

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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A Study by the HIV Prevention Trials Network

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LIST OF ABBREVIATIONS AND ACRONYMS

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

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LIST OF ABBREVIATIONS AND ACRONYMS

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
EFD	early fetal development
EFV	efavirenz
EQA	external quality assurance
FDA	(US) Food and Drug Administration
FEM-PrEP	Pre-exposure Prophylaxis Trial for HIV Prevention among African Women
FTC	emtricitabine
FTC-TP	emtricitabine triphosphate
GC	<i>Neisseria gonorrhoeae</i>
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

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LIST OF ABBREVIATIONS AND ACRONYMS

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
IQA	(DAIDS) Immunology Quality Assurance
IRB	Institutional Review Board
ISR	injection site reaction
IUD	intrauterine device
IUS	Intrauterine system
LA	long-acting (injectable)
LC	(HPTN) laboratory center
LATTE	Cabotegravir plus Rilpivirine, once a day, after Induction with Cabotegravir plus Nucleoside Reverse Transcriptase Inhibitors in Antiretroviral-naïve Adults with HIV-1 Infection
LATTE-2	Cabotegravir plus Rilpivirine as Long-Acting Maintenance Therapy
LDL	low-density lipoprotein
LDMS	(HPTN) Laboratory Data and Management System
LFTs	liver function tests
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

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LIST OF ABBREVIATIONS AND ACRONYMS

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
pSMILE	Patient Safety Monitoring and International Laboratory Evaluation
PSRC	(DAIDS) Prevention Science Review Committee
PTCA	percutaneous transluminal coronary angioplasty
PY	person-years
QA	quality assurance
QC	quality control
QT	time between the start of the Q wave and the end of the T wave
RCT	randomized clinical trial
RE	regulatory entity
RNA	ribonucleic acid
RPV	rilpivirine
RPV LA	rilpivirine long-acting (injectable)
RSC	(DAIDS) Regulatory Support Center
SAE	serious adverse events
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

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LIST OF ABBREVIATIONS AND ACRONYMS

TGW	transgender women
TP	triphosphate
TV	<i>Trichomonis vaginalis</i>
ULN	upper limit of normal
US	United States
VOICE	Vaginal and Oral Interventions to Control the Epidemic
VQA	(DAIDS) Virology Quality Assurance
WHO	World Health Organization

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Sponsored by:

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US Agency for International Development (USAID)
Office of the US Global AIDS Coordinator (OGAC)

The signature below constitutes approval of this study in full accordance with the provisions of this protocol and the attachments. I agree to conduct this study in compliance with the protocol, in-country and local regulatory requirements, applicable United States (US) Code of Federal Regulations (CFR) and ICH Good Clinical Practices (E6).

I agree to maintain all study documentation for at least two years following the date of marketing approval for the study product for the indication in which it was studied, unless otherwise specified by DAIDS, or the HPTN Leadership and Operations Center (LOC) 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 will be retained for two years after the US Food and Drug Administration (FDA) is notified that the Investigational New Drug (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.

Publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be submitted to the HPTN Manuscript Review Committee (MRC), and DAIDS for review prior to submission.

Truvada® is an approved registered drug in the USA and used as one of the study products in protocol HPTN 084. I have read and understand the information in the Truvada® package insert (PI) and the Cabotegravir Investigator Brochure (IB), including the potential risks and side effects of the products under investigation, 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 3,200 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, provision 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, provision 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, provision 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, provision of condoms.

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

SCHEMA (continued)

Study Regimen Continued: Step 2 will continue until the required number of endpoints (111) 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 provision 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.

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SCHEMA (continued)

**Tertiary
Objectives:**

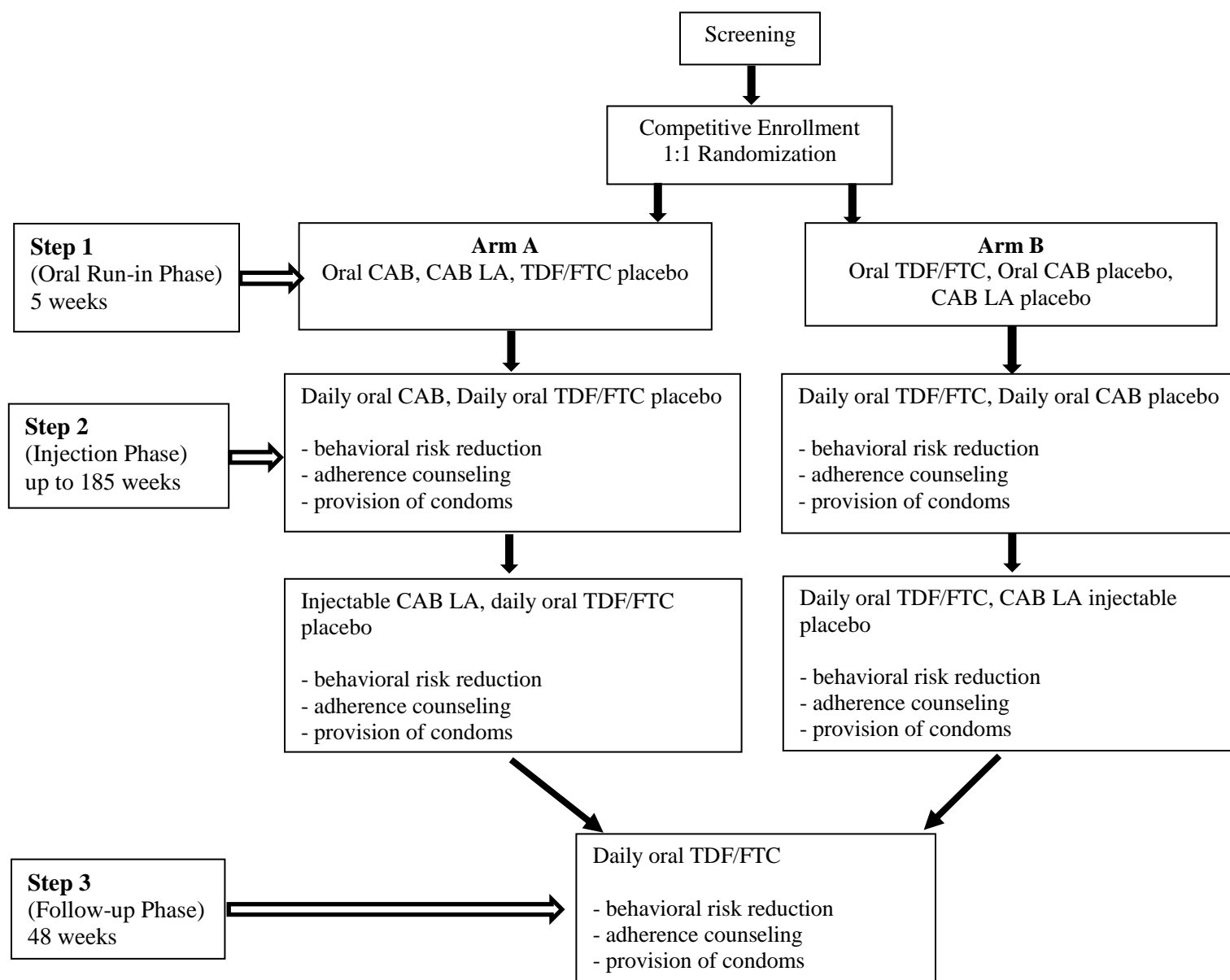
- To estimate and compare sexual risk behaviors, as measured by self-report and rates of incident sexually transmitted infections (STIs), between study arms.
- To compare Grade ≥ 2 adverse event (AE) rates in women with baseline BMI $< \geq 25$ kg/m², within each study arm.
- To compare pregnancy incidence 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 medroxyprogesterone (DMPA) or norethisterone (NET-EN) when co-administered with CAB LA.
- To determine lutenizing hormone (LH), follicular stimulating hormone (FSH), and progesterone in subjects receiving either DMPA or NET-EN when co-administered with 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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 Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women**

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 disoproxil 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 $\geq 80\%$, 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 HIV 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) V6.0, Effective Date 13 January 2016, 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 [TCID₅₀]) 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 TCID₅₀) were evaluated. The percent of challenges resulting in infection was calculated relative to the plasma CAB protein-adjusted 90% inhibitory concentration (PA-IC₉₀) value. None of 59 challenges resulted in infection when plasma levels were greater than 3 times the PA-IC₉₀, compared with 1 out of 22 challenges resulting in infection when plasma levels were between one to three times the PA-IC₉₀, and 11 out of 43 challenges resulting in infection when plasma levels were less than 1 times the PA-IC₉₀. 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 infection³⁵ 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 (AUC_{0–28d}) in vaginal secretions were compared to the values with those seen in plasma or rectal secretions. The AUC_{0–28d} values in vaginal secretions (median, 11,511 ng × day/ml; range, 3,956 to 14,011) were lower than those in rectal secretions (median, 26,717 ng × day/ml; range, 10,120 to 39,989), although the difference was not statistically significant. In contrast, AUC_{0–28d} values in vaginal secretions were lower than those in plasma (median, 70,333 ng × day/ml; range, 40,265 to 169,341) ($P = 0.002$) (Figure 1.1). 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_{0–24} and C_{max} of 547 µg·h/mL and 34.6 µg × 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 AUC_{1,440–2,160h} following once monthly IM dosing at the NOAEL (75 mg/kg/dose) in the 3-month rat CAB LA toxicity study (92,566 µg × 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_{τ}) of 0.57 $\mu\text{g/mL}$, 3.4-fold above the PA-IC₉₀ value, and was associated with a mean Day 11 HIV ribonucleic acid (RNA) change from a baseline of -2.2 log₁₀ 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_{τ} following oral CAB 10 mg and 30 mg once daily were 1.35 $\mu\text{g/mL}$, eight-fold above PA-IC₉₀, and 4.2 $\mu\text{g/mL}$, 25-fold above PA-IC₉₀, 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 7.5 $\mu\text{g/mL}$ (28%), which provides adequate safety coverage for the predicted median (90% Investigational Brochure [IB] peak concentrations following CAB LA of 4.0 $\mu\text{g/mL}$ (1.8, 8.9 $\mu\text{g/mL}$). 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-IC₉₀ value of 0.166 $\mu\text{g/mL}$, 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 $\mu\text{g/mL}$ (139%), approximately 6.7-fold above the PA-IC₉₀ 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 $\mu\text{g/mL}$ target based on 10 mg daily oral dosing with the lower bound of the 90% CI at ~four-fold PA-IC₉₀. 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-IC₉₀ following each of the three quarterly injections, while 15 to 31% were below the PA-IC₉₀. 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 $\mu\text{g/mL}$, falling between the lower limit of quantitation (LOQ) of 0.025 $\mu\text{g/mL}$ and 1 x PA-IC₉₀ (0.166 $\mu\text{g/mL}$).

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 C_{τ} of 1.49 $\mu\text{g/mL}$ at Week 48 (Figure 1.2), above the geometric mean C_{τ} 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 an ongoing 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). These additional follow-up data will be available in approximately the fourth quarter of 2017 (for Cohort 1) and the third quarter of 2018 (for Cohort 2) and will provide additional insight into how long CAB levels may be detected after terminal injection and help to inform the optimal duration of Step 3 of HPTN 084.

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 ($4.54 \times 10^{-4} \text{ hr}^{-1}$ to $9.19 \times 10^{-4} \text{ hr}^{-1}$; 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_{τ} in females of approximately 2.5 $\mu\text{g/mL}$, which is approximately 15-fold above PA-IC_{90} , with C_{τ} 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)

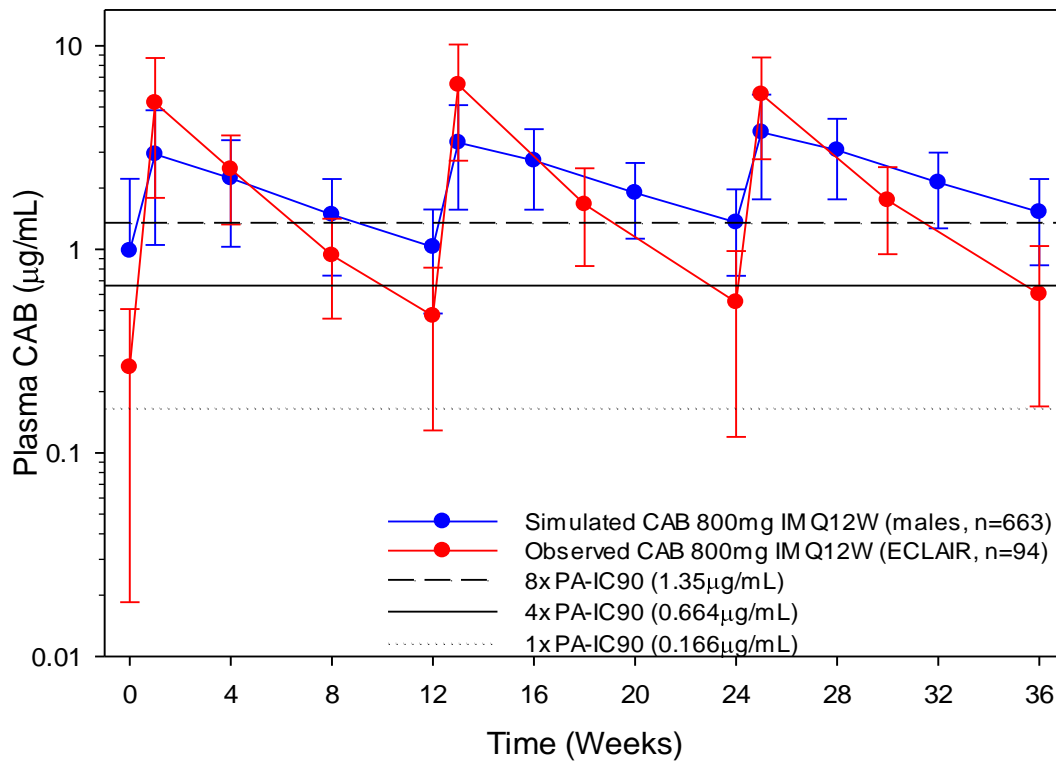


Figure 1.2. Mean (SD) Plasma CAB Concentration-Time Profile following CAB LA Q8W Regimen (800 mg IM Loading Dose, 600 mg IM Week 4, Week 8, then Q8W) in LATTE-2

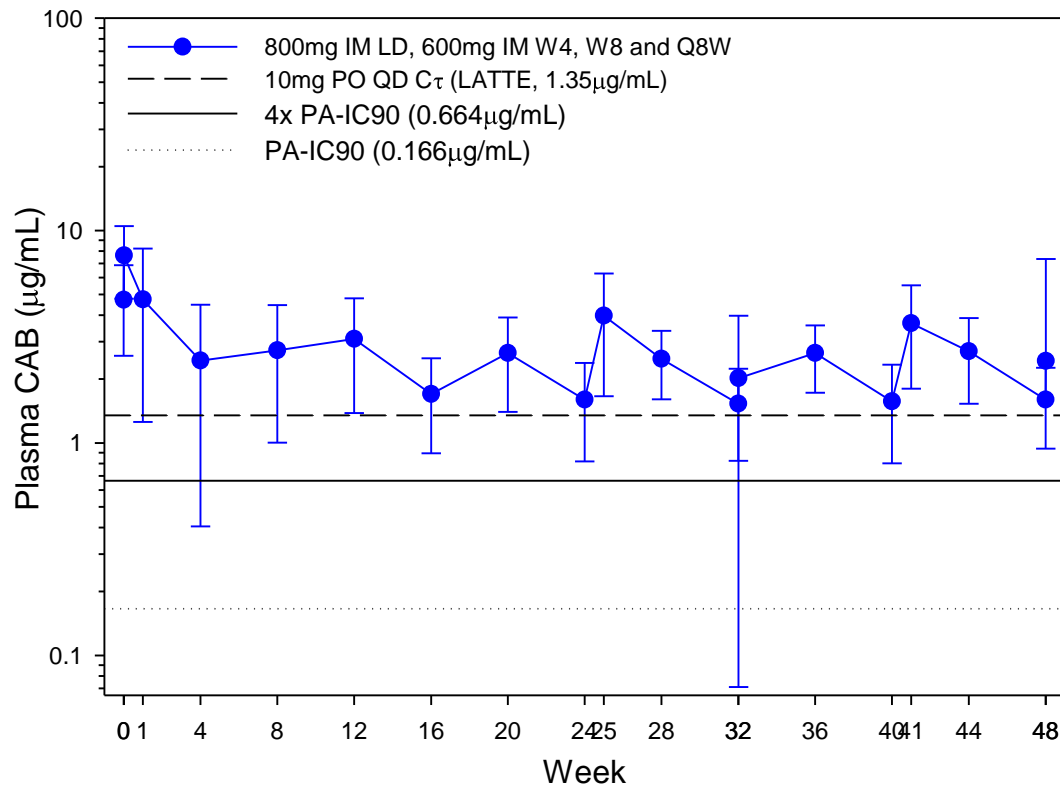


Figure 1.3. Simulated Plasma CAB Concentration-Time Profile for the Proposed Regimen (600 mg IM Day 1, Week 4 and Q8W) in Females based on Updated Population PK Model and Overlayed with Preliminary HPTN077 C2 Data in Females (semilog scale)

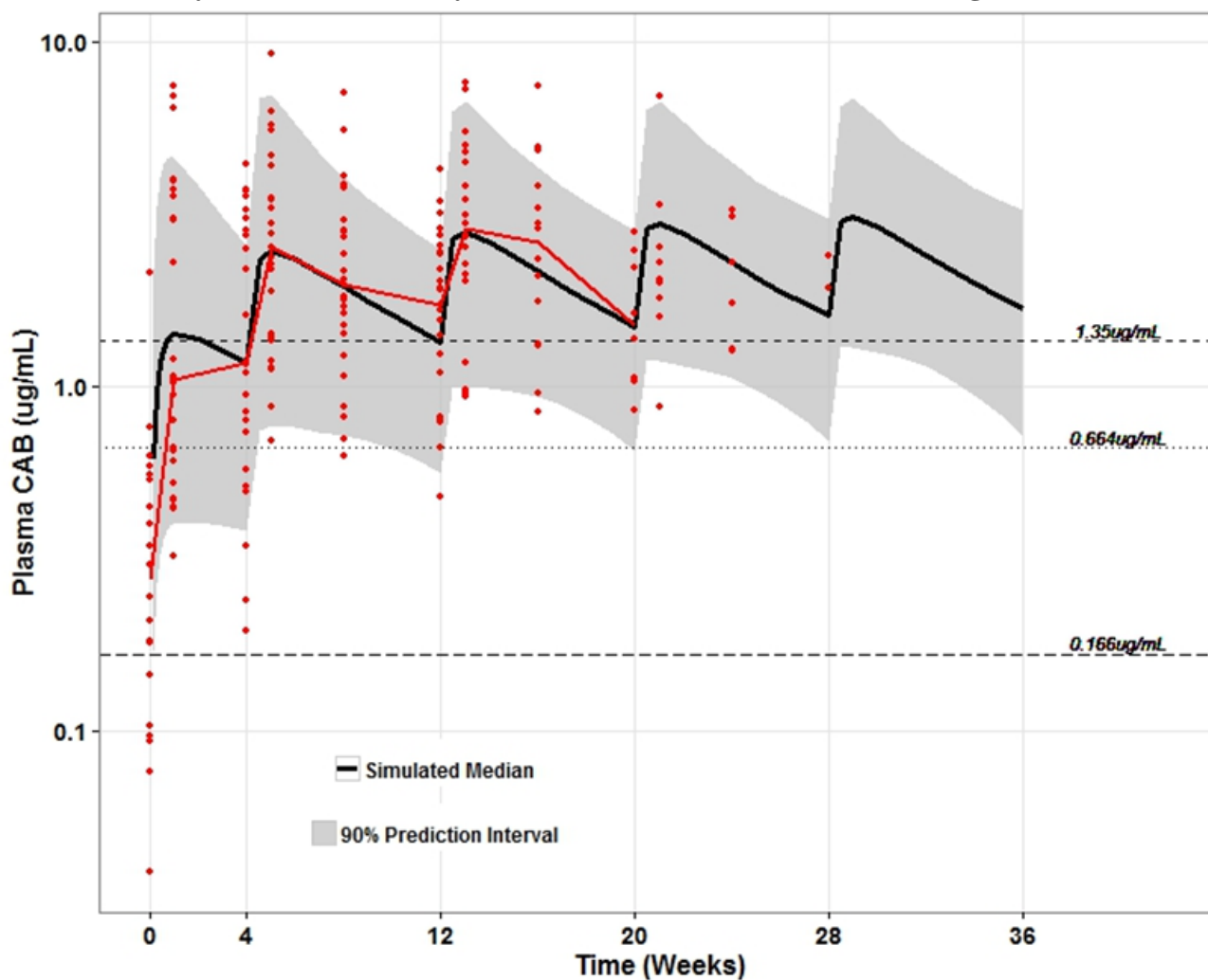
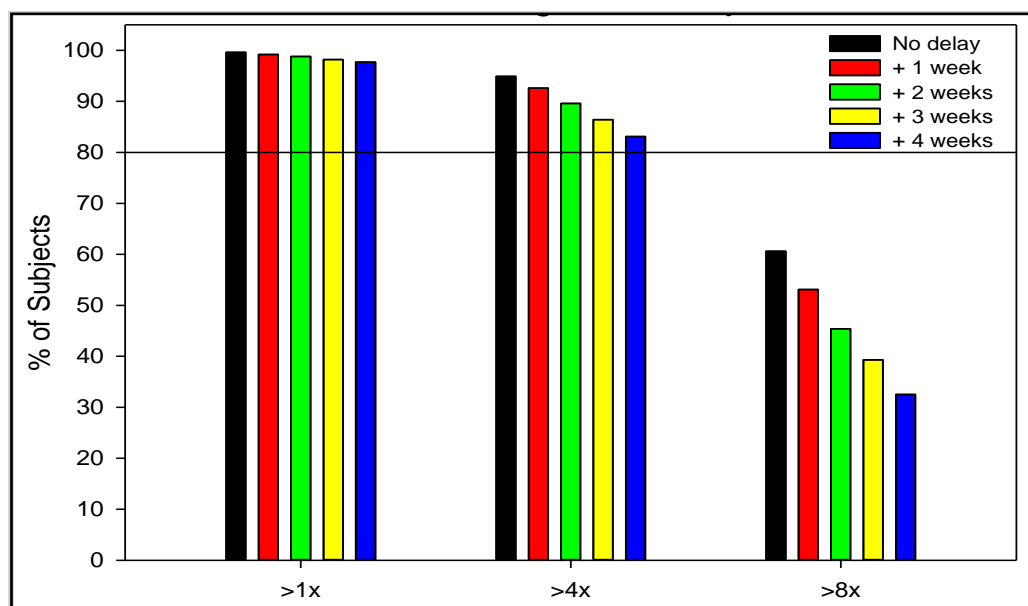


Table 1.2. Predicted Percent Above Targets for Delayed Dosing in Females

Delayed Injection	% > PA-IC90					% > 4x PA-IC90					% > 8x PA-IC90				
	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)



1.6 Clinical Experience to Date: Oral CAB and CAB LA

Through 01 July 2016, approximately 1,256 adult participants have been exposed to at least one dose of CAB (oral and/or LA) across completed or ongoing Phase 1 and Phase 2 clinical trials.

Oral CAB has been studied at doses between 5 mg and 150 mg in HIV-uninfected and HIV-infected adults. The oral formulation of CAB has been generally well-tolerated as single or repeated doses in clinical studies of HIV-uninfected adults. Among the HIV-uninfected and HIV-infected participants who received oral formulations ranging from 5 mg to 150 mg in Phase 1 and 2a studies, 11 participants receiving oral CAB were withdrawn due to potentially drug-related AEs, including dizziness, leucopenia, and aspartate aminotransferase and alanine aminotransferase [AST/ALT]/gamma-glutamyltransferase increases, creatinine phosphokinase (CPK) increases and fatigue. No drug-related Grade 3 or Grade 4 clinical AEs or Serious Adverse Events (SAEs) have been reported to date in Phase 1 and 2a studies.⁴⁰ One death from anoxic brain injury as a result of status epilepticus was reported in the HIV-infected Phase 2b treatment study; the event was in the clinical context of recreational drug use, and was not considered by the Investigator or study Sponsor to be related to study drug, but contribution from CAB or RPV cannot be ruled out.

One hundred thirty-six (136) 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. Five non-drug-related SAEs have been reported: foot osteomyelitis, uterine fibroids, appendicitis, elective hysterectomy, and seizure. An additional 94 participants have received CAB LA as 800 mg IM injections QW12 in the ÉCLAIR study. One participant was withdrawn from CAB LA prophylaxis due to a pre-existing prostate cancer diagnosis, a non-drug-related AE.

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).⁴⁰ 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.⁴⁰

In the ÉCLAIR study, 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 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 suppression⁴¹. 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.

Cumulative exposures of CAB, through 01 July 2016, are shown in Table 1.3.

Table 1.3. Cumulative CAB Exposure Estimates from Phase 1 through Phase 2b Clinical Studies Up to 01 July 2016

Treatment Population/ Dose	Duration	Completed	Ongoing/ Concluded ^a	Total
Healthy Volunteers/HIV Uninfected		423	328	751
5 to 150 mg oral	Single dose	167	23	190
10 to 30 mg once daily oral	10 to 28 days	158	305^b	463
150 mg every 12 hours oral	3 doses	40	0	40
100 – 800 mg IM/SC LA	Max 456 days ^h	136 ^c	269^d	405
HIV infected patients		15	490	505
5 to 30 mg once daily oral (Ph 2a)	10 days	15	0	15
10 to 60 mg once daily oral (Ph 2b)	Max 1408 days ⁱ	0	181	181
30 mg once daily oral (Ph 2b)	Max 775 days	0	309	309
Up to 800 mg IM LA ^e	Max 638days	0	230 ^f	230
Total		438	818^b	1256
Single dose oral (5 to 150 mg)		167	23	190
Repeat dose once daily oral (5 to 60 mg)		173	795	968
150 mg oral every 12 hours x 3		40	0	40
Single or repeat dose LA injection (100 to 800 mg)		136 ^c	499^g	635

- Concluded studies: study completed through follow-up; and/or clinical study report is in preparation
- Approximately **50** of these subjects are on placebo in study 201103
- 78 subjects received both oral and LA dosing
- 269 subjects received both oral and LA dosing and approximately 50 of these subjects are on placebo from study 201103
- Includes 400 mg Q4W and 600 mg Q8W dosing
- Subset of the subjects that received 30 mg once daily in study 200056
- 499 subjects received both oral and LA dosing and approximately 50 of these subjects are on placebo from study 201103
- Detectable CAB concentrations can remain as long as a year or more following the last CAB injection. See Section 1.5.2 of the protocol.
- As of 28 Dec 2014, all subjects had transitioned to CAB 30 mg in the Open-Label phase of study LAI116482 (LATTE-1), therefore, the longer durations apply to the 30 mg dose only

1.7 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 levonorgestrel (LNG) or ethinyl estradiol (EE) containing combination oral contraceptive.⁴² There were no apparent differences in pharmacodynamic assessments of follicular stimulating hormone (FSH), luteinizing hormone (LH) or progesterone and concomitant administration of CAB and LNG/EE was well-tolerated in the study. Because the pathways of metabolism and excretion are comparable between the oral and injectable formulation of CAB, it is expected that the results of this drug interaction study can be extrapolated to long-acting CAB. In clinical studies, combination estrogen and progestin or progestin-only hormonal contraceptives available in oral, injectable or implant formulations may be used concurrently with CAB. However, clinical data are limited evaluating the use of injectable or implantable forms of hormonal contraceptives and CAB to date. Progestin-only products such as injectable NET-EN and DMPA are commonly prescribed, specifically in SSA. Although the metabolic pathways for such products are complex and vary somewhat from ethinyl estradiol and levonorgestrel, no pharmacokinetic drug-drug interaction between CAB and progestin-only contraceptives is anticipated. This study will permit characterization of the pharmacokinetics of injectable contraceptives during concomitant CAB LA administration.

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

Genital tissue concentrations have been measured after CAB LA 400 mg IM single dose administration in 24 healthy men and 15 healthy women. Median cervical and vaginal tissue concentrations ranged from 16-28% (overall range 0-70%) of plasma concentrations, roughly 1 x PA-IC₉₀ (0.166 µg/mL). Median rectal tissue concentrations were ≤ 8% of plasma concentrations (range 0-20%).⁴³ In further tissue studies using single and multiple doses of the 800 mg IM dose are ongoing.

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 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).

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

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

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objectives

- 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 and compare sexual risk behaviors, as measured by self-report and rates of incident sexually transmitted infections (STIs), between study arms.
- To compare Grade ≥ 2 AE rates in women with baseline BMI $</\geq 25$ kg/m², within each study 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 medroxyprogesterone (DMPA) or norethisterone (NET-EN) when co-administered with CAB LA.
- To determine LH, FSH, and progesterone in subjects receiving either DMPA or NET-EN when co-administered with 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 3,200 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 (111), 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, provision 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, provision 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, provision 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, provision of condoms.

This Step will continue until the required number of incident HIV endpoints (111) 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 permanently discontinue receiving injections before their study participation ends for any reason other than HIV infection will begin open-label TDF/FTC to cover the tail phase. These participants will continue to be followed according to their Step 2 schedule and upon its completion move into Step 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 provision 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 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 100 evaluable participants will be invited to enroll a sub-study after screening to evaluate the effect of CAB LA on the injectable contraceptive drugs: DMPA and NET-EN. Participants who are currently on these drugs or are willing to use these drugs as contraceptive methods qualify for the enrollment. These participants will go through all of the study procedures as all others participants, and extra PK samples will be collected prior to when Step 1 starts and also during the Step 2. PK sampling time collections may vary depending on the injectable contraceptive schedule.

2.5.1 Participating Sites/Institutions

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

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 3,200 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 ≥ 2 using a modified VOICE risk score⁴⁴
- 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)
- Hepatitis B virus (HBV) surface antigen (HBsAg) negative and accepts vaccination
- Alanine aminotransferase (ALT) $< 2 \times$ upper limit of normal (ULN) and total bilirubin (Tbili) $\leq 2.5 \times$ 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 (β HCG) 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.
- If of reproductive potential, women must agree to use a reliable form of 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
- 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).

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)
- Current or past enrollment in an HIV vaccine 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)

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.

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 Medicines Control Council of South Africa, 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 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:** CAB 30 mg tablet, one tablet orally daily for five weeks, with or without food **AND** placebo for TDF/FTC tablet, 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 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 4 weeks apart and every 8 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 tablet, one tablet orally daily for up to 48 weeks.

4.1.1 Oral Product

Oral CAB and placebo for oral CAB

Oral CAB tablets 30 mg 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 a desiccant. The bottles should be stored up to 25 degrees Celsius (°C) and protected from moisture.

Placebo tablets for oral CAB are formulated as white to almost white oval-shaped coated tablets to visually match the active oral CAB tablets. The tablets are packaged in HDPE bottles with child-resistant closure that include an induction seal. The bottles contain a desiccant. The bottles should be stored up to 25 °C and protected from moisture.

Oral TDF/FTC and placebo for oral TDF/FTC

The TDF/FTC fixed dose combination tablet containing 200 mg of FTC and 300 mg of TDF 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).⁴⁵

TDF 300 mg/FTC 200 mg study product tablets are manufactured and provided by Gilead Sciences, Inc. under the trade name Truvada®. TDF/FTC tablets must be stored in the pharmacy in the original container. Each bottle contains a silica gel desiccant canister to protect the product from humidity. Store at 25°C. Excursions are permitted between 15°C to 30°C.

Placebo tablets match the TDF/FTC tablets in physical size and appearance. The placebo tablets contain pregelatinized starch croscarmellose sodium lactose monohydrate, denatonium benzoate purified water, lactose monohydrate manesium stearate and opadry II light blue Y-30-10701 purified water. The tablets are packaged in bottles with a child resistant cap. In addition to the tablets, the bottle contains a silica gel desiccant to protect from humidity. The bottles should be stored at 25 °C. Excursions are permitted between 15°C to 30°C. Matching placebo tablets also will be provided by Gilead Sciences, Inc.

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 coloured suspension containing 200 mg/mL of CAB LA for administration by IM. The product is packaged in a 3 mL vial. Each vial is for single use containing a nominal fill of 2mL (400 mg), and does not require dilution prior to administration. CAB LA injectable suspension is to be stored at 2° C – 30° C, do not freeze.

Placebo for CAB LA formulation

Placebo for CAB LA injectable suspension will be Intralipid 20% fat emulsion infusion. Intralipid 20% fat emulsion is made up of 20% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, and water for injection. It is supplied for IV use in 100 mL, 250 mL and 500 mL aliquots for IV use. Intralipid has been selected as an IM placebo in the HPTN 084 study on the basis of its physical appearance, which is indistinguishable from cabotegravir LA to the eye within a syringe, supporting the maintenance of the blind. It is anticipated that the IM of 2-3 mL of Intralipid will be safe and well tolerated. While Intralipid is typically administered in practice as an IV nutritional supplement, it has been used in prior studies as an IM placebo injectable product. When administered as an IV product, labeled adverse effects are as follows: a) immediate or early adverse reactions, each of which has been reported to occur in clinical trials, in an incidence of less than 1%: dyspnea, cyanosis, allergic reactions, hyperlipidemia, hypercoagulability, nausea, vomiting, headache, flushing, increase in temperature, sweating, sleepiness, pain in the chest and back, slight pressure over the eyes, dizziness, and irritation at the site of infusion, and, rarely, thrombocytopenia in neonates; b) delayed adverse reactions such as hepatomegaly, jaundice due to central lobular cholestasis, splenomegaly, thrombocytopenia,

leukopenia, transient increases in liver function tests, and overloading syndrome (focal seizures, fever, leukocytosis, hepatomegaly, splenomegaly and shock).

As a placebo IM gluteal injection in the HPTN 084 study, Intralipid 20% will be administered in much smaller volumes (2-3 mL) relative to IV infusion volumes. In a study by Berwaerts et al. 160 participants received chronic IM dosing with Intralipid 20% as placebo comparator for paliperidone palmitate. AEs reported in schizophrenic patients receiving IM placebo dosing include headache (4%), weight increased (3%), nasopharyngitis (1%), EPS-related events (3%), anxiety (12%), insomnia (12%) and decreased weight (8%). Injection site reactions were not commonly reported with IM dosing of Intralipid 20%.⁴⁶

IM Dosing Considerations

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

4.2 Study Product Acquisition and Accountability

The CAB study product (oral and LA injectable) and corresponding placebos are being provided by ViiV Healthcare. TDF/FTC oral study product and matching placebo are being provided by Gilead Sciences, Inc.

4.2.1 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 and/or NET-EN will be not be provided by the Study Sponsor.

4.2.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the CRPMC and subsequently dispensed to study participants. All study products must be stored in the pharmacy. All unused study products must be returned to the CRPMC after the study is completed, terminated or otherwise instructed by the study sponsor. The procedures to be followed are provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

4.3 Toxicity Management

Toxicity management guidelines can be found in Appendix III.

4.4 Concomitant, Prohibited, and Precautionary Medications

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

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

5.0 STUDY PROCEDURES

Overviews of the study visit and procedures schedules are presented in Appendices I 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 eligibility 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, and urinalysis from this visit are NOT required prior to randomization.

Subjects currently taking injectable contraceptives and opting to participate in the contraceptive sub-study should have PK and biomarkers (medroxyprogesterone, norethisterone, LH, FSH, progesterone) 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, 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.

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 \leq Grade 2.

Table 5.1. Management of Participants with AEs in Step 1

<u>Grade of AE</u>	<u>Brief Instruction</u>
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 Weeks 2 or 3→ continue oral product, repeat ALT labs in 1 week
	At Week 4→ permanently stop oral product, repeat ALT labs weekly until \leq Grade 1, follow annually for HIV testing until study end of Step 2
Grade 3 AE, excluding ALT & CPK	Report to CMC and if determined to be: <ul style="list-style-type: none"> • Related AE→ permanently stop oral product, follow annually for HIV testing until study end of Step 2 • 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 \leq Grade 1, follow annually for HIV testing until study end of Step 2
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 2
Grade 4 ALT	Report to CMC Regardless of CPK permanently stop oral product, repeat ALT labs weekly until \leq Grade 1, follow annually for HIV testing until study end of Step 2
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)

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.

Contraceptive Sub-study

Subjects participating in the contraceptive sub-study should have PK and biomarkers (medroxyprogesterone, norethisterone, LH, FSH, progesterone) drawn at each CAB PK sampling visit during the second and third CAB LA injection cycles (Weeks 9, 13, 17, 21, and 25), to ensure collection of an entire plasma PK for medroxyprogesterone and NET-EN. Dosing date and time 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.^{47 48} 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.

5.8 Injection Visit Windows

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

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.

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
- Participants will be followed on TDF/FTC according to the 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.

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 not 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 the CMC. 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, even if HCV RNA is undetectable. At Enrollment, participants will be tested for Hepatitis B surface antibody (HBsAb), and Hepatitis B core antibody (HBcAb). Participants who do not have evidence of immunity to HBV (e.g., negative HBsAb) will be provided HBV vaccination. For participants who do not have evidence of HBV immunity at Enrollment, HBV testing should be repeated at the discretion of the IoR or designee during the study if clinically indicated, if the participant has elevated AST/ALT results (elevated level at discretion of IoR or designee), or if the participant expresses a concern about having acquired HBV infection after enrollment. Refer to the SSP Manual for persons who have a positive result for HBcAb 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 48 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 will also provide 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

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 will be 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 recognized pregnancy 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; 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. 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.

5.15 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, a subset of participants will be invited to take part in qualitative assessments of acceptability. This may include participation in a single or repeated semi-structured interviews or a focus group discussion to provide more holistic and contextualized information on motivations, attitudes and experiences using daily oral or injectable PrEP, reasons for and circumstances related to product and/or study discontinuation, and future intentions related to PrEP use. Finally, semi-structured observations may be conducted periodically within clinic waiting rooms in order to document other aspects of the clinical trial environment that have been associated with product acceptability and adherence in past HIV prevention trials. Some examples include observations of participant wait times and brief intercepts of individuals and/or groups to assess their understanding of trial procedures, product beliefs or partner and community concerns.

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 or focus group discussions aimed at understanding acceptability of an injectable PrEP product will be conducted in a private space. During FGDs, the moderator will address participants by a unique number provided to each 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.

5.16 Interim Contacts and Visits

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

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

5.17 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 have moved to Step 3), and when all corresponding procedures at the HPTN SDMC, LC, and LOC have been completed, including final confirmation from the PTN SDMC, the study will be unblinded.

5.18 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. Site IoRs may, with the agreement of the CMC, Protocol Chairs, DAIDS MO, and study statistician withdraw participants before their scheduled termination visit to protect their safety, the safety of the staff, and/or if participants are unable or unwilling to comply with study procedures. Participants also may be withdrawn if the study sponsors, government or regulatory authorities (including the OHRP and US FDA), or site IRBs/ECs or if appropriate, the Medicines Control Council of South Africa, 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 (Grade 1 and higher, and any AE that leads to a study product hold (temporary or permanent) will be captured on CRFs) reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.0, November 2014. 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 http://rsc.tech-res.com/docs/default-source/safety/manual_for_expedited_reporting_aes_to_daids_v2.pdf?sfvrsn=.

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: <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/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 results (must be both in order to require expedited reporting):

- ALT \geq 3xULN AND total bilirubin \geq 2xULN
- 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, Version 2.0, November 2014, 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 <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

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

This study also will be monitored by a NIAID Data and Safety Monitoring Board (DSMB), 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 111 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 3 or higher clinical and laboratory AEs

7.2.3 Secondary Endpoints Endpoints

- Number of documented incident HIV infections in participants in subgroups broken down by baseline age, HSV-2 status, contraceptive use method and BMI \leq 25 kg/m²
- Plasma and DBS levels of CAB in participants randomized to CAB/CAB LA
- Plasma levels of TFV/TFV-DP in 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 [adjudicated])
- Grade 2 or higher clinical and laboratory adverse events (AEs) broken down by BMI \leq 25kg/m²

- 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 when co-administered with 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 four 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) provides an adequate degree of robustness against uncertainties in adherence rates to the two drug regimens.

Table 7.1. Four 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

¹Background 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.

Target sample size for the Contraceptive sub-study is up to 100 evaluable subjects based on contraceptive use and feasibility.

7.4 Accrual and Retention

Approximately 3,200 participants will be enrolled in approximately 24 months and followed through phases 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 last participant enrolled completes approximately 81 weeks of follow-up or the required number of endpoints or person years has been met. At a specified time directed by the HPTN SDMC, participants will be notified of their treatment assignment. In addition, as noted in Section 5.11.2, an Investigator can request unblinding to the HPTN SDMC in the event that a participant becomes infected with HIV during the study, and the SDMC will assist in directly providing the participant's provider of choice the randomized arm assignment information per their SOP; the randomized assignment will not be provided to the site where the participant was enrolled and followed.

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)

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 need to receive open-label TDF/FTC (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. We will test the hypothesis $H_0: HR = 1.0$ versus $H_a: HR < 1.0$ using $\alpha = 0.025$. 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 3 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 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 7.2), that can be incorporated into a meta-analytic model to provide a robust model of the relationship between TDF/FTC efficacy and adherence.

Table 7.2. 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 7.2 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 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 data¹. A limitation, however, is that, for women, most data are available for very low ($\leq 30\%$) and very high adherence levels ($> 75\%$) with little in the middle range of interest to HPTN 084.

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.

The fitted regression model is

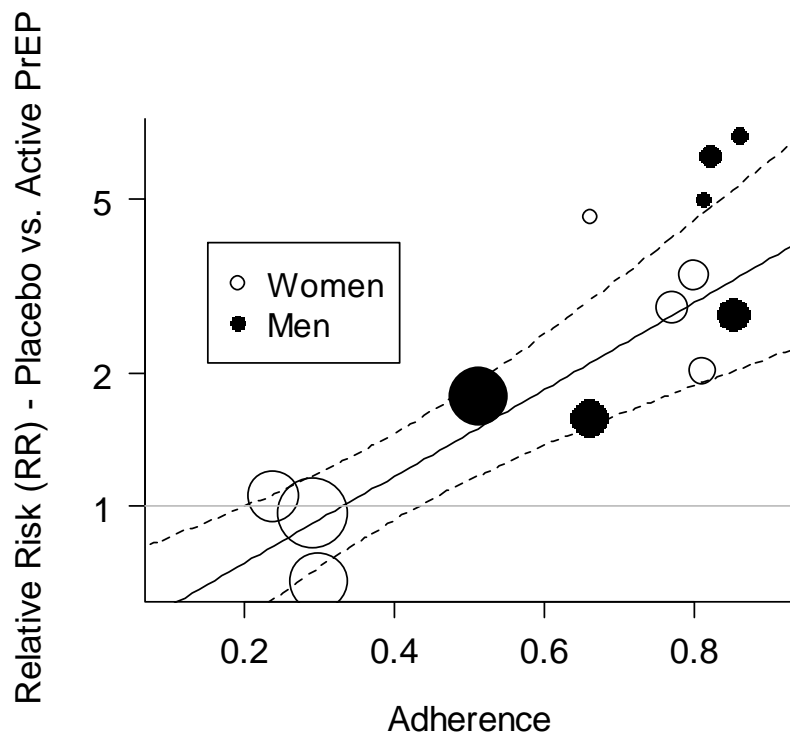
$$\log(RR) = -0.752 + 0.105 * male + 2.276 * adh \quad (1)$$

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).

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 7.2, 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. 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 3,200 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 ± 0.05 and ± 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 $(1-p) \cdot \log(RR_L)$ 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 then an appropriate NI margin may be chosen based on the meta-regression model (1) described above.

An NI trial uses the following hypotheses:

Ho: $RR = \text{margin}$

Ha: $RR < \text{margin}$

Table 7.3 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 in Figure 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 sample size of 3200.

Table 7.3. Non-inferiority Designs for Various Levels of TDF/FTC Adherence Using a Margin Based on Figure 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 Table 7.3) 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

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

where s is the standard error of the estimated log(RR), $\Phi()$ is the cumulative normal distribution, and $f(\hat{a})$ is the sampling distribution of the estimated adherence. Table 7.4 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 7.4. 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 7.3.					
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 $H_0: HR = 1.0$ versus $H_a: HR < 1.0$ 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

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

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 $H_0: \beta_3 = 0$ versus $H_a: \beta_3 \neq 0$.

- 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 levels in continuous time based on observed plasma and PBMC 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, $H_0: \beta = 0$ versus $H_a: \beta \neq 0$ 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, observations and/or focus group discussions 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 11.) A team representing core and site behavioral investigators will follow a process of reading, coding, data display and data reduction⁴⁹ in order to explore in greater depth participants' and their partners' 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. When participant and partner data have been collected, additional analysis will explore how couples' similar or divergent attitudes towards product use and trial participation may have influence acceptability and future demand for an injectable PrEP product.

7.8.6 Analyses of Tertiary Objectives

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

Key sexual behaviors (numbers of partners, unprotected sex) will be dichotomized (i.e. >1 partner, any unprotected sex) and analyzed using logistic regression methods for longitudinal data (i.e. generalized estimating equations). The outcome will be the dichotomized behavior; arm and time on study will be included as covariates. All post-randomization visits where the outcome information is collected will be included in the analysis. We will test for a difference in probability of the behavior between arms using the hypotheses, $H_0: \beta_{\text{arm}} = 0$ versus $H_a: \beta_{\text{arm}} \neq 0$ with $\alpha = 0.05$ and the RR between arms will be estimated as $RR = \exp(\beta_{\text{arm}})$. A 95% confidence interval for the RR will be reported. A test for a trend over time will be based on the hypotheses, $H_0: \beta_{\text{time}} = 0$ versus $H_a: \beta_{\text{time}} \neq 0$ with $\alpha = 0.05$. All analyses will use a robust variance.

Rates of incident STI's will be computed for each arm as number of new STI's divided by total person-years. To compare rates of incident bacterial STI's between the arms, we will fit a Poisson regression with number of incident STI's 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, $H_0: \beta_{\text{arm}} = 0$ versus $H_a: \beta_{\text{arm}} \neq 0$ with $\alpha = 0.05$.

- To compare Grade ≥ 2 AE rates in women with baseline BMI $</\geq 25 \text{ kg/m}^2$, 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) $</\geq 25 \text{ kg/m}^2$.

A multiplicative intensity model will be used to compare rates of Grade 2 or higher AE's between women with BMI $\geq 25 \text{ kg/m}^2$ versus $< 25 \text{ kg/m}^2$, 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, $H_0: \beta_{\text{bmi}} = 0$ versus $H_a: \beta_{\text{bmi}} \neq 0$ with $\alpha = 0.05$. AE's will be clustered by participant and a robust variance will be used.

- 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, $H_0: \beta_{\text{arm}} = 0$ versus $H_a: \beta_{\text{arm}} \neq 0$ 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 when co-administered with CAB LA.

- To determine LH, FSH, and progesterone in subjects receiving either DMPA or NET-EN when co-administered with CAB LA.

Concentrations of medoxyprogesterone, norethisterone, LH, FSH and progesterone will be assayed and summarized. PK analysis will be performed as permitted by the data.

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— 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 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 regulatory authorities (including the OHRP and US FDA), site IRBs/ECs or if appropriate, the Medicines Control Council of South Africa, 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 Medicines Control Council of South Africa, 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, HCV antibody tests
- Complete blood count (CBC) with differential
- Chemistry testing (blood-urea nitrogen (BUN)/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 β HCG 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 an initial 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 good laboratory practice, the HPTN Manual of Operations (MOP), the SSP Manual and local SOPs for proper collection, processing, labeling, transport, and storage of specimens to the local laboratory. Specimen collection, testing, and storage at the local laboratory will be documented using the HPTN Laboratory Data Management System (LDMS) as described in the SSP Manual.

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

9.2 Stored Specimens

Plasma 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.

Injectable Contraception Sub-Study

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.

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 may also perform testing for HSV-2 or other infections. 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 may 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), so the relevant assays are only performed on participants who received the study product.

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

9.2.3 Pharmacogenomics

Samples collected for pharmacogenomics testing will be analyzed for genetic polymorphisms associated with study drug exposure. Assays may be performed at the HPTN LC. Sites and individual participants may choose to opt out of this testing. For sites that will conduct this testing, results will 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 HPTN LC 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 inform site staff of the samples selected for QA testing, and site staff will ship the selected specimens to 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 Patient Safety Monitoring and International Laboratory Evaluation (pSMILE) 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 the DAIDS Immunology Quality Assurance (IQA) program and UNKEQAS 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 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.

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 sample lists are provided by the HPTN SDMC in consultation with the HPTN LC.

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 <http://rsc.tech-res.com/protocolregistration/>.

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 DataFax data management system. Quality control reports and 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 regulatory authorities (including the OHRP and US FDA). site IRBs/ECs or if appropriate, the Medicines Control Council of South Africa, ViiV/Gilead A site visit log will be maintained at each study site to document all visits.

10.5 Protocol Compliance

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

10.6 Investigator's Records

The IoR will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. In accordance with Federal regulations, for each of the investigational products tested, the IoR will retain all study records for at least two years following the date of marketing approval for the study product for the indication in which it was studied, or if other applicable laws, regulations, policies, or other requirements (e.g., State, country-specific, and local laws, and sponsor or institutional policies) exist, the most stringent retention period will be followed. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the US FDA is notified that the IND is discontinued, or if other applicable laws, regulations, policies, or other requirements (e.g., State, country-specific, and local laws, and sponsor or institutional policies) exist, the most stringent retention period will be followed. Study records include administrative documentation — including protocol registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened and/or enrolled in the study — 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, OGAC, ViiV Healthcare, Gilead Sciences, Inc., USAID, and BMGF for review prior to submission.

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APPENDICES I - V

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/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 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		
Plasma storage ¹¹	X	X	X	X
DBS storage ¹²				X
Whole blood storage		X		
Additional sample storage for participants enrolled in the Injectable Contraception Sub-Study ¹³		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.

² Full physical exam is to be conducted during Enrollment. A targeted physical exam will be done at all other visits.

³ The initial dose of the Hep B vaccination must be given at Week 2. 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.

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.

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.

¹¹ 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.

¹² For Arm B (TDF/FTC) participants only.

¹³ 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.

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		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		X		
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		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			X					X			
CLINICAL EVALUATIONS & PROCEDURES																																																
Adherence counseling for Arm B	X	X	X	X	X	X	X		X		X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	
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		X	
Medical history, concomitant medications, contraceptive use, targeted physical exam	X	X	X	X	X	X	X		X		X	X	X		X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		
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		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		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		X	
Dispense ISR Memory Aid	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Review ISR Memory Aid		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
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		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		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		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		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		X	
Fasting lipid profile ⁸														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									

[illegible]

FOOTNOTES FOR APPENDIX Ib

¹ The initial dose of the Hep B vaccination must be given at Week 2. 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.

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.

⁴Pregnancy 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.

⁷AST, 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.

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 For Arm B (TDF/FTC) participants only.

¹¹ 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.

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 ¹	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 for all participants	X	X	X	X	
Review ISR Memory Aid	X				
Medical history, concomitant medications, contraceptive use, targeted physical exam	X	X	X	X	X
Blood collection	X	X	X	X	X
Urine collection	X ⁷	X ⁴	X	X ⁴	X
Vaginal swab collection ²	X ⁷		X		X
LOCAL LABORATORY EVALUATIONS & PROCEDURES					
HIV testing ³	X	X	X	X	X
Pregnancy testing ⁴	X	X	X	X	X
Chemistry testing ⁵			X		X
Liver function testing ⁶			X		X
Syphilis testing	X ⁷		X		X
GC/CT and TV testing ²	X ⁷		X		X
Plasma storage ⁸	X	X	X	X	X
DBS storage			X		X

FOOTNOTES FOR APPENDIX Ic

* 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 Administer Acceptability Assessment at week 0 as final assessment if not done in the previous 24 weeks on step 2, to include a brief preference assessment.

² GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab.

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 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.

⁵ Chemistry testing includes: BUN/Urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.

⁶ Liver function testing includes: AST, ALT, TBili, and alkaline phosphatase.

⁷ Skip Day 0 if testing has occurred within the last 3 months of Day 0, and do only at Weeks 24 and 48.

⁸ 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.

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
ADMINISTRATIVE, 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	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				

¹ The HIV confirmatory visit must be held on a different day from the visit where the participant had their initial reactive/positive HIV test. The testing algorithm for the HIV Confirmation Visit is provided in the SSP Manual. If HIV rapid testing is included in the HIV testing algorithm, this testing may be performed in the clinic or the laboratory.

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

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

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

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

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. Refer to the table below for specific guidance for ALT.

Grade 1 or 2

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

Grade 3

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

Related:

For Grade 3 AEs deemed related to study product, the study product should be permanently discontinued if improvement to severity \leq Grade 2 cannot be documented within 4 weeks of receipt of the initial result. If study product is resumed and the same Grade 3 AE recurs at any time, the IoR must consult the CMC for further guidance on holding of study product, frequency of reevaluation or progression to permanent discontinuation of the study product.

Unrelated:

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

Grade 4

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

In general, study product use will not be resumed if the Grade 4 AE is considered related to study product use. If, in consultation with the CMC, study product use is resumed and the same Grade 4 AE recurs at Grade 4 level at any time, study product must then be permanently discontinued.

General Criteria for Discontinuation of Study Product

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

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

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

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

- Report of use of prohibited concomitant medications as described in 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.

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 2 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 until either the end of the participant's Step 2 schedule or for 48 weeks after beginning TDF/FTC, whichever is later.

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 viral hepatitis as the cause of elevation in AST or ALT of any Grade. The participant must be carefully assessed for any symptoms or signs of hepatotoxicity, including fatigue, malaise, anorexia and nausea, jaundice, acholic stools, right upper quadrant pain, or hepatomegaly. If the AST/ALT elevation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent, if possible, should be undertaken. If symptoms or signs of clinical hepatitis are present, study product must be held or discontinued. In addition, all participants with elevated values should be considered for testing for hepatitis A, B, and C infection.

Note the following for cases of exercise-induced CPK abnormalities:

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

Guidance on Toxicity Management for Specified Toxicities:

CONDITION AND SEVERITY	FOLLOW-UP AND MANAGEMENT
ELEVATIONS in ALT	
Grade 2 and higher	<p>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 \leq 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 \leq Grade 1.</p> <p>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 \leq Grade 1.</p> <p>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 (\leq Grade 1) in consultation with the CMC.</p>
Grade 2 and higher	<p>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 \leq 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 \leq 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 \leq 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.</p>

Guidance on Toxicity Management for Specified Toxicities:

Creatinine Clearance

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

Guidance on Toxicity Management for Specified Toxicities:

Creatine Phosphokinase (CPK)

Note the following for cases of exercise-induced CPK abnormalities:

Note the following for cases of exercise-induced CPK abnormalities: Cases of CPK abnormality \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.

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 1.0

2 March 2017

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 US Agency for International Development (USAID), Office of the US Global AIDS Coordinator (OGAC), and 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 3,200 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 also be available on www.ClinicalTrials.gov. The web site will not include information that can identify you and you may look at the web site at any time. After the study ends and the results have been reviewed by the study team, the web site will include a results summary.

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 prophylaxis (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 Medicines Control Council, [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 know 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 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 pregnancy [*site insert sample type, blood vs. urine*] and talk to you about your plans in the next years for becoming pregnant.

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 pregnancy *[site insert sample type, blood vs. urine]*. This testing may be done using a blood or urine sample.
- 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*].
- 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*].
- 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. Staff will also give you a memory aid that you can record any side effects from the shots on. You will bring the memory aid back with you at the next visit to review with staff.

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. Staff will also give you a memory aid that you can record any side effects from the shots on. You will bring the memory aid back with you at the next visit to review with staff.
- 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).

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.

Step 3 Visit Activities

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.
- Review the memory aid with staff (on Day 0 only).
- 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]*.
- 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).
- Give 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 100 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 injectable contraceptives (NET-EN and DMPA). No additional study visits are required. However, there is an additional blood draw at six of the study visits: Enrollment visit and then at Weeks 9, 13, 17, 21 and 25.]

Procedures if you become infected with HIV during the study

- 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 either 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 provide 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. 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, nausea, 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.

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.

- women of reproductive potential must agree to use a reliable form of contraception during the trial and for 52 weeks after stopping injections, or for 30 days after stopping oral study product.

PREGNANCY

To participate in this study, you must agree not to become pregnant. You must agree to use a reliable form of contraception during the trial and for 52 weeks after stopping injections, or for 30 days after stopping oral study product

If you wish to be pregnant in the next few years, you should not participate in this research study. We do not yet know how CAB LA might affect a baby during pregnancy. If you become pregnant during this study we will ask you to stop the injections. For some people CAB LA could remain in the body for a year or more after the last injection. Because we do not know how long CAB LA may stay in your body and because we do not know what effect CAB may have on a baby during pregnancy, you may wish to delay becoming pregnant after your last injection, for at least 52 weeks.

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, you will be terminated from the study.
- If 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 and followed at the regularly scheduled study visits until either the end of your planned Step 2 schedule, or for 48 weeks after beginning TDF/FTC, whichever is later.

If you become pregnant unintentionally during the study, we will refer you for obstetric care. We will stop giving you injections and switch you to open-label TDF/FTC. Your study schedule will be reduced

and we will only ask you to come to clinic one time every 12 weeks during your pregnancy. 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. The study doctor will make this information available to the study sponsor for safety monitoring follow-up.

If you become pregnant unintentionally during the study, and there is still time during Step 2, you may be able to resume full study activities after your pregnancy has ended and you are no longer breast feeding.

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 if taken daily as directed. CAB has not been shown to protect against getting HIV, which is the reason we are doing this study. You 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]), 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 Health and Human Services (DHHS), Office of Human Research Protection (OHRP)
- [insert names of applicable IRBs/ECs/other local review bodies as applicable]
- Study staff
- Study monitors
- Companies that make 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 1.0

2 March 2017

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)
(As appropriate)

Witness Signature and Date

Appendix V: Sample Qualitative 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

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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 US Agency for International Development (USAID), Office of the US Global AIDS Coordinator (OGAC), and 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 interview/ OR focus group with other women who also participated in HPTN 084]. About XX women in SSA will participate in these activities also.

Also, we would like to invite some male partners to take part in a separate qualitative interview or focus group discussion. We will only invite your partner to participate in this study if you agree that we can contact him. If we contact him, he will learn about your study participation, if he does not know about this already. His interview would be conducted separately from yours.

The qualitative interviews/focus groups will be led by a trained and experienced group leader. We are interested in learning about your thoughts, opinions, and experiences with being a part of the study, including talking with you about the injections (shots) and/or taking the TDF/FTC pill. We would like to know what you didn't like about your study products and what you did like about them. 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 focus group?

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

You do not have to join the qualitative interview/focus group.

- If you join the qualitative interview/focus group but later decide later you want to stop, you can stop taking part at any time.
- You can refuse for us to invite your partner to participate in the study. Whether he participates or not will not affect your ability to participate in the study.
- Whether or not you take part in the qualitative interview/focus groups, 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/focus group?

If you decide to join the qualitative interview/focus group, you will be asked to participate in a XX to XX minute discussion with a trained and experienced group leader. The discussion will not take place during a regular study visit. Instead, it will occur at a separate time somewhere between [*provide timeframe for planned qualitative assessment*].

The information that you share during the qualitative interview/focus group will be treated confidentially. The interview/focus group 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. Your name and any other identifying information that you mention during the focus group discussion will not be associated with your responses. No identifying information will be included in the written transcript. The recording will be destroyed after the study.

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 interview/focus group; 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. We hope that the qualitative interview/focus group procedures described above will minimize your discomfort when discussing sensitive topics. However, the greatest risk may involve your privacy and confidentiality. If you take part in a focus group discussion, other members of the focus groups are present during the discussion and we cannot guarantee that they will not discuss what you will say later. If you agree for your partner to take part in an interview/ focus group discussion, he may ask you questions about the study. Some questions may be uncomfortable. 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. If you participate in a focus group discussion, we will assign you a number instead of using your real name. If your partner takes part in an interview or focus group discussion, we will not share any of your information with him.

Your records may be reviewed by the sponsor of the study (US National Institutes of Health (NIH) their representatives), US FDA, US Department of Health and Human Services (DHHS), Office of Human Research Protection (OHRP) and other government and regulatory authorities, 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 interview/focus group discussion.

Reasons why you may be withdrawn from the study without your consent

Your participation in the focus group 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 interview/focus group 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/focus group. 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

FINAL, Version 1.0

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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