600 samples for analysis, distributed proportionately across the follow-up period. Based on this sample size, the estimate of adherence for the study cohort should have a precision (width of a 95% confidence interval) of between $\pm$0.05 and $\pm$0.0167 (depending on the magnitude of the intra-class correlation between repeated samples on the same participant).

7.8.4.3 Selection of an NI Margin

An NI margin is typically chosen to preserve (at least) p% of the proven benefit of the active control (TDF/FTC in this case). Such a margin may be defined as (1-p)*log(RR_L) where RR_L is the lower bound of the 95% confidence interval (CI) of the RR (Placebo vs PrEP). Typically, non-inferiority trials are designed to preserve at least 50% of the benefit of the active control giving a margin that is halfway (on a log scale) between RR_L and 1.0.

A critical issue in the design of NI trials is the assumption of *constancy*, namely, that the key conditions that lead to efficacy of the active control versus placebo in previous trials also hold in the current NI trial. In the context of a PrEP trial with TDF/FTC as the active control the most important constancy assumption is that adherence to TDF/FTC is comparable to previous trials where TDF/FTC has proven effective. This suggests that the NI margin of a PrEP trial with TDF/FTC as the active control should be based on the observed adherence in the current trial – if observed adherence is low then an NI margin of 1.0 (superiority) is required; if observed adherence is high than an appropriate NI margin may be chosen based on the meta-regression model (1) described above.

An NI trial uses the following hypotheses:

Ho: RR = margin
Ha: RR < margin

Table 7.5 gives, for CAB LA adherence of 85% and various levels of TDF/FTC adherence, the NI margin that preserves at least 50% of the active control benefit based on the meta- regression shown inFigure 7.1, as well as the expected RR under the alternative hypothesis, number of events needed for 90% power, and sample size. Other assumptions are as noted previously.

Based on this table an analysis with a variable, adherence-dependent margin that preserves at least 50% of the proven benefit of TDF/FTC is well-powered for TDF/FTC adherence from 55% up to 64%, assuming the original design sample size of 3200. Power will be greater for the increased sample size target of 3350.

Table 7.5. Non-inferiority Designs for Various Levels of TDF/FTC Adherence Using a Margin Based onFigure 7.1.

CAB adherence assumed to be 85%; other assumptions are the same as in Table 7.1.					
TDF/FTC Adherence	RR (Cab vs TDF)	Margin	No. HIV events for 90% power	N total	Maximum observed RR[1]
55%	.52	1.12	71	2254	.70
60%	.56	1.17	77	2572	.75
65%	.62	1.22	92	3256	.81
70%	.68	1.27	108	4062	.87

[1] Maximum observed RR which would give a non-inferiority result for this margin and this number of events.

7.8.4.4 An Adaptive Margin Preserves Type I Error Rate

In a typical NI trial a fixed margin is chosen and used to set the null and alternative hypotheses prior to trial initiation. Here we propose setting the margin and hypotheses based on the meta-regression analysis of previous trials and the adherence rate observed in the current trial. To achieve interpretable results, it is critical that adherence in the current trial be assessed in a manner that is comparable to previous trials. In addition, the calculation of adherence in the current trial must be done in a completely pre-specified manner and prior to unblinding of the HIV results. Under these conditions, our calculations show that choosing the margin and setting the hypotheses based on the adherence measured on a random subset of the trial participants does not meaningfully increase the type 1 error rate for the trial.

Specifically, we considered trials with the HPTN 084 design and true TDF/FTC adherence rates (a) of 60%, 65% and 70%. Define m(a) as the margin that preserves 50% of the proven benefit of TDF/FTC for adherence level a (see Section 7.8.4.3). Based on our meta-analysis, these levels of adherence would support NI margins (m(a)) of (1.17, 1.22, 1.27), respectively, (see) and corresponding null hypotheses of Ho: RR = m(a). If the margin is fixed a priori based on the true adherence rate, then the type I error rate for testing Ho is 0.025, by definition. If, instead, adherence is estimated by sampling and the margin is based on the estimated adherence (i.e. Ho: RR = $(\hat{a})$) then the type I error rate is given by the expression

$$\int_{\hat{a}=0}^{1} \Phi\left(\frac{\log\left(m(\hat{a})\right) - \log\left(m(a)\right)}{s} - 1.96\right) f(\hat{a}) d\hat{a}$$

where s is the standard error of the estimated log(RR), Φ() is the cumulative normal distribution, and $f(\hat{a})$ is the sampling distribution of the estimated adherence. Table 7.6 shows the results. As can be seen, there is a very slight inflation of the type I error rate – from 0.025 to 0.0254 across a range of adherence rates – associated with the adaptive margin procedure, conservatively assuming 400 independent samples are used to measure adherence. The degree of inflation declines as adherence is measured more precisely. These theoretical calculations were confirmed by simulation.

Table 7.6. Results of Simulations (based on HPTN 084 design) with Nominal Type I Error Rate of 0.025.

Number of HIV events for each scenario was chosen to provide 90% power as shown in Table 7.5.					
TDF/FTC adherence	TDF/FTC arm incidence (%/yr)	NI margin	No. HIV events	Type I rate – fixed margin	Type I rate – adapt margin
60%	1.72	1.17	78	.025	.0254
65%	1.57	1.22	92	.025	.0254
70%	1.42	1.27	108	.025	.0254.

Thus, the overall type I error rate inflation is minimal provided adherence is measured precisely.

7.8.4.5 Other Considerations

In HPTN 084 women in the CAB/CAB LA arm may receive TDF/FTC during steps 1 and 2 under certain circumstances, the most common of which is pregnancy. Such "cross-overs" bias the comparison between the arms towards non-inferiority. Thus, any non-inferiority analysis must be interpreted in light of the proportion of time that women in the CAB/CAB LA arm receive TDF/FTC.

7.8.5 Analyses of Secondary Objectives

- To compare HIV incidence among participants receiving oral CAB/CAB LA vs. daily oral TDF/FTC (Steps 1, 2 and 3)

The Hazard Ratio (HR) comparing CAB LA vs TDF/FTC and a 95% CIs will be estimated using a Cox proportional hazards model with treatment arm as the only covariate, stratified by site and using all HIV incidence data from steps 1 through 3. We will test the hypothesis Ho: HR = 1.0 versus Ha: HR < 1.0 using $\alpha = 0.025$.

- To evaluate relative efficacy of oral CAB/CAB LA vs. oral TDF/FTC in subgroups defined by the baseline factors of: age, HSV-2 serostatus, contraceptive method, and BMI.

For each of the specified baseline factors, a Cox proportional hazards model will be fit with treatment arm, baseline factor and their interaction as covariates, stratified by site. For baseline factor *x*, this model may be written as

$$\log\left(\lambda(t; arm, x, s)\right) = \log\left(\lambda_s(t)\right) + \beta_1 arm + \beta_2 x + \beta_3 arm * x$$

The hazard ratio (HR) for the baseline factor equal to each level of *x* will be estimated as $\exp(\beta_1 + \beta_3 x)$ and the corresponding treatment efficacy will be estimated as TE = 1 - HR. 95% confidence intervals for the HR for each level of *x* will be reported. The clinical significance of differences in the estimated efficacy between subgroups will be evaluated. If relevant, a test for effect modification may be conducted based on the hypotheses Ho: $\beta_3 = 0$ versus Ha: $\beta_3 \neq 0$.

- To describe and model the relationship between HIV incidence and drug concentration levels, within each arm.

A Cox proportional hazards model with drug concentration as a continuous, time-dependent covariate will be fit separately for each arm, with stratification by site. Martingale residual plots will be used to guide selection of an appropriate functional form for drug concentration, starting with the assumption of a linear relationship between drug concentration and log hazard. Separate models will be fit for different measures of drug levels (i.e. DBS, plasma). The team will also investigate using a model to predict drug concentrations in continuous time based on observed plasma and DBS drug levels; the predicted values could then be used as a covariate in the analysis proposed here. Potential confounders (e.g. age, sexual risk behaviors) will be included in the model. Once a final model is selected, the (possibly adjusted) relationship between log relative risk (y-axis) and drug concentration (x-axis), with 95% confidence intervals, will be plotted for each arm. We note that since this is an observational analysis (i.e. individuals are not randomized to drug levels), all inferences are associative, not causal.

- To describe the distribution and correlates of drug concentration levels, within each arm.

We will plot boxplots of drug concentration over follow-up overall and by age groups (<= 24 vs > 24), separately for each arm.

A mixed effects linear regression model with log of drug concentration as the outcome, a random effect for participant, and potential correlates of drug concentration as covariates will be fit to the longitudinal drug concentrations. Separate models will be fit for each arm. The association between drug concentration and each potential correlate will be evaluated by testing the corresponding regression coefficient using the hypotheses, Ho: $\beta = 0$ versus Ha: $\beta \neq 0$ with $\alpha = 0.05$.

- To compare the acceptability of and preferences for CAB LA vs. oral TDF/FTC.

Descriptive statistics will be used to summarize acceptability measures as evaluated at the end of the study. The specific statistics chosen will depend on the form of the acceptability assessment.

7.8.5.1 Qualitative Analysis

All semi-structured interviews and observations will be conducted by trained, same-sex interviewers, audio-recorded, transcribed and translated into English, and then uploaded into a qualitative software analysis program (such as NVivo 12.) A team representing core and site behavioral investigators will follow a process of reading, coding, data display and data reduction [56] in order to explore in greater depth participants' attitudes towards and experiences with the product they were assigned. Detailed memos and/or 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 or other social relationships) influence acceptability and interest in future use of an injectable PrEP product.

7.8.6 Analyses of Tertiary Objectives

- To estimate sexual risk behaviors, as measured by self-report and rates of incident STIs.

Key sexual behaviors (numbers of partners, unprotected sex) will be dichotomized (i.e. >1 partner, any unprotected sex). All post-randomization visits where the outcome information is collected will be included in the analysis. Mixed effects logistic regression will be used to estimate prevalence and 95% confidence intervals for each behavior. All analyses will use a robust variance. Results will be reported overall and by arm.

Rates of incident STI's will be computed for each arm as number of new STI's divided by total person-years. Poisson regression with a robust variance will be used to model the number of incident STI for each woman. Person-time will be used as an offset. Incidence and a 95% CI will be reported overall and by arm.

- To compare Grade $\geq$2 AE rates in women with baseline BMI </$\geq$ 25 kg/m^2, within each study arm.

Local reactions, adverse events and local laboratory values will be summarized as described in section 7.8.2 separately for women with baseline body mass index (BMI) </$\geq$ 25 kg/m2.

A multiplicative intensity model will be used to compare rates of Grade 2 or higher AE's between women with BMI $\geq$25kg/m^2 versus <25kg/m^2, with separate models for each arm. The model will include time to Grade 2 or higher AE's for each participant as the outcome and BMI category as a covariate. The coefficient of BMI category will be used to compare AE rates based on the hypotheses, Ho: $\beta_{bmi} = 0$ versus Ha: $\beta_{bmi} \neq 0$ with $\alpha = 0.05$. AE's will be clustered by participant and a robust variance will be used.

- To compare differences in weight gain and BMI, by arm

Weight gain will be computed as change from baseline (enrollment) at each follow up visit. We will plot mean weight gain over follow-up by (time-varying) current treatment (i.e. as-treated analysis). A linear mixed model will be fit with categorical intervals for time in study, (time-varying) treatment and time by treatment interaction to evaluate the effect of CAB LA on weight gain.

- To compare pregnancy incidence and outcomes between arms.

To compare pregnancy incidence between the arms, we will fit a Poisson regression with number of pregnancies for each participant as the outcome, follow-up time as an offset and arm as the covariate. Robust variances will be computed and the coefficient of arm will be evaluated using the hypotheses, Ho: $\beta_{arm} = 0$ versus Ha: $\beta_{arm} \neq 0$ with $\alpha = 0.05$.

A table describing pregnancy outcomes for each arm will be provided.

- To evaluate rates of HIV drug resistance among participants who acquire HIV infection during the study among participants receiving oral CAB/CAB LA vs. oral TDF/FTC.

The number, proportion and types of resistance mutations will be reported by arm for all post-randomization HIV seroconverters, separately for each step of the trial. No formal statistical test will be performed.

- To determine plasma concentrations of DMPA or NET-EN or etonogestrel when co-administered for contraception with study products (TDF/FTC or CAB LA).

For each contraceptive subgroup (DMPA,NET-EN, etonogestrel) we will estimate the proportion of women in the CAB LA arm with contraceptive drug levels (DMPA, NET-EN, etonogestrel for the three contraceptive subgroups, respectively) below the contraceptive threshold (0.1 ng/mL for DMPA, TBD for NET-EN and 90 pg/mL for etonogestrel). 95% confidence interval for the proportion will be provided. . The confidence interval will be based on a robust variance if multiple observations are available for each woman.

In addition, we will compare mean contraceptive drug concentrations (and/or other PK parameters) between the CAB LA and TDF/FTC arms for each contraceptive subgroup using a t-test (or a t-test with robust variance if multiple observations on each woman are available).

7.8.7 Analyses of Exploratory Objectives

- To compare the estimated programmatic cost, cost-effectiveness and disease impact indicators of CAB LA vs. daily oral TDF/FTC vs. no PrEP for HIV-uninfected women in the study sites locations.
- To perform secondary laboratory assessments that may include evaluation of factors related to HIV infection, hepatitis infection, and other infections; ARV drug use; pharmacogenomics; characterization of HIV in infected participants; and evaluation of laboratory assays related to the study objectives.

  Analysis plans for the assessments described in the laboratory Exploratory Objective will be determined at a later date based on the specific types of testing/assessments performed.

  Further details will be provided in the statistical analysis plan.

8.0 HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

This protocol and the template informed consent form contained in Appendix IV-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**s,** 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

Written informed consent will be obtained from each study participant. Each study site is responsible for developing study informed consent forms for local use, based on the template in Appendix IV 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 by signing their informed consent forms. (Further details regarding DAIDS requirements for documenting the informed consent process can be found in the DAIDS Standard Operating Procedure for Source Documentation.)

All participants will be offered a copy of their informed consent form.

8.3 Incentives

Pending IRB approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. 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; pharmaceutical sponsors; representatives of the HPTN LOC, SDMC, and/or LC; the government or other local, US, or international regulatory authorities (including the OHRP and US FDA), site IRBs/ECs or if appropriate, the SAHPRA, ViiV/Gilead.

8.5 Communicable Disease Reporting Requirements

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

8.6 Study Discontinuation

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

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

Laboratory procedures are described below and in Appendices I a-c. Refer to Appendix II 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
- Vaginal swab for Trichomonas vaginalis (TV) testing
- Plasma storage
- Dried blood spot (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 of reproductive potential 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. It will be repeated after pregnancy completion and must have returned to normal prior to recommencement of study product.

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

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

9.2 Stored Specimens

Plasma, whole blood, and DBS will be stored at the local site throughout the study. 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.

NOTE: Samples may be unblinded at the HPTN Laboratory Center (Pharmacology Laboratory only), so the relevant assays are only performed on participants who received CAB LA. In any such case, no one outside the Pharmacology Laboratory will be unblinded prior to the end of the trial (see Section 5.18).

9.2.1 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 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.

The HPTN LC will also perform testing for HSV-2 on stored plasma samples. Testing for other infections may be performed. Results will not be returned to study sites or participants.

9.2.2 Pharmacology

Plasma and DBS samples for drug concentrations will be collected throughout the study from all participants, although PK testing will be limited to a subset of the samples.

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. Results will not be returned to the study participants.

NOTE: Samples may be unblinded at the HPTN Laboratory Center (Pharmacology Laboratory only) for the adherence subset testing so the relevant assays are only performed on participants who received CAB LA. The HPTN LC (Pharmacology Laboratory) will not be unblinded for remaining analysis until the end of Step 2.

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

Injectable Contraception Sub-Study

Additional plasma and DBS will be stored for participants who enroll in the Injectable Contraception Sub-Study. Processing and storage procedures will be described in detail in the SSP. Assessments will be performed retrospectively; results will not be returned to study sites or participants.

9.2.3 Pharmacogenomics

Samples collected for pharmacogenomics testing may be analyzed for genetic polymorphisms associated with study drug exposure. Sites and individual participants may choose to opt out of this testing. For sites that collect for this testing, results would not be returned to the sites or study participants.

9.3 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.

9.3.1 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. 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.

9.3.2 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 by an External Quality Assurance Provider or specified quality assurance contractor and must demonstrate successful participation in the relevant EQA programs.

9.3.3 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 an External Quality Assurance program and must demonstrate successful participation in these programs.

9.3.4 Quality Assurance for HIV RNA Testing

Local laboratories may also perform HIV RNA/viral load testing (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.

9.3.5 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, at sites that allow this type of storage, study participants will be asked to provide written informed consent for these 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.

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.

9.4 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/networks-protocol-teams/protocol-templates.

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 and Gilead Sciences, Inc. for cross-referencing with the company's other INDs for the study product(s). Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed between DAIDS and each of the collaborating partners (ViiV Healthcare, and Gilead Sciences, Inc.).

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. 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, government or other local, US, or international regulatory authorities/entities (including the OHRP and US FDA). site IRBs/ECs or if appropriate, the SAHPRA, ViiV/Gilead. A site visit log will be maintained at each study site to document all visits.

10.4.1 Remote Study Monitoring

Due to ongoing travel restrictions during the COVID-19 pandemic, some sites are unable to accommodate onsite monitoring visits. Remote monitoring visits to date consist of quality review of study data available in the Electronic Data Capture system without verification to corresponding source documents. Review of source documentation is a critical component of ensuring data integrity.

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote

monitoring visits may be performed in place of, or in addition to onsite visits to ensure the safety of study participants and data integrity[57].

Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

Four options listed below will enable the facilitation of remote source document verification, which may vary site by site. All offered are HIPAA and 21 CFR Part 11 compliant.

Option #1 - Veeva SiteVault Platform- This platform is available for sites to self-subscribe at no cost from Veeva Systems. There is no software to download and the only requirement is internet access. Sites will upload source documents to this secure platform and assign permissions to monitors to access these data for a limited period of time. For sites that are already using this platform in some capacity, they can add specific DAIDS studies to their existing account. In the event that this platform is being used by another entity within the institution, the site can request access to the platform following their internal procedures. However, sites that are not currently using Veeva SiteVault, can obtain additional information by visiting https://www.veeva.com/products/sitevault/ or sign up to try at sites.veeva.com. Veeva SiteVault may require a signed agreement between the site and Veeva Systems.

Option #2 - Site Controlled SharePoint or Cloud-Based Portal-Some sites may already have a

platform which allows for sharing of participant source documents, which could be extended to allow monitor's access. This option must be 21CRF 11 and HIPAA compliant as applicable.

Option #3 – Direct Access to Electronic Medical Records by Monitors- This option may

be feasible for sites that use Electronic Medical Records, and whose institutional policy allows for direct access of the site's Electronic Medical Record to monitors for a limited period of time. Please contact your institution's Security Officer for required approvals and any agreements to facilitate remote access to participant source documents.

Option #4 - Medidata Rave Imaging Solution- This option does not require additional purchase of software and sign-on is through each site's existing single iMedidata account. Sites will upload source documents to this secure platform and monitor permission and access is assigned by the SDMC. There is ongoing discussion regarding the implementation timeline for MediData Rave Imaging Solutions, and the SDMC will contact sites regarding demonstration of this solution.

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 — including 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, ViiV Healthcare, Gilead Sciences, Inc., and BMGF for review prior to submission.

11.0 REFERENCES

1. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. The New England journal of medicine 2012;367:399-410.
2. Daar ES, Tierney C, Fischl MA, et al. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. Annals of internal medicine 2011;154:445-56.
3. Fauci AS, Folkers GK, Dieffenbach CW. HIV-AIDS: much accomplished, much to do. Nature immunology 2013;14:1104-7.
4. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. The New England journal of medicine 2010;363:2587-99.
5. Gulick RM, Mellors JW, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. The New England journal of medicine 1997;337:734-9.
6. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. The New England journal of medicine 2004;350:1850-61.
7. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. The New England journal of medicine 2008;358:2095-106.
8. Thigpen M. Daily oral antiretroviral use for the prevention of HIV infection in heterosexually active young adults in Botswana: results from the TDF2 study. Abstract WELBC01. 6th IAS 2011.
9. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. The New England journal of medicine 2012;367:423-34.
10. Interim guidance for clinicians considering the use of preexposure prophylaxis for the prevention of HIV infection in heterosexually active adults. MMWR Morbidity and mortality weekly report 2012;61:586-9.
11. Guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV. 2012. (Accessed August 14, 2012., at http://www.who.int/hiv/pub/guidance_prep/en/index.html.)
12. Fonner VA DS, Kennedy CE, Baggaley R, O'reilly KR, Koechlin FM, Rodolph M, Hodges-Mameletzis I, Grant RM. Effectiveness and safety of oral HIV pre-exposure prophylaxis (PrEP) for all populations: A systematic review and meta-analysis. . AIDS2016.
13. Amico KR, Mansoor LE, Corneli A, Torjesen K, van der Straten A. Adherence support approaches in biomedical HIV prevention trials: experiences, insights and future directions from four multisite prevention trials. AIDS and behavior 2013;17:2143-55.
14. van der Straten A, Van Damme L, Haberer JE, Bangsberg DR. Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. AIDS 2012;26:F13-9.
15. Woodsong C, MacQueen K, Amico KR, et al. Microbicide clinical trial adherence: insights for introduction. Journal of the International AIDS Society 2013;16:18505.
16. Patterson KB, Prince HA, Kraft E, et al. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. Science translational medicine 2011;3:112re4.
17. Louissaint NA, Cao YJ, Skipper PL, et al. Single dose pharmacokinetics of oral tenofovir in plasma, peripheral blood mononuclear cells, colonic tissue, and vaginal tissue. AIDS research and human retroviruses 2013;29:1443-50.
18. MCCormack S TD, Desai M, Dolling DI, Gafos M, Gilson R, Sullivan AK, Clarke A, Reeves I, Schembri G, Mackie N, Bowman C, Lacey CJ, Apea V, Brady M, Fox J, Taylor S, Antonucci S, Khoo SH, Rooney J, Nardone A, Fisher M, McOwans A, Phillips AN, Johnson AM, Gazzard B, Gill ON. Pre-

exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of pragmatic open-label randomised open-label trial. Lancet 2016;387 53-60.
19. Bekker LG HJ, Amico R, Roux S, Hendrix C, Andersen PL, Dye B, Elharrar V, Stirratt MJ, Grant B. HPTN 067/ADAPT Cape Town: A comparison of daily and nondaily PrEP dosing in African Women. CROI. Seattle, Washington2015.
20. Grant R FV, Rodolph M, Liegler T, Glidden D and R Baggaley. AIDS 2016. Durban, South Africa.
21. Gupta SK, Anderson AM, Ebrahimi R, et al. Fanconi syndrome accompanied by renal function decline with tenofovir disoproxil fumarate: a prospective, case-control study of predictors and resolution in HIV-infected patients. PloS one 2014;9:e92717.
22. van Griensven F, Thienkrua W, McNicholl J, et al. Evidence of an explosive epidemic of HIV infection in a cohort of men who have sex with men in Thailand. AIDS 2013;27:825-32.
23. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. The New England journal of medicine 2015;372:509-18.
24. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. The New England journal of medicine 2012;367:411-22.
25. Solomon MM, Lama JR, Glidden DV, et al. Changes in renal function associated with oral emtricitabine/tenofovir disoproxil fumarate use for HIV pre-exposure prophylaxis. AIDS 2014;28:851-9.
26. Martin M VS, Suntharasamai P, Sangkum U, Mock PA, Gvetadze RJ, Curlin ME, Leethochawalit M, Chiamwongpaet S, Cherdtrakulkiat T, Anekvorapong R, Leelawiwat W, Chantharojwong N, McNicholl JM, Paxton LA, Kittimunkong S, Choopanya K. Renal Function of Participants in the Bangkok Tenofovir Study- Thailand, 2005-2012. Clinical Infectious Diseases 2014;59:716-24.
27. Choopanya K MM, Suntharasamai P, Sangum U, Mock PA, Leethochawalit M, Chiamwongpaet S, Kitisin P, Natrujirote P, Kittimunkong S, Chuachoowong R, Gvetadze RJ, McNicholl JM, Paxton LA, Curlin ME, Hendrix CW, Vanichseni S. 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. Lancet 2013;381:2083-90.
28. Mulligan K, Glidden DV, Anderson PL, et al. Effects of Emtricitabine/Tenofovir on Bone Mineral Density in HIV-Negative Persons in a Randomized, Double-Blind, Placebo-Controlled Trial. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2015.
29. Liu AY, Vittinghoff E, Sellmeyer DE, et al. Bone mineral density in HIV-negative men participating in a tenofovir pre-exposure prophylaxis randomized clinical trial in San Francisco. PloS one 2011;6:e23688.
30. Mugwanya KK, Wyatt C, Celum C, et al. Changes in glomerular kidney function among hiv-1–uninfected men and women receiving emtricitabine–tenofovir disoproxil fumarate preexposure prophylaxis: A randomized clinical trial. JAMA Internal Medicine 2015;175:246-54.
31. Spreen WR, Margolis DA, Pottage JC, Jr. Long-acting injectable antiretrovirals for HIV treatment and prevention. Current opinion in HIV and AIDS 2013;8:565-71.
32. Bureau PR. Family Planning Worldwide: 2013 Data Sheet. 2013.
33. Reece M, Herbenick D, Schick V, Sanders S, Dodge B, Fortenberry J. 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;7:266–76.
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;7:270ra5.

35. Andrews CD, Spreen WR, Mohri H, et al. Long-acting integrase inhibitor protects macaques from intrarectal simian/human immunodeficiency virus. Science 2014;343:1151-4.
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]. 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;14:192-203.
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. 21st Conference on Retrovirus and Opportunistic Infections 2014; Boston, MA.
39. Ford S; Stancil B; Markowitz M ea. ECLAIR Study of Cabotegravir LA Injections: Characterization of Safety and PK During the "PK Tail" Phase. HIV Research for Prevention 2016 October 17-21; Chicago, Illinois, USA.
40. Landovitz R, Li S, Eron J, et al. Tail-phase safety, tolerability and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected individuals: HPTN 077 final results. Abstract OA15.06LB HIV R4P. Madrid2018.
41. Han Kelong, Patel Parul, Baker Mark, et al. Cabotegravir (CAB) Long-acting (LA) Phase 3 (Ph3) PrEP Dose Selection Based on Population Pharmacokinetics (PPK) in Healthy and HIV-infected Adults. Abstract OA15.05 HIV R4P. Madrid2018.
42. Spreen W, Ford SL, Chen S, et al. GSK1265744 pharmacokinetics in plasma and tissue after single-dose long-acting injectable administration in healthy subjects. J Acquir Immune Defic Syndr 2014;67:481-6.
43. Lou M, Gould E, Chen S, et al. Meta-Analysis of Safety Data from 8 Clinical Studies with GSK 1265744, an HIV Integrase Inhibitor, Dosed Orally or as Injection of Long-Acting Parenteral Nanosuspension. Poster Presentation #1752. 53rd ICAAC 2013; 2013; Denver, CO, USA.
44. Margolis D PD, Stellbrink HJ, Lutz T, Angel J, Richmond G, Clotet B, Gutierrez F, Sloan L, Griffith S, St Clair M, Dorey D, Ford S, Mrus J, Crauwels H, Smith K, Williams P, Spreen B. Cabotegravir + rilpivirine as long-acting maintenance therapy: LATTE ‑ 2 week 48 results. ADIS 2016; Durban, South Africa.
45. Landovitz RJ, Donnell D, Clement M, et al. HPTN083 interim results: Pre-exposure prophylaxis (PrEP) containing long-acting injectable cabotegravir (CAB-LA) is safe and highly effective for cisgender men and transgender women who have sex with men (MSM,TGW). AIDS 2020. Virtual.
46. 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.
47. WHO statement on dolutegravir. 2018. (Accessed May 20, 2018, at https://www.who.int/medicines/publications/drugalerts/Statement_on_DTG_18May_2018final.pdf?ua=1.)
48. Zash R, Holmes L, Diseko M, et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo study, Botswana. AIDS 2020. Virtual.
49. Hill A, Waters L, Pozniak A. Are new antiretroviral treatments increasing the risks of clinical obesity? Journal of Virus Eradication 2019;5:41-3.
50. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. The New England journal of medicine 2019.

51. Landovitz RJ, Zangeneh SZ, Chau G, et al. Cabotegravir is Not Associated with Weight Gain in HIV-uninfected Individuals in HPTN 077. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2019.
52. Balkus J BE, Palanee T, Nair G, Gafoor Z, Zhang J, Richardson BA, Chirenje ZM, Marrazzo JM, Baeten JM. An Empiric HIV Risk Scoring Tool to Predict HIV-1 Acquisition in African Women. J Acquir Immune Defic Syndr 2016;72:333-43.
53. Gilead Package Insert For Truvada. at http://www.gilead.com/~/media/Files/pdfs/medicines/hiv/truvada/truvada_pi.PDF.)
54. Prevention CfDCa. Preexposure prophylaxis for the prevention of HIV infection in the United States-2014: a clinical practice guideline. Atlanta: Centers for Disease Control and Prevention 2014;67.
55. (WHO) WHO. Policy brief: consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: what's new. 2015.
56. Tolley EE, Ulin, Priscilla R., Mack, Natasha, Robinson, Elizabeth T., Succop, Stacey M. . Qualitative Methods in Public Health: A Field Guide for Applied Research Second ed: San Francisco: Jossey-Bass Inc. ; 2016.
57. FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, Updated on January 27, 2021. Accessed at: https://www.fda.gov/media/136238/download

APPENDICES I - VIII

Appendix Ia: Schedule of Evaluations – Screening and Step 1, Oral Run-in Phase

	Screening	Step 1		
		DAY 0/ Enrollment	WEEK 2	WEEK 4
ADMINISTRATIVE, BEHAVIORAL, REGULATORY				
Informed consent	X			
Locator information	X	X	X	X
Demographic information		X		
Randomization		X		
HIV prevention counseling	X	X	X	X
Offer condoms	X	X	X	X
Baseline acceptability assessment		X		
Baseline behavioral assessment		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/contraception counseling[13]/pill count (pill count Weeks 2 and 4 only)		X	X	X
Medical history (including bleeding history at Screening), contraceptive use, con meds, physical exam (with pulse, BP, weight and BMI calculated at each visit)[2]	X	X	X	X
Hep B vaccination (if needed)[3]			X	
Blood collection	X	X	X	X
Urine collection	X[6]	X	X[6]	X[6]
Vaginal swab collection[4]		X		
LOCAL LABORATORY EVALUATIONS & PROCEDURES				
HIV testing[5]	X	X	X	X
Pregnancy testing[6]	X	X	X	X
HBV and HCV testing[7]	X	X		
CBC with differential	X	X	X	X
Chemistry testing[8]	X	X	X	X
Liver function tests[9]	X	X		X
Fasting lipid profile[10]		X		
Syphilis testing		X		
GC/CT and TV testing[4]		X		
Urinalysis (protein and glucose)		X		

	Screening	Step 1		
		DAY 0/ Enrollment	WEEK 2	WEEK 4
Plasma storage[11]	X	X	X	X
DBS storage				X
Whole blood storage[14]		X		
Additional sample storage for participants enrolled in the Injectable Contraception Sub-Study[12]		X		

FOOTNOTES FOR APPENDIX Ia

[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 at all visits except Screening.

[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] GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing using the swab may be performed at that later visit.

[5] The HIV testing algorithm is provided in the SSP Manual. Testing for acute HIV must be negative and must be performed within 14 days of 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 the same day as sample collection and before product is administered.

[6] 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.

[7] At Screening: HBsAg and HCV antibody testing. At Enrollment: HBsAb and HBcAb testing. Note: These tests can all be done at Screening at the discretion of the IOR.

[8] At Screening: Creatinine. At and after enrollment: BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.

[9] At Screening: ALT and TBili. At and after Enrollment: AST, ALT, total bilirubin, and alkaline phosphatase.

[10] Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

[11] Stored plasma will be used for Quality Assurance testing, HSV-2 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 Section 9.0

[12] Additional serum and/or plasma will be stored for participants who enroll in the Injectable Contraception Sub-Study. Processing and storage procedures will be described in detail in the SSP. Assessments will be performed retrospectively; results will not be returned to study sites or participants.

[13] Refer to the SSP Manual.

[14] Whole blood collection and storage is only required for participants who consent to genetic testing.

Appendix Ib: Schedule of Evaluations - Step 2, Injection Phase

WEEKS in Study (shaded column = injection/ dispense pills visit)	**5**	**6**	**9**	**13**	**17**	**21**	**25**		**33**		**41**	**42**	**49**		**57**		**65**		**73**		**81**		**89**		**97**		**105**		**113**		**121**		**129**		**137**		**145**		**153**		**161**		**169**		**177**		**185***
ADMINISTRATIVE, BEHAVIORAL, REGULATORY																																														
Locator information	X	X	X	X	X	X	X		X		X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
HIV prevention counseling	X	X	X	X	X	X	X		X		X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
Offer condoms per local SOC	X	X	X	X	X	X	X		X		X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
Acceptability assessment					X						X						X						X										X														X
Behavioral assessment	X		X		X		X		X		X		X		X		X		X		X		X		X				X				X						X								X
CLINICAL EVALUATIONS & PROCEDURES																																															
Adherence counseling / contraception counseling[10]	X	X	X	X	X	X	X		X		X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
Dispense oral products to all participants	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
Medical history, concomitant medications, contraceptive use, targeted physical exam (with pulse, BP, weight and BMI calculated at each visit)	X	X	X	X	X	X	X		X		X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
Hep B vaccination (if needed) [1]		X							X																																						
Blood collection	X	X	X	X	X	X	X		X		X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
Urine collection	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]		X[4]		X[4]	X[4]	X[4]		X		X[4]		X[4]		X[4]		X[4]		X[4]		X		X[4]		X[4]		X[4]		X[4]		X[4]		X		X[4]		X[4]		X[4]		X[4]
Vaginal swab collection[2]									X						X						X						X						X						X						X		
Injections for all participants	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
ISR evaluation		X		X		X						X																																			
LOCAL LABORATORY EVALUATIONS & PROCEDURES																																															
HIV testing[3]	X	X	X	X	X	X	X		X		X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
Pregnancy testing[4]	X	X	X	X	X	X	X		X		X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
HCV testing[5]															X												X												X								
CBC with differential	X	X	X	X	X	X	X		X		X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
Chemistry testing[6]	X	X	X	X	X	X	X		X		X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
Liver function testing[7]	X	X	X	X	X	X	X		X		X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X

WEEKS in Study (shaded column = injection/ dispense pills visit)	**5**	**6**	**9**	**13**	**17**	**21**	**25**		**33**		**41**	**42**	**49**		**57**		**65**		**73**		**81**		**89**		**97**		**105**		**113**		**121**		**129**		**137**		**145**		**153**		**161**		**169**		**177**		**185***
Fasting lipid profile[8]									X						X												X																				
Syphilis testing									X						X						X						X						X						X						X		
Vaginal GC/CT and TV testing[2]									X						X						X						X						X						X						X		
Urinalysis (protein, glucose)															X												X												X								
Plasma storage[9]	X	X	X	X	X	X	X		X		X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
DBS storage									X						X						X						X						X						X						X		

* Participants in Step 2 may be followed for longer than 185 weeks. Any participant who reaches Week 185 prior to the implementation of the Open-Label Amendment, Protocol Version 3.0, should continue to be followed according to procedures at Week 185 every eight weeks. Once the Open-Label amendment is implemented on site, the participant must be transitioned to that amendment.

FOOTNOTES FOR APPENDIX Ib

[1] The initial dose of the Hep B 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.

[2] GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing using the swab may be performed at that later visit.

[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 the same day as sample collection and before product is administered. product is administered. Additional HIV testing may be requested by the 084HIV alias committee.

[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. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

[5] HCV antibody testing.

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

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

[8] Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

[9] 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 Section 9.0.

[10] Refer to the SSP Manual.

Appendix Ic: Schedule of Evaluations - Step 3, Follow-up Phase

Time in Step 3	Step 3, Day 0*	Step 3, Week 12	Step 3, Week 24	Step 3, Week 36	Step 3, Week 48
ADMINISTRATIVE, BEHAVIORAL, REGULATORY					
Locator information	X	X	X	X	X
HIV prevention counseling	X	X	X	X	X
Offer condoms	X	X	X	X	X
Acceptability assessment	X				
Behavioral assessment (if done in last 4 weeks, skip D0 and start at W12)	X		X		X
CLINICAL EVALUATIONS & PROCEDURES					
Dispense pills to all participants	X	X	X	X	
Adherence counseling/ contraception counseling[8] for all participants	X	X	X	X	
Medical history, concomitant medications, contraceptive use, targeted physical exam (with pulse, BP, weight and BMI calculated at each visit)	X	X	X	X	X
Blood collection	X	X	X	X	X
Urine collection	X[6]	X[3]	X	X[3]	X
Vaginal swab collection[1]	X[6]		X		X
LOCAL LABORATORY EVALUATIONS & PROCEDURES					
HIV testing[2]	X	X	X	X	X
Pregnancy testing[3]	X	X	X	X	X
Chemistry testing[4]			X		X
Liver function testing[5]			X		X
Syphilis testing	X[6]		X		X
GC/CT and TV testing[1]	X[6]		X		X
Plasma storage[7]	X	X	X	X	X
DBS storage			X		X

FOOTNOTES FOR APPENDIX Ic

Follow this SOE for participants on open label TDF/ FTC. Also, please note that for applicable participants who complete this schedule and move to annual HIV testing visits, procedures for those visits are described in the SSP.

* Day 0 of Step 3 should be scheduled no later than 8 weeks after the last injection. Attempts should be made to bring the participant in earlier rather than later than the target date. See SSP Manual for further details.

[1] GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing using the swab may be performed at that later visit.
[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 at all visits where this testing is indicated. 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 pregnancy is still ongoing.
[4] Chemistry testing includes: BUN/Urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.
[5] Liver function testing includes: AST, ALT, TBili, and alkaline phosphatase.
[6] Skip Day 0 if testing has occurred within the last 3 months of Day 0, and do only at Weeks 24 and 48.
[7] Stored plasma will be used for Quality Assurance testing, HSV-2 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 Section 9.0.
[8] Refer to the SSP Manual.

Appendix Id: 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)
ADMINISTRATIVE, BEHAVIORAL, REGULATORY				
Locator information	X	X	X	X
HIV prevention counseling	X	X	X	X
Offer Condoms per local SOC	X	X	X	X
Acceptability assessment		X		
Behavioral assessment		X		X
CLINICAL EVALUATIONS & PROCEDURES				
Adherence counseling	X	X	X	X
Dispense TDF/FTC to all participants	X	X	X	X
Medical history, concomitant medications, targeted physical exam (with pulse, BP, weight and BMI calculated at each visit)	X	X	X	X
Blood collection	X	X	X	X
Urine collection	X		X	
Vaginal swab collection[1]	X		X	
LOCAL LABORATORY EVALUATIONS & PROCEDURES				
HIV testing[2]	X	X	X	X
Pregnancy testing[3]	X			
Chemistry testing[4]			X	
Liver function testing[5]			X	
Syphilis testing	X[7]		X	
Vaginal GC/CT and TV testing [1]	X[7]		X	
Plasma storage[6]	X	X	X	X
DBS storage	X	X	X	X

FOOTNOTES FOR APPENDIX Id

All participants who continue to breastfeed beyond the initial "Quarterly Visit 3" will continue to be followed quarterly (approximately every 12 weeks). Visit procedures will alternate between those done for "Quarterly Visit 2" and those done for "Quarterly Visit 3."

[1] GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing using the swab may be performed at that later visit.
[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). Assessments will be performed retrospectively; results will not be returned to study sites or participants, except as noted in Section 9.0.
[7] If not done within 4 weeks of initial positive pregnancy test

Appendix Ie: Schedule of Evaluations - Contraceptive Substudy ONLY

WEEKS in Study (shaded column = injection/ dispense pills visit)	**Enrollment**	**5**	**6**	**9**	**13**	**17**	**21**	**25**		**33**		**41**	**42**	**49**		**57**		**65**		**73**
CLINICAL EVALUATIONS & PROCEDURES																				
Draw blood for PK samples[2]	X							X						X						X
LOCAL LABORATORY EVALUATIONS & PROCEDURES																				
Plasma storage[1]	X							X						X						X
DBS	X							X						X						X

FOOTNOTES FOR APPENDIX Ie

[1] Additional stored plasma will be used for PK evaluations and DMPA, NET-EN, Etonogestrel

[2] Blood must be collected prior to study product administration during the visit. Also, record the date that the participant's LARC was last injected/inserted.

Appendix II: Schedule of Additional Procedures for Reactive/ Positive HIV Tests

(For enrolled participants)

Note 1: The procedures listed for the HIV Confirmation Visit apply to participants who acquire HIV infection at any time during the study. The procedures listed for Weeks 12, 24, 36, and 48 apply to participants who acquire HIV infection in Step 2. 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 084HIV@hptn.org. 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**[6]
ADMININISTRATIVE, BEHAVIORAL, REGULATORY					
Locator information	X	X	X	X	X
Offer condoms	X	X	X	X	X
HIV counseling	X				
CLINICAL EVALUATIONS AND PROCEDURES					
History, con meds, physical exam (with pulse, BP, weight and BMI calculated at each visit)	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 II

[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. Additional HIV testing may be requested by the 084HIV alias committee.

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

[3] Required chemistry testing: BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.

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

[5] Stored plasma will be used for Quality Assurance testing and other assessments at the HPTN LC (see Section 9). Assessments will be performed retrospectively; results will not be returned to study sites or participants, except as noted in Section 9.0. Additional HIV testing may be requested by the 084HIV alias committee.

[6] For participants in Arm A who received injections, the Week 48 visit should be timed as closely as possible to 52 weeks after the participant received the last injection.

Appendix III: 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, creatinine clearance (absolute and change from baseline), and CPK. Refer to the tables below for specific guidance about these laboratory abnormalities.

Grade 1 or 2
In general, participants who develop a Grade 1 or 2 AE regardless of relatedness to study product, and that is not specifically addressed 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 also temporarily or 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 temporary or 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 temporarily 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

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

- Report of use of prohibited concomitant medications as described in the SSP Manual. 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.

- During Step 2, if a participant becomes pregnant or declines to continue using long-acting contraception, and subsequently changes her mind she may continue in the study on blinded study product once she has documentation of a negative pregnancy test and of resuming long acting contraception; she must also meet all other standard visit criteria.

Step 1

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. Regardless of randomization, all of these participants will be followed until the study end of Step 3 for annual HIV testing.

Step 2

Participants who have received at least one injection and refuse further injections or discontinue due to an AE will be managed as follows:

- Participants will be transitioned to open-label TDF/FTC no later than eight weeks after the last injection.

- Participants will be followed on TDF/FTC according to the SOE for 48 weeks after beginning TDF/FTC, and then followed for annual HIV testing until the end of Step 3.

Step 3

Participants in Step 3 who refuse further TDF/FTC or discontinue due to an AE will be managed on a per participant basis and in accordance with CMC guidance until the end of the participant's Step 3 schedule. Participants will be instructed to return all remaining study product as soon as possible.

Guidance on Toxicity Management for Specified Toxicities:

Nausea, Vomiting, and Diarrhea

CONDITION AND SEVERITY	IMMEDIATE ACTION	FOLLOW-UP AND MANAGEMENT
Nausea, Vomiting, and Diarrhea		
Grade 1 and 2	Continue study product (reminder to take oral study product with food)	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 infectious 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. Contact the CMC for further guidance on investigation and study product administration.

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 Step 2 injection phase. If the repeat value is Grade 2 or higher at Week 4, study product should be stopped, and the participant will be followed annually for HIV testing only. 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 reported at Week 2 or Week 4, regardless of relatedness to the study product, will result in 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. A Grade 3 ALT will lead to permanent study product discontinuation, and the participant will be followed annually for HIV testing only until the conclusion of Step 2 of the study. AEs will be followed until resolution (≤ Grade 1) in consultation with the CMC.
Grade 2 and higher	**Injection phase**: The CMC should be notified as soon as possible. For a Grade 2 ALT, the CMC will determine whether further injections may be given in cases where levels are ≤ Grade 2 prior to the next scheduled injection. Unless otherwise specified by the CMC, for Grade 2 ALT, repeat testing should be performed weekly until levels are ≤ Grade 1. For Grade 3 and higher ALT, study product will be permanently discontinued.* For Grade 3 and 4 ALT, repeat testing should be performed as soon as possible, and participants should be followed weekly until levels are ≤ Grade 1. Participants who are permanently discontinued from study product should continue to be followed on study/off study product, following the Step 3 Schedule of Evaluations.

Guidance on Toxicity Management for Specified Toxicities:

Creatinine Clearance

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

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 for adjudication and recommendation for further testing and follow-up.
Confirmed CrCl< 60 mL/min	Permanently discontinue study product	If the calculated creatinine clearance is confirmed to be <60 mL/min, the 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 annually for HIV testing only until the conclusion of Step 2 of the study. 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 on study/off study product. Participants should be treated as clinically appropriate and followed until resolution of the AE.

Appendix IV: Sample Screening and Enrollment Informed Consent Form

HPTN 084:
A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women

FINAL Version
Protocol Version 3.0, dated 12August2021
DAIDS Document ID: 38070

Sponsored by: Division of AIDS, United States (US) National Institute of Allergy and Infectious Disease, US National Institutes of Health.

Study products are provided by ViiV Healthcare and Gilead Sciences, Inc. Additional support is provided by the Bill & Melinda Gates Foundation (BMGF).

PRINCIPAL INVESTIGATOR: *[Insert Name*]

PHONE: [Insert Number]

GENERAL OVERVIEW

You are being invited to take part in an investigational research study related to the Human Immunodeficiency Virus (HIV) because you live in a part of the world where women have a high risk of becoming infected with the virus. The HIV virus causes Acquired Immunodeficiency Syndrome (AIDS). As many as five to ten women out of 100 in SSA are newly infected with HIV each year. This study will be offered to about 3,350 other women who live in SSA, are HIV-uninfected, and have sex with men.

Before you decide whether to join the study, we will explain the purpose of the study, the risks and benefits, and what is expected of you. This form includes all of that information in the later pages.

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

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

- **Your participation is voluntary. You do not have to participate in the study.**
- If you join the study and later on want to stop participating, you may leave the study at any time. You will continue to receive the same services that you would normally get here at [insert clinic name].
- 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 cannot join this study if you are taking part in another study of drugs, HIV vaccines, or medical devices. You are asked to 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.

So that you can make an informed decision about participating in this study, we will explain all of the possible risks and benefits of this study. It is important that you understand there may be no direct benefit to participating in this study and there may be some risks associated with taking part in the study. The information included in this form will be discussed with you and you may ask as many questions as you wish after you review it.

Once you understand the study, and if you decide 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.

BACKGROUND AND PURPOSE OF THE STUDY

Women in SSA are at high risk for HIV, and new methods of HIV prevention are needed. Current HIV prevention methods for women include condoms or pre-exposure prohylaxis (PrEP). Taking medication to prevent becoming HIV-infected is called "PrEP."

The main purpose of this study is to find out if a new drug called cabotegravir (CAB), an antiretroviral used as PrEP, will protect women from getting HIV. CAB comes in the form of a pill and also as an injection (shot). CAB has shown to be effective in treating HIV, but researchers do not yet know if CAB protects people from getting HIV. Neither CAB pills nor CAB injections are approved by the US FDA for the treatment and prevention of HIV infection. CAB pills and CAB injections are considered investigational drugs. In this study, we want to find out whether the injection form of CAB, which is active for a longer time in the body than the pill form, can protect people from HIV.

In this study, CAB injections (the long acting form of CAB) are given as one injection in the buttocks. The first two doses are given four weeks apart. After these first two doses, an injection will be given every eight weeks. Over the course of the study, and depending on what point in time you join the study, you could receive up to 24 injections. The injections are NOT HIV vaccinations.

CAB pills are also used in the study. CAB pills are taken every day for five weeks to make sure that no one has a bad reaction to CAB before getting an injection. The injection form of CAB (the long acting form) is active in the body for weeks. It is important to take the CAB pills because once an injection of the long acting CAB is given, the drug takes a long time to leave the body.

Researchers want to study the long acting, injection form of CAB, as an alternative method of HIV prevention. Right now, there is a pill approved by the US Food and Drug Administration (FDA), the South African Health Products Regulatory Authority (SAHPRA), [or country-specific regulatory agency], and recommended by the World Health Organization that can be taken daily by people who do not have HIV but are at risk to become infected. *[Non-US sites to fill in the current status of approval for TDF/FTC here.]* That pill contains two drugs called "TDF" and "FTC." For the TDF/FTC pill to work best at preventing HIV infection, it must be taken every day. When taken every day, TDF/FTC can be more than 90% protective against HIV infection. However, some people have a hard time remembering to take a daily pill, so it is a good idea to have another HIV prevention option. If the CAB injections work, people could get injections every eight weeks and would not have to remember to take a pill every day.

This research study will evaluate the safety of oral CAB followed by injectable CAB versus daily oral TDF/FTC. It will also see which drug works better to prevent HIV.

STUDY GROUPS

If you decide to be in this study, you will be placed into one of two groups, either Group A or Group B. Each group will have about 1,600 women in it. The study group that you will be in will be chosen randomly, like flipping a coin. You cannot choose your group, and the study staff cannot choose your group for you. You have an equal chance of being placed in Group A or in Group B. Both groups are very important to the study. You will not be told which group you are in and study clinic staff will not know which group you are in either.

We do not want you or the study researchers to know which group you are in, because we want to know which drug works better to protect you from getting HIV. By not knowing, then we do not favor one group over the other.

Each person in each group will get injections and a daily pill. The pill must be taken every day to protect against HIV. Injections are given as one shot in the buttock. The shot is given over time like this: you get one shot, then a month later you get another shot, and then after that you get a shot every two months.

There are two types of study pills used. One pill will be the active ("real") product. The other type of pill is called a "placebo" ("dummy") pill that will look and feel like the real product, but it will not contain any of the "active" ("real") drug or any other medicines.

There are also two types of injections used in the study. One injection will be the "active" ("real") product. The other type of injection is called a "placebo" ("dummy") that will look and feel like the real product, but it will not contain any of the active ("real") drug or any other medicines.

In order to keep the groups secret, women in both groups will get the same number of pills and the same number of injections. One study group will get the real CAB drug in a pill and CAB injections plus "placebo" TDF/FTC pills, and the second group will get the real TDF/FTC pills and "placebo" CAB pills and CAB injections. The placebo for the CAB injection is a nutrition injection called Intralipid.

Both groups will move through three steps (stages) in the study. The steps look like this [*sites may show a graphic to depict the groups and the steps*]:

- **Group A**: This group gets CAB pills and CAB injections plus TDF/FTC placebo pills.
    - Step 1: CAB pill plus a TDF/FTC placebo pill every day for five weeks
    - Step 2: CAB injections given as a shot, then another shot a month later, and then every 2 months after that up to three and half years plus a TDF/FTC placebo pill every day
    - Step 3: TDF/FTC pill every day for about a year, then move to local HIV prevention services

- **Group B**: This group gets TDF/FTC pills plus placebo CAB pills and placebo CAB injections.
    - Step 1: TDF/FTC pill plus placebo CAB pill every day for five weeks
    - Step 2: TDF/FTC pill everyday plus placebo CAB injections up to three and a half years
    - Step 3: TDF/FTC pill every day for about a year, then move to local HIV prevention services.

If you decide to join the study, at the most, your participation could last up to 4.5 years and include a maximum of 36 study visits at this clinic. Most of those visits would happen about every two months. We do not know exactly how long you will participate because we do not how long the study will continue after you join it. Some women will join early in the study and others may join as long as two years after the first women join. As the study goes on, we will keep you updated you on how long your participation will be.

No matter what group you are in, neither daily TDF/FTC nor CAB will protect you from getting sexually transmitted infections, like gonorrhea, chlamydia, syphilis, warts, or herpes. Neither TDF/FTC nor CAB will prevent pregnancy. **One of the best things you can do to protect yourself from getting HIV or other sexually transmitted infections during sex is to use a condom every time you have sex.**

STUDY PROCEDURES

Screening Visit Activities

Your screening visit may occur after you read, discuss, understand, and sign this form. We will help you understand the form and answer all of your questions before you sign it. The procedures done for the screening visit will take about [*site to fill in time required*], and may be done at one or more visits.

During the screening visit, the study staff will:

- Ask you where you live and other questions about you, your medical health, your sexual practices, including if you are at a higher risk of getting HIV, and whether you use alcohol or drugs.
- Give you a brief physical exam to make sure you are healthy.
- Talk with you about HIV and ways to protect yourself from getting it and offer condoms.
- Collect ~XX mL (about x teaspoons) of blood for HIV testing, hepatitis B and C testing, to check your general health, to check the health of your liver, and for storage for study-related testing.
- Test you for pregancy *[site insert sample type, blood vs. urine]* and talk to you about your plans in the next years for becoming pregnant as well as available forms of long acting contraception. We will require proof of contraception if you have received it elsewhere.

The results of the HIV test will be available *[site to insert timeframe of RNA testing, and also EIA testing if being used]*. You will be contacted about the results of your other tests when they are available.

Step 1 Visit Activities

Step 1: Enrollment Visit (Week 0) Activities

If you are eligible for this study and decide to take part in it, you will be asked to return for the enrollment visit within a specific window of time after the screening visit (usually within two weeks). This visit will last about xx hours, *[sites to add appropriate timeframe]*. During the visit, the study staff will:

- Confirm where you live and how to contact you.
- Ask you some questions about yourself, like your age, and your racial/ethnic group [*sites that want to collect this during screening should move this to screening section.*]
- Talk with you about HIV and ways to protect yourself from getting it.
- Give you a complete physical exam, to include measuring your height, weight, temperature, blood pressure, ask you about any other medicines you are taking, and whether you use alcohol or drugs.
- Collect a urine sample to see if there is sugar or protein in your urine. This sample may also be used to test for pregnancy or for sexually transmitted infections.
- Collect ~XX mL (about x teaspoons) of blood for: HIV testing, hepatitis B testing, hepatitis C, and syphilis testing, to check how much cholesterol is in your blood (a fatty substance in your blood), to check your general health, to check the health of your liver, and for storage for study-related testing and long-term storage (if you provide consent) *[Sites to delete if long term storage is not allowed]*. [*Sites to add this if allowed at your site. If not, delete: Additionally, if you provide consent, we will use a sample of your blood to see how the HIV drugs work in your body by looking at your genes. Information about the testing related to your genes is found later in this consent form.*] For the cholesterol test, you will be instructed to not eat or drink anything other than what the study staff tell you is acceptable for 8-12 hours before your blood is drawn.
- Test you for pregancy *[site insert sample type, blood vs. urine]*. This testing may be done using a blood or urine sample.
- Talk with you about long term contraception. If you are not currently utilizing implants, injections or intrauterine devices we will offer them to you in the clinic or refer you for services. We will require proof of contraception if you have received it elsewhere. If you are receiving a long-acting injectable contraceptive, we will also require proof that you received your most recent dose.
- Ask you questions about your sexual behavior.
- Ask you questions about your opinions about taking pills and getting injections.
- Test a vaginal swab to test for sexually transmitted infections; urine may also be used for some of this testing.
- Randomize you into one of the two study groups.
- Give you your study pills, explain how to take them, watch you take one, and explain any side effects they may cause.
- Have a discussion about any challenges of taking a pill every day.

- Give you the results of tests when they are available.
- Offer you condoms.

Step 1: Weeks 2 and 4 Visit Activities

These visits will last about XX minutes. During these visits, the study staff will:

- Confirm where you live and how to contact you.
- Talk with you about HIV and ways to protect yourself from getting it.
- Site staff will count your study pills, watch you take one, and talk with you about ways to help you remember to take your pills. If it seems to you or to the study staff that you are having challenges, we will try to help by working through these with you.
- Give you a brief physical exam, ask you if you have experienced any side effects from the study drugs, and ask you about any other medicines you are taking.
- Collect ~XX mL (about x teaspoons) of blood for HIV testing, to check your general health, the health of your kidneys, the amount of the study drug that is in your blood, and for storage. Blood will also be used to test liver health at Week 4.
- At Week 2 but not Week 4, you will be given the hepatitis B vaccination if testing shows you are not already immune (first vaccination at Week 2, and then boosters at approximately Weeks 6 and 33).
- Test you for pregnancy *[site insert sample type, blood vs. urine]*.
- Talk with you about long term contraception. If you are not currently utilizing implants, injections or intrauterine devices we will offer them to you in the clinic or refer you for services. We will require proof of contraception if you have received it elsewhere. If you are receiving a long-acting injectable contraceptive, we will also require proof that you received your most recent dose.
- Give you the results of your blood tests when they are available.
- Offer you condoms.

Step 2 Visit Activities

Step 2: Visit Activities

In this step of the study, there may as many as 24 visits during which participants will receive injections and pills. The number of these visits in Step 2 is dependent on when you join the study.

In Step 2 of the study, everybody will also attend 4 safety visits that will take place at Weeks 6, 13, 21 and 42.

At all Step 2 visits, the following activities will occur:

- Confirm where you live and how to contact you.
- Talk with you about HIV and ways to protect yourself from getting it.

- Give you a brief physical exam. Ask you if you have experienced any side effects from the study drugs (either the pills or shots). Everyone will be asked about any other medicines they are taking, and whether they use alcohol or drugs.
- Collect ~XX mL (about x teaspoons) of blood for HIV testing, the amount of the study drug that is in your blood, and for storage.
- Test you for pregnancy *[site insert sample type, blood vs. urine]*.
- Talk with you about long term contraception. If you are not currently utilizing implants, injections or intrauterine devices we will offer them to you in the clinic or refer you for services. We will require proof of contraception if you have received it elsewhere. If you are receiving a long-acting injectable contraceptive, we will also require proof that you received your most recent dose.
- Give you the results of your blood tests when they are available.
- Offer you condoms.

Step: 2: Week 5 Visit Activities

This visit will last up X hours. During this visit, in addition to the activities described above for all Step 2 visits, the study staff will:

- Ask you to answer questions about your sexual behavior.
    - Staff will give you more pills. Staff will also count your leftover pills and talk with you about ways to help you take your pills. If it seems to you or to the study staff that you are having challenges, we will try to help by working through these with you.
    - The first shot will be given in your buttock.

Step 2: CAB LA Injection or TDF/FTC Dispensing Visit Activities

These visits will take place at Weeks 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 137, 145, 153, 161, 169, 177, 185. [*Note: Sites may remove Week numbers in the text if easier to depict it in a table or refer to the Schedule of Procedures and Evaluations*].

These visits will last up to XX hours. During these visits, in addition to the activities described above for all Step 2 visits, the study staff will:

- Collect ~XX mL (about x teaspoons) of blood for:
    - Hepatitis C testing about every year (Weeks 57, 105 and 153 only)
    - Syphilis testing about every 6 months throughout Step 2 (Weeks 33, 57, 81, 105, 129, 153 and 177 only)
    - Testing to see how much cholesterol is in your blood two times during the study, one year apart (Weeks 57 and 105 only). For the cholesterol test, you will be instructed to not eat or drink anything other than what the study staff tell you is acceptable for 8-12 hours before your blood is drawn.

- Collect a urine sample to see if there is sugar or protein in your urine about every year for 3 years (Weeks 57, 105, and 153 only).
- Ask you to answer questions about your sexual behavior at every visit for about 2 years, and then every other visit for the rest of Step 2 (Weeks 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 121, 137, 153, 169, 185 only)
- Staff will give you more pills. Staff will also count your leftover pills and talk with you about ways to help you take your pills. If it seems to you or to the study staff that you are having challenges, we will try to help by working through these with you.
- A shot will be given in your buttock. Shots will be given approximately every 2 months (8 weeks) after the first two are given.
- Ask you questions about how you feel about taking pills and getting injections about every 6 months for two years and then once more a year later (Weeks 17, 41, 65, 89, 137 and 185).
- Test a vaginal swab for sexually transmitted infections about every 6 months throughout Step 2 (Weeks 33, 57, 81, 105, 129, 153 and 177 only).
- Talk with you about long term contraception. If you are not currently utilizing implants, injections or intrauterine devices we will offer them to you in the clinic or refer you for services. We will require proof of contraception if you have received it elsewhere. If you are receiving a long-acting injectable contraceptive, we will also require proof that you received your most recent dose.

Step 2: Weeks 6, 13, 21 and 42 Safety Visit Activities

In this step of the study, there will be 4 safety visits following each injection visit. The visits will take place at Weeks 6, 13, 21 and 42.[*Note: Sites may remove Week numbers in the text if easier to depict it in a table or refer to the Schedule of Procedures and Evaluations*].

These visits will last up to XX hours. During these visits, the study staff will:

- count your pills and talk with you about ways to help you take your pills. If it seems to you or to the study staff that you are having challenges, we will try to help by working through these with you.
- Talk with you about long term contraception. If you are not currently utilizing implants, injections or intrauterine devices we will offer them to you in the clinic or refer you for services. We will require proof of contraception if you have received it elsewhere. If you are receiving a long-acting injectable contraceptive, we will also require proof that you received your most recent dose.

<u>Step 3 Visit Activities</u>

Step 3: Follow-up Visits

Step 3 includes 5 visits over about a year (Step 3: Day 0, Weeks 12, 24, 36, and 48). Each visit will last up to XX hours. During these visits, the study staff will:

- Confirm where you live and how to contact you.

- Talk with you about HIV and ways to protect yourself from getting it.
- Give you a brief physical exam and ask you about any other medicines you are taking.
- Collect ~XX mL (about x teaspoons) of blood for HIV testing, syphilis testing, to check your general health, the health of your liver, the amount of the study drug in your blood, and for storage.
- Test you for pregnancy *[site insert sample type, blood vs. urine]*.
- Talk with you about long term contraception. If you are not currently utilizing implants, injections or intrauterine devices we will offer them to you in the clinic or refer you for services. We will require proof of contraception if you have received it elsewhere. If you are receiving a long-acting injectable contraceptive, we will also require proof that you received your most recent dose.
- Test a vaginal swab for sexually transmitted infections (Day 0, Week 24 and 48 only). If you have had these tests within 3 months of joining this part of the study, you will only have this done at Week 24 and Week 48 only; urine may also be used for some of this testing.
- You will be given TDF/FTC pills. Staff will count your leftover pills and talk with you about ways to help you take your pills. If it seems to you or to the study staff that you are having challenges, we will try to help by working through these with you. (Day 0, Weeks 12, 24, and 36 only).
- Ask you to answer questions about your sexual behavior (Day 0, Week 12, 24 and 48 only).
- Ask you questions about what it was like getting the injections and taking the study pills (this will only be asked if you have not been asked this in the few months before you started this step).
- Offer you condoms.

While you are attending study visits, sitting in the waiting room or attending events with other participants, staff members may take notes on what is said about using the study pills, injections or taking part in this study. We are doing this to help us learn more about women's experiences with taking study medication. We will not record your name or participant ID on these notes.

After these visits are over, we will help you seek additional HIV prevention care *[sites to add information here or elsewhere in the consent form]*.

[*This text is only relevant for sites which will do the Contraceptive Sub-study:*
Injectable Contraceptive Sub-Study

A subset of approximately 180 participants will be invited to join the Contraceptive Sub-Study. The sub-study will help researchers find out if CAB LA has any impact on implant (etonogestrel) and injectable contraceptives (NET- EN and DMPA). No additional study visits are required. However, there is an additional blood draw at four of the study visits: Enrollment visit and then at Weeks 25, 49 and 73.]

[*This text is only relevant for the four sites which will do the Qualitative Sub-study:*
Qualitative Sub-Study

At a subset of approximately four sites, a qualitative sub-study will be done. This sub-study will help us understand how the women in the study feel about the injectable product and other HIV prevention methods. We will collect their opinions during interviews. We will also observe the waiting room for up to an hour at about four different times each year. Each time the waiting room is observed notes will be taken about topics of discussion and any information participants wish to share. No identifying information (such as a woman's name or birthdate) will be written down about the participants observed.

Women who are invited to participate in the qualitative sub-study will also need to sign a separate consent form that fully explains the sub-study.]

Procedures if you become infected with HIV during the study

During the study, if you have a positive HIV test result the site will have you come back for an additional visit (s). The site will also need to draw some more blood from you. The additional blood will be used for further testing to confirm whether you have become infected with HIV.

- If you get HIV during Step 1 of the study, you will stop taking any study pills and you will be referred for local care and treatment of HIV and will be discontinued from the study.

- If you get HIV during Step 2 of the study, you will stop taking any study drug and you will be referred for local care and treatment of HIV. You will stop receiving the injections and stop taking study pills.

  We will ask you to come back for a visit every 3 months for about a year. During these visits we will take xx amount of blood [*sites to fill in*] to check your immune system, the amount of HIV in your blood, the health of your blood and liver, and for storage. We also will give you a brief physical exam during these visits, and ask you about any other medications that you are taking. We will also update your contact information and offer you with condoms.

- If you get HIV during Step 3 of the study, you will stop taking the TDF/FTC. People in both groups will be referred for local care and treatment of HIV. We may ask you to come in for additional visits to check on your health.

Testing 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.

Permanently Stopping Your Study Product

There may be certain situations that occur where you will no longer get the study drugs while in the study. For example, you may decide you do not want to take study drug any more, you may get HIV, or we may find out the drugs are no longer safe for you to take. We may ask you to continue to come to the study visits even if you no taking pills or getting shots. Depending on the reason that study product is stopped, you may be asked to come to the site at least once a year for HIV testing until the study ends. We will fully explain to you what will be expected if you permanently stop taking the study drugs.

USE OF STUDY SAMPLES

In addition to the laboratory tests performed at each study visit, further study-related testing may be performed on samples. This will include testing related to HIV and other infections, including testing for the drugs used in this study and other anti-HIV medications. If you get infected with HIV or hepatitis B or C during the study, some the stored blood may also be used to study the HIV and hepatitis virus, and the body's response to these infections. The samples used for this testing will be labeled with your study number and will be tested at special laboratory facilities that may be located in the US and other countries outside of [insert site country]. Results of this specialized testing will not be returned to the study site or you.

POSSIBLE FUTURE TESTS ***[Sites may require a separate consent form for this]***

If you agree, your stored samples may also be used for future research related to HIV infection, hepatitis infection, and other infections, and to better understand laboratory tests related to this study. *[For sites that opt in for pharmacogenomics testing:]* If you agree, your stored samples may also be used to study genes related to HIV infection and use of anti-HIV medications to prevent HIV infection. This testing is described in more detail below. You can agree to have your samples used for future research, even if you do not agree to have your samples used to study genes.

The stored samples will be labeled with your study number and will be tested at special laboratory facilities that may be located in the US and other countries outside of *[insert site country]*. Only approved researchers will have access to them. Results from this testing will not be returned to the study site or you. You will be asked to sign at the end of this consent form to give permission to use your stored samples for future research. Even if you do not give permission to store your blood for possible future research, you can still be in this study. You may also withdraw your consent to use your stored samples for future research at any time. We will then destroy your samples after all of the study-related testing has been completed. If you agree to have your stored samples used for future research, your left over blood will be stored for an indefinite period of time after the study ends. Results from possible future tests will not be given to either the site or to you.

RISKS AND/OR DISCOMFORTS
Study Medications

The side effects of CAB include:

Headaches, diarrhea, and fatigue. With the CAB that you get as an injection, people in other studies have said they had pain, irritation, skin redness, bumps, swelling, itching, bruising where they got the injection. Other reported side effects include muscle aches, irritated nasal passages, runny nose, sore throat, upper respiratory tract infection, difficulty sleeping, abnormal dreams/nightmares, depression, increase in the level of enzymes in the muscle (creatine phosphokinase), nausea, vomiting (being sick), flatulence (gas or wind), fever and dizziness. There have been some people who were taking this medicine who have had liver side effects. Some of these people were HIV-infected (HIV positive) and some, but not all, had damage to their liver before taking the CAB study medication. While taking the study medication, their blood tests showed that their liver was irritated, although they felt well. The medications were stopped, and the liver blood tests returned to normal. In this study, anyone with HIV-infection, Hepatitis C (or B), or any liver irritation will not be allowed to be in the study.

Some people who have had a prior history of seizures (epilepsy) have had seizures (spells) while taking CAB. One person who did not have a previous history of seizures died after prolonged seizures. If you have ever had a seizure you will not be allowed to be in the study.

The injections you receive in this study are long acting, meaning they can potentially stay in your body as long as a year or more, although for most people the drug is processed and eliminated from the body within 6 months. If you are in the group that gets the CAB, we will monitor your health for a year after your last injection. If you get infected with HIV while on the CAB, it is possible that HIV may be resistant to CAB and other HIV drugs that are like it, called integrase inhibitors, may not work to fight the virus. For this reason, we will ask you to take an oral PrEP pill daily to reduce your chance of becoming infected with HIV.

If you develop a symptom from these drugs while the drugs are still in your body, every effort will be made to treat the side effects. The amount of drug will decrease overtime and will eventually disappear.

We will update you on any new side effects that we see in this study and other on-going studies, if those side effects appear to have come from the drug. If you have questions concerning the additional study drug side effects, please ask the medical staff at your site. As stated above, some of these risks are seen in HIV-infected people taking these medications. It is not known if these side effects will occur as often and it could be that some of these side effects might be more or less serious in HIV-uninfected people.

The side effects of Intralipid include:
Side effects of Intralipid when used as an intramuscular injection placebo include headache, anxiety, difficulties with sleeping feeling restless or sleepy, stomach upset, extremity pain, upper respiratory infection, cough, urinary tract infection, decreased weight, and increased muscle tone.

Side effects of TDF/FTC include:
Like all other medicines, you may have symptoms or side effects while taking TDF/FTC. 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. You will be given a telephone number so you can contact the clinic. You should call them if you/she experience any symptoms.

In TDF/FTC research studies, nausea and diarrhea were the most common side effects, but happened in only about 10% or one in ten people. Nausea and diarrhea mainly happened in the first month and then went away. A small number (<1% or one in one hundred people) in these PrEP studies showed a slight decline in their kidney function, but this stopped when the people stopped taking the drug.

Other side effects, such as changes in bone mineral density (how much calcium and other minerals are in your bone which keep them strong) were very rare in people taking the drug who did not have HIV and have gotten better when the drug was stopped.

You could have these side effects or other side effects that we do not know about. Please tell the staff here if you have any side effect that bothers you or does not go away.

Blood Draws

Taking blood samples may cause some pain, bruise your arm, or make you feel lightheaded. In rare cases you may faint. There is also a slight chance of infection when blood is drawn. You may be nervous while you are waiting for your test results, particularly your HIV and sexually transmitted infection tests. You will receive counseling before and after these tests to help address your concerns.

Possible Injection (Shot) Side Effects:
The shots will be given in the muscles of your buttocks (bottom "cheeks"). The shot could be given too deeply or not deeply enough, missing the muscle and entering your skin, blood, or a nerve. The risk of this is unknown, but may result in higher or lower levels of the injected study medication in your system.

Getting shots could also cause some people to feel lightheaded or feel like they might pass out, or 'faint'. People may also 'see black spots', sweat, or feel sick to their stomach. This reaction, called a 'vasovagal reaction', can occur with many medical procedures and usually passes quickly.

Sensitive Questions

The questions we will ask you about your sexual behavior may make you feel uneasy. However, you do not have to answer any question that you do not want to and you can stop answering the questions at any time.

Genetic Testing

[*Sites that are able to conduct this testing should keep this section included; otherwise, this should be removed, as well as the signature lines on the signature page*]

We want to look at your genes that affect how your body changes and removes the drug used in this study. Gene differences between people can lead to different amounts of drug in the body. This may affect how well a drug protects people from HIV infection. If you consent, we will test your blood to get information about how your genes may have affected the drug levels in your body. The tests we will use to look at your genes are research tests and will be performed in a research laboratory. All of the samples will be identified with a coded number. The laboratory doing the testing will not know who you are. The results obtained for individual study participants (like you) will not be reported to the study sites or back to you. However, the combined results of the testing for all of the study participants will be available to the study sites and to the study participants at their request, once the analysis has been completed.

Your genetic information may also be shared for future research purposes and may be stored in a central genetic database, but your personal information (like your name or anything else about you) will not be shared.

Social

There may also be some social risks to participating in this study. You may feel embarrassed or uncomfortable with some of the questions you will be asked, some of the procedures that will be done, or some of the test results that you will receive. The questions we will ask you about your sexual behavior may make you feel uneasy. However, you do not have to answer any question that you do not want to and you can stop answering the questions at any time. You may also experience stigma as a result of being involved in a study about HIV because people may assume that you are HIV-infected. In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to the researchers immediately.

Confidentiality

We will make every effort to protect your confidentiality during the study. However, 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 infection with HIV. Because of this you could have trouble finding or keeping a job. You could also have problems with your family, friends and community.

This study has been reviewed and approved by a local IRB (an Ethics Committee). The name of your local IRB is [site to insert IRB info here]. The IRB is a committee that watches over the safety and rights of research participants.

HIV Infection

We told you earlier that we do not know if CAB works to protect you from getting HIV. If you are in the group that gets the CAB, you still may be at risk of getting HIV. We do know that taking TDF/FTC every day can be very effective at preventing HIV infection. If it is not taken every day, you may not be well protected. Neither of these methods prevent pregnancy or sexually transmitted infections. Because of these risks, you may still need to use condoms every time you have sex, no matter what group you are in.

Because the study medication is itself being studied to be an HIV treatment medication, if you become HIV-infected while taking the study medication, there is a chance that other drugs used to treat HIV infection might not work. This is called drug resistance. If you become infected, we will test your HIV for resistance to help guide treatment decisions for your HIV infection.

To reduce the possibility of developing drug resistance, you will be asked to work with your local study clinic team to begin HIV treatment after your last study medication injection. The study will not provide this treatment but may be able to help you find and/or pay for that treatment.

PREGNANCY

To participate in this study, you must agree not to become pregnant. You must agree to use a reliable form of long acting contraception (either injectables, implants or IUD/IUS) during the trial and for 52 weeks after stopping injections, or for 30 days after stopping oral study product. If you have received your contraception at another site which is not this study clinic, we may ask you to provide proof that you are on an effective long-acting contraceptive method. If you wish to be pregnant in the next few years, you should not participate in this research study.

We would like you to be cautious about falling pregnant. We do not yet know how CAB LA might affect a baby during pregnancy. There are few data from humans on the effects of CAB in pregnancy. Most of the information we have comes from animal studies. In studies done in pregnant rats and their newborns, using very high amounts of CAB, there were more baby rats that died when they were born or right after they were born. This did not happen to the baby rats when the mother got lower amounts of the drug, or no drug. The amount of CAB that we are giving in this study is expected to be more than 7-times lower than the amount given to the pregnant rats. We do not know whether what happened to the baby rats has any impact on what will happen in pregnant humans taking this drug. That is why if you are female and participating in this study, you cannot be pregnant, and we want you to take long acting contraception the entire time you are in the study and also for a year after.

We do not know if CAB can cause birth defects in babies. Birth defects have not been found in any animal studies of CAB so far. We have information from a different study conducted in Botswana with

dolutegravir (DTG), a medicine that is similar to but not the same as cabotegravir (CAB), the medicine being studied in HPTN 084. In that study, some women living with HIV were taking DTG for treatment of HIV infection around the time of conception. That study, known as the Tsepamo study, collected information on 153,899 deliveries at government hospitals throughout Botswana from August 2014 April 2020 and reported on babies that had birth defects of the spinal cord and brain (neural tube defects). These defects occur early on in the development of the pregnancy.

The latest results show that about 2 out of 1000 infants born to women who used DTG around the time of conception had a neural tube defect, compared to 1 in 1000 infants born to women using any non-DTG regimen. The difference between the two groups is not statistically significant. When this new unexpected finding was first reported in May 2018, there were concerns that the rate of nervous system defects in babies of mothers using dolutegravir at the start of pregnancy was much higher than for other antiretroviral drugs. However, we now know that the difference in the rate of these birth defects between the two groups is essentially the same.

Cabotegravir is not the same as dolutegravir, and we still do not know if CAB can cause birth defects in babies. We share this information with you so that you can be cautious about becoming pregnant, and so that you can decide if you want to participate in the HPTN 084 study.

During the study, you will receive counseling about your options for preventing pregnancy. You can receive some forms of contraception from the study clinic or be referred to an appropriate clinic for contraception.

- If you change your mind after enrolling in the study and do wish to become pregnant prior to Week 5, we will ask you to stop study product and continue with follow up visits only.
- If you change your mind and desire to become pregnant at any time point after Week 5, we will stop giving you injections as we don't know how CAB LA might impact a baby. You will be started on open-label oral TDF/FTC ("open-label" means you will know you are receiving TDF/FTC) and followed at the regularly scheduled study visits until either the end of your pregnancy or breastfeeding period.

If you decide to re-start your long-acting contraception and you are still in Step 2, you may be allowed to restart your blinded study pills and injections provided all other safety requirements are met.

If you become pregnant during the study, we will refer you for obstetric care. We will stop giving you injections, we will tell you and your doctor which study group you were assigned to and switch you to open-label TDF/FTC. We will refer you for an ultrasound and evaluation by an obstetric specialist approximately 12 weeks into your pregnancy so that we can examine the health of your unborn baby. Ultrasound imaging uses sound waves and allows an inside view of soft tissues and body cavities without the use of invasive techniques. There is no evidence that any danger occurs from doing an ultrasound during pregnancy. The study will not pay for the ultrasound. If the ultrasound shows anything unusual we will refer you for further care.

Your study schedule will be reduced and we will only ask you to come to clinic one time every 12 weeks during your pregnancy and until your baby is 1 year of age or you have stopped breastfeeding. During these study visits, we will collect blood and urine samples and at some visits we will also collect

vaginal swabs. We will perform some, but not all, of the same study lab tests you agreed to. Although you will stop injections, if you were receiving CAB it is likely that the levels of CAB will last in your body throughout your pregnancy up until delivery. If available at this site, you may be offered enrollment in a separate study to measures levels of cabotegravir in the babies of mothers who received cabotegravir injections. Once your pregnancy has ended and you have completed breastfeeding you may resume taking the study product you were allocated to (injection OR pills) and resume your previous visit schedule, provided that you agree to use an approved long-acting contraceptive method. If you do not wish to use an approved long-acting contraceptive method, then we will ask you to continue taking open-label TDF/FTC for up to 48 weeks after your last CAB LA injection and attending quarterly study visits. After that we will ask to see you at least once a year for HIV testing until the study has ended.

If you are still pregnant after your last visit, we will ask you or your doctor to provide updates on the progress of your pregnancy and its outcome for the first year of the baby's life. The study doctor will make this information available to the study sponsor for safety monitoring follow-up.

BENEFITS

There may be no direct benefit for you if you participate in the study.

TDF/FTC is known to protect people from getting HIV <u>if taken daily</u> as directed. The recent results from the HPTN 083 study comparing CAB to TDF/FTC conducted in men who have sex with men and transgender women at 43 sites globally showed that participants given daily TDF/FTC pills had about three times the number of HIV infections compared to participants getting long-acting CAB. CAB has not yet been shown to protect against HIV infection in cisgender women, which is the reason we are doing this study.

Neither you nor we will know which real drug you are getting in this study. We will test you for HIV, hepatitis B and hepatitis C during this study, and other sexually transmitted infections. We will refer you for Hepatitis B vaccination if it is indicated. The counseling you get during this study may help you to avoid HIV and other sexually transmitted infections. If you have or become infected with HIV, this counseling may help you to learn how to better care for yourself and avoid passing HIV to your sexual partners. If you become HIV-infected, or have another sexually transmitted infection, we will refer you for care and/or treatment. During the study you will also have other tests to check on the health of your blood, and liver. If any health problems are found, you will be referred for care. At every visit you will be offered condoms free of charge.

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.

NEW INFORMATION

You will be told any new information learned during this study that might affect your willingness to stay in the study. For example, if information becomes available that shows that the medication may be causing bad effects, you will be told about this. You will also be told when the results of the study may be available, and how to learn about them.

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

You may be withdrawn from the study without your consent if any of the following occur:

- You are unable or unwilling to follow all of the study procedures or instructions.
- You could be harmed by continuing to take the pill or getting an injection.
- The study is stopped or canceled.
- The study staff feels that staying in the study would be harmful to you.
- You are not able to attend clinic visits or complete all of the study procedures.
- Other reasons, as decided by the study staff.

ALTERNATIVES TO PARTICIPATION

It is possible that TDF/FTC is available in your local area as an HIV prevention method. Because we do not know if CAB LA will protect you against HIV, if you prefer to take TDF/FTC instead of joining the study where you may receive CAB LA instead, 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.]*

COSTS TO YOU

There will be no cost to you for study related visits, study products, physical examinations, laboratory tests, or other procedures specifically related to the study.

REIMBURSEMENT

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

CONFIDENTIALITY

To keep your information private, your samples will be labeled with a code that can only be traced back to your study clinic. Your name, where you live, and other personal information will be protected by the study clinic. The results of any tests done on these samples 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 personal information may be disclosed if required by law.

Efforts will be made to keep your study records and test results confidential to the extent permitted by law. However, we cannot guarantee absolute confidentiality. You will be identified by a code, and personal information from your records will not be released without your written permission. Any publication of this study will not use your name or identify you personally. However, 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 U.S., local, and international regulatory entities may also review study records, as well as the [*insert name of site*] Institutional Review Board (IRB), Ethic Committee (EC) study staff,

study monitors, the companies that make the drugs used in this study, and (*insert applicable local authorities*].

The study staff will also use your personal information, if needed, to verify that you are not taking part in any other research studies. This includes other studies conducted by [site name] and studies conducted by other researchers that study staff know about.

Your records may be reviewed by:

- US FDA
- US NIH
- US Department of Heath and Human Services (DHHS), Office of Human Research Protection (OHRP)
- other U.S., local, and international regulatory entities
- [insert names of applicable IRBs/ECs/other local eview bodies as applicable]
- Study staff
- Study monitors
- Companies that makes the study drug (ViiV Healthcare and Gilead Sciences, Inc.)

[*Sites to include/amend the following if applicable:] [Local/state/national]* regulations require study staff to report the names of people who test positive for [HIV and other infections] passed during sex to the [*local health authority*]. Outreach workers from the [*health authority*] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [*health authority*].

RESEARCH-RELATED INJURY

[*Sites to specify institutional policy*:] It is unlikely that you will be injured as a result of study participation. If you are injured, the [institution] will give you immediate necessary treatment for your injuries. You [*will/will not*] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries either through this institution or the NIH. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

If you ever have any questions about the study, or if you have a research-related injury, you should contact [*insert name of the investigator or other study staff*] at [*insert telephone number and/or physical address*].

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

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

SIGNATURE PAGE

HPTN 084:
A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women

FINAL Version
Protocol Version 3.0, dated 12August2021
DAIDS Document ID: 38070

SCREENING AND ENROLLMENT CONSENT

Insert signature blocks as required by the local IRB:] If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to join the study, please sign your name or make your mark below. Samples will be stored from all study participants for study-related testing. Also, please indicate by providing your initials in the spaces below if you agree to long-term sample storage for other future testing and/or use of your samples for genetic testing.

_____ I agree to take part in this study.

_____ I agree to have samples of my blood stored long-term for future testing.

_____ I do not agree to have samples of my blood stored and long-term for future testing.

_____ I agree to allow my blood to be tested to see how my genes make drugs work in my body.

_____ I do not agree to allow my blood to be tested to see how my genes make drugs work in my body.

[_____ I agree to take part in the Contraceptive Sub-study. **If relevant to site*.]

[_____ I do not agree to take part in the Contraceptive Sub-study. **If relevant to site*.]

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

(As appropriate)

Appendix V: Sample Qualitative Informed Consent Form

HPTN 084:
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Sponsored by: Division of AIDS, United States (US) National Institute of Allergy and Infectious Disease, US National Institutes of Health.

Study products are provided by ViiV Healthcare and Gilead Sciences, Inc. Additional support is provided by the Bill & Melinda Gates Foundation (BMGF).

PRINCIPAL INVESTIGATOR: *[Insert Name*]

PHONE: [Insert Number]

GENERAL OVERVIEW

You have been invited to take part in a qualitative substudy for the HPTN 084 main study. The goal of the qualitative substudy is to understand how you feel about topics related to this study, HIV risk and HIV prevention methods. The substudy will include one to three interviews during which you will be asked to share your experiences about participating in HPTN 084. This qualitative substudy is being conducted in four of the HPTN 084 sites in Africa. It will include a total of 80-110 women.

The interviews will be led by a trained and experienced interviewer. We are interested in learning about your thoughts, opinions, and experiences with being a part of the study. For example, we would like to know how you decided to join the study. We would also like to know what you like and do not like about the injections (shots) and about the oral pills. Finally, we would like to know how you feel about contraception and getting pregnant during the study. We hope that the information learned from this study will help us to better understand what kind of HIV prevention options women prefer.

What happens if you do not want to join the qualitative interviews?

Before you learn more about the study it is important that you know the following:

- You do not have to join the qualitative interview.
- If you join the qualitative interview study but later decide later you want to stop, you can stop taking part at any time.
- Whether or not you take part in the qualitative interview study, you can still participate in the main study (HPTN 084). Also you will still continue to receive the same services you get at

[insert clinic].

What will happen if you do want to join the qualitative interview study?
If you decide to join the qualitative interview study, you will be asked to participate in a minimum of one and a maximum of 3 interviews during the time that you participate in HPTN 084. Each interview will be conducted by a trained interviewer and last from one hour to one and a half hours. The interviewer will contact you to arrange the next interview. In general, interviews will occur when you move to another stage of the HPTN 084 study.

The information that you share during the qualitative interviews will be treated confidentially. The interviews will be audio-recorded to help assure that we get the best understanding possible from each discussion. This recording will be used to make a written transcript of the interview. The recording and transcript will only have a Participant ID number. No identifying information will be included in the written transcript.

Although we hope that you will be comfortable answering all of the questions and talking openly and honestly, please keep in mind that you do not have to answer any of the questions. You may stop participating completely at any time.

What are the potential benefits?
You will not receive any direct benefit from being in the qualitative interviews; however, you or others in your community may benefit from this study later. The information gathered during this study may help to prevent HIV and other infections. This may be beneficial to you and your community.

What are the possible risks or discomforts?
The questions we will ask you may make you feel uncomfortable. Your partner or others may not like for you to talk about the study and how it affects your home life. We hope that the qualitative interview procedures described above will minimize your discomfort when discussing sensitive topics. However, the greatest risk may involve your privacy and confidentiality. Additional steps that the study team has taken to protect your privacy are described below.

How will your privacy be protected?
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, and anything else that might identify you personally, will not be used in any publication of information about this study.

Your records may be reviewed by the sponsor of the study (US National Institutes of Health (NIH) their representatives), US FDA, US Department of Heath and Human Services (DHHS), Office of Human Research Protection (OHRP) and other government and local, US and International regulatory entities, authorized representatives of US NIH and/or its contractors, [insert names of applicable IRBs/ECs/other local review bodies as applicable] IRB, study staff, study monitors, and companies that makes the study drug (ViiV Healthcare and Gilead Sciences, Inc.).

We cannot guarantee absolute confidentiality.

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

What are the alternatives to participating in this study?
You do not have to participate in the interviews.

Reasons why you may be withdrawn from the study without your consent
Your participation in the interviews may be ended early without your consent for the following reasons:

- The research study, or the qualitative part of the research study, is stopped or canceled.
- The study staff feels that participating in the interviews would be harmful to you.

What happens if you are injured by this research?
It is unlikely that you will be injured as a result of taking part in a qualitative interview. If you are injured, the [institution] will give you the treatment needed for your injuries. You [*will/will not*] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries through the United States NIH. You do not give up any legal rights by signing this consent form.

Who can you contact if you have any questions?
We are happy to answer any questions that you may have. It may be that you have questions about your rights as a study participant or that you think you have been injured because you were in this study. In this case you can contact [insert name of the investigator or other study staff] at [insert telephone number and physical address].

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

What is the cost of study participation?
There is no cost to you for being in this study. You will receive [insert local amount] for your time, effort, and travel to and from the clinic for each study visit.

SIGNATURE PAGE

HPTN 084:
A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women

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Sponsored by: Division of AIDS, United States (US) National Institute of Allergy and Infectious Disease, US National Institutes of Health.

Study products are provided by ViiV Healthcare and Gilead Sciences, Inc. Additional support is provided by the Bill & Melinda Gates Foundation (BMGF).

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

Study Participation
If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to join the study, please sign your name or make your mark below.

_____	_____	_____
Participant Name (print)	Participant Signature	Date

For staff: I have explained the purpose of the screening to the volunteer and have answered all of her questions. To the best of my knowledge, she understands the purpose, procedures, risks and benefits of this study.

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

Appendix VI: Guidance on study conduct during the COVID-19 pandemic

PRIORITIZATION OF STUDY VISIT PROCEDURES

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

  Note: If locally available, feasible, and at the discretion of the IoR, home HIV self-tests can be sourced and distributed to participants for participant use, and results demonstrated by video or photo-sharing to study sites as corroborative evidence of testing and test results. Such photos should be placed in the participant research record. Absence of home-testing results will NOT be considered a protocol deviation, nor reportable.

- Sites that are able may also conduct study visits — in full or in part — off-site if permitted by applicable government, health authority, and institutional policies. This is including but not limited to home-based visits. Where this option is permitted, site staff should communicate with participants to determine in advance where and when such visits will take place, with adequate protections for safety, privacy, and confidentiality. Offsite visit procedures should be conducted by site staff who are adequately qualified and trained to conduct the procedures, as determined by the site Investigator of Record (IoR), with attention paid to occupational health, biohazard containment, and specimen and data chain of custody. These staff should also be adequately qualified and trained to immediately assess and/or manage any adverse events or social impacts that may occur during the visits. If adverse events requiring further evaluation or management are identified during an off-site visit, staff conducting the visit should arrange for appropriate clinical management, in consultation with the IoR or designee as needed. NOTE: Step 2 BLINDED study product cannot be provided at an off-site visit.

Finalized Guidance for STEPS 1, 2 and 3 sent out 17 April 2020
These recommendations are made with the goal of ensuring both participant and staff safety and respecting the public health recommendations to minimize disease transmission.

1. Screening and enrollment were paused until further notice at all sites effective close of business local time Tuesday, March 17, 2020. This means that any screening and enrollment

appointments scheduled have to be deferred until after the pause is lifted.

2. For participants on study, follow-up visits should continue to ensure safety of the participants in alignment with local guidance and protocol where possible. We encourage all sites to plan for contingencies regarding HPTN 084 participants on study.

3. In the event that CRS operations are diminished or suspended entirely, and where conduct of study visits is not possible either because of staffing or operational concerns, please note the following:
    a. For participants in Step 1 (applicable to sites in South Africa and Eswatini), we recommend that where safe and feasible, participants be transitioned to step 2. At some sites, it may be possible to conduct week 4 testing and receive same-day results. In this case, sites may then proceed to complete week 5 procedures at that visit if protocol requirements for transition to step 2 are met.

       Where it is not possible to complete week 4 visits, participants should continue study product. Site staff should provide participants with sufficient product to cover this time period and ensure that they have sufficient contraceptive protection. Please counsel participants on the need to adopt additional HIV and pregnancy preventive measures if they are unable to return to site per schedule, and to record their pill taking and when that ended. We will follow routine procedures for assessing the transition to step 2 for delayed week 4/5.

       We do not anticipate significant product-related adverse events during this period, but if participants report significant symptoms, they should contact the site by phone. The IoR may consult the CMC, but in case responses are delayed, the IoR may use clinical judgement to hold or continue product.

    b. For participants in step 2: Sufficient product should be provided to cover the 8-week interval between injections plus a buffer of 30 days per the SSP - even for visits prior to week 41. This may allow the visit interval to extend up to 12 weeks. Contraception coverage should be verified to cover the entire interval.

       Participants need to receive both blinded study products during step 2. If injections cannot be administered, oral product should also be held. In this scenario, participants are advised to take additional measures to prevent HIV infection and exposure by all means available until they can return to study site. If they use non-study provided open-label PrEP during this period they should be encouraged to keep a log of dates of use should they use this option.

    c. For participants in step 3: we recommend continuation on daily unblinded oral product. Where participants cannot report for quarterly visits, participants should continue study product and where possible sites should explore delivery of product directly to participants from site investigational pharmacies. If not feasible, participants should be counselled to use other available means to protect themselves against HIV exposure and infection and pregnancy prevention until they are able to return to study participation.

IoRs can use their judgement about ongoing dispensation of oral product in these extraordinary circumstances without routine HIV and creatinine testing, based on known previous renal function, risk and adherence. Self-testing for HIV may also be useful in this setting if practical. The same guidance would apply to pregnant participants.

d. For participants in step 2 where early pregnancy cannot be excluded including a lapse in contraception, we suggest providing the participant with up to four weeks of TDF/FTC. The site can provide the participant with a pregnancy test kit to repeat pregnancy testing at home. Where the second test is negative, see guidance re step 2. Where the test is positive, see guidance re step 3.

e. For annual follow up: Annual visits should be delayed until study conduct can be resumed at the site.

4. PLEASE NOTE: These measures may not all be needed at your site immediately and are to be deployed as needed. Before any of these above is implemented, and should you update your plans, please inform the people copied on this email, including your site-specific DAIDS OCSO Program Officer. Please note that additional guidance was issued to CTU PIs and CRS leaders regarding considerations for visits during this extraordinary time (see attachment).

5. Please follow Data Communique #8, sent on 2 April 2020, regarding data collection procedures and documentation of missed visits or missed procedures, and any associated protocol deviations.

6. Please consider whether partial or full participant reimbursements may be provided for telephonic visits during this pandemic. This decision must be made in conjunction with your IRB and CTU.

7. Finally, as the situation unfolds in our countries, sites will also need to consider procedures for symptom screening, isolation of suspected cases and linkage to testing based on national guidelines. It may be useful to anticipate these contingencies ahead of time.

STUDY PRODUCT CONSIDERATIONS

- For emergency cases, and if possible given local considerations, the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks permits shipment or courier of oral study product from the site directly to participants. The pharmacist should refer to the section on “Shipping Study Product to a Participant” in this manual for detailed procedures. If this method is to be implemented, each site pharmacist must develop appropriate procedures for the shipment or courier of oral study product to identified participant in accordance with these guidelines and must include appropriately documented chain of custody. This method should only be used if permissible per local institutional and IRB/EC policies.

- All questions related to study product management should be directed to Katie Shin – kashin@niaid.nih.gov.

DOCUMENTATION

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for HPTN 084.
- Participant-specific documentation should be entered in participant study charts in real-time to the extent possible.

- Specific guidance regarding coding visits and instructions therein is forthcoming from SCHARP in a separate communication to all sites.

- In consultation with the Division of AIDS, the HPTN Network is developing comprehensive guidance for documenting and/or reporting protocol deviations that may occur due to limited site capacity to conduct study visits or procedures during the COVID-19 pandemic. Once this Network-level guidance is available, it will be provided in a separate communication to all sites.

Appendix VII: Study conduct post 5 November 2020 DSMB meeting (LoA #4)

All modifications included in this Letter of Amendment are based on results of a pre-planned interim efficacy and safety review by the National Institute of Allergy and Infectious Diseases (NIAID) Multinational Data and Safety Monitoring Board (DSMB). On 5 November 2020, the NIAID Multinational DSMB was in agreement that the primary question of whether long-acting cabotegravir prevents HIV infection has been answered in the affirmative and was highly statistically significant. Because of these results, the DSMB recommended that blinded portion of the study be stopped, participants unblinded to their study allocation and that the trial results be made available as soon as possible. The study's sponsor (NIAID) accepted the Board's recommendation. A full protocol amendment will be developed; however, the modifications specified below reflect an interim approach to be employed until that amendment is finalized and approved by the sponsor and the IRBs/ECs/other national and local regulatory authorities.

The immediate modifications are summarized below:

- No further screening or enrollment will occur under Version 2.0 of the protocol, dated November 6, 2019, meaning that the portion of the LoA that outlines the recommendation for an increase to 3,350 participants in LoA #3 is null and void.

- Investigators of Record (IoR) will be provided the randomization assignment for their enrolled participants. Each site IoR will then be responsible for informing participants of her randomization assignment as soon as is feasible following approval of a Participant Letter to be administered at the time of unblinding.

- Upon being informed of randomized study drug assignment, participants still receiving study drug will no longer receive the respective placebo study product and will be offered to continue the active study drug to which they were originally assigned until further notice as follows:

    - Participants in Step 1: If any participants remain in Step 1, contact the HPTN 084 Clinical Management Committee for guidance. (084cmc@hptn.org).

    - Participants in Step 2 assigned to active CAB LA: These participants will be offered to continue active CAB LA on the current Step 2 study visit schedule**.**

    - Participants in Step 2 assigned to active oral TDF/FTC: These participants will be offered to continue active TDF/FTC on the current Step 2 study visit schedule**.** These participants will be offered CAB when it becomes available.

    - Participants in Step 3 will continue visits per the current Step 3 visit schedule. Participants who reach the final visit of Step 3 prior to obtaining additional CAB drug supply will transition to annual follow-up and be referred to local HIV prevention services. When CAB supply is obtained, these participants will be contacted and offered CAB.

    - In consultation with the study's Clinical Management Committee (CMC), participants who have already completed or terminated study participation for reasons other than HIV infection, an adverse event assessed as related to study product, or other exclusionary reasons as identified by the CMC, will be offered to re-enroll via the upcoming full amendment of the protocol.

- Upon implementation of LoA #4, participants who choose to continue study follow-up as outlined above will follow the current applicable Step-associated Schedule of Procedures and Evaluations with the exception of

pill counts at Weeks 2 and 4 and dispensing blinded product and placebo. Only unblinded products will be dispensed.

Sample HPTN 084 Participant Letter/Information Sheet

PRINCIPAL INVESTIGATOR: [Insert PI Name/Affiliation]

Dear HPTN 084 Participant:

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

The HPTN 084 Study:

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

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

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

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

Results of the DSMB review:

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

The HPTN 084 study will continue. The study team wants you to keep coming to this clinic for follow up visits and procedures. In the near future, the protocol will be amended to allow for slight changes to the study visit requirements depending on which active product you are taking and whether you change from TDF/FTC to CAB. You will be given the information and offered an updated consent form at that time. For now, you will stay in the group that you were put in at the beginning of the study. We will tell you what this group is at your visit today.

[To be inserted for sites with participants on Step 1: If you are in the first part of the study (Step 1) and you are on real CAB, you will finish Step 1 and then you will come to the clinic for your first injection and then four weeks

later for another injection, and then every 8 weeks after that. If you are on real TDF/FTC, you will finish Step 1 and then come to the clinic every 8 weeks.]

If you are in part of the study where you are getting injections (Step 2), you will come to the clinic as originally planned which is about every 8 weeks. Participants assigned to real CAB will continue to receive real CAB injections but will no longer receive TDF/FTC placebo pills.

Participants assigned to real TDF/FTC will continue to receive real TDF/FTC pills but will no longer receive CAB placebo injections. If this is the real TDF/FTC group, we want to remind you that TDF/FTC works very well to prevent HIV infection if it is taken as prescribed.

If you are in the group that got real TDF/FTC and you want to get CAB, you will be offered CAB when it is available. The study team is working to get more CAB for participants that want it. The study team will also let you know how long you will stay in the study, the new study visits and study procedures now that we have this new information. Any changes in the study must be approved by a group of people that protect your rights and safety *(insert regulatory authorities and Ethics Committees as appropriate)*. This group oversees research at this clinic. We will tell you of any decisions about changes in the study and fully explain any changes to you.

Staying in HPTN 084 is entirely your choice. You may choose to leave the study now or at any time in the future without losing any of the care you get at this [*or name local referral clinic or other required local language*] clinic.

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

Your participation in the HPTN 084 study has led to a very important discovery about a new way to prevent HIV infection. Staying in this study will help to increase our knowledge. Thank you for participating in HPTN 084.

Sincerely,

[Insert name and contact information of Investigator of Record]

_____

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

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

Appendix VIII: Procedures for Offering Open Label (OL) Cabotegravir- The Next Part of HPTN 084

Background, Purpose and Overview, Description of Steps

1. Background

Given the results of the HPTN 084 trial[1], in keeping with the Data and Safety Monitoring Board (DSMB) recommendations after the 5 November 2020 review to discontinue the blinded portion of the trial, and in keeping with the HPTN 083 trial results and DSMB recommendations, HPTN 084 is amending the version 2.0 protocol to add an open-label (OL) evaluation of long-acting cabotegravir (CAB LA) for all participants, irrespective of original study arm. Please note that as an interim measure between the DSMB's recommendation and this full protocol amendment, a Letter of Amendment (LoA) (LoA #4 dated 16 November 2020) was issued. That LoA ended the blinded portion of the study and included a descriptive Dear Participant Letter. This full protocol amendment will permit participants to choose which of the two active study agents (CAB LA or TDF/FTC) they wish to take for a 48-week OL evaluation. In addition, it makes provision for participants to continue active dosing with CAB LA through pregnancy and breastfeeding upon reconsent.

The procedures for the amendment and an addendum to the main informed consent form (ICF) are contained within this Appendix. The amended protocol signature page is within the main body of the protocol. The only other changes made to the main body of the protocol were to incorporate previously issued updates to the v2.0 protocol made via Clarification Memo (CM) and LoAs. Specifically, the main protocol was edited to include changes made by the previously issued:

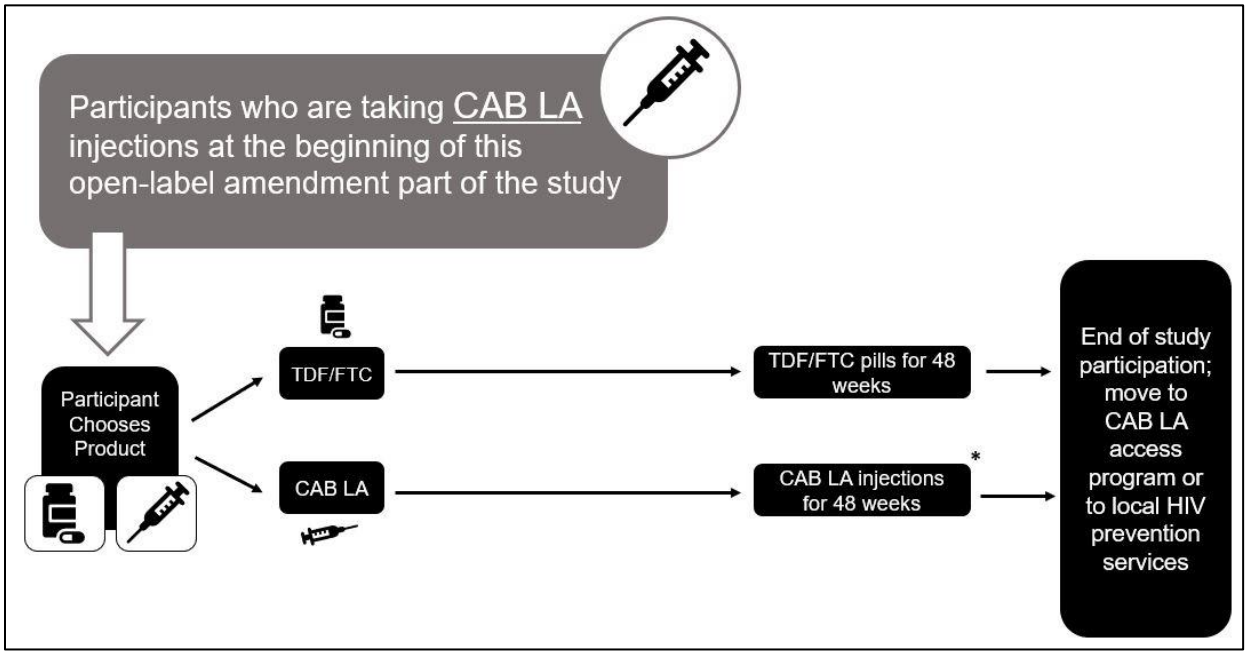
- CM#1, Version 1.0 dated 22Jan2020
- LoA#1, Version 1.0 dated 23June2020
- LoA#2, Version 1.0 dated 10Sep2020
- CM#2, Version 1.0 dated 16Sep2020
- LoA#3, Version 1.0 dated 22Oct2020
- LoA#4, Version 1.0 dated 16Nov2020

A few minor wording changes were made to Sections 9.0, Laboratory Specimens and Biohazards Containment to reflect a network change in quality assurance. A footnote was added to Appendix 1b (Schedule of Evaluations- Step 2. Injection Phase), to address participants who reach Week 185 on Step at a site awaiting implementation of this amendment. No other changes were made to the main body of the protocol.

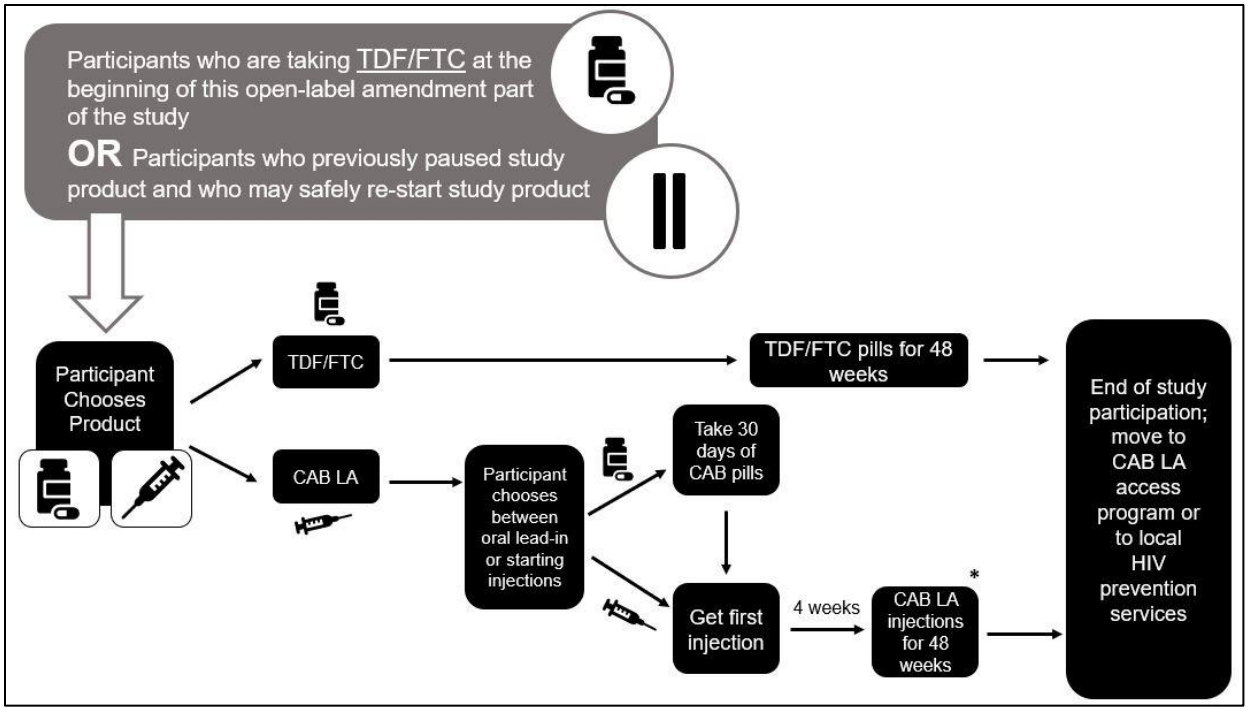
2. Purpose and Overview

The purpose of this Appendix is to provide instructions for the OL portion of the study.

Participants will be offered the opportunity to either take OL CAB LA 600 mg IM every eight weeks (with the exception of participants who previously discontinued CAB LA for confirmed safety reasons) or to take OL daily TDF/FTC. Participants switching from TDF/FTC or re-starting CAB LA may choose to start CAB LA immediately or they may start at a later time point but no later than 24 weeks after they begin the OL portion of the study. Participants initiating CAB LA during this amendment will be permitted to choose between an oral lead-in (OLI) prior to the first injection or initiating injections immediately. Participants may also choose to discontinue study products, (e.g., if they have reduced HIV risk); participants discontinuing study products will be asked to continue in follow-up for 48 weeks off of study product. Below are two images illustrating the options participants will have during the open-label portion of the study.



* Note that participants who elect to stop taking CAB LA injections will be offered 48 weeks of TDF/FTC to cover the PK tail.



* Note that participants who elect to stop taking CAB LA injections will be offered 48 weeks of TDF/FTC to cover the PK tail.

This Appendix includes procedures for new Steps, Step 4 (OL CAB LA or OL TDF/FTC) and Step 5 (OL TDF/FTC following premature discontinuation of CAB LA), the respective visit schedule for each participant group, updated toxicity management instructions, an updated sample ICF, and other relevant information from the original protocol that pertains to study procedures for Steps 4 and 5. Please note, this section also contains an SOE for following pregnant and breastfeeding participants.

Implementation of this Appendix will go into effect at a given site when: 1) all required IRB/EC/other regulatory entity approvals are in place; 2) adequate supply of cabotegravir for this purpose has been received at the site; 3) the site has confirmed that training of all active personnel for Version 3.0 has been completed; and 4) the site receives notification from the DAIDS Protocol Registration Office that the site-specific informed consent addendum is approved and indicates successful completion of the amendment protocol registration process. **The HPTN Leadership and Operations Center (LOC) will issue an approval notice to begin implementation of Version 3.0 upon confirmation that all items outlined above are in place.**

2.1 Duration

For the majority of participants, the HPTN 084 OL component will last a minimum of approximately 48 weeks and a maximum of 52 weeks, per participant. In specific circumstances, participants may be in the study for longer timeframes:

- Participants starting/re-starting CAB LA who elect to do the oral run-in will be followed for 56 weeks. These participants will complete 4 weeks of an oral run-in plus a 4-week injection loading period.

- Only a minority of participants will be followed for up to 100 weeks (those who discontinue CAB LA prematurely during the OL component and are offered 48 weeks of TDF/FTC to cover the pharmacokinetic (PK) “tail").

- Pregnant participants may be enrolled in the study for up to 148 weeks (four-week OLI optional, plus 48 weeks OL CAB LA (and only if pregnancy occurs within 8 weeks of last injection) plus 96 weeks of follow-up through pregnancy and post-partum period with final assessment of infant outcome at 48 weeks post-partum).

The OL evaluation period will be 48 weeks of either OL study product (CAB LA or TDF/FTC). Following that initial 48-week period participants will take one of two paths:

1) Participants who elected to take OL TDF/FTC will have completed all study activities and will be provided information to access local Pre-Exposure Prophylaxis (PrEP) programs.

2) Participants who elected to take OL CAB LA may choose to transition to locally available CAB LA (through a post-trial access program) or to a local PrEP program. These participants will have completed all study activities, unless they are pregnant.

2.2 Study sites and population

Only participants at sites who participated in the original HPTN 084 study, or participants in the adolescent sub-study HPTN 084-01 will be included. HPTN 084-01 participants may transition to this HPTN 084 protocol amendment any time after Step 2 of HPTN 084-01.

2.3 Special considerations:

Optional Oral Lead-In (OLI): Following review of the preliminary safety data from HPTN 083, HPTN 084 and safety data across the entire CAB LA clinical program, ViiV Healthcare has agreed to permit an **optional** OLI in the OL extension for participants switching from TDF/FTC to CAB LA.

Justification for an optional OLI:
Based on the totality of the safety data obtained during Step 1 of HPTN 083 (n=2281 participants in the CAB group Step 1 Safety population, of whom 2117 were included in the Step 2 Safety population), no significant concerns regarding safety or tolerability of oral CAB have been identified. A review of AEs, SAEs, Grade 3 or 4 AEs, AEs leading to discontinuation of study drug, and drug-induced liver injury (DILI) cases in participants receiving CAB do not indicate any specific safety concerns that would require mandatory use of OLI to mitigate severe adverse drug reactions (ADRs) prior to initiating CAB LA.

To date, the OLI has been included in the CAB LA clinical development program to reduce the theoretical risk of a severe adverse drug reaction following initiation of CAB LA. The duration up to five weeks of OLI for HPTN 084 was selected given that approximately 80-90% of severe hypersensitivity drug-related reactions (in general, and not necessarily for CAB) occur within the first four weeks of dosing. HPTN 084 was launched approximately three years ago, in November 2017, and HPTN 083 was launched in December 2016. A total of 7,143 subjects have received at least 1 dose of CAB oral or LA through 18 October 2020 in ViiV sponsored and supported studies, of whom 6,279 of these received CAB LA. Approximately 90,000 CAB injections have been administered to date. No confirmed hypersensitivity cases were reported in the CAB treatment program in HIV infected patients. The AE data for the combined OLI CAB + rilpivirine (RPV) periods in Phase 3 Studies 201584 (FLAIR), 201585 (ATLAS), and 207966 (ATLAS-2M) did not identify any new AE trends. One case of possible DILI was identified during OLI in a participant for ATLAS-2M (Overton, Lancet 2020 article[2] and additional Sponsor information). Based on FLAIR Week 124 results, CAB + RPV LA with or without an OLI, was found to be a well-tolerated, safe and effective maintenance regimen up to Week 124. Switching directly to CAB + RPV LA was comparable in terms of safety and tolerability to treatment with OLI (cite Glasgow 2020 presentation).[3]

An OLI is not required for achievement of therapeutic concentrations on initiation of injections or at steady state. The contribution of oral dosing to the profile is limited to the first week following the final OLI dose and has no impact on trough levels 4-weeks following the initiation injection as observed in HIV-infected participants [geometric mean (5th, 95th percentile): 1.43 µg/mL (0.403, 3.90) without OLI, 1.56 µg/mL (0.551, 3.61) with OLI], which were similar to observed values for uninfected participants in HPTN083 where OLI dosing was stopped 1 day prior to initiation injections [1.86 µ/mL (0.43, 4.73)]. Initiation of injections without OLI did not impact efficacy in HIV-1 infected participants in the CAB-LA/RPV-LA treatment program [plasma HIV-1 RNA ≥50 c/mL 24-weeks after initiation: 1 of 111 (0.9%) participants without OLI compared with 1 of 121 (0.8%) participants with OLI].

The CAB LA HIV prevention program, relative to the treatment program, has unique considerations that need to be better understood to fully inform the risk/benefit of using CAB LA as PrEP. People using PrEP are HIV un-infected and desire PrEP to protect themselves. Adherence to oral PrEP is difficult for many, and suboptimal oral adherence during the OLI in HPTN 083 may have played a role in three incident cases in the CAB LA arm during the OLI period.[4] In addition to adherence challenges, many countries are also resource constrained. Access to providers and to PrEP may be limited. Operationally, countries may desire simplified programs once CAB LA is available.

In the HIV treatment arena, the evaluation of an optional OLI dosing was first undertaken in a controlled clinical trial setting. Our proposal for an optional OLI approach in the prevention arena, rather than outright removal of the oral lead-in period, will allow us to explore considerations around participant choice, provider choice and comfort level, uptake and utilization, and safety data collection in detail in a trial setting.

Pregnancy: Following a review of available safety data, the long-acting, reversible contraceptive (LARC) requirement for the OL evaluation of HPTN 084 will be relaxed to allow

for more real-world approach to fertility intentions. Participants will not be required to take any form of contraception during the OL Steps 4 and 5, although they will be counselled about risks and benefits of CAB use during pregnancy and breastfeeding and about ways to avoid pregnancy if they so desire. Participants who become pregnant during the HPTN 084 OL will be permitted to continue active dosing with CAB LA, after they provide additional consent.

Justification for relaxed contraceptive requirements and CAB LA dosing during pregnancy: Addressing the use of CAB LA for HIV PrEP in pregnancy is important and timely. Women in high HIV prevalence settings may be at increased risk for HIV when planning to conceive, and need HIV prevention options, like PrEP that go beyond condoms. Pregnancy may also be a vulnerable period for HIV acquisition. A systematic review in 2018 that included 37 studies contributing 100,758 person-years of follow-up estimated that the average HIV incidence in pregnant and breastfeeding women was 3.6 per 100 person years. This HIV incidence is consistent with the threshold recommended for offer of PrEP in at-risk populations. While the review did not find any evidence of excess HIV risk associated with pregnancy and breastfeeding, there was significant heterogeneity in the data.[5] Pregnancy and breastfeeding are periods marked by significant biological and behavioral changes that may have varying effects on the risk of HIV. Pregnancy is associated with biological changes including higher concentrations of estrogen and progesterone that may promote a cascade of synergistic changes in the female genital tract, including changes in C-C chemokine receptor type 5 (CCR5) and C-X-C chemokine receptor type 4 (CXCR4) expression, increased inflammation, decreased integrity of the vaginal epithelium, and alterations in vaginal microbiota, all of which have been associated with increased HIV acquisition susceptibility.[6] An analysis of prospective data from 2,751 HIV serodiscordant couples found that the per-coital act probability of HIV acquisition was higher in late pregnancy and early post-partum compared to the non-pregnant state, after adjusting for sexual behavior, leading authors to hypothesize that this increased risk may be due to biological changes that occur in the late pregnancy and post-partum period.[7] These biological changes and associated risks may be offset in some settings by changes in sexual behavior and reduced frequency of sexual intercourse. The direction of an observed association between pregnancy and the breastfeeding and HIV, may therefore depend on the context as well as the balance of these behavioral and biological factors.[5] Nevertheless, preventing HIV in high-risk populations who are also at risk for pregnancy remains a priority for reducing both maternal and infant morbidity and mortality. As access to PrEP expands, data on the safety, acceptability and dosing requirements of PrEP agents during pregnancy are a priority.

During the blinded portion of HPTN 084 it was not possible to continue dosing with blinded study product during pregnancy. In May 2018, the study protocol was modified to require all participants of child-bearing potential to use a long-acting reversible contraceptive (LARC); all participants who became pregnant discontinued blinded product and were transitioned to OL TDF/FTC for the duration of pregnancy. This was in response to a safety signal observed in women living with HIV and using dolutegravir (DTG) around the time of conception in the Tsepamo study. (see section 1.7.1) Since the initial reports from the Tsepamo study, studies done in several other cohorts have not confirmed this safety signal.[7] These studies however have been conducted in high-income countries (e.g., Canada, Germany, France, and the UK) and have included few exposed pregnancies. Neural Tube Defect (NTD) cases have also been reviewed using pharmacovigilance databases; one review lacked sufficient data on DTG exposure in pregnant women necessary to make any conclusion.[8] A subsequent review of NTD data from the

World Health Organization (WHO) pharmacovigilance database that includes 20 million case safety reports from over 130 million countries did not find strong support for the NTD signal associated with DTG use.[9] In 2020, updated data from expanded and ongoing surveillance in Botswana (where the original Tsepamo study was conducted) between April 1, 2019, and April 30, 2020, revealed a decrease in the NTD prevalence difference between women receiving DTG and those receiving other antiretrovirals from 0.20% in the earlier report to 0.09%, a difference that is not statistically significant.[10]

Current guidance from WHO recommends the use of DTG in pregnant women and those of child-bearing potential, and encourages counselling of women so that they can make an informed choice about treatment based on an understanding of the risks and benefits associated with their choice.[11] While structurally similar, cabotegravir is not the same as DTG. Pre-clinical studies did not find any effect of CAB on embryofetal development (see section 1.7 of original protocol). In HPTN 084, prior to 5 November 2020, pregnancy incidence in the context of LARC use was 1.3 per 100 person years (95% confidence interval [CI] 1.0, 1.7). Of 50 confirmed pregnancies, 27 (54%) had confirmed pregnancy outcomes while the remainder were ongoing. Reassuringly, no congenital anomalies were observed.[1]

Data on the safety and PK of CAB LA in pregnant women compared to non-pregnant women are critical. In particular, data on PK are important for informing the need for dose adjustments in pregnancy. Drug metabolism may be altered during pregnancy. Pregnant women experience unique physiological changes that may result in clinically significant alterations in drug PK and pharmacodynamics. With respect to long-acting injectable antiretroviral products, the following physiological changes beginning early in gestation may be relevant: (a) large changes in total body water and fat, increasing drug distribution volume; (b) decreased albumin and increased alpha-1 acid glycoprotein (AAG) concentrations that may cause clinically relevant changes in drug protein binding; (c) increased cardiac output, ventilation, and hepatic and renal blood flow which may impact drug metabolism and elimination; and (e) increased concentrations of endogenous glucocorticoids that may affect the activity of hepatic enzyme systems that regulate drug metabolism. [12-17] These physiological changes have the potential to result in lower drug exposures with consequent loss of HIV protection if significant. While few data exist, an analysis of samples from three women living with HIV who received CAB LA with RPV during ViiV-sponsored trials provide some reassurance. Although CAB LA was discontinued at the time of pregnancy confirmation, the rate of decline of CAB concentrations during the PK tail in pregnancy was within the expected range for non-pregnant women. The CAB LA PK profile is primarily determined by its absorption rate, which appears to be unaffected by changes in metabolic enzymatic profile.[18] More data in a larger sample size could confirm this.

Data on CAB LA concentrations in breastmilk are extremely limited. In pre-clinical pre- and post-natal development studies in female rats, no effect of CAB on lactation was seen at any dose.[19] There was also no effect on rat pup growth and development, or AEs with exposure to CAB in maternal milk. Data from DTG may provide some indication of expected breast milk concentrations. In 17 breastfeeding mothers, the median ratio of DTG in breast milk to maternal plasma was 0.03. Their infants had a median maximum DTG concentration of 66.7 ng/mL (range 21–654 ng/mL) and a median minimum concentration of 60.9 ng/mL (range 16.3–479 ng/mL) at a median age of 10 days (range 7–18 days). It appears that elimination by newborn infants is

prolonged but no AEs have been reported and DTG has been used safely in HIV-positive mothers during breastfeeding.[20] Collection of similar data on CAB concentrations in breastmilk and infant plasma will be important for providing clear guidance to health care providers and PrEP users about CAB use during breastfeeding, particularly if HIV risk is elevated in the early post-partum period and effective PrEP is required. These data may also be informative for women who may breastfeed for a prolonged period (up to 2 years) but who also want an effective method of HIV prevention.

Historically, pregnant women have been seen as a vulnerable population and excluded from clinical trials in order to protect the mother and fetus from potential harm. The consequence of this exclusion, however, has been off-label use of medicines in pregnancy in the absence of robust evidence of safety, PK and efficacy of during this period. More recently there has been a recognition that pregnant women are better served through targeted enrollment in research that meets their needs, and that is able to provide appropriate protections within the framework of a clinical trial where adequate monitoring can take place.[21] The HPTN 084 amendment provides an opportunity to offer participants the chance to reconsent to active CAB LA dosing during pregnancy and breastfeeding, while ensuring adequate monitoring of safety in both mother and infant. These data will provide important information on acceptability, tolerability, safety and PK of CAB LA during pregnancy and breastfeeding prior to widescale implementation in demonstration projects and national programs where extensive monitoring may be limited.

3. Description of Steps 4 and 5

3.1 Overview

All participants will be offered OL CAB LA, except for those participants who discontinued CAB LA for safety reasons earlier in the study. Participants who permanently discontinued study products during the blinded portion of the study due to HIV infection, HBV infection or for a study product-related AE that would deem the continuation or initiation of CAB unsafe are NOT eligible to restart or begin CAB. The CMC may be contacted for questions related to study product AEs of concern for participants interested in continuing or initiating CAB and whether it is safe to do so.

All participants will be followed for at least 48 weeks in Step 4 (unless they decline consent for further participation). Step 5 will be offered to all participants who receive at least one injection of CAB LA in Step 4 but who prematurely discontinue CAB LA in Step 4. In Step 5 participants will be followed for 48 weeks on OL TDF/FTC to cover the CAB LA tail. Details of Steps 4 and 5 are included below.

An addendum to the main informed consent form is included in this Appendix and will document the participant's continued participation in the OL portion of the study. A site may opt to discuss the choice of participating in the OL evaluation via telephone or telemedicine at the discretion of the Investigator of Record (IoR) and if allowable by local ethics committees. If this discussion does occur off-site and the participant chooses to continue in the study, once the participant reports to the study site, product dispensation can only occur after signature of the addendum informed consent form. Contact the CMC (084cmc@hptn.org) for guidance if there

are other scenarios for a discussion about choice and obtaining informed consent that are not outlined here.

The following Steps will be followed during the OL evaluation:

1) Step 4a- Procedures for Participants Initially Randomized to TDF/FTC Who Elect to Move to OL CAB LA with Optional Oral Lead-in first
2) Step 4b- Procedures for Participants Initiating or Re-starting CAB LA without the Optional Oral Lead-in; the Initial Dose Visit
3) Step 4c- Procedures for Participants on Maintenance Doses of CAB LA or TDF/FTC
4) Step 4d- Procedures for Pregnant/Breastfeeding Participants
5) Step 5- Procedures for Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation

Step 4

During Step 4c, all participants will be followed for 48 weeks, irrespective of OL study product choice (CAB LA or TDF/FTC), at visits every eight weeks for a total of six visits.

Participants who were taking CAB LA during the original study will move directly into Step 4c (if they wish to continue taking CAB LA).

Participants who transition from TDF/FTC or re-start CAB LA may choose from two options before starting Step 4c:

> Option A: Step 4a- Participants will receive daily oral CAB pills for four weeks prior to starting injectable CAB LA. Once Step 4a is completed, participants will move to Step 4b.
>
> Option B: Step 4b- Participants will start immediately with injectable CAB LA. Once a participant completes Step 4b, she will move to Step 4c four weeks later for the first injection of the 48-week OL evaluation.

Step 4d is for participants who become pregnant in Step 4 and first 8 weeks of Step 5, who have had at least one CAB LA injection ever: This step does not apply to participants who have never received a CAB LA injection. At the first pregnancy test positive visit, participants will have their pregnancy confirmed on a second independent sample. Participants should be counselled about the risks and benefits of continuing CAB through pregnancy and breastfeeding, and offered an opportunity to re-consent to receive CAB LA injections during pregnancy. Participants who need more time to consider their decision can have their CAB LA injection temporarily deferred, within the remaining visit window. Participants who decline to continue CAB LA during pregnancy and breastfeeding will be offered OL TDF/FTC. All pregnant participants who have had at least one CAB LA injection will be followed up in accordance with the pregnancy schedule of evaluations in Step 4d. CAB LA injections will be administered every eight weeks in those that consent. Additional safety assessments and PK samples will be collected at study visits four weeks after every injection.

At delivery, a maternal blood sample and cord blood sample will be collected from the mother, and where feasible an infant blood sample will be collected (week 0). During the post-partum period blood and breastmilk samples will be collected from the mother, and blood samples from the infant per the Step 4d SOE. Infant outcomes will be assessed at delivery up to approximately 12 months later (Week 48 of Step 4d).

Participants who do not have a live birth outcome will be followed up in accordance with Step 4c visits. Pregnancy outcome data will still be collected in these participants at the time of the pregnancy outcome.

Participants who have never received a CAB LA injection will be followed up through Step 4c and through to pregnancy outcome. They will remain on the Step 4c SOE.

All participants who complete Steps 4c or d will have the option to link to a CAB LA access program or local HIV prevention program if preferred.

Step 5

Only participants who received OL CAB LA in Step 4 and who discontinue CAB LA early for safety or other reasons will have the option to transition to Step 5.

During Step 5, participants will be followed for 48 weeks on OL TDF/FTC according to the Step 5 SOE. Once participants complete Step 5 they will be offered information for local PrEP/standard of care HIV prevention programs.

a. Step 4a

Appendix VIII: Schedule of Evaluations for Step 4a-Procedures for Participants Initially Randomized to TDF/FTC Who Elect to Move to OL CAB LA with Optional Oral Lead-in first

	DAY 0/ of Step 4a
ADMINISTRATIVE, BEHAVIORAL, REGULATORY	
Informed consent	X
Locator information	X
Offer CAB LA and counseling on direct to inject vs. oral lead in	X
Acceptability assessment	X
Behavioral assessment	X
HIV prevention counseling	X
Offer condoms	X
CLINICAL EVALUATIONS & PROCEDURES	
Medical history, con meds, targeted physical exam (with pulse, BP, weight and BMI calculated at each visit)	X
Blood collection	X
Urine collection[1]	X
For those who select oral lead in: Dispense study product (enough for 4 weeks)	X
Adherence counseling[2]	X
LOCAL LABORATORY EVALUATIONS & PROCEDURES	
HIV testing[3]	X
HIV viral load testing[4]	X
Pregnancy testing[1]	X
CBC with differential, if not done in Step 4a	X
Chemistry testing[5]	X
Liver function tests[6]	X
Fasting lipid profile, if not done in Step 4a[7]	X
Plasma storage[8,9]	X
DBS storage[9]	X

[1] 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.
[2] Refer to the SSP Manual.
[3] The HIV testing algorithm and instruction for VL testing are provided in the SSP Manual. HIV rapid 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.
[4] This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.
[5] Albumin, BUN/urea, creatinine. Additional testing may be required if abnormalities of clinical significance are detected.

[6] AST, ALT, total bilirubin.
[7] Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit
[8] Stored plasma may be used for Quality Assurance testing, possible HSV-2 testing and other assessments at the HPTN LC.
[9] Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP.

b. Step 4b

Appendix VIII: Schedule of Evaluations for Step 4b- Procedures for Participants Initiating or Re-starting CAB LA without the Optional Oral Lead-in; the Initial Dose Visit

	DAY 0 of Step 4b
ADMINISTRATIVE, BEHAVIORAL, REGULATORY	
Informed consent, if not obtained in Step 4a	X
Locator information	X
Offer CAB LA and counseling on direct to inject vs. oral lead in, if not done in Step 4a	X
Acceptability assessment, if not done in Step 4a	X
Behavioral assessment, if not done in Step 4a	X
HIV prevention counseling	X
Offer condoms	X
CLINICAL EVALUATIONS & PROCEDURES	
Medical history, con meds, targeted physical exam (with pulse, BP, weight and BMI calculated at each visit)	X
Blood collection	X
Urine collection[1]	X
Adherence counseling[2]	X
Dispense and administer CAB LA [±]	X
LOCAL LABORATORY EVALUATIONS & PROCEDURES	
HIV testing[3]	X
HIV viral load testing [4]	X
Pregnancy testing[1]	X
CBC with differential, if not done in Step 4a	X
Chemistry testing[5]	X
Liver function tests[6]	X
Fasting lipid profile, if not done in Step 4a[7]	X
Plasma storage[8,9]	X
DBS storage[9]	X

[±] All participants initiating or re-starting CAB LA, will receive their initial CAB LA injection during Step 4b. The second injection will occur during Step 4c. The second injection must be given 4 weeks after the initial injection.

[1] 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.

[2] Refer to the SSP Manual.

[3] The HIV testing algorithm and instruction for VL testing are provided in the SSP Manual. HIV rapid 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.

[4] This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.

[5] Albumin, BUN/urea, creatinine. Additional testing may be required if abnormalities of clinical significance are detected.
[6] AST, ALT, total bilirubin.
[7] Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit
[8] Stored plasma may be used for Quality Assurance testing, possible HSV-2 testing and other assessments at the HPTN LC.
[9] Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP.

c. Step 4c

Appendix VIII: Schedule of Evaluations for Step 4c- Procedures for Participants on Maintenance Doses of CAB LA or TDF/FTC

Time on OL Study Product	Week 0 of Step 4c[+]		Week 8		Week 16		Week 24		Week 32		Week 40		Week 48
Informed Consent**	X												
Locator information	X		X		X		X		X		X		X
Acceptability assessment	X						X						X
Behavioral assessment	X		X		X		X		X		X		X
HIV prevention counseling	X		X		X		X		X		X		X
Offer condoms per local SOC	X		X		X		X		X		X		X
CLINICAL EVALUATIONS & PROCEDURES													
Medical history, concomitant medications, targeted physical exam (with pulse, BP, weight and BMI calculated at each visit)	X		X		X		X		X		X		X
Blood collection	X		X		X		X		X		X		X
Urine collection[1]	X		X		X		X		X		X		X
Vaginal swab collection[2]	X						X						X
Adherence counseling[3]	X		X		X		X		X		X		X
Dispense/administer product as is appropriate	X		X		X		X		X		X		X
LOCAL LABORATORY EVALUATIONS & PROCEDURES													
HIV testing[4]	X		X		X		X		X		X		X
HIV viral load testing[5]	X		X		X		X		X		X		X
Pregnancy testing[1]	X		X		X		X		X		X		X
CBC with differential, if not done in Step 4a or 4b	X						X						X
Chemistry testing, if not done in Step 4a or 4b[6]	X						X						X
Liver function testing[7]	X						X						X
Fasting lipid profile[8]													X
Syphilis testing	X						X						X
Vaginal GC/CT and TV testing[2]	X						X						X
Urinalysis (protein, glucose)	X						X						X
Plasma storage[9,10]	X		X		X		X		X		X		X
DBS storage[10]	X		X		X		X		X		X		X

** for those that have not already re-consented as part of step 4 a or b

** for those that have not already re-consented as part of step 4 a or b

[+] For participants transitioning from Step 4b this will not be Week 0 of CAB LA. This is Week 0 of Step 4c but must implemented 4 weeks after the initial injection for women who completed Step 4b.

[1] 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 a participant has a positive pregnancy test, follow her according to Step 4d.
[2] GC/CT and TV testing to be done only if not performed in the past 3 months. GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing u9sing the swab may be performed at that later visit.
[3] Refer to the SSP Manual.
[4] The HIV testing algorithm is provided in the SSP Manual. HIV rapid testing 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.
[5] This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.
[6] Only for those that did not have this collected in steps 4a and b. Albumin, BUN/urea, creatinine. Additional testing may be required if abnormalities of clinical significance are detected.
[7] AST, ALT, total bilirubin.
[8] Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.
[9] Stored plasma may be used for Quality Assurance testing, possible HSV-2 testing and other assessments at the HPTN LC.
[10] Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP.

d. Step 4d

Participants who become pregnant during Step 4 and who received at least one CAB LA injection during HPTN 084 are eligible to participate in the Pregnancy and Infant Sub-Study. In addition, participants in Step 5 who received a CAB LA injection within 8 weeks of pregnancy confirmation may join the Pregnancy and Infant Sub-Study. All participants interested in participating in Step 4d will be provided informed consent for this Step prior to any study activities.

Appendix VIII: Schedule of Evaluations for Step 4d- Procedures for Pregnant/Breastfeeding Participants

Time on Pregnancy and Infant Sub-study	Week 0	Wee k 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Delivery	Week 2, pp	Week 4, pp	Week 8, pp	Week 16 pp	Week 24, pp	Week 32, pp	Week 40, pp	Week 48, pp
Maternal assessments																				
Informed Consent	X																			
Locator information	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X
Acceptability assessment	X			X					X								X			X
Behavioral assessment	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X
HIV prevention counseling	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X
Offer condoms per local SOC	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X
Medical history, concomitant medications (including folate intake)	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X
Targeted physical exam including antenatal assessment per SOC	X	X	X	X	X	X	X	X	X	X	X				X					X
Ultrasound or refer to ultrasound				X																
Blood collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine collection [1]	X						X								X	X	X	X	X	X
Vaginal swab collection[1]	X						X								X					X
Breastmilk Collection, 5mLs[4]													X	X	X	X	X			
Adherence counseling[2]	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X
Contraceptive counseling															X	X	X	X	X	X
Dispense/administer study product, as is appropriate	X		X		X		X		X		X				X	X	X	X		X
ISR Assessment, only for PPTs receiving CAB LA injections		X		X		X		X		X					X					X
HIV testing[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV viral load testing [4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy testing[5]															X	X	X	X	X	X
CBC with differential	X						X			X					X					X

Time on Pregnancy and Infant Sub-study	Week 0	Wee k 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Delivery	Week 2, pp	Week 4, pp	Week 8, pp	Week 16 pp	Week 24, pp	Week 32, pp	Week 40, pp	Week 48, pp
Chemistry testing[6]	X						X			X					X					X
Liver function testing[7]	X						X			X					X					X
Syphilis testing	X						X								X					X
Vaginal GC/CT and TV testing[1]	X						X								X					X
Urinalysis (protein, glucose)	X						X			X					X					X
Plasma storage[8,9]	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Breastmilk storage[9,10]													X	X	X	X	X			
DBS storage for women on TDF/FTC only[9,11]	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X			
Infant assessments																				
Pregnancy outcome assessment including abbreviated infant examination[12]															X					X
Infant feeding history															X	X	X			
Infant HIV testing, if the mother is confirmed to have HIV infection[13]																				
Cord blood storage[9,14]												X								
Infant plasma storage[9,14]												X	X	X	X	X	X			X

NOTE: PK analysis will be performed on cord blood and infant plasma samples at an offsite laboratory.

[1] GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing using the swab may be performed at that later visit.
[2] Refer to the SSP Manual.
[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 the same day as sample collection and before product is administered.
[4] This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.
[5] Pregnancy testing may be done if indicated. Pregnancy testing may be performed in the clinic or the laboratory. 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.
[6] Albumin, BUN/urea, creatinine.
[7] AST, ALT, total bilirubin
[8] Stored plasma may be used for Quality Assurance testing and other assessments at the HPTN LC (see Section 9).
[9] Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP.
[10] Breastmilk collection does not need to be performed if the mother is not breastfeeding or producing milk.
[11] DBS will be stored for participants who elect to receive TDF/FTC. Processing and storage procedures will be described in detail in the SSP. Assessments will be performed retrospectively; results will not be returned to study sites or participants.

[12] Whenever feasible, use delivery notes plus complete assessment in clinic.
[13] If HIV testing indicates that an infant has HIV infection, a second confirmatory visit should be conducted to confirm HIV infection in the infant. If infant infection is confirmed, resistance testing should be performed locally using a separate (additional) infant sample collected for this purpose.
[14] Samples will be used for PK analysis and may be used for other assessments, including virology testing.

e. Step 5

Appendix VIII: Schedule of Evaluations for Step 5- Procedures for Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation

Time in Step 5	Step 5, Day 0*	Step 5, Week 12	Step 5, Week 24	Step 5, Week 36	Step 5, Week 48
ADMINISTRATIVE, BEHAVIORAL, REGULATORY					
Locator information	X	X	X	X	X
Acceptability assessment	X				X
Behavioral assessment (if done in last 4 weeks, skip D0 and start at W12)	X		X		X
HIV prevention counseling	X	X	X	X	X
Offer condoms	X	X	X	X	X
CLINICAL EVALUATIONS & PROCEDURES					
Medical history, concomitant medications, targeted physical exam (with pulse, BP, weight and BMI calculated at each visit)	X	X	X	X	X
Blood collection	X	X	X	X	X
Urine collection	X[7]	X	X	X	X
Vaginal swab collection[1]	X[7]		X		X
Adherence counseling[2]	X	X	X	X	
Dispense pills to all participants	X	X	X	X	
LOCAL LABORATORY EVALUATIONS & PROCEDURES					
HIV testing[3]	X	X	X	X	X
HIV viral load testing[4]	X	X	X	X	X
Pregnancy testing[5]	X	X	X	X	X
Chemistry testing[6]	X		X		X
Liver function testing[7]	X				X
Syphilis testing	X[7]		X		X
GC/CT and TV testing[1]	X[7]		X		X
Plasma storage[8,9]	X	X	X	X	X
DBS storage[9]	X	X	X	X	X

FOOTNOTES FOR Step 5, SOE

* Day 0 of Step 5 should be scheduled no later than 8 weeks after the last injection. Attempts should be made to bring the participant in earlier rather than later than the target date. See SSP Manual for further details.

[1] GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing using the swab may be performed at that later visit.

[2] Refer to the SSP Manual.

[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 the same day as sample collection and before product is administered.

[4] This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.

[5] Pregnancy testing may be performed in the clinic or the laboratory at all visits where this testing is indicated. 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 pregnancy is still ongoing. For Step 5, ONLY PARTICIPANTS WHO HAVE RECEIVED CAB LA WITHIN THE PAST EIGHT WEEKS may join the pregnancy sub-study (see Step 4d).Pregnancy outcome data will be collected from participants who join Step 4d.

[6] Chemistry testing includes: Albumin, BUN/Urea, creatinine. Skip Day 0 if testing has occurred within the last 3 months of Day 0, and do only at Weeks 24 and 48.

[7] Liver function testing includes: AST, ALT, Total bilirubin.

[8] Stored plasma may be used for Quality Assurance testing and other assessments at the HPTN LC.

[9] Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP.

Schedule of Additional Procedures for Women with Reactive/ Positive HIV Tests

It is possible that some participants may test positive for HIV during the OL portion of this trial. Site staff will follow procedures, see below, to confirm a participant's HIV status and must contact the HIV alias group (084HIV@hptn.org) for guidance.

Participants with a confirmed HIV infection must be linked to care as soon as possible (care is not provided by the study) and subsequently, the IOR must confirm that the participant has achieved viral suppression on antiretroviral treatment. The participant's ART regimen must be documented as concomitant medication. Once viral suppression is confirmed, the participant will be terminated from the study.

Note 1: The procedures listed for the HIV Confirmation Visit apply to participants who acquire HIV infection at any time during the study. Procedures will be determined by the members of 084HIV@hptn.org.

Participants who acquire HIV infection	
	HIV Confirmation Visit
ADMININISTRATIVE, BEHAVIORAL, REGULATORY	
Locator information	X
Offer condoms	X
HIV counseling	X
CLINICAL EVALUATIONS AND PROCEDURES	
History, con meds, physical exam (with pulse, BP, weight and BMI calculated at each visit)	X
Blood collection	X
LOCAL LABORATORY EVALUATIONS	
HIV testing[1]	X
CD4 cell count	X
HIV viral load testing[2]	X
HIV resistance testing[3]	X
Chemistry testing[4]	X
Liver function testing[5]	X
Plasma storage[6,7]	X
DBS Storage[7]	X

[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. Additional HIV testing may be requested by the 084HIV alias committee.
[2] This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.
[3] Sites may collect specimens for resistance testing at a local laboratory to assist with clinical management; results from resistance testing performed at local laboratories will not be reported to the SDMC. Stored plasma may not be used real-time/local resistance testing; additional samples must be collected for this testing.
[4] Required chemistry testing: Albumin, BUN/urea, creatinine,
[5] Required LFTs: AST, ALT, total bilirubin,
[6] Stored plasma will be used for Quality Assurance testing and other assessments at the HPTN LC.
[7] Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP. Additional HIV testing may be requested by the 084 HIV alias committee.

A. Information in the Main Protocol that is Not Relevant to Protocol, Version 3.0

Many sections of text, but not all, from the original/main protocol are no longer applicable; they pertain specifically to the original study design under protocol versions 1.0 and 2.0. Material from the original protocol that is not relevant to this amendment is delineated in this Section, Section A (Information in the Main Protocol that is Not Relevant to Protocol, Version 3.0, dated 12 August 2021).

Information from the following sections of the protocol are **not** relevant to Protocol Version3.0, dated 12 August 2021:

- Schema
- Overview of Study Design and Randomization Scheme
- Section 1.1 through Section 1.6, Section 1.8 through 1,11
- Section 2.0, in full
- Section 3.0: Sections 3.1, 3.2 and 3.3
- Section 4.0: Section 4.5
- Section 5.0: Section 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.9, 5.13, 5.15, and 5.18
- Section 6.6
- Section 7.0 in full (analyses from endpoints outlined are ongoing and pertain to the original study design and are not repeated in this Appendix)
- Section 9.0 in full (all relevant information from this section of the protocol is included in the updated SSP section pertaining to this Appendix)
- Section 10.2

B. Information in the Main Protocol that is Relevant to Protocol, Version 3.0

Material from the original protocol that is relevant to this amendment is delineated in this Section, Section B (Information in the Main Protocol that is Relevant to Protocol, Version 3.0, dated 12 August 2021).

The following front matter of Protocol, Version 3.0, dated 12 August 2021 is applicable:

- Title page
- Table of Contents
- Protocol Signature Page
- List of Abbreviations and Acronyms
- Protocol Team Roster
- Terminology for Cabotegravir and TDF/FTC Formulations

SECTION 3.0 (MODIFIED FROM THE MAIN PROTOCOL)

3.4 Co-Enrollment:

Participants may join a COVID-19 vaccine or treatment study, provided that participant study burden and American Red Cross-mandated limitations on per-unit-time phlebotomized blood volumes are not exceeded. There is no need to consult the CMC for participation in this type of

COVID study. However, the CMC should be consulted for participation in any other biomedical/intervention or observational study. Co-enrollment in IMPAACT 2026 is prohibited.

3.5 Participant Retention:

Sites will continue to implement all existing retention strategies and are encouraged to develop new strategies as needed.

3.6 Participant Withdrawal:

Participants may voluntarily withdraw from the study for any reason at any time. Participants may be withdrawn from the study if the study sponsor, government or regulatory authorities (including Office for Human Research Protections [OHRP] and the FDA) or site IRBs/ECs or if ViiV/Gilead terminate the study prior to its planned end date. Every reasonable effort will be made to complete a final evaluation of participants who terminate from the study prior to the final protocol-dictated study week, and study staff will record the reason(s) for all withdrawals from the study in participants' study records. In such cases, the IoR or designee must contact the CMC for guidance regarding final evaluation procedures.

SECTION 4.0 (MODIFIED FROM THE MAIN PROTOCOL)

4.1 Study Product Regimens/Administration/Formulation Content:

Study Product Regimens

Step 4

Step 4a - CAB 30 mg tablets

- Oral CAB tablets, 30 mg, one tablet orally daily for four weeks, with or without food

Step 4b – CAB LA 600 mg

- CAB LA 600 mg administered as one 3 mL (600 mg) IM injection in the gluteal muscle one time

Step 4c – CAB LA 600 mg OR TDF 300 mg/FTC 200 mg tablets

- CAB LA 600 mg administered as one 3 mL (600 mg) IM injection in the gluteal muscle every 8 weeks for no longer than a total of 48 weeks
- TDF/FTC 300 mg/200 mg fixed dose combination tablet, one tablet orally daily, with or without food for no longer than a total of 48 weeks

Step 4d – CAB LA 600 mg OR TDF 300 mg/FTC 200 mg tablets

- CAB LA 600 mg administered as one 3 mL (600 mg) IM injection in the gluteal muscle every 8 weeks for the duration of the pregnancy and up to 48 weeks after delivery
- TDF/FTC 300 mg/200 mg fixed dose combination tablet, one tablet orally daily, with or without food for the duration of the pregnancy and up to 48 weeks after delivery

Step 5

Step 5- TDF 300 mg/FTC 200 mg tablets

- TDF/FTC 300 mg/200 mg fixed dose combination tablet, one tablet orally daily, with or without food for no longer than a total of 48 weeks

The CAB study product (oral and LA injectable) being tested in this study is investigational and not yet approved by the US FDA for the prevention of HIV-1 infection. Injectable CAB-LA in combination with RPV-LA (CABENUVA®) is approved for the treatment of HIV-1 infection by the U.S. FDA.

Further information on the study product is available in the Investigator's Brochure (IB), which will be provided by the DAIDS Regulatory Support Center (RSC).

Oral Study Products

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

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

Injectable Study Product

- 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 2mL or 3 mL glass vial. Each vial is for single use containing 2mL (400 mg), or 3mL (600mg), and does not require dilution prior to administration. CAB LA injectable suspension is to be stored up to 30° C (86°F), do not freeze.

4.2 Study Product Preparation:

Prescription

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

Study Product Preparation

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

Preparation of Oral Study Product

CAB 30 mg Oral Product

The pharmacist will take the following steps to prepare and dispense un-blinded active oral CAB to the participant:

1) Retrieve oral active CAB 30mg tablet bottle with two part-label from Step 2 supply.

2) Retain both the un-blinded part and the blinded part of the two-part label on the CAB bottle. Do not tear off the un-blinded part of the two-part label from the bottle.

3) Place pharmacist-prepared, participant- specific, un-blinded label in such a way that the blinded part of the two-part label on the bottle is covered.

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

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

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

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

The pharmacist will take the following steps to prepare and dispense un-blinded active oral TDF/FTC to the participant:

1) Retrieve oral active TDF 300 mg/FTC 200 mg with two-part label from Step 2 supply.
2) Retain both the un-blinded part and the blinded part of the two-part label on the TDF/FTC bottle. Do not tear off the un-blinded part of the two-part label from the bottle.
3) Place pharmacist prepared participant-specific un-blinded label in such a way that the blinded part of the two-part label on the bottle is covered.

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

Alternatively, retrieve open-label oral active TDF/FTC supply from Step 3 supply if the site no longer has oral active TDF/FTC bottles with a two-part label from Step 2 supply. Place pharmacist prepared participant-specific un-blinded label on the bottle and dispense

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

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

Injectable CAB LA 600 mg/3mL

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

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

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

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

Preparation Steps:

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

- Hold the vial firmly and vigorously shake the vial(s) for a full 10 seconds.

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

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

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

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

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

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

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

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

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

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

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

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

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

- Record the time that the suspension was withdrawn from the vial and into the syringe in the participant's pharmacy log. This is the time of preparation.
- The overlay tape that covers the syringe barrel of the prepared unblinded, injectable CAB LA in a syringe is not required

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

  After withdrawal of the CAB-LA suspension from the vial into a syringe, it is recommended to inject the suspension immediately. Once the CAB LA suspension has been drawn into the syringe, the medication can remain in the syringe for up to 2 hours before injecting. If 2 hours are exceeded, the medication, syringes, and needles must be discarded.

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

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

4.3 Study Product Acquisition and Accountability

CAB 30 mg tablets and CAB LA injectables are manufactured and provided by ViiV Healthcare. TDF 300 mg/FTC 200 mg tablets and Placebo for TDF/FTC tablets are manufactured and provided by Gilead Sciences, Inc.

All study products 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.

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

4.4 Other Study Product Dispensing Considerations

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

4.6 Concomitant, Prohibited, and Precautionary Medications

All concomitant medications/preparations (prescription and non-prescription) including alternative/complementary medications/preparations (e.g., herbs, vitamins, etc.) will be collected in the study participant's chart and on study case report forms (CRFs).

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 PI for TDF/FTC and the 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.

For any precautionary or prohibited drug listed in the TDF/FTC 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 was written) are listed below.

<u>Cabotegravir:</u>

- Not to be administered concurrently:
  - Cytotoxic chemotherapy or radiation therapy
  - barbiturates
  - carbamazepine
  - oxcarbazepine
  - phenytoin
  - pheonobarbital
  - rifabutin
  - rifampin
  - rifapentine
  - St. John's wort

    NOTE: Prohibition of concurrent immunomodulators and systematically administered immunomodulators has been removed per the updated IB, version 10.0, Effective Date 06 January 2021. Co-administration of methotrexate and CAB LA is now permitted.

- 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

TDF/FTC (Truvada®):

- Not to be administered concurrently:
  - emtricitabine or tenofovir disoproxil fumarate (e.g. ATRIPLA®, COMPLERA®, EMTRIVA, GENVOYA®, ODEFSEY®, STRIBILD®, or VIREAD, Descovy).
  - lamivudine (e.g. Combivir, Dutrebis, Epivir, Epivir-HBV, Epivir A/F, Epzicom, Triumeq, or Trizivir)
  - adefovir (e.g. HEPSERA®)
  - tenofovir alafenamide (e.g. Vemlidy)
  - didanosine (e.g. Videx EC)
  - atazanavir (e.g. Reyataz, Evotaz (atazanari/cobicistat))
  - ledipasvir/sofosbuvir (e.g. HARVONI®)
  - darunavir (e.g. Prezista)
  - lopinavir/ritonavir (e.g. Kaletra)
  - orlistat (e.g. Alli, Xenical)

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

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

SECTION 5.0 (MODIFIED FROM THE MAIN PROTOCOL)

Procedures for protocol version 3.0, dated 12 August 2021, are included in the Schedules of Evaluation for Steps 4a, 4b, 4c, 4d, and 5. The HIV testing algorithm is included in the updated SSP. Sites will refer to that and will follow the Schedule of Additional Procedures for Reactive/Positive HIV Tests as is appropriate.

5.8 Injection Visit Windows

Target windows for all visits are outlined in the SSP Manual. It is not required to contact the CMC regarding visit window timing as long as injections are administered in accordance with the below:

- For the Week 0 injection of Step 4c, the injection must be given with a minimum of 3 weeks' time and a maximum of 10-12 weeks' time from the injection in Step 4b.
- For all other injections during Steps 4c and 4d, injections must be given with a minimum of 3 weeks.

An injection visit may never be completed without preceding safety laboratory assessments being completed and all the assessments being resulted and protocol-allowable.

The CMC must be contacted for guidance for any scenarios that deviate from the above parameters.

5.10 Procedures for Participants in Step 4 Who Do Not Complete the Full Course of Study Product

<u>Premature Discontinuations for Step 4a</u>
Participants in Step 4a of the study who are unable to transition to Steps 4b and 4c for any reason AND who have not had a dose of CAB LA in the past 48 weeks – including HIV infection - will be referred to local care and terminated from the study.

<u>Premature Discontinuations for Steps 4b and 4c</u>
Participants in Step 4b or 4c of the study who prematurely stop injections will transition to Step 5, unless study product is discontinued for HIV infection or for an AE/circumstance where OL TDF/FTC is contraindicated. Participants for whom OL TDF/FTC is contraindicated will be followed according to the SOE for Step 5, excluding study product dispensing and adherence counseling.

Participants with HIV infection detected in Steps 4b or 4c will be followed per the Schedule of Additional Procedures for Reactive/Positive HIV Tests.

5.11 Participants with Suspected of Confirmed HIV Infection

Refer to the updated SSP as well as the Schedule of Additional Procedures for Reactive/Positive HIV Tests in this protocol Appendix.

Sites will continue to contact the 084HIV@hptn.org email alias any time a participant has a reactive HIV test result for guidance regarding clinical management or other questions.

5.12 STIs

Testing for Neisseria gonorrhoeae (GC)/Chlamydia trachomatis (CT), Trichomonas vaginalis (TV) and syphilis will occur throughout the study. Testing will be performed at local laboratories.

Participants will be referred for treatment of STIs as per local guidelines. Symptomatic screening for STIs beyond what is required by the protocol will be at a site's discretion and cost.

Testing may be adjusted or prioritized at the discretion of the site investigator if there is a potential for shortage of supplies for collection and testing. Please see CDC recommendation September 8 2020. https://www.cdc.gov/std/general/DCL-Diagnostic-Test-Shortage.pdf.

5.14 Pregnancy

Confirmed Pregnancies

Participants with a positive pregnancy test will require confirmation of pregnancy at a subsequent visit at least TWO weeks later. All pregnancies that occur during the course of the study must be reported to the CMC within seven days of site awareness (either upon confirmation by urine or blood pregnancy testing during a study visit or as reported by the participant between study visits). Site staff will refer to their SOP for detailed management.

The site IoR or designee will refer pregnant participants to all applicable pregnancy-related services and will be provided 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.

Participants who have received at least one injection of CAB LA during HPTN 084 or HPTN 084-01, or who received an injection within the previous eight weeks and are in Step 5 are eligible to join the Pregnancy and Infant Sub-Study. Procedures in Step 4d for Pregnant/Breastfeeding Participants must be followed.

5.16 Acceptability Assessments

Acceptability of CAB LA and daily use of TDF/FTC will be continued to be assessed through administration of brief behavioral surveys conducted every six months during this amendment. The surveys will include, but not be limited to, questions about participants' attitudes/beliefs towards CAB LA and TDF/FTC; product-related preferences and choice. In addition, the qualitative sub-study, conducted in four sites, will continue with some additional modifications.

Qualitative Sub-study

Qualitative sub-study participants who were recruited during the blinded trial (both "continuing" participants and those recruited as "special cases") will be invited for a final interview. This final interview will explore women's preferences and choice of PrEP product (or no product), including how her perception of HIV risk, desires for pregnancy, partner dynamics or other contexts influence that choice. The interview will also elicit recommendations for additional information and service delivery strategies that might support women's access and use of CAB LA and PrEP more generally beyond clinical trial settings.

Several additional activities will be conducted within the qualitative sub-study, including interviews with male partners and other key informants and up to two participatory workshops. As is appropriate, separate informed consent will be collected.

1. In each site, a total of 5-6 male partners of qualitative sub-study participants will be invited to participate in a qualitative interview. The qualitative study team in each site will identify sub-study participants who represent different product-related experiences and who would be interested/willing to facilitate their partner's engagement in the study. Male partner interviews will explore disclosure and/or couple decision-making about trial participation and product use, perceived risks and benefits of injectable and oral PrEP use, questions about product use during pregnancy, use by a partner, and impact of trial participation on couple relationship.

2. In each site, a total of 5-6 community-based healthcare providers and/or other key informants (CBO stakeholders or others) will be invited to participate in a qualitative interview to explore perceptions about CAB LA and other PrEP modalities, required information, tools and strategies to integrate delivery of CAB LA into other services, and perspectives about how to increase demand for and uptake of injectable and oral PrEP within different populations (e.g., adolescents and young women, pregnant and breastfeeding women etc).

3. Finally, teams in each site will convene one to two participatory workshops that include a mix of participants who represent target end-user group(s), providers and community representatives. They will review findings from the qualitative sub-study, make use of design strategies (e.g., personnas, journey maps, scenario development); and draft potential messages and/or strategies that support uptake, use and/or transitions between PrEP products, including CAB LA.

5.17 Interim Contacts and Visits

Refer to SSP Appendix for guidance.

5.19 Criteria for Early Termination of Study Product

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 ViiV/Gilead terminate the study prior to its planned end date. Study staff will record the reason(s) for all withdrawals in participants' study records.

SECTION 6.0 (NOT MODIFIED FROM THE MAIN PROTOCOL)

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

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).

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.

6.2 EAE Reporting

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.

6.2.1 Reporting to DAIDS

The DAIDS Adverse Event Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE form. For questions about DAERS, please contact CRMSSupport@niaid.nih.gov. Site queries may also be sent with the DAERS application itself.

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

6.2.2 Reporting Requirements for This Study

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

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

- 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); TDF/FTC fixed dose combination tablet containing 200 mg of FTC and 300 mg of TDF (also outlined in Section 4.0).

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.

6.2.3 Grading Severity of Events

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.

6.3 Safety Monitoring

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.). Sites will be instructed to not solicit guidance from the CMC regarding HIV seroconversions in order to ensure to the extent possible that the team is blinded to the number of infections occurring in the study. The HPTN LC will be available for questions regarding HIV confirmation testing.

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 Study Monitoring Committee (SMC), which will meet by conference call approximately every 6 months. More frequent or *ad hoc* reviews may be conducted by the SMC as needed.

This study also will be monitored by a NIAID Data and Safety Monitoring Board (DSMB), 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 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 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 will also be collected and reported into the database.

SECTION 7.0 (MODIFIED FROM THE MAIN PROTOCOL)

Throughout this section the start of OL Cab LA period will be defined as the (site-specific) date that the OLE extension is approved for those originally randomized to the Cab LA arm and as the date that a participant begins use of Cab (injectable or OLI) for those originally randomized to the TDF/FTC arm.

Participants will be censored from the OL Cab efficacy and safety analyses using an On-Blinded-Study-Product (OBSP) approach i.e. at the end of study participation or 10 weeks after the date of last Cab injection (6 weeks, if only one injection has been given), whichever comes first.

ITT analyses of Cab vs TDF/FTC incidence will be restricted to the blinded and unblinded study periods. OBSP estimates of Cab incidence will use data from the blinded, unblinded and OLE periods.

OLE objectives:

- To estimate the incidence of HIV among participants who use CAB LA, combining blinded, unblinded and OL periods

The number of infections and cumulative person-years will be computed by combining the total follow-up time of those randomized to the CAB LA arm together with the follow-up time from start of OL Cab LA in those randomized to the TDF/FTC arm. The HIV incidence rate will be calculated as the total number of participants with confirmed incident HIV infection follow-up, divided by the accumulated person-years. OBSP censoring will be used. Corresponding 95% CIs will be calculated based on Poisson assumptions. Additional estimates will be made for each subperiod (blinded, unblinded, OL).

- To evaluate the safety of open-label CAB LA with and without an oral lead-in over 48 weeks

We will tabulate all AEs with maximum grade >2 for those receiving OL CAB LA overall among those with and without an oral lead-in. Event rates and 95% robust confidence intervals will be calculated using a log-linear model for counts using log(person-time) as an offset, assuming a Poisson distribution and using a robust variance (i.e. generalized estimating equations). OBSP censoring will be used.

Laboratory findings for CBC, chemistries (urea, creatinine, glucose, calcium), liver function (AST, ALT, total bilirubin, alkaline phosphatase) and fasting lipid profile (total cholesterol, triglycerides, HDL, LDL) will be reported by grade, as defined in the "Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events". The proportion of laboratory findings qualifying as Grade 2 or above will be presented. Laboratory values as median, 1st and 3rd quartiles, min and max.

In a supplementary analysis we will compare AE rates during the OL CAB LA period to AE rates in the CAB LA arm and the TDF/FTC arm (separately) during the blinded and unblinded periods.

- To evaluate the acceptability (uptake, continuation, discontinuation) of OL CAB LA over 48 weeks

The proportion of participants who start/continue CAB LA during the OL period will be reported overall and by original randomization arm, along with 95% CI. Time from initiation of injections to discontinuation, defined as not receiving an injection within 12 weeks of the prior injection, will be plotted using the product limit method i) using all follow-up time on CAB LA (blinded, unblinded and OL) and ii) for those starting CAB LA during the OL period only.

- To estimate the incidence of pregnancy among participants during the OL period

Tables will summarize the number of pregnancies and pregnancy rate. The pregnancy rate and 95% robust confidence interval will be calculated from a log-linear model for counts using log(person-time) (excluding time spent pregnant) as an offset, assuming a Poisson distribution, and using a robust variance (i.e. generalized estimating equations).

- To evaluate safety and infant outcomes among pregnant participants

Safety events, as described above, will be tabulated before, during and up to 24 weeks after pregnancy for women who become pregnant. Events will be reported overall and separately for women who did and did not receive CAB injections during pregnancy. Infant outcomes will be tabulated and all congenital anomalies individual reported.

- To evaluate the PK of CAB LA among pregnant participants, combining blinded, unblinded and OL periods

The mean and SD of log CAB LA PK concentrations before, during and after (up to 24 weeks postpartum) pregnancy will be described, combining data from the blinded, unblinded and OL periods (since injections were discontinued when pregnancy was confirmed in the blinded and unblinded periods, these data will contribute primarily to PK during the tail phase). Specifically,

plots of PK concentrations as a function of time since last injection will be provided, separately for pre-pregnant, pregnant and postpartum periods, using the data from all women who become pregnant. A linear mixed model with log drug concentration as the outcome and time since last injection, pregnancy (yes/no), baseline BMI, and a pregnancy x time since last injection interaction will be fit with random effects (intercept and slope) for each participant. The effect of pregnancy as a on mean PK concentrations and as a modifier of time since last injection will be tested using $\alpha = 0.05$.

- To describe the diagnostic test profile, PK, HIV drug resistance, and response to antiretroviral treatment in those who become infected after CAB LA exposure, combining blinded, unblinded and OL periods

The number of cases of drug resistance will be summarized by period (blinded, unblinded, OL) for those receiving CAB LA who become infected. Case reports including information on testing profile, resistance, drug resistance and response to treatment will be developed for each confirmed incident infection in for those who receive CAB.

- To characterize pharmacokinetics and duration of detectable drug among those who discontinue CAB LA injections, combining blinded, unblinded and OL periods.

Starting with the third (17 week) injection (to allow steady state to be achieved), we will tabulate and plot the mean and SD of log CAB LA levels as a function of time since the last injection. Data will be presented overall and separately by pregnancy status. These data will be input into a mechanistic PK model and estimated parameter values from the fitted model will be reported.

- To evaluate concentration in breastmilk and infants among women who receive CAB LA injections during pregnancy and/or the early post-partum period.

We will present descriptive statistics (median, quartiles, geometric mean) of cabotegravir concentrations in breastmilk and infant plasma samples collected at multiple time points following delivery among women who receive CAB LA injections during pregnancy and breastfeeding. We will also summarize infant plasma/maternal plasma ratios and breast milk/maternal plasma ratios to help understand drug transfer and deposition, respectively.

SECTION 8.0 (NOT MODIFIED FROM THE MAIN PROTOCOL)

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

Written informed consent for the OL amendment will be obtained from each study participant. If a participant becomes pregnant, consent will also be obtained from her before joining the Pregnancy-Infant Sub-Study. Each study site is responsible for developing study informed consent forms for local use, based on the template in Appendix IV 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 by signing their informed consent forms. (Further details regarding DAIDS requirements for documenting the informed consent process can be found in the DAIDS Standard Operating Procedure for Source Documentation.)

All participants will be offered a copy of their informed consent form.

8.3 Incentives

Pending IRB approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. 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; pharmaceutical sponsors; representatives of the HPTN LOC, SDMC, and/or LC; the government or other local, US, or international regulatory authorities (including the OHRP and US FDA), site IRBs/ECs or ViiV/Gilead.

8.5 Communicable Disease Reporting Requirements

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

8.6 Study Discontinuation

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

SECTION 10.0 (MODIFIED FROM THE MAIN PROTOCOL)

10.1 Protocol Registration

Full protocol amendments require submission of a protocol registration packet to the DAIDS PRO. DAIDS PRO WILL review and approve site-specific ICFs for the Version 3.0 protocol amendment. Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites must submit documents to DAIDS PRO and must wait for written approval prior to implementation. 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.

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

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 and Gilead Sciences, Inc. for cross-referencing with the company's other INDs for the study product(s). Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed between DAIDS and each of the collaborating partners (ViiV Healthcare, and Gilead Sciences, Inc.).

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. 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, government or other local, US, or international regulatory authorities/entities (including the OHRP and US FDA). site IRBs/ECs or ViiV/Gilead A site visit log will be maintained at each study site to document all visits.

10.4.1 Remote Study Monitoring

Due to ongoing travel restrictions during the COVID-19 pandemic, some sites are unable to accommodate onsite monitoring visits. Remote monitoring visits to date consist of quality review of study data available in the Electronic Data Capture system without verification to corresponding source documents. Review of source documentation is a critical component of ensuring data integrity.

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to onsite visits to ensure the safety of study participants and data integrity[22].

Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

Four options listed below will enable the facilitation of remote source document verification, which may vary site by site. All offered are HIPAA and 21 CFR Part 11 compliant.

Option #1 - Veeva SiteVault Platform- This platform is available for sites to self-subscribe at no cost from Veeva Systems. There is no software to download and the only requirement is internet access. Sites will upload source documents to this secure platform and assign permissions to monitors to access these data for a limited period of time. For sites that are already using this platform in some capacity, they can add specific DAIDS studies to their existing account. In the event that this platform is being used by another entity within the institution, the site can request access to the platform following their internal procedures. However, sites that are not currently using Veeva SiteVault, can obtain additional information by visiting https://www.veeva.com/products/sitevault/ or sign up to try at sites.veeva.com. Veeva SiteVault may require a signed agreement between the site and Veeva Systems.

Option #2 - Site Controlled SharePoint or Cloud-Based Portal-Some sites may already have a platform which allows for sharing of participant source documents, which could be extended to allow monitor's access. This option must be 21CRF 11 and HIPAA compliant as applicable.

Option #3 – Direct Access to Electronic Medical Records by Monitors- This option may be feasible for sites that use Electronic Medical Records, and whose institutional policy allows for direct access of the site's Electronic Medical Record to monitors for a limited period of time. Please contact your institution's Security Officer for required approvals and any agreements to facilitate remote access to participant source documents.

Option #4 - Medidata Rave Imaging Solution- This option does not require additional purchase of software and sign-on is through each site's existing single iMedidata account. Sites will upload source documents to this secure platform and monitor permission and access is assigned by the SDMC. There is ongoing discussion regarding the implementation timeline for MediData Rave Imaging Solutions, and the SDMC will contact sites regarding demonstration of this solution.

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 — including 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, ViiV Healthcare, Gilead Sciences, Inc., and BMGF for review prior to submission.

TOXICITY MANAGEMENT (MODIFIED- APPENDIX III IN MAIN PROTOCOL)

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, creatinine clearance (absolute and change from baseline), and CPK. Refer to the tables below for specific guidance about these laboratory abnormalities.

Grade 1 or 2
In general, participants who develop a Grade 1 or 2 AE regardless of relatedness to study product, and that is not specifically addressed 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
Any Related, Grade 4 or higher clinical or laboratory AE observed prior to first injection (i.e. in STEP 4a) will prompt permanent study product discontinuation.

Participants who develop a Related, 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 also temporarily or 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 temporary or 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 temporarily 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

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

- Report of use of prohibited concomitant medications as described in the SSP Manual. 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.

Participants who temporarily or permanently discontinue study product and are taking pills (either TDF/FTC or oral CAB) will be instructed to return all study products as soon as possible.

Guidance on Toxicity Management for Specified Toxicities:

Nausea, Vomiting, and Diarrhea

CONDITION AND SEVERITY	IMMEDIATE ACTION	FOLLOW-UP AND MANAGEMENT
Nausea, Vomiting, and Diarrhea		
Grade 1 and 2	Continue study product (reminder to take oral study product with food)	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 infectious 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. Contact the CMC for further guidance on investigation and study product administration.

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

Guidance on Toxicity Management for Specified Toxicities:

Creatinine Clearance, only applicable to TDF/FTC recipients

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

NOTE: Adverse events related to creatinine clearance should be based on examination of BOTH the absolute creatinine clearance AND the change in creatinine clearance from baseline (Enrollment/ Visit 2.0). When gradable, only the higher grade of these two assessments should be entered on the Adverse Event e-CRF. Clinical Management of Grade 3 and Grade 4 changes in creatinine clearance should follow the "Toxicity Management General Guidance" ONLY when the absolute creatinine

clearance is < 90 mL/min. That is, changes in creatinine clearance of >30% from baseline that DO NOT result in an absolute creatinine clearance < 90 mL/min do NOT need to be reported to the CMC or more frequent clinical monitoring. Additionally, changes in creatinine clearance of > 30% that are accompanied by a creatinine that remains within normal limits also do not need to be reported to the CMC and do not require more frequent clinical monitoring.

CONDITION AND SEVERITY	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 for adjudication and recommendation for further testing and follow-up.
Confirmed CrCl< 60 mL/min	Permanently discontinue study product	If the calculated creatinine clearance is confirmed to be <60 mL/min, the 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 annually for HIV testing only until the conclusion of Step 2 of the study. 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)

ISR discomfort can be managed if the reaction is interfering with the participant's ability to perform activities of daily living. Recommended interventions include:

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

- Post-treatment NSAID or other analgesic preparations, topically or orally

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

Guidance for Allergic Reactions

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

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

ADDENDUM TO THE MAIN SAMPLE INFORMED CONSENT FORM

HPTN 084:
A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women

FINAL Version
Protocol Version 3.0, dated 12August2021
DAIDS Document ID: 38070

Sponsored by: Division of AIDS, United States (US) National Institute of Allergy and Infectious Disease, US National Institutes of Health.

Study products are provided by ViiV Healthcare and Gilead Sciences, Inc. Additional support is provided by the Bill & Melinda Gates Foundation (BMGF).

PRINCIPAL INVESTIGATOR: *[Insert Name*]

PHONE: [Insert Number]

You are currently taking part in either HPTN 084 (for adult women) or HPTN 084-01 for adolescent girls). This consent form update contains information to help you decide if you want to participate in the "open label" portion of HPTN 084.

Your participation is voluntary

This consent form gives you information about the next part of this study, the "open label" piece. Once you understand the next part, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep. Your continued participation in this research is voluntary. You may decide to not take place in the next part of the study now or at any time without a loss of benefits to which you are otherwise entitled. We will also review the information in the main consent form that you already signed (either for HPTN 084 or for HPTN 084-01), if you would like us to do that.

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?

We'd like to learn more about women's HIV prevention choices including during pregnancy and breastfeeding now that we know that CAB LA is safe and effective in preventing HIV infection in women.

2. How long will I participate in the study?

For most participants the study will last an additional 7 visits over 48 weeks (11 months). If you choose to start or re-start CAB you may take 1-2 extra visits over 8 weeks over and above the 48 weeks. If you become pregnant you will be asked to be in follow up until your baby is one year old. If you have had at least one CAB injection you will be asked to attend additional visits during pregnancy and after delivery for a total of 19 visits.

3. What will happen to me during the study?

Participants can choose to stay on their current study medication or to change. We will offer participants who received TDF/FTC the chance to take CAB LA if they wish for an additional 48 weeks. Participants starting or re-starting CAB can choose to start injections directly or to take 30 days or oral CAB pills first before starting injections. We would like you to continue your study visits even if you choose neither TDF/FTC or CAB LA.

You will be asked to come for study visits every 8 weeks. At each of these visits we will ask you questions about your health, the medications you are taking, any side effects of study medications, and any alcohol or drug use. We will talk with you about ways to avoid HIV. We will ask you about your plans to become pregnant and ways to avoid pregnancy if you wish. We will not require you to use long acting contraceptives anymore. We will collect blood samples for HIV, syphilis, drug level testing and to test your general health. We will collect urine samples for pregnancy testing and to test the health of your kidneys. We will collect vaginal samples to test for sexually transmitted infections (STIs) You will be given your preferred study medication and offered condoms. If you are having trouble taking your oral pills or attending your injection visits on time we will talk with you about strategies to help with that.

4. Will I benefit from the study?

You will receive information about your health and access to effective HIV prevention, including oral or injectable PrEP, as well as treatment for STIs. The counselling you receive may help you to avoid HIV, STIs or pregnancy. If you become pregnant you and your baby will receive monitoring during pregnancy and breastfeeding.

5. Will taking part in the study expose me to risks?

Taking part in research may expose you to some risks. We know that both CAB LA and TDF/FTC are safe and well tolerated in women. Injection site reactions were the most common side effect in women receiving CAB LA. The risks are similar to those described during the blinded part of the study.

[*Sites: For pregnant women only.*

If you become pregnant during the study and choose to take CAB LA during pregnancy and while breastfeeding, we want to be sure you know that while we think CAB LA will be safe for your baby there is not much information available yet. The lack of information is why we are doing this study. So far, in the women who have become pregnant and breastfed their babies while taking CAB LA, no problems in their babies have occurred.

We do know that in studies of another drug, called dolutegravir, which is very similar to CAB LA no

nursing babies had any problems. These babies were breastfed by mothers who had HIV and were taking dolutegravir as treatment. Small amounts of dolutegravir were found in the breastmilk. It is possible some CAB LA may pass to a baby through breastmilk.]

6. Will I be paid to participate?

You will be reimbursed for costs associated with your visits, as was done in the blinded part of the study.

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

New Information about CAB LA

We now know for certain that CAB LA is effective in preventing people from getting infected with HIV, the virus that causes AIDS.

As a quick reminder, in November 2020, an independent Data Safety and Monitoring Board or DSMB checked the HPTN 084 study data and found that both CAB and TDF/FTC were very good at preventing new HIV infections. They also found that both CAB and daily TDF/FTC pills were safe and well tolerated. They saw that CAB was much better at preventing HIV than TDF/FTC. Participants given daily TDF/FTC pills had approximately nine times the number of HIV infections than participants getting long-acting cabotegravir injections (real CAB, also called CAB LA). The DSMB recommended that the blinded part of the study be stopped, that participants be informed of their study group, and that the results be made public. Study teams shared the data with their country regulators and with their permission, have begun to tell participants which study product they were taking.

Since we first shared the study results with you, we have some new updates based on the testing of samples in those people that became infected with HIV. One of the reasons that women in the CAB LA group had fewer infections is because it may be easier to take an injection every 8 weeks than a pill every day. TDF/FTC works very well when taken daily but it cannot protect you if you do not take it every day. The participants in HPTN 084 in the TDF/FTC group who became infected with HIV were not taking TDF/FTC every day. We know they weren't taking pills every day because we measured the amount of study drug in their blood. We know that some people find it hard to take a pill every day. Four women in the CAB LA group in HPTN 084 became infected with HIV. Two women became infected before they received any CAB LA injections. When we measured the amount of drug in their blood, we learned that they weren't taking their oral pills every day. Two other participants became infected with HIV while receiving injections; one of those participants was late for several of her injections and this may have led to her becoming infected with HIV. All participants who became infected with HIV were counselled about starting antiretroviral therapy.

Did any participants develop HIV infections that were resistant to CAB LA?

None of the participants who received CAB LA and later became infected with HIV had any resistance to CAB or other drugs like CAB called integrase inhibitors. For example, dolutegravir which is commonly used to treat HIV infection in many parts of Sub-Saharan Africa, is an integrase inhibitor. Resistance means that the drug, and sometimes other drugs like it, might not work as well to control the

HIV infection as part of HIV treatment. In another study however called HPTN 083 that involved men who have sex with men and transgender women, they did see several cases of resistance to CAB LA and other drugs like CAB LA called integrase inhibitors. These people all had to use different anti-retroviral drugs that are not like CAB to control their HIV.

In HPTN 084, one participant in the TDF/FTC group who became infected with HIV had resistance to FTC. Similarly, in HPTN 083 several people in the TDF/FTC group has resistance to one or both drugs.

What happens next?
We'd like to offer you the chance to continue taking CAB LA or TDF/FTC for the next 48 weeks. We want to learn more about women's HIV prevention choices now that we know that CAB LA is safe and works to prevent HIV. We also want to learn more about CAB LA use during pregnancy and breastfeeding. In the next part of the study, the "open-label" part of the study you will be able to:

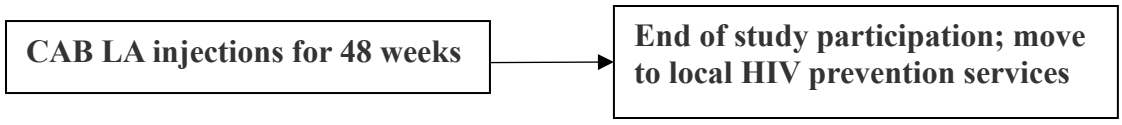
- Stay on CAB LA if you are already on it
- Stay on TDF/FTC if you are already on it
- Switch to CAB LA if you are on TDF/FTC and it is safe for you to do so
- Start or re-start CAB LA if you have been on the annual visit schedule and it is deemed safe for you to take CAB LA
- Stop from CAB LA to TDF/FTC

If you think you are no longer at risk for HIV, you may stop both study product. We'd still like you to come for study visits for 48 weeks. Study staff will take with you and help you to decide whether you are at risk for HIV and still need to take pre-exposure prophylaxis or PrEP (either oral or injectable) to prevent HIV.

What will happen during the open-label part of the study?
If you decide to continue with the study you will have visits similar to those in the earlier part of the study. Most study visits will be spaced eight weeks apart (every other month). These next study visits will happen for at least 48 weeks (11 months). If you become pregnant you may be on study for longer (1 year and 10 months).

<u>If you choose CAB LA injections</u>

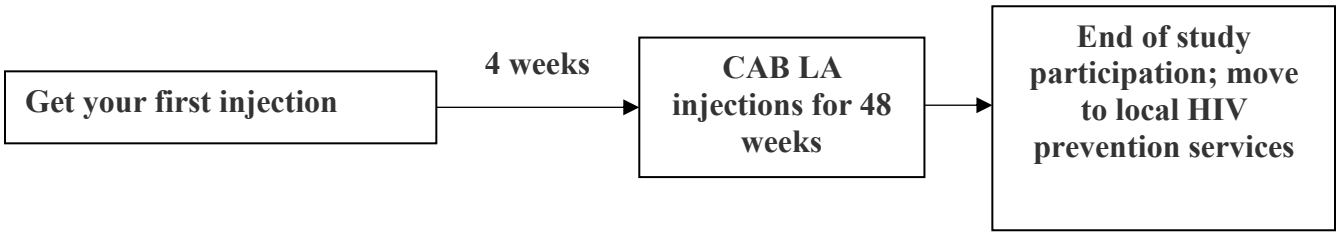
- If you were previously receiving CAB LA injections during the blinded part of HPTN 084 and you choose to continue CAB LA injections you will be in the next part of the study for 48 weeks. You will have at least seven more study visits. These visits will be spaced eight weeks apart. At the end of 48 weeks, if you want to keep taking CAB LA you can choose to move to locally provided CAB LA that is not part of the study. Your participation in the study will end. If you prefer, we can refer you to a local HIV prevention program for ongoing PrEP access.



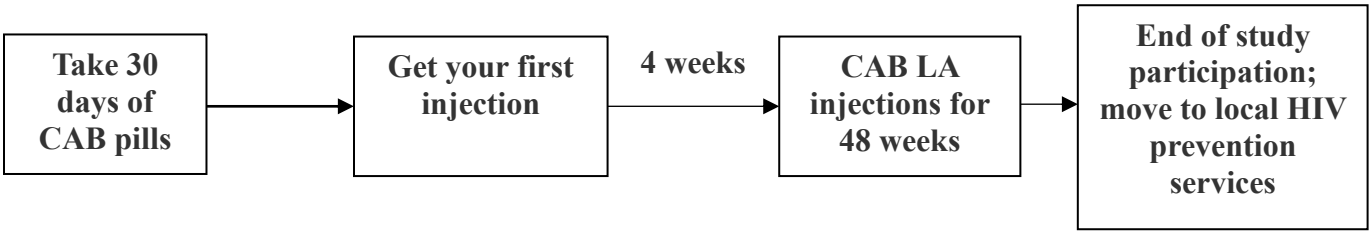
- If you were previously receiving TDF/FTC during the blinded part of HPTN 084, or if you stopped taking CAB LA injections (and it is safe for you to restart), and you choose to take CAB LA injections during the open-label part of the study you will be in the next part of the study for either 52 or 56 weeks. You will have 8 or 9 more study visits. . These visits will be spaced eight weeks apart, except for the first two injections which are 4 weeks apart. At the end of all these visits, your participation in the study will end. You would have the choice then to join a locally available program for CAB LA injections (the company that makes CAB LA is working to make it available locally for study participants). If you prefer, we can refer you to a local HIV prevention program for ongoing PrEP access.

  To start you on CAB LA injections you may choose from two options:

Option 1- start injections directly



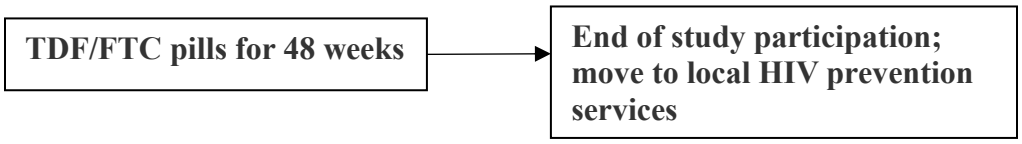
Option 2- take oral pills for 30 days and then start injections



During the blinded part of the study, you may remember that everyone was required to take cabotegravir pills before getting injections. This process was in place because we did not have enough information then about CAB LA to know if it was safe to start getting injections right away. Based on what we learned in the blinded part of the study, we now know that it is safe to begin injections right away. However, if you feel more comfortable taking 30 days of cabotegravir pills first you may do so. [Note to sites: If your IRB/EC requires this step, or if the IoR requires this step, then update this language to make it non-optional].

<u>If you choose TDF/FTC pills</u>

- If you choose to take TDF/FTC pills, you will be in the next part of the study for 48 weeks. You will have a total of seven more study visits. At the end of the 48 weeks, your participation in the study will be over. If you prefer, we can refer you to a local HIV prevention program for ongoing PrEP access.



What will happen during open-label study visits?
During the new, open-label part of the study clinic visits will be very similar to those you are used to. Because you will be allowed to choose between CAB LA and TDF/FTC and some people may switch products, the number of study visits will depend on each person's choices. Visits will be spaced eight weeks apart and will last for at least 48 weeks. Below are descriptions of what will happen depending on participant choices.

<u>For people that stay on their current study medication</u>,
During the study visits we will:

- At the first visit we will talk with you about your choice of study products.
- Confirm where you live and how to contact you.
- Ask you questions. We will ask about about your sexual behavior, how your health is, whether you have experienced any side effects from taking study medication, whether you have taken any other medicines, and whether you have used alcohol or drugs. We will also ask how you feel about taking pills or getting injections at the first visit and then at weeks 24 and 48.
- Give you a brief physical exam.
- Collect blood samples. We will collect ~XX mL (about x teaspoons) of blood for HIV testing, to measure the amount of the study drug that is in your blood, and for storage. At this visit, and every 6 months we will also collect ~XX mL (about x teaspoons) of blood to testing your general health, including the on the health of your liver, and for syphilis.
- At Week 48, we will also collect ~XX mL (about x teaspoons) of blood to check how much cholesterol is in your blood (a fatty substance in your blood. For this cholesterol test, you will be instructed to not eat or drink anything other than what the study staff tell you is acceptable for 8-12 hours before your blood is drawn.
- Collect urine samples to Test you for pregnancy *[site insert sample type, blood vs. urine]*. At your first visit, and every 6 months we will also test to see if there is sugar or protein in your urine.
- Collect vaginal swabs at the first visit and every 6 months to test for sexually transmitted infections.
- Provide you with the results of your tests and talk with you about what they mean. Talk with you about HIV and ways to protect yourself from getting it.
- Talk with you about ways to avoid pregnancy if you wish to.
- If it seems to you or to the study staff that you are having challenges taking the pills or attending study visits, we will try to help by working through these with you.

- Staff will give you study medication (pills or injections) and offer you condoms.

For people that choose to start or re-start CAB LA

- **Option 1 – start injections directly**

  In addition to the procedures above, if you choose to start taking injections directly, we will check your previous results to make sure that it is safe to start CAB LA. After you receive your first CAB LA injection, you will be asked to return to the clinic in four weeks where you will receive your second CAB LA injection. Once you have received two CAB LA injections, at four weeks apart, the CAB LA levels in your body will be high enough to let you space injections out to every eight weeks. From this point in the study, you will have at least seven more study visits.

- **Option 2 - take oral pills for 30 days and then start injections**

  If you chose to take 30 days of CAB pills, you will complete the visit procedures listed above and will be given pills to take daily for 30 days. You will be asked to return to the clinic after the pills are finished. The study procedures listed above will be repeated and you will receive your first CAB LA injection.

  After you receive your first CAB LA injection, you will be asked to return to the clinic in four weeks where you will receive your second CAB LA injection. Once you have received two CAB LA injections, at four weeks apart, the CAB LA levels in your body will be high enough to let you space injections out to every eight weeks. From this point in the study, you will have at least seven more study visits.

What happens if you need to stop taking CAB LA during the injection period?

During the open-label part of the study, if you stop taking CAB LA because of a safety concern we will offer you TDF/FTC for 48 more weeks to cover the CAB LA "tail". If you remember, this is to protect you from potentially developing resistant HIV infection if you become HIV infected while the levels of CAB in your blood are decreasing. We know from our HPTN 084 study results that this risk is very small. Please note that that we will only cover the tail for this sub-group of women who stop CAB LA early. While you are taking TDF/FTC, you will return the clinic for a total of five more visits spaced 12 weeks apart. At that point, your participation in the study will end. If you prefer, we can refer you to a local HIV prevention program for ongoing PrEP access.

During these visits we will:

- Confirm where you live and how to contact you.
- Talk with you about HIV and ways to protect yourself from getting it.
- Offer you condoms.
- At the first visit and at the last visit, we will ask you and about how you feel about taking pills. We will ask you if you have experienced any side effects from the TDF/FTC. At the first visit

and again at Weeks 24 and 48, we will also ask you questions about your sexual behavior. Everyone will be asked about any other medicines they are taking, and whether they use alcohol or drugs.

- Give you a brief physical exam and ask how your health is.
- Collect ~XX mL (about x teaspoons) of blood for HIV testing, to measure the amount of the study drug that is in your blood, and for storage.
- Collect ~XX mL (about x teaspoons) of blood at the first visit and at Week 24 and Week 48 for checking your general health.
- Collect ~XX mL (about x teaspoons) of blood at the first visit and Week 48 to check the health of your liver.
- Give you the results of your blood tests when they are available.
- Test you for pregnancy *[site insert sample type, blood vs. urine]*.
- Test a vaginal swab for sexually transmitted infections at the first visit and then at Week 24 and Week 48.
- If it seems to you or to the study staff that you are having challenges taking the pills or attending study visits, we will try to help by working through these with you.
- Staff will give you more pills.

At this point, your participation in the study will end. We will refer to locally provided HIV prevention services.

What happens if you become pregnant during the next part of this study?

During HPTN 084, women were required to be on a long-acting, reversible contraceptive (LARC). This was because:

1) we did not know how well CAB LA worked in women and

2) a report from Botswana was released raising the possibility that a drug called dolutegravir (DTG) may have caused a very serious birth defect of the spinal cord and the brain in women who were taking DTG at the time they became pregnant for treatment of HIV. DTG is similar to CAB LA so we wanted to be careful during HPTN 084. Ever since the first Botswana report, doctors have continued to monitor babies born to mothers who have taken DTG during pregnancy. It now seems much less likely that DTG was the cause of the birth defects in babies. We now know that the difference in the rate of birth defects in mothers who took DTG and those that used other antiretrovirals for HIV treatment is essentially the same. Other studies that study large groups of pregnant women that use medications, including DTG during have not found this problem. CAB LA is not the same as DTG. CAB LA has not been shown to cause birth defects in animal studies. In blinded portion of HPTN 084 there were 50 confirmed pregnancies; none of the babies born to women in HPTN 084 had any birth defects.

Now that we know that CAB LA is safe and works to prevent HIV in women, we no longer will require you to use a LARC during this study. We will talk with you about ways to avoid pregnancy if you wish

to do so. We will test for pregnancy at every study visit. If you do become pregnant, please note that we will refer you to a clinic that routinely manages pregnant women; the study will not pay for this medical care.

We know that many women wish to conceive safely, but are worried about the risk of HIV during pregnancy and breastfeeding. If you become pregnant during the study you will be given the chance to continue taking CAB LA injections during pregnancy and breastfeeding. If you prefer, you can switch to TDF/FTC. TDF/FTC has been used much longer than CAB LA and is not known to cause any health problems for babies. All women who become pregnant in the study will be followed up. We would like to know about the health of your baby when born and again at one year of age.

For women who have received at least one CAB LA injection in this study, we would like you to invite you to complete additional study visits during pregnancy and for about one year after the birth of your baby. You will have 11 study visits that are very similar to study visits that occurred before you were pregnant. Those study visits will happen every 4 weeks. You will receive your preferred study product every 8 weeks as before. We will ask you to sign this form to confirm that you agree to these additional visits for you and your infant.

[This section is only for women who become pregnant and have <u>ever</u> received a CAB LA injection.

<u>Study activities for women who become pregnant</u>
Most study activities will be very similar to previous visits. During these visits we will do the following:

- At the first visit we will talk with you about your choice of study products. If you have been taking CAB LA and wish to continue taking it, you may do so after providing consent by signing the end of this form.
- Confirm where you live and how to contact you.
- Ask you questions. We will ask about about your sexual behavior, how your health is, whether you have experienced any side effects from taking study medication, whether you have taken any other medicines, and whether you have used alcohol or drugs. We will also ask how you feel about taking pills or getting injections at the first visit and then at weeks 12 and 32.
- Give you a brief physical exam.
- Collect blood samples. We will collect ~XX mL (about x teaspoons) of blood for HIV testing and to measure the amount of the study drug that is in your blood, and for storage.
- We will collect ~XX mL (about x teaspoons) of blood at the first visit and again at Weeks 24 and 36 to test your general health, including the on the health of your liver.
- Collect urine samples at the first visit and again at Weeks 24 and 36 to see if there is sugar or protein in your urine.
- Collect vaginal swabs at the first visit and again at Week 24 to test for sexually transmitted infections.
- Provide you with the results of your tests and talk with you about what they mean. Talk with you about HIV and ways to protect yourself from getting it.

- [*Sites to include this if local SOC permits offer of condoms.* At each study visit we will offer you condoms.]

Here are some study activities that will be new and are specific to pregnancy:

At the visit where your pregnancy test is positive, we will

- confirm your pregnancy on a second sample
- collect a swab to test for sexually transmitted infections
- talk with you about whether you want to continue with CAB LA injections or whether you want to start TDF/FTC. If you are not sure, you can take some time to think about it and return for your injection visit at a later date (within the visit window). You can start TDF/FTC then if you prefer.
- If you choose to take CAB LA injections during pregnancy, we will check the injection location carefully at the following visit s: Weeks 4, 12, 20, 28 and 36.

- At Week 12, we will either perform an ultrasound to check on the baby (or refer you to a local office for this).

-At Week 24, we will test you for sexually transmitted infections like syphilis, chlamydia, gonorrhea and trichomonas.

<u>At Delivery</u>
Please know that we do not want to disrupt the special time that you spend with your new baby, family and friends. We would like to know about the health of you and your baby at the time of delivery. If you choose to deliver in a healthcare facility, we would like to make arrangements ahead of time with the facility to collect some blood from you, some blood from the umbilical cord and some blood from the baby.

<u>After Delivery</u>
Once you have your baby, you will have 8 more study visits. These visits will happen at Weeks 2, 4, 8, 16, 24, 32, 40 and 48. We will use these visits to check on the health of you and your baby.

Study visits are very similar to study visits that occurred before you were pregnant. For example, at Weeks 8 and 48 we will do a targeted physical exam, vaginal swab collection, and blood collection to check on your general health, including liver health.

Here are some study activities that will be new and others that are similar to those that occurred during previous visits:

-At Weeks 24 and 48, we will ask how you feel about taking pills or getting injections.

- At Weeks 2, 4, 8, 16 and 24 we collect 5mLs (1 teaspoon) of breastmilk to learn about levels of CAB in breastmilk.

-At Weeks 8, 16, 24, 32 40 and 48 we will collect urine to test you for pregnancy and at Weeks 8 and 48 we will also check the amount of sugar and protein in your urine.

-At Week 8 and again at Week 48, we will test you for sexually transmitted infections like syphilis, chlamydia, gonorrhea and trichomonas.

-If you choose to take CAB LA injections during breastfeeding, we will check the injection location carefully at Week 8 and Week 48.

What happens to babies during study visits?

We would love the opportunity to meet your baby and to collect some information about them. With the information we have right now, we think it is unlikely that CAB LA causes problems for babies. If we can examine babies born to moms in this study, the information will help us and will help other women in the future.

You can bring your baby to the same study visits that you attend after delivery. Those visits happen at Weeks 2, 4, 8, 16, 24, 32, 40 and 48. Here is what happens at those visits:

-We would like to do a brief infant exam at Week 8 and Week 48.

-We would like to ask you about your baby's eating habits at Weeks 8, 16 and 24.

-We would like to collect a small amount of blood from your baby at Weeks 2, 4, 8, 16, 24 and 48.

At the end of 48 weeks your participation in the study will end. At that time, if you want to keep taking CAB LA you can choose to move to locally provided CAB LA that is not part of the study. The company making CAB LA is working to offer it to study participants after this research study ends. If you prefer, we can refer you to a local HIV prevention program.

[End of section only for women who become pregnant.]

What happens if you become infected with HIV during this part of the study?
If you become infected with HIV during this next part of the study, you will be immediately referred for local care and treatment of HIV. We will not provide care for HIV infection as part of this study.

We will ask you to come back to the study clinic for a few appointments. At the first visit, we will confirm your contact information, we will offer you condoms, provide HIV counseling, do a physical exam and collect blood. Some blood will be stored, if you agree to that. The rest of the blood will be used to help us better understand how the infection occurred and how the early course of infection may be impacted by the study drug you were taking. This includes testing for HIV resistance. If you get infected with HIV while on CAB, you might need to take medications that are not like CAB to treat the HIV infection. We will also want to make sure that the amount of HIV virus in your blood is responding well to treatment. Once we have confirmed that your HIV is responding well to treatment, you participation in the study will end.

Problems or Questions

If you ever have any questions about the study, or if you have a research-related injury, you should contact [*insert name of the investigator or other study staff*] at [*insert telephone number and/or physical address*].

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

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

SIGNATURE PAGE

HPTN 084:
A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women

FINAL Version
Protocol Version 3.0, dated 12August2021
DAIDS Document ID: 38070

[The section immediately below is only for ADULTS who participated in HPTN 084 or HPTN 084-01. The signature block for minors is further down the page.]

***[Insert signature blocks as required by the local IRB*:]**

If you have read this addendum to the main consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to continue in this part of the study, please sign your name or make your mark below. Also, please indicate by providing your initials in the spaces below the additional sample collection, genetic testing, or long-term storage that you agree to.

_____ I agree to take part in this OL amendment of the HPTN 084 of the study.

_____ I do not agree to take part in this OL amendment of the HPTN 084 of the study.

_____ I agree to have samples of my blood stored long-term for future testing.

_____ I do not agree to have samples of my blood stored and long-term for future testing.

_____ I agree to allow my blood to be tested to see how my genes make drugs work in my body.

_____ I do not agree to allow my blood to be tested to see how my genes make drugs work in my body.

[_____ I agree to continue taking part in the Contraceptive Sub-study. **If relevant*]

[_____ I do not agree to continue taking part in the Contraceptive Sub-study. **If relevant*]

_____ _____
Participant Name (print) Participant Signature and Date

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

[End of the ADULT, OL amendment Signature Block.]

[The section below is only for MINORS who participated in HPTN 084-01.]

***[Insert signature blocks as required by the local IRB*:]**

If you have read this addendum to the main consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to continue in this part of the study, please sign your name or make your mark below. Also, please indicate by providing your initials in the spaces below the additional sample collection, genetic testing, or long-term storage that you agree to.

_____ I agree to take part in this OL amendment of the HPTN 084 of the study.

_____ I do not agree to take part in this OL amendment of the HPTN 084 of the study.

_____ I agree to have samples of my blood stored long-term for future testing.

_____ I do not agree to have samples of my blood stored and long-term for future testing.

_____ I agree to allow my blood to be tested to see how my genes make drugs work in my body.

_____ I do not agree to allow my blood to be tested to see how my genes make drugs work in my body.

Participant Name (print)	Participant Signature and Date

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

[End of the MINOR, OL amendment Signature Block.]

[This consent section is separate because it is ONLY for participants who 1) become pregnant during the OL amendment, 2) who have received at least one CAB LA injection, and 3) want to join the Pregnancy Infant Sub-study. Only women meeting the criteria need to read and complete the below.]

***[Insert signature blocks as required by the local IRB*:]**

If you have read this addendum to the main consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to join the Pregnancy Infant Sub-Study, please sign your name or make your mark below. Also, please indicate by providing your initials in the spaces below whether you agree for your baby to participate.

_____ I agree to take part in the Pregnancy Infant Sub-Study of the HPTN 084 OL amendment.

_____ I do not agree to take part in the Pregnancy Infant Sub-Study of the HPTN 084 OL amendment.

_____ I agree to take CAB LA injections during the pregnancy and while breastfeeding.
_____ I do not agree to take CAB LA injections during the pregnancy and while breastfeeding.

_____ I agree to let the team collect blood from me.

_____ I do not agree to let the team collect blood from me.

_____ I agree to let the team collect some blood from the umbilical cord at delivery.

_____ I do not agree to let the team collect some blood from the umbilical cord at delivery.

_____ I agree to let the team collect blood from my baby.

_____ I do not agree to let the team collect blood from my baby.

_____ I agree to let the team collect breastmilk samples.

_____ I do not agree to let the team collect breastmilk samples.

_____ I agree to let the team store umbilical cord blood, blood from my baby and breastmilk samples for future research.

_____ I do not agree to let the team store umbilical cord blood, blood from my baby and breastmilk samples for future research.

[Immediately below is a signature block for ADULT participants. There is a separate signature block for pregnant, minor participants further down.]

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

[End of the ADLUT Pregnancy Infant Sub-Study Signature Block.]

[Immediately below is a signature block for MINOR participants. There is a separate signature block for pregnant, adult participants above.]

Participant Name (print)	Participant Signature and Date
Parent or Guardian Name (print)	Parent or Guardian Name Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
Witness Name (print) (As appropriate)	Witness Signature and Date

[End of the MINOR Pregnancy Infant Sub-Study Signature Block.]

REFERENCES TO OLE APPENDIX

1. S Delany-Moretlwe, JP Hughes, P Bock, et al. Long acting injectable cabotegravir is safe and effective in preventing HIV infection in cisgender women: interim results from HPTN 084. Paper presented at: R4P; January, 2021; Online.
2. Overton ET, Richmond G, Rizzardini G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. Lancet. 2021;396(10267):1994-2005.
3. Susan Swindells, Thomas Lutz, Lelanie Van Zyl, et al. Cabotegravir + Rilpivirine Long-Acting as HIV-1 Maintenance Therapy: ATLAS Week 96 Results. HIV Glasgow – Virtual, 5–8 October 2020; 2020.
4. Marzinke MA, Grinsztejn B, Fogel JM, et al. Characterization of HIV infection in cisgender men and transgender women who have sex with men receiving injectable cabotegravir for HIV prevention: HPTN 083. J Infect Dis. 2021.
5. Graybill LA, Kasaro M, Freeborn K, et al. Incident HIV among pregnant and breast-feeding women in sub-Saharan Africa: a systematic review and meta-analysis. Aids. 2020;34(5):761-776.
6. Thomson KA, Hughes J, Baeten JM, et al. Increased Risk of HIV Acquisition Among Women Throughout Pregnancy and During the Postpartum Period: A Prospective Per-Coital-Act Analysis Among Women With HIV-Infected Partners. The Journal of Infectious Diseases. 2018;218(1):16-25.
7. Thomson KA, Hughes J, Baeten JM, et al. Increased Risk of HIV Acquisition Among Women Throughout Pregnancy and During the Postpartum Period: A Prospective Per-Coital-Act Analysis Among Women With HIV-Infected Partners. J Infect Dis. 2018;218(1):16-25.
8. Chouchana L, Beeker N, Treluyer JM. Is There a Safety Signal for Dolutegravir and Integrase Inhibitors During Pregnancy? J Acquir Immune Defic Syndr. 2019;81(4):481-486.
9. van De Ven NS, Pozniak AL, Levi JA, et al. Analysis of Pharmacovigilance Databases for Dolutegravir Safety in Pregnancy. Clin Infect Dis. 2020;70(12):2599-2606.
10. R. Zash, L. Holmes, M. Diseko, et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo study, Botswana. IAS; 2020; Virtual.
11. In: World Health Organization. Policy brief: update of recommendations on first- and second-line antiretroviral regimens.; 2019.
12. Odagiri E, Ishiwatari N, Abe Y, et al. Hypercortisolism and the resistance to dexamethasone suppression during gestation. Endocrinol Jpn. 1988;35(5):685-690.
13. Markham A. Bictegravir: First Global Approval. Drugs. 2018;78(5):601-606.
14. J C, SK W, S C, Vu A XD, H M. Pharmacokinetics of Bictegravir Adminstered Twice Daily in Combination with Rifambin. 25th Conference on Retroviruses and Opportunistic Infections. Paper presented at: CROI2018; Boston, MA.
15. Zhang H, Custodio JM, Wei X, et al. CLINICAL PHARMACOLOGY OF THE HIV INTEGRASE STRAND TRANSFER INHIBITOR BICTEGRAVIR. Paper presented at: CROI2017; Seattle, WA.
16. Kityo C, Hagins D, Koenig E, A. A. Switching to Bictegravir/Emtricitabine/Tenfovir Alfenimide (B/F/TAF) in Women. Paper presented at: CROI2018; Boston, MA.
17. Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet. 2017;390(10107):2063-2072.

18. Parul Patel, Shanker Thiagarajah, Susan Ford, et al. CABOTEGRAVIR PHARMACOKINETIC TAIL IN PREGNANCY AND NEONATAL OUTCOMES. Paper presented at: CROI2020; Boston, MA.
19. GSK1265744, Cabotegravir. In: 11 V, ed. Investigator's Brochure. February 2021.
20. Waitt C, Orrell C, Walimbwa S, et al. Safety and pharmacokinetics of dolutegravir in pregnant mothers with HIV infection and their neonates: A randomised trial (DolPHIN-1 study). PLoS Med. 2019;16(9):e1002895.
21. Risa M Hoffman, Rosie Mngqibisa, Dawn Averitt, Currier JS. Accelerating drug discovery for pregnant and lactating women living with HIV. JIAS. 2021;Volume24(3).
22. FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, Updated on January 27, 2021. Accessed at: https://www.fda.gov/media/136238/download