HPTN 083

A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men

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LIST OF ABBREVIATIONS AND ACRONYMS

ABC/3TC	abacavir/lamivudine
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ALT	alanine aminotransferase
AUC	area under the curve
BCRP	breast cancer resistance protein
BGRG	Black Gay Research Group
BMD	bone mineral density
BMSM	black men who have sex with men
BUN	blood urea nitrogen
CAB	cabotegravir, oral and LA formulations
CAB LA	long-acting injectable formulation of cabotegravir
CABG	coronary artery bypass grafting
CBC	complete blood count
CBO	community-based organizations
CDC	(US) Centers for Disease Control and Prevention
CFR	(US) Code of Federal Regulations
CI	confidence interval
CK or CPK	creatine phosphokinase
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	Chlamydia trachomatis
DAERS	DAIDS Adverse Event Reporting System
DAIDS	Division of AIDS
DAIDS-ES	DAIDS Enterprise System

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LIST OF ABBREVIATIONS AND ACRONYMS

DAIDS PRO	DAIDS Protocol Registration Office
DAIDS RSC	DAIDS Regulatory Support Contract
DBS	dried blood spot
DSMB	Data and Safety Monitoring Board
DXA	dual-energy X-ray absorptiometry
EAE	expedited adverse event
EC	Ethics Committee
ECG	Electrocardiogram
ÉCLAIR	A Phase IIa Study to Evaluate the Safety, Tolerability and Acceptability of Long Acting Injections of the HIV Integrase Inhibitor, GSK1265744, in HIV Uninfected Men
EQA	External Quality Assurance
FDA	(US) Food and Drug Administration
FEM-PrEP	Phase 3, double-blind, randomized, placebo-controlled effectiveness and safety study among 3900 women at high risk of HIV infection at 6 sites in 4 African countries
FTC	Emtricitabine
FTC-TP	emtricitabine triphosphate
GC	Neisseria gonorrheae
GT	Genital tract
HBcAb	hepatitis B virus core antibody
HBsAb	hepatitis B virus surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
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	herpes simplex virus

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LIST OF ABBREVIATIONS AND ACRONYMS

IATA	International Air Transport Association
ICF	informed consent form
ID	Identification
IM	Intramuscular
IND	investigational new drug
IoR	Investigator of Record
iPrEX OLE	iPrEx Open Label Extension
IQA	(DAIDS) Immunology Quality Assurance
IQR	interquartile range
IRB	Institutional Review Board
ISR	injection site reaction
LA	long-acting (injectable)
LATTE-2	A Phase IIb, Dose Ranging Study of Oral GSK1265744 in Combination With Nucleoside Reverse Transcriptase Inhibitors for Induction of Human Immunodeficiency Virus -1 (HIV-1) Virologic Suppression Followed by an Evaluation of Maintenance of Virologic Suppression When Oral GSK1265744 is Combined With Oral Rilpivirine in HIV-1 Infected, Antiretroviral Therapy Naive Adult Subjects
LDL	low-density lipoprotein
LFTs	liver function tests
LGBT	lesbian, gay, bisexual, and transgender
MSM	men who have sex with men
NGO	non-governmental organization
NI	non-inferiority
NIAID	(US) National Institute of Allergy and Infectious Diseases
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleotide reverse transcriptase inhibitor
OHRP	Office for Human Research Protections
Oral CAB	oral formulation of cabotegravir
PA-IC90	protein-adjusted 90% inhibitory concentration
PAT	presence at the table
PEP	post-exposure prophylaxis
PI	package insert
Pgp	permeability glycoprotein
PK	Pharmacokinetic
PO	by mouth/orally

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LIST OF ABBREVIATIONS AND ACRONYMS

PrEP	pre-exposure prophylaxis
PROUD	PRe-exposure Option for reducing HIV in the UK: an open-label randomisation to immediate or Deferred daily Truvada for HIV negative gay men
PSMILE	Patient Safety Monitoring and International Laboratory Evaluation
PTCA	percutaneous transluminal coronary angioplasty
PY	person-years
QA	quality assurance
QC	quality control
RE	regulatory entity
RNA	ribonucleic acid
RPV	rilpivirine
RPV LA	rilpivirine long-acting (injectable)
SAE	serious adverse events
SC	subcutaneous
SHIV	simian human immunodeficiency virus
SMC	Study Monitoring Committee
SOP	standard operating procedure
SSP	Study Specific Procedures Manual
STI	sexually transmitted infection
TBili	total bilirubin
TCID	tissue culture infective dose
TDF	tenofovir disoproxil fumarate
TDF/FTC	tenofovir/emtricitabine (trade name: Truvada®)
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TGW	transgender women
TP	triphosphate
UKNEQAS	United Kingdom National External Quality Assessment Service
ULN	upper limit of normal
US	United States of America
VCT	voluntary counselling and testing
VOICE	Vaginal and Oral Interventions to Control the Epidemic
VQA	(DAIDS) Virology Quality Assurance
WHO	World Health Organization

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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 pharmacokinetic measurement.
Oral CAB	When written as shown, this refers to the oral tablet formulation of cabotegravir.
CAB LA	When written as shown, this refers to the long-acting injectable formulation of cabotegravir.
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.
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-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), for pre-exposure prophylaxis (PrEP) in HIV-uninfected cisgender men and transgender women who have sex with men (MSM and TGW).

Design: Multi-site, double blind, two-arm, randomized (1:1), controlled non-inferiority trial of the efficacy of CAB LA compared to daily oral tenofovir disoproxyl fumarate (TDF)/emtricitabine (FTC) for HIV prevention.

Population: HIV-uninfected MSM and TGW at risk for acquiring HIV infection, ages 18 or older.

Study Size: Approximately 4500, 2250 per arm.

Study Duration: Approximately 4.5 years total, with individual participants being followed between 1.5 years (for the latest enrolling participants) to 4.5 years (for the earliest enrolling participants). Accrual will require approximately 130 weeks. In Step 1, participants will receive oral tablets for 5 weeks. In Step 2, participants will receive injections (as a single injection at two time points 4 weeks apart and every 8 weeks thereafter) and daily oral tablets. Step 2 will be continued until the required number endpoints is reached, estimated to be approximately when the final participant reaches 60 weeks on Step 2 (week 65 for the final participant). Participants will be all simultaneously unblinded at the conclusion of Step 2. In Step 3, all participants will receive open-label daily oral TDF/FTC for up to 48 weeks. Participants will therefore be followed between 113 weeks to 233 weeks (between 65 and 185 weeks on blinded study medication and up to 48 weeks on open-label daily oral TDF/FTC). All participants will be transitioned to locally-available HIV prevention services, including services for PrEP, if available, at the end of their participation in the study.

Study Sites: Study sites will be listed in the Study Specific Procedures (SSP) Manual, and will include sites in the Americas, Asia, and South Africa.

SCHEMA (continued)

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

Step 1:

Arm A – **Daily oral CAB** (30 mg tablets) and oral TDF/FTC placebo for five weeks

Arm B – **Daily oral TDF/FTC** (300 mg/200 mg fixed-dose combination tablets) and oral CAB placebo for five weeks

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

Step 2:

Arm A – **CAB LA** (600 mg as a single intramuscular [IM] injection at two time points 4 weeks apart and every 8 weeks thereafter) and daily oral TDF/FTC placebo.

Arm B – **Daily oral TDF/FTC** (300/200 mg fixed-dose combination tablets) and IM placebo at two time points 4 weeks apart and every 8 weeks thereafter (matching vehicle, identical volume as active injectable product in Arm A).

This step will continue until the required number of endpoints is reached.

A participant that becomes HIV-infected during Step 2 of the study will permanently discontinue study product, be placed on immediate suppressive ART, and will be followed at quarterly intervals for 52 weeks after their last injection prior to diagnosis of HIV in order to test for safety parameters, as well as CD4 cell count and HIV viral load. After 52 weeks, they will be terminated from the study and transitioned to continued HIV-related care.

Step 3:

Both arms: **Open-label daily oral TDF/FTC** no later than 8 weeks after the last injection (in order to cover the pharmacokinetic (PK) tail for Arm A participants), for up to 48 weeks. Participants will then transition to locally-available HIV prevention services, including services for PrEP, if available.

A participant with confirmed HIV infection during Step 3 will be followed at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by the Clinical Management Committee (CMC).

SCHEMA (continued)

Primary Objectives:

- To compare HIV incidence among participants randomized to oral CAB/CAB LA (oral lead in and injections) vs. oral TDF/FTC (Steps 1 and 2)
- To compare the safety of oral CAB/CAB LA vs. oral TDF/FTC

Secondary Objectives:

- To compare HIV incidence among participants receiving CAB LA injections vs. oral TDF/FTC (each step independently and all steps in aggregate)
- To compare HIV incidence among participants receiving CAB LA injections vs. oral TDF/FTC (Steps 1, 2, and 3 combined)
- To compare HIV incidence among participants randomized to CAB LA injections vs. oral TDF/FTC while taking open label TDF/FTC (Step 3 only, descriptive)
- To compare the change in risk of HIV acquisition between CAB and oral TDF/FTC strategies (Arm A and Arm B) as participants progress from Step 2 to Step 3
- To compare HIV incidence among the subgroups of participants receiving oral CAB/CAB LA vs. oral TDF/FTC by region, age, race, ethnicity, baseline risk, and gender identity
- To compare changes in renal function, liver function, and bone mineral density (BMD) among participants receiving oral CAB/CAB LA vs. oral TDF/FTC
- To evaluate and compare 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 compare the acceptability of and preferences for CAB LA vs. oral TDF/FTC

Tertiary Objectives:

- To examine the association between levels of adherence and HIV incidence
- To compare and describe the rates, patterns, and correlates of adherence to CAB LA vs oral TDF/FTC, in aggregate and by psychosocial/demographic variables
- To estimate changes in sexual-risk behavior as measured by self-report and rates of incident gonorrhea, chlamydia, and syphilis in the study population

- To compare the resource utilization and programmatic costs of long-acting injectable PrEP vs. daily oral PrEP vs. no PrEP for HIV uninfected MSM and TGW in the US, Brazil, South Africa and India

- To use mathematical simulation to project the short- and long-term clinical impact, cost projections, budgetary impact, and incremental cost-effectiveness of long-acting injectable PrEP vs. daily oral PrEP vs. no PrEP for HIV uninfected MSM and TGW in the US, Brazil, South Africa and India

Exploratory Objectives:

- To perform secondary laboratory assessments that may include evaluation of factors related to HIV infection, hepatitis infection, or sexually transmitted infections (STIs); antiretroviral (ARV) drug use; pharmacogenomics; characterization of HIV in infected participants; and evaluation of laboratory assays related to the study objectives
- To explore possible drug-drug interactions between cross-sex hormone therapy (csHT) and cabotegravir and TDF/FTC in a subset of TGW taking commonly prescribed cross-sex hormone therapy regimens

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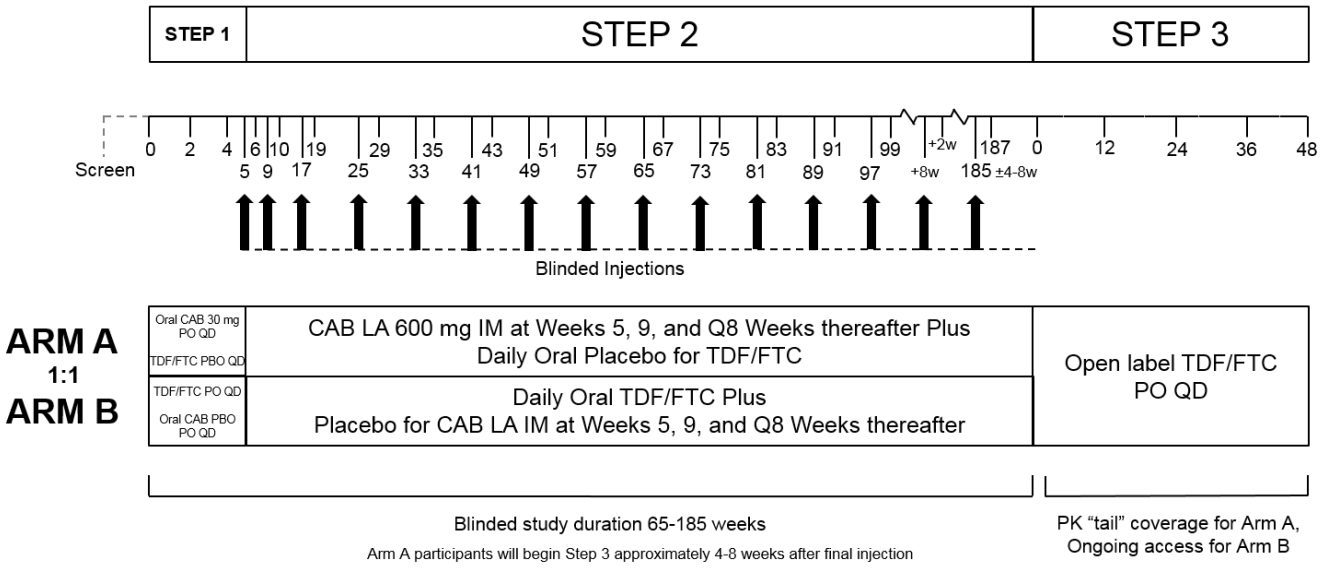
OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME



1.0 INTRODUCTION

1.1 Background and Rationale

Cabotegravir LA (CAB LA) is a long-acting injectable integrase inhibitor, also known as GSK 1265744 LA or 744 LA. This is a Phase 2b/3 study designed to establish the efficacy of CAB LA for pre-exposure prophylaxis (PrEP) in HIV-uninfected men who have sex with men (MSM) and in transgender women (TGW). Small single-dose and multiple-dose studies and Phase 2a safety/tolerability studies have been performed for CAB LA. This PrEP efficacy study is the next developmental investigation of CAB LA in healthy, HIV-uninfected MSM and TGW. CAB LA is the first antiretroviral (ARV) drug being studied as an intervention for HIV prevention prior to regulatory approval of the drug for HIV treatment. A parallel development program for use of cabotegravir (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 ARV drug use for both HIV treatment and prevention has provided consistent and compelling evidence of efficacy.[1-9] A challenge in the use of current oral ARV formulations for both indications is the requirement for adherence to daily or near-daily dosing strategies.[10,11] In healthy HIV-uninfected and HIV –infected individuals, sustaining adherence over time becomes increasingly challenging.[12] In the treatment setting, sub-optimal adherence to an ARV treatment (ART) regimen can lead not only to ART failure, but also to the development of HIV drug resistance.[13-16] HIV transmission in the setting of ARV PrEP is relatively rare; the majority of transmission events have occurred in the context of absent or sub-therapeutic drug levels, indicating poor adherence. Resistance to PrEP agents has been observed in individuals who initiated PrEP with undiagnosed primary HIV infection.[1,4,17] Resistance appears to emerge less frequently in individuals who acquire HIV infection after initiating a PrEP regimen;[1,4,9,17-21] however, recent studies using more sensitive drug resistance tests have revealed the presence of minority variants with resistance mutations in some individuals.[17,18] In these cases, resistance may arise in individuals with suboptimal PrEP adherence who become infected, but continue to take their PrEP regimen before their HIV infection is diagnosed.[18]

Despite tremendous therapeutic advances in HIV treatment and prevention, the HIV epidemic persists worldwide.[22] The United States (US) Food and Drug Administration (FDA) approved oral tenofovir disoproxil fumarate/emtricitabine (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.[23,24] The safety and efficacy of TDF/FTC in combination with other ARV drugs for ART,[25-29] and results from TDF/FTC PrEP studies in a rhesus macaque simian-HIV (SHIV) exposure model,[30,31] supported the development and evaluation of TDF/FTC for PrEP. Five randomized clinical trials (RCTs) have evaluated oral TDF or TDF/FTC as PrEP.[1,4,8,20,21] These five trials differ in several ways, but suboptimal adherence,[32,33] with a daily pill regimen was noted in all five studies. In fact, the FEM-PrEP and VOICE trials, both conducted in sexually-active, young women in sub-Saharan Africa and requiring adherence to a daily regimen, were either stopped for futility or showed no efficacy on completion. On further investigation, very poor adherence by trial participants to study product was confirmed in both studies. Analyses of the available RCT data suggest a strong correlation between adherence to study product and observed efficacy. The iPrEX open label extension (iPrEX OLE) suggests that individuals with sustained adherence averaging 4-7 doses of TDF/FTC PrEP weekly conferred

100% protection;[34] however the impact of timing of HIV exposures relative to missed doses on protective efficacy remains to be clarified. Recent open-label data from the United Kingdom PROUD study suggests that in particularly high-incidence populations of MSM, daily oral TDF/FTC can be as effective as 86% compared to a strategy of "standard of care" risk reduction and deferred TDF/FTC.[35] A strategy of "on demand" TDF/FTC, using a 2-dose pre-coital dose and then daily dosing until the completion of sexual activity, followed by two additional daily doses, also demonstrated 86% reduction in HIV acquisition compared to a placebo intervention, but the mean monthly use was 16 tablets (IQR 12-24) with a median 10 sexual partners per month roughly equating to 4 or more doses per week. Notably, only 43% of the study participants were able to adhere to the pre- and post-coital dosing as prescribed.[36] While TDF-based PrEP provides an exciting new prevention tool, adherence to daily oral dosing has proven a challenging obstacle to consistent, preventive success. There are several additional reasons why alternative PrEP agents are needed, including: 1) TDF/FTC causes side effects that may impede adherence;[4] 2) TDF/FTC has been associated with increased creatinine levels and decreased bone density;[37-39] and 3) TDF/FTC is a key component of many first-line ART regimens;[40] resistance that might emerge with its use as a PrEP agent is highly undesirable.

PrEP may only reach its full potential 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.[41] Injectable agents have been used by women for contraception, although adherence even to quarterly injections is imperfect. In the US, insurance claims showed that only 41.4% of new users had a second injection at three months.[42] Data from Brazil show that 64% of injectable contraception users discontinued use in the first 12 months, 27% related to side effects.[43] Increased choice in type and method of delivery of contraceptive methods has increased acceptability.[44] It is our hypothesis that expanded choices for HIV prevention will similarly increase utilization, satisfaction, and effectiveness.

1.2 Overview of Oral Cabotegravir (Oral CAB) and long-acting injectable (CAB LA)

The majority of information contained in this section of the protocol is a summary of information provided in the cabotegravir Investigator's Brochure V5.0, Effective Date 06 January 2016, unless otherwise noted.

Cabotegravir (GSK 1265744) is an investigational HIV integrase strand transfer inhibitor (INSTI) that has attributes favorable for both HIV treatment and prevention indications. Currently in Phase 2 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 cabotegravir (oral CAB) is also under development 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 SHIV infection in non-human primate models[45]. In a preclinical study evaluating the potential of CAB LA for PrEP, 2 weekly doses of CAB LA (50 mg/kg intramuscularly [IM]) were highly protective against weekly rectal challenges with SHIV162p3 (50 tissue culture infective dose $[TCID]_{50}$) for up to eight exposures. In these protected animals, the plasma concentrations of CAB LA throughout the period of virus challenges were comparable to clinically-relevant concentrations in humans. In follow-up studies, a single dose of CAB LA 50 mg/kg IM one week prior to the serial weekly viral challenges with SHIV162p3 (50 $TCID_{50}$) were evaluated. The percent of challenges resulting in infection was calculated relative to the plasma cabotegravir protein-adjusted inhibitory concentration (PA-IC_{90}) value. None of 59 challenges resulted in infection when plasma levels were greater than 3 times the PA-IC_{90}, compared with 1 out of 22 challenges resulting in infection when plasma levels were between 1 to 3 times the PA-IC_{90}, and 11 out of 43 challenges resulting in infection when plasma levels were less than 1 times the PA-IC_{90}. Twelve out of 26 challenges resulted in infection in control animals; rectal tissue levels of cabotegravir were approximately 20% of plasma levels.[45]

1.2.2 Metabolism

Cabotegravir 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 via the 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).

1.2.3 Preclinical Studies

The cabotegravir toxicology package supports the careful conduct of clinical studies with cabotegravir up to the no observed adverse effect level (NOAEL) exposure in the 39-week monkey toxicity study (Week 39 gender mean area under the curve (AUC_{0-24}) and Cmax 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 Cmax plasma concentration observed at the NOAEL in the 39-week monkey oral CAB toxicity study (34.6 μg/mL) or the mean AUC1,440-2,160h following once monthly IM dosing at the NOAEL (75 mg/kg/dose) in the 3-month rat CAB LA toxicity study (92,566 μg·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 postnatal 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 4 (10 offspring/litter vs. 11.5 in

control on post-natal day 4). 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 pharmacokinetics of CAB LA in HIV uninfected, at 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.

1.3 Dose Rationale

1.3.1 Oral CAB

CAB is readily absorbed following oral administration in healthy and HIV infected participants with a median T_{max} of approximately 2 hours. The apparent terminal phase half-life following oral administration is approximately 40 hours.

In a short-term monotherapy study, seven HIV-infected participants received oral CAB 5 mg once daily for 10 days, which achieved a geometric mean Day 10 plasma trough concentration ($C\tau$) of 0.57 μg/mL, 3.4-fold above the PA-IC_{90} value, and was associated with a mean Day 11 HIV ribonucleic acid (RNA) change from a baseline of -2.2 $\log_{10}$ c/mL.[46,47] In LAI116482 (LATTE), the Phase 2b study in HIV-infected, ART-naïve adult participants,[48] suppression of HIV replication was accomplished with oral CAB at doses of 10 mg to 60 mg once daily in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs), and was maintained below 50c/mL at similar rates across oral CAB 10 mg to 60mg doses through >72 weeks when combined with oral rilpivirine (RPV). The geometric mean individual average plasma $C\tau$ following oral CAB 10 mg and 30mg once daily were 1.35 μg/mL, 8-fold above PA-IC_{90}, and 4.2μg/mL, 25-fold above PA-IC90, respectively.

CAB 30mg once daily has been used as the oral lead-in in both ECLAIR and LATTE-2, where it achieved a similar pre-dose CAB concentration at baseline as observed in LATTE. The geometric mean (CVb%) C_{max} following CAB 30mg once daily is 7.5μg/mL (28%), which provides adequate safety coverage for the predicted median (90%PI) peak concentrations following CAB LA of 4.0μg/mL (1.8, 8.9μg/mL). Therefore, CAB 30mg once daily has been selected for the oral lead-in regimen for this study.

Relevant pharmacokinetic parameters following oral administration are listed in Table 1.

1.3.2 CAB LA

Following a single IM or subcutaneous (SC) injection of CAB LA, plasma drug concentrations increased rapidly over the first week, followed by a general trend to plateau for the remainder of the 12-week follow-up period. The drug was detected in plasma up to 52 weeks, and the mean absorption-limited apparent terminal phase half-life ranged from 21 to 50 days, reflecting absorption from depot site rather than elimination from the systemic circulation.

The CAB LA PrEP dose has been selected to deliver adequate drug concentrations to prevent sexual transmission of HIV. The proposed dosing schedule for evaluation in humans is based on maintaining CAB LA plasma concentrations well above the PA-IC_{90} value of 0.166 μg/mL, a concentration range shown to have significant antiviral activity.

A small cohort of healthy participants receiving two quarterly doses (Q12W) of CAB LA 800 mg IM achieved a geometric mean (CVb%) C_{tau} (C_τ) of 1.11 μg/mL (139%), approximately 6.7-fold above the PA-IC_{90} and between the 5 mg and 10 mg oral doses (Table 1). These data, as well other PK data following CAB LA following single or repeat doses ranging from 100mg to 800mg IM, were included in the initial population PK model. Based on the initial population PK model, CAB LA 800 mg IM given every 12 weeks (Q12W) was predicted to achieve a mean concentration above the 1.35 μg/mL target based on 10 mg daily oral dosing with the lower bound of the 90% confidence interval (CI) at ~4-fold PA-IC_{90}. The overall range of predicted CAB C_τ values following CAB LA 800 mg IM was similar to that following once daily dosing of oral CAB 10 mg.

The Phase 2a 201120 (ÉCLAIR) study was undertaken to evaluate PK and safety following Q12W CAB LA 800mg IM doses in healthy male participants. Evaluation of PK data from ÉCLAIR showed that 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). 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 800mg Q12W may not maintain sufficient exposures in all participants, particularly in males. The ongoing Phase 2a study HPTN 077, which is similar to ÉCLAIR, studying CAB LA 800mg IM Q12W in healthy male and female participants, was amended to enroll a second cohort with dosing of CAB LA 600 mg IM at two time points 4 weeks apart and every 8 weeks (Q8W) thereafter for 5 injection visits. A similar regimen (CAB LA 800mg IM initial dose followed by 600mg IM at two time points 4 weeks apart and Q8W thereafter) has been evaluated in HIV infected participants (n=115; 107 males and 8 females) in combination with rilpivirine (RPV) LA in study 200056 (LATTE-2). This regimen achieved a mean CAB Cτ of 1.53μg/mL (median 1.45 μg/mL) at Week 32 (Figure 2), above the geometric mean Cτ value for the 10mg oral dose in LATTE. At Week 32, the proportion of participants maintaining suppression of HIV in the Q8W arm was 95% as compared to 94% in the Q4W arm (CAB LA 800mg IM initial dose followed by 400mg IM every 4 weeks from Week 4, n=115).

The CAB population PK model has been updated with PK data from ÉCLAIR (an additional 94 males) and LATTE-2 (an additional 230 participants; 216 males and 14 females), significantly increasing the data in the population PK dataset. The absorption rate constant following CAB LA was increased approximately 2-fold (4.54×10^{-4} hr^{-1} to 9.19×10^{-4} hr^{-1}; i.e., more rapid absorption) and resulted in higher peak to trough ratios than previously observed.

Simulations based on the updated population PK model have been conducted to evaluate several potential dosing regimens. The proposed regimen for this study is CAB LA 600mg IM as a single injection at two time intervals 4 weeks apart and every 8 weeks thereafter (Figure 3). This dosing regimen is predicted to yield a median steady-state Cτ in males of approximately 1.35 μg/mL, which is approximately 8-fold above PA-IC90 (Figure 3), with Cτ above the PA-IC_{90} for 95% of participants, and 4-fold above PA-IC_{90} for 80% of participants (Figure 4). A one week delay in dosing of 600mg IM at steady state resulted in a drop in the median Cτ to 1.08μg/mL,

and the 5th percentile to 0.10μg/mL, with 92% of Cτ values remaining above the PA-IC_{90} (Figure 5).

Relevant PK parameters following CAB LA in healthy and HIV infected subjects and following simulations based on the initial and updated population PK models are listed in Table 1.

Table 1: Summary of Cabotegravir Pharmacokinetic Parameters Following Oral and LA (IM) Administration and Pharmacokinetic Simulations in Healthy and HIV-Infected Participants

Route Study Population N	Cabotegravir Regimen	Cabotegravir 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	5 mg oral once daily x10 d monotherapy	0.57 [33%]	1.02 [25%]	17.7 [31%]	3.4
Ph2b - LAI116482 (LATTE) HIV infected N=14	10 mg oral once daily with 2NRTIs	1.35 [45%] (n=57)	2.77 [33%]	45.7 [32%]	8.1
Ph2b - LAI116482 (LATTE) HIV infected N=12	30 mg oral once daily with 2 NRTIs	4.20 [40%] (n=53)	7.49 [28%]	134 [32%]	25
LA Data					
Ph1 - LAI115428 HVs N=9	800 mg IM every 12weeks x 2 (2nd dose interval)	1.11 [139%]	3.35 [56%]	4417 [53%]	6.7
Ph2a - 201120 (ECLAIR) HVs[c]	800 mg IM every 12 weeks x 3 (third dose) (n=85)	0.387 [150%] (n=66)	4.91 [67%]	4021 [36%]	2.3
Ph2b – 200056 Q4W (LATTE-2[a]) HIV infected (N=115)	800mg IM Day 1, 400mg 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 – 200056 Q8W (LATTE-2[a]) HIV infected(n=115)	800mg IM LD, 600mg 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[d]	8.7
Modeling and Simultation					
PopPK simulation (Initial PopPK model) (N=1000)	800 mg IM every 12 weeks x 5 (last dose)	1.57 [56%]	ND[d]	ND[d]	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[d]	8.0

a. Data presented as geometric mean, [CVb%], LATTE-2 data presented as median (range), Current Population PK model predictions median (90% prediction interval (PI))
b. PA-IC90=0.166 μg/mL
c. Healthy volunteers
d. Not Determined

Figure 1. Mean (SD) Plasma CAB Concentration-Time Profile following CAB LA 800mg IM Q12W in ÉCLAIR and Original Simulated Phase 2 Dose Rationale Model Predictions (Sparse Time Points)

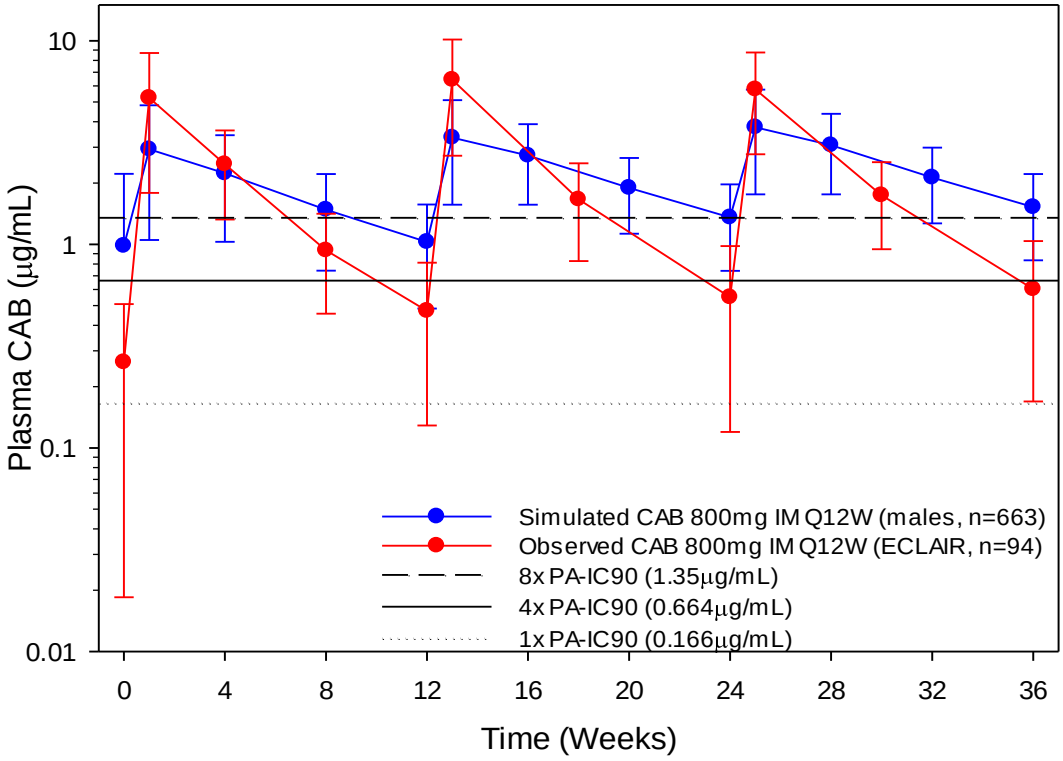


Figure 2. Mean (SD) Plasma CAB Concentration-Time Profile following CAB LA Q8W Regimen (800mg IM Loading Dose, 600mg IM W4, W8, then Q8W) in 200056 (LATTE-2)

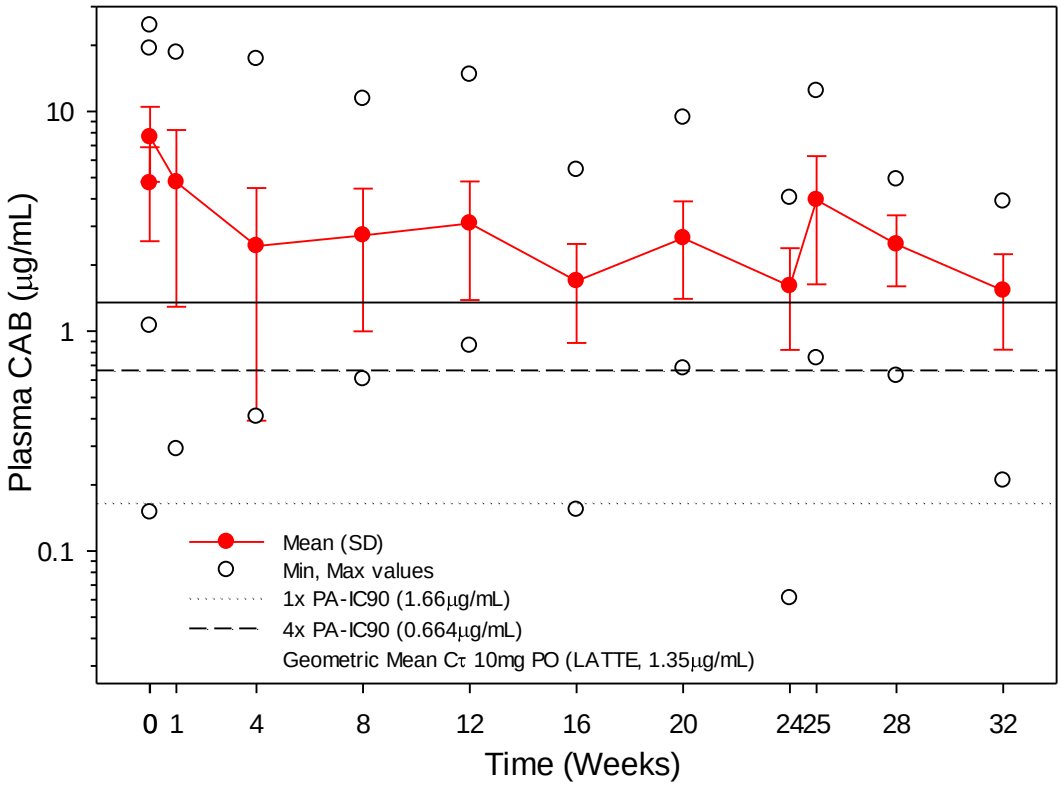


Figure 3. Simulated Median (90% PI) Plasma CAB Concentration-Time Profile for the Proposed Regimen (600mg IM Day 1, W4 and Q8W) in Males based on Updated Population PK Model (linear scale)

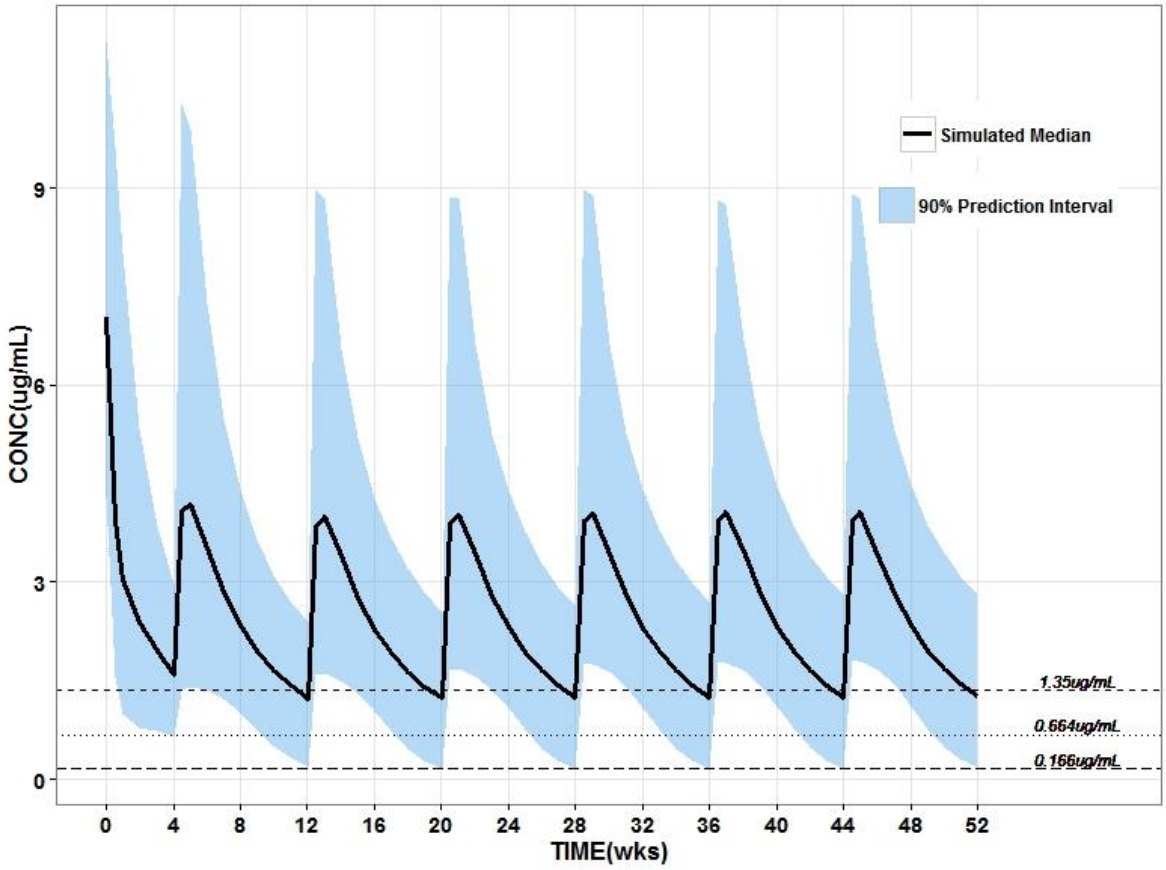


Figure 4. Simulated Plasma CAB Concentration-Time Profile for the Proposed Regimen (600mg IM Day 1, W4 and Q8W) in Males based on Updated Population PK Model (semilog scale)

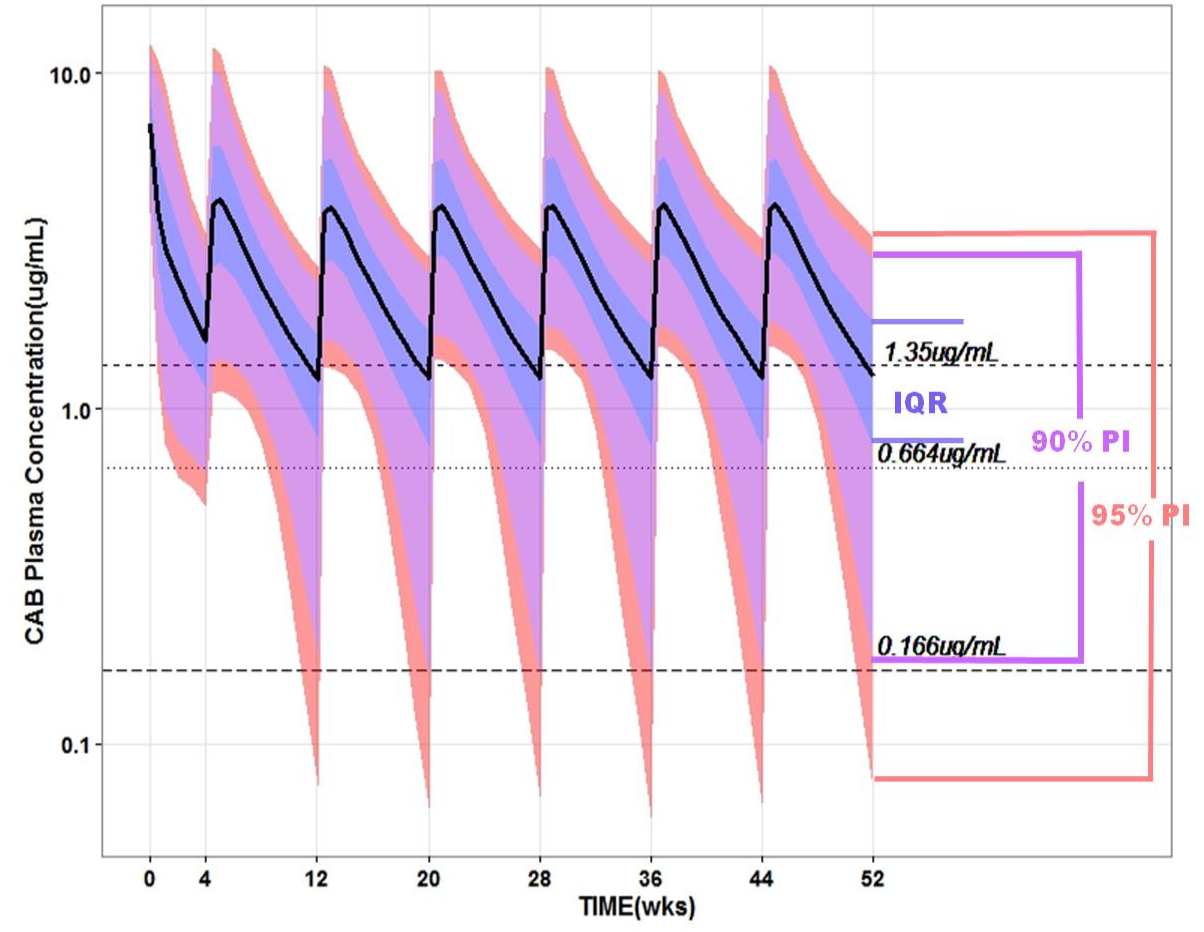
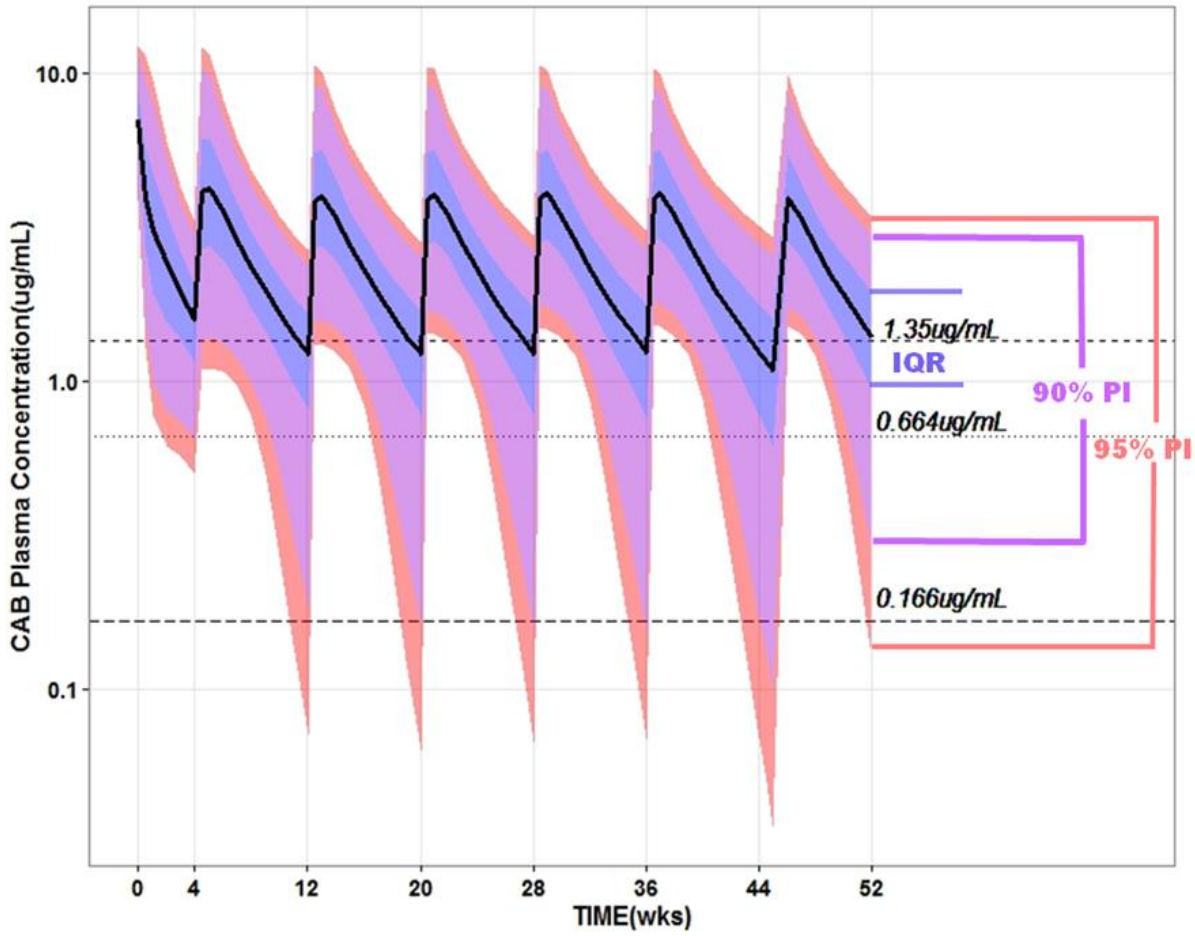


Figure 5. Simulated Plasma CAB Concentration-Time Profile for the Proposed Regimen (600mg IM Day 1, W4 and Q8W) with a One-Week Delay in Dosing at Steady State (W44) in Males based on Updated Population PK Model (semilog scale)



1.4 Clinical Experience to Date: Oral CAB and CAB LA

Through 1 July 2015, approximately 1056 adult participants have been exposed to at least one dose of CAB (oral and/or long acting) across 18 completed or ongoing Phase 1 and Phase 2 clinical trials.

Oral CAB has been studied at doses between 5 mg - 150 mg in HIV-uninfected and HIV-infected adults. The oral formulation of GSK 1265744 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-150 mg in Phase 1 and 2a studies, eleven participants receiving oral CAB were withdrawn due to potentially drug-related adverse events (AEs), including dizziness, leucopenia, and aspartate aminotransferase and alanine aminotransferase [AST/ALT]/gamma-glutamyltransferase increases, 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.[49] 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, but contribution from oral CAB could not 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 every 12 weeks in the ongoing 201120 (ÉCLAIR) study. One participant was withdrawn from CAB LA therapy due to a pre-existing prostate cancer diagnosis, a non-drug-related adverse event.

Injection site reactions (ISR) occurred in the majority of participants following IM (76% 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).[49] 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%)C 2013). Median IM ISR durations were approximately 5 days for pain and erythema, and approximately 22 days for nodules.[49]

A Phase 2a safety and acceptability study (ÉCLAIR), designed similarly to HPTN 077, is currently in the follow-up phase of the study at 10 US-based sites. In this 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, eleven participants withdrew prior to their first injection, all of whom were randomized to CAB LA, seven for adverse events 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) randomized to CAB LA completed all three of their injections. The participant on the placebo arm that did not complete all three injections reached a protocol-defined stopping criteria, subject acquired HIV, 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 abnormality of 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 744LA 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.

Two Phase 2b clinical trials are in progress (GSK protocol LAI116482 [LATTE] and 200056 [LATTE-2]). In the LAI116482 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.[47] (ABC/3TC). 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 < 50c/mL prior to week 24 were transitioned to a regimen maintaining their 744 dosing but substituting oral rilpivirine 25 mg daily for the nucleosides. Efavirenz-treated participants were kept on their "induction" regimen of dual nucleosides with efavirenz. 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 10mg, 30mg, and 60mg daily, and 83% for the efavirenz control participants. One participant randomized to oral CAB 10mg who successfully transitioned to rilpivirine plus oral CAB 10 mg daily experienced virologic failure at week 48 in the context of subtherapeutic (<50% expected) CAB and rilpirivine plasma levels (partially confounded by an extreme calorie-restricted diet during weeks 40-48), and developed treatment-emergent high level integrase (Q148R) and NNRTI (E138Q) resistance[48].

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 LAI116482. 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 rilpivirine 25 mg developed ALT values >10x ULN at Week 96 likely due to acute Hepatitis C infection.

Plasma exposures 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 CABLA in HIV-infected and HIV-uninfected participants supports continued clinical development for HIV treatment and PrEP.

A second Phase 2b study in HIV-infected, antiretroviral naïve adults is currently underway (LATTE-2), with 310 participants enrolled to receive oral CAB 30mg + ABC/3TC for 20 weeks followed by a long acting regimen containing CAB LA + TMC278LA or continuation of oral medications. Data from this study is limited and preliminary. One participant with Hepatitis C infection and underlying stage 3/4liver fibrosis received oral CAB 30mg + ABC/3TC and developed possible drug induced liver injury and a second subject on oral CAB 30 mg + ABC/3TC, with steatohepatitis, developed possible drug induced liver injury approximately 6 months after initiating oral CAB. Two deaths have occurred on study, one due to a motor vehicle accident (unrelated to study products), and as noted above, one due to anoxic brain injury from status epilepticus in the setting of recreational drug use; contribution from oral CAB could not be ruled out.

Cumulative exposures of GSK1265744, through 01 July 2015, are shown in Table 2.

Table 2: Cumulative Cabotegravir Exposure Estimates from Phase 1 through Phase 2b Clinical Studies Up To 01 July 2015

Treatment Population/Dose	Duration	Completed	Ongoing/ Concluded[a]	Total
HIV uninfected healthy participants		**351**	**200**	**551**
5 to 150 mg	Single dose	115	37	152
10 to 30 mg once daily	10 to 28 days	138	163[b]	301
150 mg every 12 hours	3 doses	40	0	40
100 – 800 mg IM/SC LA	Max 252 days	136[c]	114[d]	250
HIV-infected participants		**15**	**490**	**505**
5 to 30 mg once daily (Ph IIa)	10 days	15	0	15
10 to 60 mg once daily (Ph IIb)	Max 1022 days[i]	0	181	181
30 mg once daily (Ph IIb)	Max 394 days	0	309	309
Up to 800 mg IM LA[e]	Max 232 days[h]		229[f]	229
Total		**366**	**690[b]**	**1056**
Single dose oral (5 to 150 mg)		115	37	152
Repeat dose once daily oral (10 to 60 mg)	-	153	653	806
150 mg oral every 12 hours x 3		40	0	40
Single or repeat dose LA (100 – 800 mg)	-	136[c]	343[g]	479

a. Concluded studies: study completed through follow-up; and/or clinical study report is in preparation
b. Approximately 10 are on placebo in study 201103
c. 78 received both oral and LA dosing
d. 114 received both oral and LA dosing and approximately 5 are on placebo from study 201103
e. Includes 400 mg Q4W and 600 mg Q8W dosing
f. Subset that received 30 mg once daily in study 200056
g. 343 received both oral and LA dosing and approximately 5 are on placebo from study 201103
h. Detectable CAB concentrations can remain for up to 52 weeks following the last CAB injection
i. As of 28 Dec 2014, all participants had transitioned to oral CAB in the Open-Label phase of study LAI116482 (LATTE), therefore, the longer durations apply to the 30 mg dose only

1.4.1 Evidence for Clinically Significant Anti-viral Activity in HIV-infected Individuals

Two Phase 2b clinical trials are in progress (GSK protocol LAI116482 [LATTE] and 200056 [LATTE-2]). 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).[48] 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 oral 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 oral CAB doses who had viral loads <50 c/mL prior to week 24 were transitioned to a regimen maintaining their oral CAB dosing but substituting oral rilpivirine (RPV) 25 mg daily for the NRTI. 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 administered at 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 sub therapeutic (<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) resistance with the E138Q mutation.[48] Two additional participants experienced virologic failure on CAB-containing therapy with evidence of NNRTI-resistance only (K101K/E and E183E/K at weeks 48 and 72, respectively).[50]

1.4.2 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. Median rectal tissue concentrations were ≤8% of plasma concentrations (range 0-20%).[51] Further tissue studies using single and multiple doses of the 800 mg IM dose are ongoing.

1.5 Hepatic and Central Nervous System Adverse Events

As part of the early phase development of cabotegravir (Phase 2b LATTE and LATTE-2), some participants with HIV infection and pre-existing liver disease 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 an MRI was unrevealing for pathology. An EEG was consistent with benign juvenile epilepsy; the participant recovered without additional events.

A second participant in the ongoing Phase 2b LATTE-2 trial of HIV-infected individuals received oral ABC/3TC with CAB 30mg 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 ICU, 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 third 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 30mg (or placebo) was administered for 4 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 IP dosing.

1.6 Background of TDF/FTC for Pre-exposure Prophylaxis

In 2010, results became available from the first efficacy trial of an ARV-based PrEP, known as "iPrEX".[4] Close to 2,500 HIV-uninfected MSM and transgendered women who have sex with men in South Africa, South America, Thailand, and the US were randomized to daily oral TDF/FTC or placebo. Overall 44% fewer incident HIV infections occurred in the TDF/FTC group (36 incident infections) compared to the placebo group (64 incident infections). A key finding of the study was that drug detection in blood (intracellular and plasma levels) was highly correlated with protection among those who self-reported TDF/FTC use on at least 90% of days, incident HIV infection was 73% lower when compared with the placebo arm. AEs were similar between the two groups, with Grade 3 and 4 events occurring among 12% of participants in each arm. Some Grade 2 and higher AEs were reported significantly more frequently in the TDF/FTC arm than the placebo arm: moderate nausea (22 vs. 10 events) and unintentional weight loss (34 vs. 19 events). Serum creatinine elevations occurred more frequently in the TDF/FTC arm than placebo arm (25 vs. 14 events). All elevations in the serum creatinine level resolved after discontinuation of study drug. There were 10 participants who were HIV infected at enrollment, of whom three had FTC-resistant infections. There were no TDF-resistant infections. Of the participants who became infected during follow-up, no FTC or TDF resistance was detected. Of interest, participants in the study reported increased condom use and decreased number of sexual partners. The Partners PrEP Study enrolled 4,758 HIV-serodiscordant African heterosexual couples, and compared TDF once daily and TDF/FTC once daily regimens to placebo. The TDF and TDF/FTC PrEP demonstrated definitive reduced risk of HIV acquisition, by 67% ($P<0.001$) and 75% ($P<0.001$) respectively, in these men and women.[1] The CDC TDF-2 trial showed that daily TDF/FTC was safe and effective for prevention of HIV infection among African heterosexual men and women compared to placebo.[8] In a modified intent-to-treat analysis that excluded three participants who were HIV-infected at enrollment, the overall protective efficacy

was 62.2% (P=0.03); an "as-treated" analysis demonstrated a protective efficacy of 77.9% (P=0.01).[9] In all of these studies, PrEP regimens were well-tolerated.

After consideration of these results (primarily iPrEX and Partners PrEP), the US FDA, in July 2012, approved Truvada® (TDF/FTC fixed dose combination) "to be taken once daily and used in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults who do not have HIV but are at high risk of becoming infected."[52]

Modeling data based the iPrEX dataset estimate that the protective efficacy for those who took the TDF/FTC 7 days per week (as prescribed) had 99% reduction in the risk of HIV acquisition; those who took 4 doses per week had 96% reduction, and those who took 2 doses per week had 76% protection;[53] further, in the iPrEX Open Label Extension (OLE) study, no seroconversions were observed among MSM and TGW who had intraerythrocytic TFV-DP levels consistent with 4-7 doses per week.[34]

Despite these estimates of high-levels of efficacy when taken as prescribed, it remains clear that many populations have challenges achieving the level of adherence to daily oral tablets required for these high levels of protection. Studies in African women in particular (FEM-PrEP, VOICE) have failed to demonstrate protective efficacy for oral TDF-based PrEP due to a combination of low-levels of adherence and a need for greater adherence fidelity to achieve HIV protection from vaginal exposures compared to rectal exposures.[54,55]

In addition to adherence challenges inherent to daily oral tablet regimens, additional concerns related to the safety of TDF-based PrEP have propelled the evaluation of additional agents (and delivery systems) for potential use in prevention settings: 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. Across randomized Phase 3 PrEP studies, the rate of HIV seroconversion with resistant virus among active-exposed participants was 0.06%,[1,4,9,17-21] although rates of resistant virus generated by the initiation of TDF-based PrEP during occult primary HIV infection was approximately 25%.

Concerns also remain about longer-term side effects of these drugs, including renal toxicity and decreased bone mineral density (BMD). Renal toxicity occurs with TDF use, including acute renal failure and Fanconi's syndrome.[56,57] 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.[1,9,20,21,58] BMD changes of approximately 1% were seen in dual-energy X-ray absorptiometry (DXA) subsets of MSM who received 48 weeks of TDF-based PrEP with some reversion towards baseline after PrEP medication withdrawal; no interventions have been shown to mitigate such bone loss to date.[37,59,60] Fractures were not observed to be associated with observed levels of BMD loss.

1.7 Rationale for Study Design

This study is a Phase 2b/3 randomized double-blind non-inferiority trial of CAB-LA versus TDF/FTC designed to evaluate the ability of long-acting injectable Cabotegravir (CAB LA) to prevent HIV infection in high-risk transgender women (TGW) and men who have sex with men (MSM) when used as pre-exposure prophylaxis (PrEP). A non-inferiority trial comparing CAB

LA to an active control group taking oral TDF/FTC is appropriate because robust evidence now exists supporting a strong protective effect of oral TDF/FTC against rectal exposure to HIV[4,35,36] and the US FDA has approved licensure of TDF/FTC for HIV prevention in high risk populations. The WHO has provided guidance suggesting that the current level of evidence for MSM and TGW is sufficient for placebo-controlled designs to be unacceptable.[61] Although TDF/FTC has been shown to be effective, adherence to a daily oral regimen can be difficult in many settings, and no efficacy was observed when adherence was low (FEM-PrEP, VOICE). An effective, long-acting PrEP agent could offer substantial advantages in achieving sustained efficacy because of increased convenience and higher adherence.

A non-inferiority design has been selected because TDF/FTC has been shown to be highly effective in high-risk MSM populations so that it is sufficient to establish that CAB-LA has similar effectiveness to TDF/FTC, particularly if CAB-LA is shown to be safe and effective, and to have an adherence advantage over daily TDF/FTC. Using existing randomized, controlled trial data for TDF/FTC in MSM populations an appropriately robust non-inferiority margin can be established that would substantially preserve clinical efficacy in a randomized comparison of CAB-LA to oral TDF/FTC.[62] The proposed randomized trial does also allow for establishing superiority of CAB-LA in the event that it is substantially more effective than TDF/FTC.

The study is double blind to achieve a direct comparison of the two drugs in the absence of the additional differential effect of adherence to daily pills and difference in risk behavior. With the double blind, all participants are required to take a daily pill and receive the injections, thus differences in pill adherence between the arms are likely to be small (based on prior trials). HIV risk is also expected to be similar in both groups. An un-blinded trial was considered; however, the strong potential for knowledge of the active agent to modify daily adherence, retention in the trial and risk behavior was judged to threaten the interpretability of the study. A double blind trial of CAB-LA, with all participants offered TDF/FTC could also be considered, but this would not lead to licensure of CAB-LA as a single agent with a potential for a long-acting drug without the adherence burden of daily drug dosing.

Although treatment paradigms for HIV typically include three or more agents in order to achieve durable suppression of viral replication, HIV prevention using ARVs agents does not obligate three or even multiple agents. For example, the Partners PrEP study demonstrated statistically similar prophylaxis efficacy against HIV acquisition among heterosexual men and women for tenofovir monotherapy and TDF/FTC dual therapy.

There is a risk that too few HIV infections will occur in the trial to be able to definitively establish non-inferiority. This could occur if the population was not truly at risk for HIV, or if both products were highly effective in preventing HIV: that is, that adherence to TDF/FTC was high and CAB-LA was similarly effective. We plan to establish whether adherence to TDF/FTC is high by measuring intraerythrocytic TFV-DP levels, relying on the robust database for TDF/FTC that allows extrapolation of intraerythrocytic TFV-DP level data to levels of protective efficacy. Risk behavior and non-HIV STIs will be carefully monitored to provide a benchmark for HIV-exposure risk of the enrolled population and to support the statistical design assumptions.

1.8 Rationale for Bone Mineral Density Subset

As noted above, BMD loss was associated with receipt of TDF-based PrEP in HIV-uninfected participants, making BMD loss one of three "signature" toxicities of TDF/FTC-based PrEP (including a gastrointestinal "start-up" syndrome and potential nephrotoxicity). Although there are no data to suggest that integrase inhibitors as a class or CAB specifically should impact BMD, it has not been studied. In order to evaluate further the risk-benefit of a long-acting injectable compared to daily oral TDF/FTC, it is critical to compare the known toxicity profile of TDF/FTC to any comparator agent.

At sites that have the ability to perform DXA scans, 175 participants in each arm (350 participants in total) will be offered participation in a DXA sub study. DXA evaluations will be conducted for sub study participants at Enrollment and Weeks 57 and 105. An additional informed consent will be required for substudy participation, and participation will be stratified across regions to provide broad geographic and racial/ethnic representation in the sub study.

1.9 Recruiting and Retaining Most At Risk Populations

The study aims to recruit a large population of highest-risk individuals from a broad geography. 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.

The study will be targeted towards most at-risk populations of MSM and TGW in each geographic setting (i.e., those with highest HIV incidence). In the US, this will entail close collaboration with community and leadership of the African-American and Latino MSM communities, as well as the transgender community. Such collaborations are being planned or have already occurred, including planned discussions with the Black Gay Research Group (BGRG) and the Black Caucus within the HPTN, as well as engagement with the transgender community at a transgender workshop that took place during the HPTN Annual Meeting in June 2015. In the US, HPTN 061, a cohort engaging African American MSM in a longitudinal observational study, found localized epidemics where HIV incidence among young (age 18-29) Black MSM was 5.9%, and approximately 3% overall for the population.[63] US recruitment in this study will be guided by the recommendations set forth by the Black Caucus on future research with BMSM, including using the "Presence at the Table"[64] strategy at US sites at the time of initiation.

In order to target most at-risk populations, sites will be encouraged to enroll the majority of participants 30 years of age and younger. Additionally, the protocol will strive to enroll 50% of the US-based recruitment with Black MSM, particularly young (<30 years) Black MSM. Efforts to enrich enrollment with young Black MSM will be a focus of education and outreach at US based sites. The study overall will strive to enroll 10% TGW, and again, efforts to enrich enrollment with TGW will be a focus of education and outreach at all sites.

Within South America, young MSM and TGW have the highest risk of HIV infection.[65] Previous studies in the region have found that this population has a high willingness and acceptability for

the use of PrEP.[66] To help identify potential study participants, alliances will be made between the study team and local specialized resources, including Lesbian/Gay/Bisexual/Transgender-based non-governmental organizations, trans-advocacy and support groups and mobile HIV testing units. Because of the work with iPrEX and other PrEP studies underway in the region, the foundation for many of these recruitment partnerships has already been established across South America. Recent epidemiologic data from 3 voluntary counseling and testing sites in Rio de Janeiro found 24.8% (95% CI 19.9-29.7) prevalence among MSM, and conservatively estimated incidence among MSM to be 8.55% (95% CI 4.36-12.74).[67] MSM and TGW in Brazil have a very high willingness to use PrEP to prevent HIV.[68]

A cohort of 718 MSM/TW in Peru showed an HIV incidence was 3.6 cases per 100 person-years, with HIV incidence being highly associated with having an incident STI (aHR 3.73).[69] In Thailand, the situation is similar, with MSM at high risk of HIV infection and younger MSM at even higher risk. MSM cohorts from 2006-2013 found HIV incidence rates of 5–6 per 100 PY, with incidence among MSM aged 24 years or less to be 7 per 100 PY.[70] The overall HIV incidence rate among MSM is 180 times as high as the estimated incidence of 0.03% in 2011 among adults in Thailand.[71] Risk factors for HIV infection in this population have been found to be younger age, drug use for sexual pleasure, inconsistent condom use, group sex, and seropositivity for herpes simplex virus type 1 and 2 (HSV-1, HSV-2) and syphilis at baseline.[57] The MSM population has a high willingness to participate in PrEP trials, and the civil society links between community-based organizations and researchers are strong. Interest in injectable forms of PrEP is high among MSM community based organizations.

Sub-Saharan Africa was long believed to have an exclusively heterosexual epidemic. Nevertheless, HIV rates have been found to be higher than the background male population rates in both gay-identified and non-identified MSM. HIV prevalence rates of up to 50% have been described.[72-76]

1.10 HIV and Risk Reduction Counseling

HIV testing and risk reduction counseling will be provided at each study visit, in accordance with local standards of care, and will include messaging about consistent condom use, and the known effectiveness of daily oral TDF/FTC when taken with high adherence. Condoms and lubricant will be offered to all participants at each study visit. In addition, counseling will emphasize the unknown efficacy of the injectable study product in preventing HIV infection.

1.11 Adherence Counseling and Monitoring

It is clear that the effectiveness of daily oral TDF/FTC is tightly correlated with adherence. Therefore, a critical component of the comparison between daily oral TDF/FTC and CAB LA will be participants' ability/willingness to take a daily pill compared to a clinic-administered injection on a quarterly schedule. To evaluate the clinical applicability of this difference, the study will provide adherence support at baseline and at all follow-up visits for all participants in a manualized/standardized fashion commensurate with an intervention that could be easily implemented in diverse clinical settings. Any participant who has self-reported or actual returned pill-count evidence of challenges with adherence to AT MINIMUM the level of 4 doses weekly

will be provided an individualized adherence intervention designed to problem-solve individual barriers to adherence.

When approximately 50% of the study population has enrolled, a random sample of plasma and/or dried blood spot (DBS) specimens from TDF/FTC-arm participants from a variety of time points will be assayed for drug levels (TFV in plasma and/or intra-erythrocytic TFV-DP in DBS). If adherence rates suggest adherence levels <50-60%, additional adherence support for daily oral tablets will be provided to all participants.

1.12 Rationale for use of oral lead-in prior to injectable dosing

The CAB LA formulation has a pharmacokinetic decay rate that exposes the injected individual to detectable levels of cabotegravir for up to 52 weeks after an injection. In order to maximally identify any acute toxicity prior to administration of a non-dialyzable, non-removable depot injection, a 5-week lead-in period of daily oral (short acting) cabotegravir 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 4 weeks of oral drug exposure. The 5-week exposure in this study is designed to provide uninterrupted study product coverage while awaiting return of the Week 4 safety laboratory assessments.

1.13 Rationale for exploring cross-sex hormone therapy and PrEP medication drug-drug interactions

Although no drug-drug interactions would be expected between the components of TDF/FTC or CAB and cross-sex hormone therapy (csHT) in HIV-uninfected individuals, there are currently no data to support that assumption. Lower TFV-DP levels observed in TGW in the iPrEX OLE study, which were attributed to poor adherence may, in fact, be partly attributable to drug-drug interactions.[34] Focus groups among TGW have also noted a high level of interest in interactions between PrEP agents and csHT. TGW will often prioritize csHT use above other health concerns, further emphasizing the importance of formally evaluating such drug-drug interactions.[77] In order to best characterize interactions, csHT regimens would need to be limited to most-common regimens composed of oral 17-beta estradiol, with or without spironolactone or progestagens. PK data (plasma TFV and/or TFV-DP levels) and plasma CAB levels from a subset of TGW participants taking stable regimens of csHT and a subset of TGW not taking csHT from each arm could then be compared.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objectives:

- To compare HIV incidence among participants randomized to oral CAB/CAB LA (oral lead in and injections) vs. oral TDF/FTC (Steps 1 and 2)
- To compare the safety of oral CAB/CAB LA vs. oral TDF/FTC (Steps 1 and 2)

2.2 Secondary Objectives:

- To compare HIV incidence among participants receiving CAB LA injections vs. oral TDF/FTC (each step independently and all steps in aggregate)
- To compare HIV incidence among participants receiving CAB LA injections vs. oral TDF/FTC (Steps 1, 2, and 3 combined)
- To compare HIV incidence among participants receiving CAB LA injections vs. oral TDF/FTC (Step 3 only, descriptive)
- To estimate the change in hazard of HIV acquisition between CAB and oral TDF/FTC strategies (Arm A and Arm B) as participants progress from Step 2 to Step 3
- To compare HIV incidence among the subgroups of participants receiving oral CAB/CAB LA vs. oral TDF/FTC by region, age, race, ethnicity, baseline risk, and gender identity
- To compare changes in renal function, liver function, and bone mineral density (BMD) among participants receiving oral CAB/CAB LA vs. oral TDF/FTC
- To evaluate and compare 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 compare the acceptability of and preferences for CAB LA vs. oral TDF/FTC

2.3 Tertiary Objectives:

- To examine the association between levels of adherence and HIV incidence
- To compare and describe the rates, patterns, and correlates of adherence to CAB LA vs oral TDF/FTC, in aggregate and by psychosocial/demographic variables.
- To estimate changes in sexual-risk behavior as measured by self-report and rates of incident gonorrhea, chlamydia, and syphilis in the study population
- To compare the resource utilization and programmatic costs of long-acting injectable PrEP vs. daily oral PrEP vs. no PrEP for HIV uninfected MSM and TGW in the US, Brazil, South Africa and India
- To use mathematical simulation to project the short- and long-term clinical impact, cost projections, budgetary impact, and incremental cost-effectiveness of long-acting

injectable PrEP vs. daily oral PrEP vs. no PrEP for HIV uninfected MSM and TGW in the US, Brazil, South Africa and India

2.4 Exploratory Objectives:

- To perform secondary laboratory assessments that may include evaluation of factors related to HIV infection, hepatitis infection, or sexually transmitted infections (STIs); antiretroviral (ARV) drug use; pharmacogenomics; characterization of HIV in infected participants; and evaluation of laboratory assays related to the study objectives
- To explore possible drug-drug interactions between cross-sex hormone therapy (csHT) and cabotegravir and TDF/FTC in a subset of TGW taking commonly prescribed cross-sex hormone therapy regimens

2.5 Study Design and Overview

This is a Phase 2b/3, randomized, multi-site, two-arm, study of CAB LA compared to daily oral TDF/FTC for HIV prevention. 4500 participants will be enrolled, randomized 1:1 to Arm A and Arm B through the following 3 steps:

Step 1:

- Arm A - Daily oral CAB (30 mg tablets) and daily oral placebo for TDF/FTC for 5 weeks.
- Arm B - Daily oral TDF/FTC and daily oral placebo for CAB for 5 weeks.

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

Step 2:

- Arm A – Injections of CAB LA at two time points four weeks apart and every 8 weeks thereafter beginning at Week 5, and daily oral placebo for TDF/FTC. Injections will consist of 600 mg of CAB LA administered as one 3 mL injection.

- Arm B: Daily oral TDF/FTC and injections of placebo for CAB LA on the same schedule as Arm A beginning at week 5. Injections will consist of the same volume (3 mL) as Arm A participants.

This step will continue until the required number of incident HIV endpoints is reached, estimated to be when the final participant reaches approximately 60 weeks on Step 2 (week 65 for the final participant).

Participants who permanently discontinue receiving injections before their study participation ends for any reason other than HIV infection will remain blinded to their study assignment and will follow the schedule in Step 3, starting no later than 4-8 weeks after their last injection.

Any participant that becomes HIV infected during Step 2 of the study will permanently discontinue study product and will be followed at quarterly intervals for approximately 52 weeks in order to test for safety parameters, as well as CD4 cell count and HIV viral load.

Step 3:

When the study reaches the required number of incident HIV endpoints or when the last participant enrolled completes their participation in Step 2, all participants will be unblinded. All participants will begin open-label daily oral TDF/FTC for approximately 48 weeks (for Arm A, to "cover the tail"), starting no later than 8 weeks after their last injection (the timing of the last injection visit and duration of provision of daily oral TDF/FTC may vary according to when the last participant reaches their final Step 2 visit or if the study endpoints are reached earlier). All participants will be transitioned to locally-available HIV prevention services when their participation in Step 3 ends.

Participants with confirmed HIV infection during Step 3 will be followed at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by the CMC.

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

2.5.1 Participating Sites/Institutions

Participating sites are listed in the SSP Manual, and are located in Asia, North and South America, and South Africa.

2.5.2 Study Duration

The study will last approximately 4.5 years total, with individual participants being followed between 1.5 years (for the latest enrolling participants) to 4.5 years (for the earliest enrolling participants). Accrual will require approximately 130 weeks. In Step 1, participants will receive oral tablets for 5 weeks. In Step 2, participants will receive injections (as a single injection at two time points 4 weeks apart and every 8 weeks thereafter) and daily oral tablets. Step 2 will be continued until the required number endpoints is reached, estimated to be approximately when the final participant reaches their last scheduled visit in Step 2 (approximately week 65 for the final participant). Participants will be all simultaneously unblinded at the conclusion of Step 2. In Step 3, all participants will receive open-label daily oral TDF/FTC for up to 48 weeks. Participants will therefore be followed between 113 weeks to 233 weeks (between 65 and 185 weeks on blinded study medication and for Arm A participants up to 48 weeks on open-label daily oral TDF/FTC). All participants will be transitioned to locally-available HIV prevention services, including services for PrEP, if available, at the end of their participation in the study.

3.0 STUDY POPULATION

Four thousand five hundred (4500) HIV-uninfected MSM and TGW will be included in this study. Each site will be asked to work with their Community Advisory Board and outreach, education and recruitment teams to develop a recruitment plan appropriate for their 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:

- MSM and TGW, 18 years or older at the time of screening (male at birth)
- Willing to provide informed consent for the study
- At high risk for sexually acquiring HIV infection based self-report of at least one of the following:
    - Any condomless receptive anal intercourse in the 6 months prior to enrollment (condomless anal intercourse within a monogamous HIV seronegative concordant relationship does not meet this criterion)
    - More than five partners in the 6 months prior to enrollment (regardless of condom use and HIV serostatus, as reported by the enrollee)
    - Any stimulant drug use in the 6 months prior to enrollment
    - Rectal or urethral gonorrhea or chlamydia or incident syphilis in the 6 months prior to enrollment
- In general good health, as evidenced by the following laboratory values, which must be from specimens obtained within 45 days prior to study enrollment:
    - Non-reactive / negative HIV test results*
    - Hemoglobin > 11 g/dL,
    - Absolute neutrophil count > 750 cells/mm^3
    - Platelet count ≥ 100,000/mm^3
    - Calculated creatinine clearance ≥ 60 mL/minute using the Cockcroft-Gault equation
    - Alanine aminotransferase (ALT) < 2 times the upper limit of normal (ULN)
    - Total bilirubin ≤ 2.5 times ULN
    - Hepatitis B virus (HBV) surface antigen (HBsAg) negative
    - HCV Ab negative
    - No Grade 3 or higher laboratory abnormalities

*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 obtained at the Enrollment visit must be obtained prior to randomization in to the study and must be negative/non-reactive. Individuals who have one or more reactive or positive HIV test results will not be enrolled, even if subsequent confirmatory testing indicates that they are not HIV-infected (see SSP Manual).

- 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)
- Willing to undergo all required study procedures

3.2 Exclusion Criteria

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

- One or more reactive or positive HIV test result at Screening or Enrollment, even if HIV infection is not confirmed
- Active or recent use of any illicit intravenous drugs ("recent" defined as in the 90 days prior to enrollment)
- Co-enrollment in any other interventional research study or other concurrent studies that may interfere with this study (as provided by self-report or other available documentation. Exceptions may be made if appropriate after consultation with the CMC.)
- Past or current participation in HIV vaccine trial. An exception will be made for participants that can provide documentation of receipt of placebo (not active arm).
- 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 intramuscular (IM) injections, per the discretion of the Investigator of Record. Mild skin conditions may not be exclusionary at the discretion of the Investigator of Record or designee in consultation with the CMC
- Has a tattoo or other dermatological condition overlying the buttock region which in the opinion of the IoR or designee, in consultation with the CMC, may interfere with interpretation of injection site reactions
- 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)

- Coagulopathy (primary or iatrogenic) which would contraindicate IM injection (concomitant anticoagulant or anti-platelet therapy use should be discussed with the CMC)
- Active or planned use of prohibited medications as described in the Investigator's Brochure or listed in the SSP Manual (provided by self-report, or obtained from medical history or medical records). In particular, future use of TDF/FTC at any point during the study.
- Known or suspected allergy to study product components (active or placebo)
- Surgically-placed buttock implants, per self-report
- Alcohol or substance use that, in the opinion of the study investigator, would jeopardize the safety of the participant on study (e.g., provided by self-report, or found upon medical history and examination or in available medical records).
- History of seizure disorder, per self-report

3.3 Recruitment Process

Sites will be responsible for developing appropriate recruitment processes that are geared toward their respective local communities. See also Section 1.9. All advertising materials must undergo approval by each participating site's Institutional Review Board (IRB)/Ethics Committee (EC).

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 participant study burden, American Red Cross-mandated limitations on per-unit-time phlebotomized blood volumes, to avoid potential unblinding of this or other studies, and to avoid confounding in the interpretation of the study data. The Clinical Management Committee (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 him or 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 7.5% 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 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.
- Immediate and multifaceted follow-up on missed visits.
- 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 Investigator also may withdraw participants from the study 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, Division of AIDS (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 also may be withdrawn if the study sponsor, government or regulatory authorities (including Office for Human Research Protections [OHRP] and the FDA) or site IRBs terminate the study prior to its planned end date.

Every reasonable effort will be made to complete a final evaluation of participants who terminate from the study prior to the final protocol-dictated study week, and study staff will record the reason(s) for all withdrawals from the study in participants' study records. In such cases, the Investigator of Record 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 - Participants will be randomized 1:1 to one of two study arms:

- Arm A: Oral CAB tablets 30 mg and placebo for TDF/FTC tablets, two tablets daily for 5 weeks, with or without food
- Arm B: TDF/FTC 300 mg/200 mg fixed dose combination tablets and placebo for oral CAB tablets, two tablets daily for 5 weeks, with or without food

Step 2 – Blinded injections and blinded daily oral pills:

- Arm A: CAB LA 600 mg administered as one 3 mL (600 mg) IM injection in the gluteal muscle at two time points 4 weeks apart and every 8 weeks thereafter, and placebo for TDF/FTC daily oral tablet
- Arm B: TDF/FTC 300 mg/200 mg fixed dost combination daily oral tablets, and placebo for CAB LA administered as one 3mL (600 mg) injection in the gluteal muscle as two time points 4 weeks apart and every 8 weeks thereafter

Step 3: For all participants, including those who permanently discontinue receiving injections before their Step 2 participation in the study ends, open-label TDF/FTC 300 mg/200 mg fixed dose combination daily oral tablets, one tablet daily for up to 48 weeks.

4.2 Study Product Formulations

4.2.1 Oral product

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 (25^{o} 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 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 (25^{o} C) and protected from moisture.

FTC 200 mg/TDF 300 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° to 30°C. Matching placebo tablets also will be provided by Gilead Sciences, Inc.

Placebo tablets match the TDF/FTC tablets in physical size and appearance. 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.

4.2.2 Injectable Suspension

CAB LA is formulated as a sterile white to slightly colored suspension containing 400mg/2mL of CAB LA for administration by intramuscular (IM). The product is packaged in a 3 mL vials. 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 degrees celsius to 30 degrees celsius (2° C – 30° C), do not freeze.

Placebo for CAB LA Injectable Suspension will be Intralipid 20% fat emulsion infusion.

The cabotegravir study product 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 Investigator's Brochure, which will be provided by the DAIDS Regulatory Support Center (RSC).

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.[78]

4.3 Study Product Acquisition and Accountability

Cabotegravir study product (oral and LA) is being provided by ViiV Healthcare. TDF/FTC oral study product is being provided by Gilead Sciences, Inc.

4.3.1 Study Product Acquisition

All study products (active drug and placebo) will be supplied by 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.

4.3.2 Study Product Accountability

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

4.4 Toxicity Management

Toxicity management guidelines can be found in Appendix III.

4.5 Concomitant, Prohibited, and Precautionary Medications

Information regarding prohibited and precautionary concomitant medications can be found in the SSP Manual. 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). Alcohol and recreational or street drug use reported by a participant during the study will be recorded in the participant's study chart only (and not captured on the concomitant medication log for inclusion in the study database).

5.0 STUDY PROCEDURES

Overviews of the study visit and procedures schedules are presented in Appendices I a-c, and Appendix II in the event of suspected and confirmed HIV infection. Presented below is additional information on 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 (except for HIV RNA, which must be collected and results obtained within 14 days before enrollment) for the clinical and laboratory evaluation and procedures outlined below. The following evaluations and procedures will occur as part of screening:

Administrative, Behavioral, and Regulatory Procedures

- Informed consent
- Locator information
- HIV counseling
- Offer condoms and lubricant

Clinical Procedures

- Target medical history (including bleeding history) and targeted physical exam for ascertainment of eligibility, and concomitant medications
- ECG (will serve as baseline value)
- Blood collection

Laboratory Evaluations

- HIV testing (see SSP Manual), including testing for acute HIV infection within 14 days prior to enrollment
- Hepatitis testing (HBsAg and HCVAb testing required at Screening)
- CBC with differential
- Chemistry testing (creatinine is the only required chemistry at Screening)
- Liver function testing (LFT) (ALT and total bilirubin are the only required LFTs at Screening)

- Plasma storage (can be discarded if participant does not enroll utilizing sample lists provided by the HPTN SDMC in consultation with the HPTN LC)

Sites will follow the HIV testing algorithm for Screening included in the SSP Manual. If a reactive/positive result is obtained for any HIV test, the person is not eligible for the study. Additional testing to confirm suspected HIV infection during Screening will be performed in accordance with local guidelines. If HIV infection is confirmed, participants will receive counseling and be referred for appropriate care, as necessary.

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

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

Eligible participants should be reminded that the use of anticoagulant and/or antiplatelet medications as outlined in the SSP Manual are prohibited within 7 days before and 7 days after injections. Reminders should be built in to the concomitant medication history.

5.2 Step 1: Week 0 - Enrollment

Administrative, Behavioral, and Regulatory Procedures

- Locator information
- Demographic information (sites may collect this information at Screening at IoR discretion)
- Randomization
- HIV counseling
- Offer condoms and lubricant
- Baseline acceptability assessment
- Baseline behavioral assessment
- Adherence counseling

Clinical Procedures

- Complete medical history and complete physical exam, including concomitant medications (may be performed during screening at the discretion of the Investigator of Record or their designee)

- DXA (only if part of BMD subset, and may be performed -14 days/+ 14 days of enrollment), and dietary calcium and Vitamin D assessment
- Blood collection (collect prior to administration of study product)
- Urine collection for urinalysis
- Urine collection for Neisseria gonorrheae (GC) and Chlamydia trachomatis (CT)
- Rectal swab for GC/CT testing
- Dispense oral study product (enough for 5 weeks) (Dosing should begin on the day of Enrollment or no later than 24 hours of Enrollment)

Laboratory Evaluations

- HIV testing (see SSP Manual)
- Hepatitis B testing (HBsAb and HBcAb required at enrollment)
- CBC with differential
- Chemistry testing (see Appendix Ia)
- Liver function testing (see Appendix Ia)
- Fasting lipid profile (participants should be fasting for at least 8 [preferably 12] hours prior to sample collection) (see Appendix Ia)
- Syphilis serology
- BMD Subset only: 25-OH-Vitamin D
- Urine GC/CT testing
- Rectal swab GC/CT testing
- Urinalysis (protein and glucose)
- Plasma storage
- Whole blood storage for Pharmacogenomics testing (at the discretion of the study site). For sites that store samples for this testing, participants must provide specific consent).

NOTE 1: All HIV test results including testing for acute HIV testing from Screening and at least one HIV test result from Enrollment must be available and confirmed to be negative/non-reactive PRIOR to provision of study product. Results from the chemistry testing, LFTs, lipid profile, hematology testing, and urinalysis from this visit are NOT required prior to the issue of study product.

5.3 Step 1: Weeks 2 and 4 – Oral Safety Visits

Administrative, Behavioral, and Regulatory Procedures

- Locator information
- HIV counseling
- Offer condoms and lubricant
- Adherence counseling
- Pill count

Clinical Procedures

- Targeted medical history and targeted physical exam, including concomitant medications
- Blood collection

Laboratory Evaluations

- HIV testing (see SSP Manual)
- CBC with differential
- Chemistry testing (see Appendix 1a)
- Liver function testing (see Appendix 1a)
- Plasma storage
- DBS storage (Week 4 only)

NOTES for 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 should be discontinued.

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 2, 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.

A Grade 3 or higher ALT abnormality reported at Week 2 or Week 4, regardless of relatedness to the study product, will prohibit a participant from entering the injection phase of the study, and the participant will be followed annually for HIV testing only until the conclusion of Step 2 of

the study. All such cases must be reported to the CMC. In addition, participants will be followed with weekly ALT assessments until they return to ≤ Grade 1.

Excluding ALT, any grade 3 clinical or laboratory AE observed prior to Week 5 will prompt consultation with the CMC prior to any injectable dosing.

Grade 3 adverse events deemed related to study product, or a Grade 3 ALT, or any Grade 4 adverse event will lead to permanent study product discontinuation, and the participant will be followed annually for HIV testing only until the conclusion of Step 2 of the study. AEs will be followed until resolution (≤ grade 1) in consultation with the CMC.

Note the following for cases of exercise-induced CK abnormalities: Cases of CK abnormality at the Grade 3 or higher level accompanied by ALT abnormalities of Grade 3 or lower up to and including Grade 3 should be brought to the attention of the CMC for adjudication of further management and further administration of study product. Grade 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.

The CMC should be contacted for guidance regarding pill counts resulting in less than 75% adherence prior to the Week 5 First Injection Visit, or any other concerns regarding adherence.

5.4 Step 2: Weeks 5 – First injection visit in Step 2

Administrative, Behavioral, and Regulatory Procedures

- Locator information
- HIV counseling
- Offer condoms and lubricant
- Behavioral assessment
- Adherence counseling

Clinical Procedures

- Targeted medical history and targeted physical exam, including concomitant medications
- Blood collection
- Administer injection
- Dispense pills

Laboratory Evaluations

- HIV testing (see SSP Manual)
- Plasma storage

NOTE: All HIV test results from previous visits and at least one HIV test result from the Week 5 visit must be available and confirmed to be negative/non-reactive PRIOR to injection of study product. The injection must not be given if any HIV test is reactive/positive.

Results from all Week 4 clinical and laboratory evaluations (e.g., chemistry, LFTs, hematology) must be available and be reviewed by the IoR or their designee prior to injection.

5.5 Step 2: Week 6 – Safety visit following first injection

Administrative, Behavioral, and Regulatory Procedures

- Locator information
- HIV counseling
- Offer condoms and lubricant
- Adherence counseling

Clinical Procedures

- Targeted medical history and targeted physical exam, and concomitant medications
- Blood collection
- ISR evaluation

Laboratory Evaluations

- HIV testing (see SSP Manual)
- CBC with differential
- Chemistry testing (see Appendix 1b)
- Liver function testing (see Appendix 1b)
- Plasma storage

5.6 Step 2: All remaining visits where injections occur - Weeks 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 137, 145, 153, 161, 169, 177, 185

Administrative, Behavioral, and Regulatory Procedures

- Locator information
- HIV counseling
- Offer condoms and lubricant
- Behavioral assessment (only at Weeks 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 121, 137, 153, 169, 185)
- Acceptability assessment (only at Weeks 17, 41, 65, 89, 137, and 185)

- Adherence counseling

Clinical Procedures

- Targeted medical history and targeted physical exam, including concomitant medications
- ECG (only at Weeks 57, 105, 153)
- DXA (in BMD subset only, and only at Weeks 57, 105) and dietary calcium and Vitamin D assessment
- Blood collection
- Urine collection for urinalysis (only at Weeks 57, 105, 153)
- Urine collection for GC/CT testing (only at Weeks 33, 57, 81, 105, 129, 153, 177)
- Rectal swab for GC/CT testing (only at Weeks 33, 57, 81, 105, 129, 153, 177)
- Administer injection
- Dispense pills

Laboratory Evaluations

- HIV testing (see SSP Manual)
- HCV testing (only at Weeks 57, 105, 153)
- CBC with differential
- Chemistry testing (see Appendix 1b)
- Liver function testing (see Appendix 1b)
- Fasting lipid profile (only at Weeks 57, 105) (see Appendix 1b)
- Syphilis serologic testing (only at Weeks 33, 57, 81, 105, 129, 153, 177)
- Urinalysis (only at Weeks 57, 105, 153)
- Urine GC/CT testing (only at Weeks 33, 57, 81, 105, 129, 153, 177)
- Rectal swab GC/CT testing (only at Weeks 33, 57, 81, 105, 129, 153, 177)
- Plasma storage
- DBS storage

NOTE: All HIV test results from previous visits and at least one HIV test result from the current injection visit must be available and confirmed to be negative/non-reactive PRIOR to injection of study product. The injection must not be given if any HIV test is reactive/positive.

Results from the other laboratory evaluations (e.g., chemistry, LFTs, hematology) from the visit prior to the injection visit must be available and be reviewed by the IoR or designee prior to injection.

5.7 Step 2: All remaining safety visits, with Week 10 occurring 1 week after the Week 9 injection, and every 2 weeks after each injection visit thereafter as - Weeks 10, 19, 27, 35, 43, 51, 59, 67, 75, 83, 91, 99, 107, 115, 123, 131, 139, 147, 155, 163, 171, 179, 187

Administrative, Behavioral, and Regulatory Procedures

- Locator information
- HIV counseling
- Offer condoms and lubricant
- Adherence counseling

Clinical Procedures

- Targeted medical history and targeted physical exam, and concomitant medications
- Blood collection
- ISR evaluation

Laboratory Evaluations

- HIV testing (see SSP Manual)
- CBC with differential
- Chemistry testing (see Appendix 1b)
- Liver function testing (see Appendix 1b)
- Plasma storage

Note: Refer to Appendix II for any participant who becomes infected with HIV during Step 2.

5.8 Step 3: Open-label extension

(Day 0, Weeks 12, 24, 36, 48)

Administrative, Behavioral, and Regulatory Procedures

- Locator information (Week 48 location information to be collected for reporting of or follow up safety labs/HIV testing after study exit)
- HIV counseling
- Offer condoms and lubricant
- Acceptability assessment (Only administer acceptability assessment at week 0 as final assessment if not done in the previous 24 weeks on Step 2)
- Behavioral assessment (only at Day 0, Weeks 24 and 48; if conducted within the last month before entering Step 3, skip Day 0 and conduct at Weeks 12, 24, and 48)

- Adherence counseling (only at Day 0, Weeks 12, 24, and 36)

Clinical Procedures

- Targeted medical history and targeted physical exam, including concomitant medications
- Blood collection
- Urine collection for GC/CT testing (only at Day 0, Weeks 24, 48. Skip Day 0 if testing occurred within 3 months prior to Day 0, and conduct at Weeks 24 and 48 only)
- Rectal swab collection for GC/CT testing (only at Day 0, Weeks 24, 48. Skip Day 0 if testing occurred within 3 months prior to Day 0, and conduct at Weeks 24 and 48 only)
- Dispense pills (only at Day 0, Weeks 12, 24, 36)

Laboratory Evaluations

- HIV testing (see SSP Manual)
- Chemistry testing (only at Weeks 24 and 48) (see Appendix 1c)
- Liver function testing (only at Weeks 24 and 48) (see Appendix 1c)
- Syphilis testing (only Day 0, Weeks 24, 48. Skip Day 0 if testing occurred within 3 months prior to Day 0, and conduct at Weeks 24 and 48 only)
- Urine GC/CT testing (only Day 0, Weeks 24, 48. Skip Day 0 if testing occurred within 3 months prior to Day 0, and conduct at Weeks 24 and 48 only)
- Rectal swab GC/CT testing (only Day 0, Weeks 24, 48. Skip Day 0 if testing occurred within 3 months prior to Day 0, and conduct at Weeks 24 and 48 only)
- Plasma storage

NOTE: 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.

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.

5.9 Injection Visit Windows

The visit windows for all visits, including injection visits, are outlined in the SSP Manual. In brief, the visit window for injection visits for the Week 5 and 9 injections is +/- 3 days, and is +/- 7 days for all other injections visits. If a participant is unable to report to the visit during this time frame, or if the participant misses their appointment within this time frame, the CMC must be contacted for consultation regarding whether rescheduling outside of the visit window is allowable.

5.10 Procedures for Continued Oral and Injectable Dosing

Appendix III, Toxicity Management, must be referred to regarding general toxicity management, as well as specific clinical and laboratory toxicity management guidelines, including directions regarding temporary and permanent study product holds.

5.11 Procedures for Participants Who Do Not Complete the Full Course of Injections

Participants on either arm who have received at least one injection and refuse further injections or discontinue due to an AE will enter Step 3 and be followed on open-label TDF/FTC according to Step 3 Arm A assessments; such participants will remain blinded to their original randomized assignment.

Participants who are unable to receive the first injection for any reason will be terminated from the study. If the reason is due to HIV infection, those participants will be referred for care and will be terminated from the study.

5.12 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, and when all corresponding procedures at the HPTN SDMC, LC, and LOC have been completed), the study will be unblinded. Participants will move to Step 3 and be unblinded following final confirmation from the HPTN SDMC.

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

5.13.1 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 the Screening and Enrollment (at 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 will be included in the SSP Manual.

5.13.2 Follow-up (after study Enrollment)

Frequent testing for HIV acquisition during the study period 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. Therefore, HIV testing will be performed at all scheduled study visits. In addition, if a participant has signs or symptoms consistent with acute HIV infection (see above), or expresses a concern about recent HIV acquisition, HIV testing will be performed using an ribonucleic acid (RNA) test that, in the opinion of the Investigator of Record 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 testing, 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. Samples from participants with confirmed HIV infection should be sent both 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 for email alias regarding suspected HIV infection), including the HPTN LC. Refer to the SSP Manual for instructions regarding HIV testing.

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.

Participants with confirmed HIV infection during Step 2 will not receive additional injections or oral study product, and will be followed per the Schedule of Evaluations and Procedures in Appendix II for approximately 52 weeks. In these cases, the randomized study product assignment will be provided by the HPTN SDMC directly to the participant's primary care provider. See the SSP Manual. 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 immediate suppressive ART treatment to prevent persistent-monotherapy-related resistance complications for a minimum of 52 weeks post-final injection. The sites will not be responsible for the actual provision/payment of ART. ART or funds for provision of ART will not be provided by the study.

Participants with confirmed HIV infection during Step 3 will be followed at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by the CMC.

5.14 Sexually Transmitted Infections

Testing for GC/CT and syphilis will occur throughout the study. Testing will be performed at the local laboratory. For rectal swabs, if testing cannot be performed at the local laboratory, testing at another laboratory may be arranged (see SSP Manual).

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.

Positive testing for syphilis should be referred to the CMC for adjudication accompanied by any prior testing and treatment results.

5.15 Hepatitis B and Hepatitis C

Testing for HBV and HCV will be performed at Screening (HBsAg and HCAb)). Persons positive for these tests will not be allowed to enroll in the study and will be referred to their primary provider for management. Persons with a positive HCV antibody test at Screening will be excluded from the study, even if confirmatory HCV RNA is undetectable. At Enrollment, participants will be tested for HBV surface antibody (HBsAb), and HBV Core antibody (HBcAb). Participants who do not have evidence of immunity to HBV (e.g., negative HBsAb) will be referred for 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.

5.16 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 case report forms. 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 case report form, and provide or refer the participant to appropriate medical care.

5.17 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 approval of the CMC, withdraw participants before their scheduled termination visit to protect their safety, 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 terminate the study prior to its planned end date. Study staff will record the reason(s) for all withdrawals in participants' study records.

5.18 Pharmacokinetic Monitoring

Plasma and DBS will be collected throughout the study for PK studies. The specimen type(s) used to assess adherence to TDF/FTC will be determined by the HPTN LC. Results of this testing will not be provided to study sites or participants.

6.0 SAFETY MONITORING AND ADVERSE EVENT (AE) REPORTING

6.1 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 team will have regularly scheduled conference calls during the period of study implementation, and additional ad hoc calls will be convened if required.

The study site Investigators are responsible for continuous close monitoring and management of AEs in conjunction with IoRs. 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 Clinical Management Committee (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.

6.2 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 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.

The SDMC will prepare routine study conduct and safety reports for the SMC, which will meet by conference call approximately every 6 months and will review accrual and retention data, as well as safety data. 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, which will meet at least annually to review safety and efficacy data.

6.3 Adverse Event 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 2 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.

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 AE to study product will be assessed as specified in Version 2.0, January 2010 of the DAIDS Expedited Adverse Event (EAE) Reporting Manual.

6.4 Expedited Adverse Event Reporting

Requirements, definitions, and methods for expedited reporting of adverse events are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the DAIDS Regulatory Support Center (RSC) website at http://rsc.tech-res.com/safetyandpharmacovigilance.

6.4.1 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.

Where DAERS has not been implemented, 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/safetyandpharmacovigilance/. For questions about EAE reporting, please contact the RSC at DAIDSRSCSafetyOffice@tech-res.com.

6.4.2 Reporting Requirements for this Study

The Serious Adverse Event (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≥3xULN AND total bilirubin≥2xULN
- Any seizure event

These reporting requirements are required for each study participant from enrollment (week 0) until their 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 or placebo; CAB LA injectable suspension (200mg/mL) or placebo; TDF/FTC fixed dose combination tablet containing 200 mg of FTC and 300 mg of TDF or placebo (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 2 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.

6.4.3 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 adverse events. The DAIDS grading table is available on the DAIDS RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

6.5 Social Impact Reporting

It is possible that participants' involvement in the study could become known to others, and that a social impact may result (i.e., because participants could be perceived as being HIV-infected or at risk or "high risk" for HIV infection). For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities. A social impact 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 impacts will be collected and reported on CRFs during regular visits. In the event that a participant reports a social impact, 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 CAB in exploring the social context surrounding instances of social impacts, to minimize the potential occurrence of such an impact.

7.0 STATISTICAL CONSIDERATIONS

7.1 Review of Study Design

This is a Phase 2b/3 randomized, multi-site, two-arm, double-blinded, double-dummy study of the safety and efficacy of CAB LA vs. TDF/FTC for MSM and TGW. Eligible participants will be randomized 1:1 to receive either oral CAB/CAB LA or matching placebo or daily oral TDF/FTC or matching placebo, and move through 3 steps. Participants will be assigned either active cabotegravir or active TDF/FTC – no participant will receive placebo only. In Step 1, study participants will receive oral tablets for 5 weeks, followed by entering Step 2 and undergoing a single injection at two time points 4 weeks apart and every 8 weeks thereafter and daily oral tablets until the required number of incident HIV endpoints is accrued (172), estimated to be when the final participant reaches 60 weeks on Step 2 (week 65 for the final participant). In Step 3, all participants will receive open-label daily oral TDF/FTC for up to 48 weeks. Participants will therefore be followed between 113 weeks to 233 weeks (between 65 and 185 weeks on blinded study medication and up to 48 weeks on open-label daily oral TDF/FTC). All participants will transition to local HIV prevention services after their completion of Step 3.

7.2 Considerations in Non-Inferiority Trials

Large, high-quality clinical trials have previously established that TDF/FTC can be a highly effective HIV PrEP agent when adherence to the drug is high (iPrEx, TDF2, Partners-PrEP, and presumably PROUD and IPERGAY). When good evidence exists that supports the use of a readily available, FDA-approved product, and in particular when the endpoint of interest is serious (such as HIV infection), it is generally considered unethical to conduct a placebo-controlled trial. The International Conference on Harmonization guidance E10 on *Choice of Control Group and Related Issues in Clinical Trials* (ICH E10) states:

In cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control. [The term "generally" leaves room for a placebo control if the known effective treatment is very toxic.]

In addition, recent guidance from UNAIDS/WHO on Ethical Considerations in Biomedical HIV Prevention Trials (Guidance Point 15) states that "the use of a placebo control arm is ethically acceptable in a biomedical HIV prevention trial only when there is no HIV prevention modality of the type being studied that has been shown to be effective in comparable populations." Providing a placebo in the context of HIV PrEP would be the same as withholding the effective drug, TDF/FTC, which is nontoxic and has few serious side effects (iPrEx, TDF2, Partners-PrEP, PROUD, iPERGAY). Therefore, rather than comparing CAB LA to placebo, a non-inferiority trial is proposed to evaluate whether CAB LA is not unacceptably worse than ("non-inferior" to) the active comparator TDF/FTC. If CAB LA is shown to be non-inferior to TDF/FTC, it can be inferred with reasonable certainty that CAB LA is effective.

7.2.1 Constancy

A positive result in a non-inferiority trial must be interpreted with caution. Establishing non-inferiority could mean either that both treatments are similarly effective, or that both treatments

are similarly ineffective. In order to assure that a positive trial indicates efficacy, it is critical to select a study population in which the standard regimen has been shown to work and is expected to work in the future. The term "constancy" is often used to describe the degree to which the active control is effective in a new study population. A critical factor defining constancy for TDF/FTC is drug adherence. TDF/FTC efficacy (as with most drugs) is highly dependent on adherence, hence the degree to which CAB LA would be judged to be effective based on a comparison with oral TDF/FTC would depend heavily on observed TDF/FTC adherence.

Although there is some suggestion that oral TDF/FTC may have higher efficacy for rectal exposures than for vaginal exposures, strong evidence does not yet exist to conclude this. Regardless, HPTN 083 will recruit only TGW and MSM, both of whom are expected to have the highest risk of HIV acquisition based on rectal exposure, and prior studies suggest that TDF/FTC is effective in this population.

7.3 Justification of the Non-inferiority Margin

The protocol design is based on a pre-specified NI margin that preserves 50% of the lower bound of proven efficacy in this risk population, using a combination of statistical, prevention and clinical judgment. This section describes the data that support the margin, the effect of different adherence assumptions on the choice of margin and interprets the margin as an absolute increase in number of infections.

7.3.1 Selecting a Non-inferiority Margin (M1 versus M2)

The non-inferiority margin is the degree to which the experimental intervention can have lower efficacy than the active control, but not be considered "clinically unacceptably worse." Defining the non-inferiority margin requires knowledge of the effect size provided by the active control, preferably based on multiple high-quality controlled trials. This is the M1 margin. It also requires an assessment of the "clinically acceptable" degree of inferiority, or the proportion of the active drug effect that must be preserved. This is the M2 margin, which is always stricter than M1.

When defining the effect size of TDF/FTC, it is fortunate to have results from five large, high-quality, controlled trials (iPrEX, TDF2, Partners-PrEP, VOICE, FEM-PrEP), as well as two smaller studies in MSM (PROUD and iPERGAY) which allow to estimate TDF/FTC efficacy. Meta-analysis can be used to combine results from existing trials, and estimate confidence bounds (see next section).

A standard practice to define the margin is to define M1, or the active-control efficacy, as the lower bound of the 95% confidence interval for the efficacy estimate for placebo compared to the standard of care (TDF/FTC). The lower bound is used as a conservative estimate of efficacy, acknowledging both the uncertainties associated with sampling variation and the potential that the constancy assumption may not be perfectly met in a new study. M2 is defined relative to this M1. In a successful trial, the upper 95% confidence bound on the relative efficacy (experimental treatment versus active control) will fall below the pre-specified non-inferiority margin. This method, requiring that the upper bound of the NI study's 95% CI falls below some fraction of the lower bound of the 95% CI from the originator's studies is referred to as the "95-95" method.

The key question is where to determine the M2 margin. Clinical judgment comes into play when defining this margin. One metric for acceptability of the margin is the absolute effect: in this setting, the number of additional infections per (e.g.) 10,000 patient years of exposure in the studied population were cabotegravir to be licensed. A second metric is the relative effectiveness: to set M2 to preserve a fixed proportion of M1, e.g., select M2 to preserve at least half of the (lower bound of) active-control efficacy. Both measures should be taken into account. Because it is believed to be clinically and ethically important that a new PrEP modality provide not just minimal efficacy, but also preserve a meaningful amount of TDF/FTC's effect, the protocol is designed using an M2 margin that preserved 50% of the M1 margin.

7.3.2 Deriving the M1 Margin Using Meta-analysis of Existing PrEP Trial Results

Estimating efficacy for the active control in a non-inferiority trial requires results from prior trials, if available, and meta-analysis is often used to combine those prior results. It is fortunate to have five large, high-quality, controlled trials (iPrEX, TDF2, Partners-PrEP, VOICE, FEM-PrEP), as well as two smaller studies in MSM (PROUD and iPERGAY), all of which can be incorporated in to meta-analytic models. The difficulty, however, is that these existing trials were conducted in widely varying populations with widely varying levels of adherence. To satisfy the constancy assumption, TDF/FTC efficacy must be estimated using settings that closely match the setting of the proposed study. Given the heterogeneity between existing PrEP trials, directly combining the results from those trials (e.g., using fixed-effects meta-analysis) may not be appropriate.

Several approaches are possible. First, the iPrEX trial is the only major trial of TDF/FTC among MSM and TGW in study locations that are similar to the locations planned for HPTN 083: the iPrEx study locations were primarily in the Americas, but also included participants from Thailand and South Africa. Based on transmission risk factors and demographic similarities, it could make sense to use the iPrEx results alone to estimate TDF/FTC efficacy and the corresponding non-inferiority margin. However, the adherence level to TDF/FTC in iPrEx was only moderate (reported as 51%[1]). After publication of iPrEx results, and in combination with the strong positive results from Partners PrEP, TDF2, iPERGAY, and PROUD, there is broad confidence in TDF/FTC. This confidence may translate into higher overall adherence in HPTN 083, and consequently increase TDF/FTC's efficacy in HPTN 083 as compared to iPrEx.

A second option would be to combine the results from the three trials conducted in MSM, namely iPrEx, iPERGAY, and PROUD. The latter two trials are relatively small, but their higher efficacy presumably resulted from higher adherence (not published), and the combined results from these three trials (using a fixed-effects meta-analysis) may represent an average effect that better represents TDF/FTC efficacy in a more adherent population. The two smaller studies, however, were conducted in MSM recruited in England (PROUD), Canada and France (iPERGAY), a population that is quite different demographically than the iPrEx population.

A third option is to use the results from the five large trials and explicitly model TDF/FTC adherence as an effect moderator. By using a mixed-effects modeling approach, the meta-

[1] Defined as the proportion of specimens with quantifiable drug > 10 ng/mL in 43 matched control specimens from HIV-uninfected participants randomized to Truvada.

analysis can account for the known heterogeneity between study populations (random effects component), and explicitly estimate the relationship between adherence and efficacy (fixed effects component). A broad range of adherence levels is represented in these trials, and this makes it possible to estimate efficacy at moderate (e.g., 55%) or moderately high (e.g., 75%) levels of adherence without extrapolating beyond the range of observed data[2]. Incorporating results from all five major trials should provide a more robust, precise estimate of TDF/FTC efficacy than estimates based on fewer or smaller studies, and the ability to estimate efficacy at specific adherence levels allows for computing a non-inferiority margin tailored to the projected adherence levels in HPTN 083.

The iPrEx study alone gives a Placebo-versus-TDF/FTC estimate (95% C.I.) equal to 1.79 (1.20, 2.67) yielding a M2 non-inferiority margin of 1.09. A fixed-effects (using inverse variance weighting) meta-analysis of the three MSM trials gives a larger Placebo-versus-TDF/FTC relative risk (95% C.I.) of 2.20 (1.52, 3.18), which gives a M2 non-inferiority margin equal to 1.23. A mixed-effects meta-analysis[79] of the five major PrEP trials reveals a range of potential TDF/FTC efficacy depending on adherence (Table 3), and a corresponding range of non-inferiority bounds. Figure 6 shows the individual efficacy results and the results of the random effect meta-analysis with adherence as an effect modifier.

[2] 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. This generally corresponds to evidence of TDF/FTC taken within 2-3 days of the visit.

Figure 6: A Random Effects Meta-analysis of PrEP Trials with Adherence as Effect Modifier

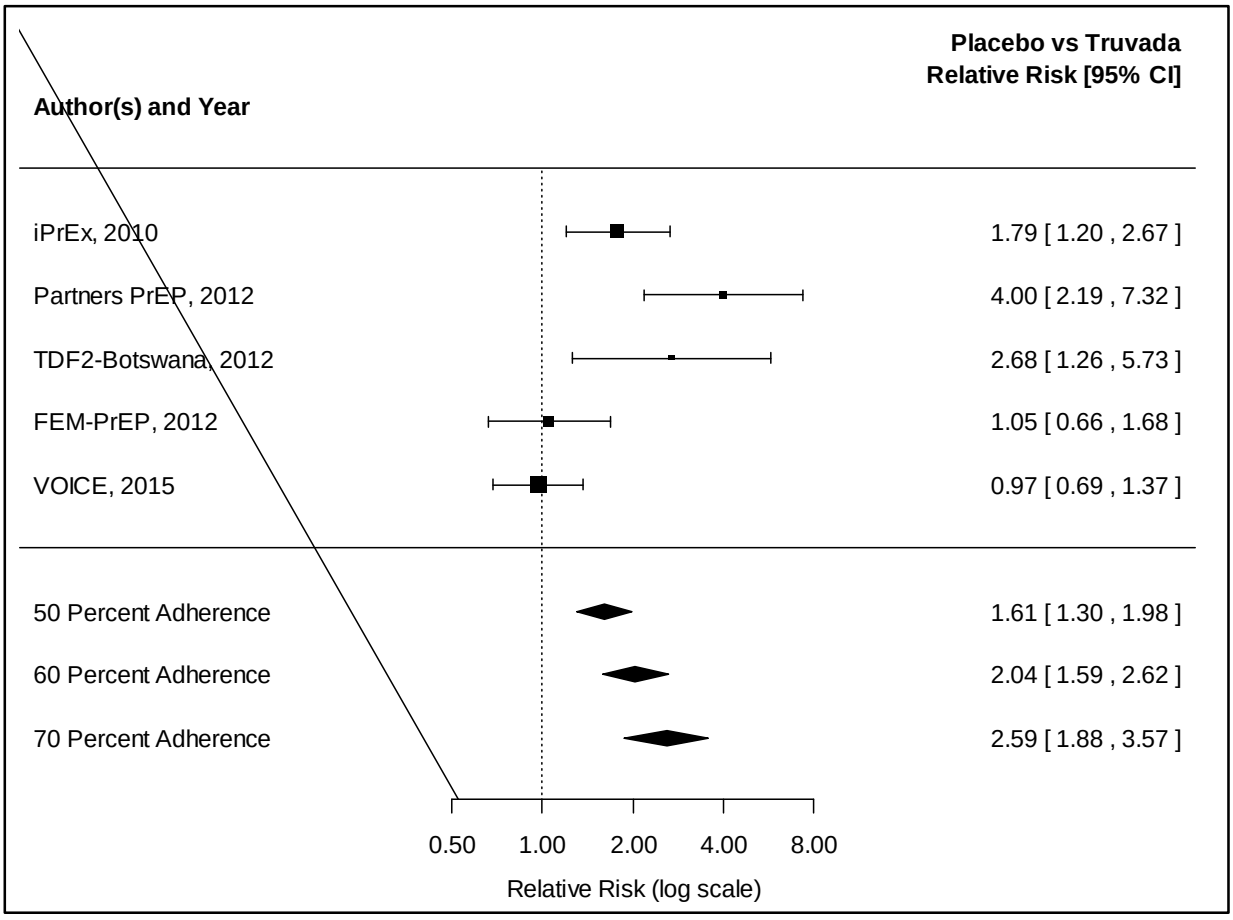


Table 3: The M2 non-inferiority margins based on fixed and random effects meta-analysis

Fixed Effects				
Trials Included	Placebo/TDF/FTCRR	95%LB	95%UB	NI Margin (M2=50%)
iPrEx	1.79	1.20	2.67	1.09
iPrEx, PROUD, iPERGAY	2.20	1.52	3.18	1.23
Mixed Effects: Includes five major placebo controlled trials of TDF/FTC as PrEP, adjusting for measured drug adherence as an effect moderator.				
TDF/FTC Adherence[2]	Placebo/TDF/FTCRR	95%LB	95%UB	NI Margin (M2=50%)
40%	1.26	1.02	1.57	1.01
50%	1.61	1.30	1.98	1.14
60%	2.04	1.59	2.62	1.26
70%	2.59	1.88	3.57	1.37

Of note is the similarity between the 1.23 margin given by the combined three MSM studies, as compared with the 1.26 margin given by the mixed-effects model at 60% adherence. As expected, the mixed-effects model that includes all five major trials gives a more precise estimate (narrower confidence interval), and it is reassuring the two estimates are well aligned.

7.3.3 Selection of the NI Margin.

The random effects meta-analysis suggests that different NI margins could be justified depending on TDF/FTC adherence. In addition, given that injection of CAB LA should confer an adherence advantage, the relative efficacy of CAB LA vs TDF/FTC may increase as TDF/FTC adherence decreases. Table 4 describes potential pairings of NI margins and relative risks for assumed levels of adherence to daily TDF/FTC. These choices imply differing sample sizes, expressed here as the total number of events required.

Table 4: Number of Events Required for a Non-inferiority Trial of CAB-LA vs TDF/FTC, Under a Range of Non-inferiority Margins Implied by Different Levels of Adherence to TDF/FTC, and Relative Risks that Decrease as Adherence Increases.

TDF/FTC Adherence	NI Margin	CAB LA vs TDF/FTC	Non-treated HIV-incidence of 4%		Non-treated HIV-incidence of 5%		# of Events Needed for 90% Power
			TDF/FTC Incidence*	CAB LA incidence	TDF/FTC Incidence	CAB LA incidence	
45%	1.08	0.65	2.82%	1.83%	3.52%	2.29%	164
50%	1.14	0.65	2.50%	1.62%	3.12%	2.03%	134
55%	1.20	0.75	2.21%	1.66%	2.77%	2.08%	191
57.5%	1.23	0.75	2.09%	1.56%	2.61%	1.95%	172
60%	1.26	0.75	1.96%	1.47%	2.45%	1.84%	157
70%	1.37	0.85	1.54%	1.31%	1.93%	1.64%	185
75%	1.43	0.85	1.37%	1.16%	1.71%	1.46%	156

* Using effectiveness estimates from meta-analysis

The current trial design is designed with a NI margin of 1.23. Using the random effects modeling of the 5 major trials with an adherence biomarker assessment this corresponds to an assumption of ~55-60% TDF/FTC adherence. This is also the estimated effect from the fixed effect modeling of the three MSM studies.

7.3.4 The NI margin: Absolute Difference in Proportion Infected

A non-inferiority margin also requires consideration of the "acceptable" number of additional infections per (e.g.) 10,000 patient years of exposure in the studied population were cabotegravir to be licensed on the basis of a finding of non-inferiority. In this trial design, because it is assumed CAB LA is somewhat more effective that TDF/FTC, a non-inferiority finding requires an observed relative risk less than one, i.e., fewer infections with CAB LA than TDF/FTC. Nonetheless, respecting the interpretation of the 95-95 rule, the prevention impact implied by the upper 95% confidence limit is presented.

In Table 5, the number of additional HIV infections that would be expected among people treated with CAB LA as compared to TDF/FTC if the risk ratio were equal to the margin (i.e., the worst case scenario) is computed. Note that this corresponds to the upper bound of the trial's 95% confidence interval, which would be more extreme than the risk ratio actually observed in the trial. For example, if a 1.23 margin were ruled out just at the boundary under the proposed trial design, 90 infections in the TDF/FTC arm and 82 in the CAB LA arm (i.e., a RR = 0.91) would be observed, but the upper 95% confidence limit would imply CAB LA could be as much as 23% worse than TDF/FTC. This corresponds to the potential for 48 additional infections per 10,000 person years on CAB LA vs TDF/FTC at the NI margin. Note that, without treatment, the expected number of infections for background rates of 4% and 5% incidence is 400 and 500, respectively**.**

Table 5: Prevention Impact Implied by the Choice of Non-inferiority Margin Under Selected TDF/FTC Adherence and Relative Risk Assumptions.

TDF/FTC Adherence	NI Margin	RR of CAB LA vs TDF/FTC RR	Trial results if just rule out the NI margin		Implied prevention impact	
			Observed[†] CAB Infections	Observed TDF/FTC Infections	Additional CAB Infections per 10,000 pyrs implied *at the NI margin*[§]	
					4% HIV Incidence*	5% HIV Incidence*
45%	1.08	0.65	73	91	23	28
50%	1.14	0.65	60	74	35	44
55%	1.20	0.75	91	100	44	55
57.5%	1.23	0.75	82	90	48	60
60%	1.26	0.75	75	82	51	64
70%	1.37	0.85	94	91	57	71
75%	1.43	0.85	80	76	59	74

[†] Observed number of events in the trial if the upper bound of the 95% CI is at the NI margin.

* Background HIV incidence in the untreated study population; per arm incidence and total number of events for each row as in Table 4.

[§] Estimated at the upper 95% confidence bound exactly equal to the NI margin. Additional infections computed as (TDF/FTC incidence x NI margin – TDF/FTC incidence) x 10,000.

7.4 Re-assessing the NI margin at the Completion of the Trial

The study is designed with a fixed non-inferiority margin specified in advance. However, the appropriate margin at completion could be broader or narrower than that specified in the protocol. For low levels of TDF/FTC adherence, HPTN 083 may demonstrate superior efficacy of directly observed, injectable, long-acting therapy. A narrow non-inferiority margin is consistent with the trial objectives in this setting. For high levels of TDF/FTC adherence, the rate of infection on TDF/FTC is expected to be low and a comparatively higher M2 margin expressed as an RR may still lead to an acceptable non-inferiority margin.

The study will obtain a rigorous, objective, assessment of adherence to TDF/FTC from dried blood spots and/or plasma throughout the trial. At the completion of the trial, to assist in the interpretation of the relative efficacy results of CAB-LA vs TDF/FTC, a post-trial NI margin using a fully pre-specified algorithm will be computed. Using pre-existing, external data incorporating all available randomized, placebo controlled trials with known TDF/FTC adherence and efficacy, a pre-specified algorithm to derive the meta-analytic estimate of the M2 boundary corresponding to the TDF/FTC adherence observed in HPTN 083 will be used. Full details of the pre-specified algorithm will be provided in a separate document, updated with all available relevant data on adherence and efficacy prior to the final analysis of the trial.

If observed adherence is higher than 65% or lower than 50%, this recomputed NI margin will be a critical secondary analysis to gauge the prevention efficacy of CAB LA.

7.4.1 Justification for Recomputing the NI Margin

The fixed NI margin selected for the study design is justified by a meta-analysis combining trials that in all likelihood had different adherence levels. Whether this NI margin establishes that CAB LA is substantial better than placebo depends on the actual adherence to TDF/FTC in the current study. In reality, the selected NI margin of 1.23 could either be insufficient to establish CAB LA prevents HIV infection or be overly conservative.

Table 6 details the absolute change in HIV incidence that would be implied under CAB LA if the true efficacy of CAB LA is lower than TDF/FTC by the upper bound of the CAB LA/TDF/FTC relative-risk confidence bound, i.e., when true relative efficacy of TDF/FTC vs CAB LA is equal to the non-inferiority margin. This is the worst-case-scenario expected based on a clinical trial that just concludes non-inferiority.

Higher than expected TDF/FTC adherence: If adherence to TDF/FTC is as high as 75%, efficacy similar to that seen in PROUD and iPERGAY would be anticipated. In this case, even assuming CAB LA were a modest 15% more effective than TDF/FTC (i.e. RR = 0.85), a 172 event trial has only 46% power to rule out a HR of 1.23, under reasonable assumptions of implied efficacy of TDF/FTC. As Table 4 suggests, if adherence is 75%, a larger margin of 1.43 could be justified. Against this margin, a 172 endpoint trial would retain 82% power. Table 6 illustrates the absolute increase in infection rates implied by this margin. In 75% adherence setting, assuming a background incidence of 5/100 PY, we expect TDF/FTC incidence to be reduced to 1.7/100 PY; the upper bound of the CAB LA incidence in a NI trial with a 1.43 margin would be 2.4/100 PY, still substantially lower than 5/100 PY and an **absolute increase of 0.7/100 PY compared to TDF/FTC**.

Lower than expected TDF/FTC adherence: If adherence to TDF/FTC is as low as 40%, we anticipate efficacy lower than that seen in iPrEX, in which case the trial has >99% power to rule out a HR of 1.23 if the RR of CAB LA to TDF/FTC is 0.75. However, as Table 6 indicates, if adherence is 40%, ruling out a HR of 1.23 would likely not provide adequate evidence for effectiveness of CAB-LA over placebo. In this lower adherence setting, the justified NI margin is close to 1.0, implying that CAB-LA should have to achieve close to superiority relative to TDF/FTC to ensure it is in fact better than placebo. Table 6 illustrates that the 1.23 bound in this

scenario corresponds to an expected incidence rate with Cabotegravir of 4.9/100 PY - virtually the same as no treatment at all.

Table 6: HIV incidence Under Cabotegravir if the True Efficacy of Cabotegravir is Lower than TDF/FTC by the Upper Bound of the CAB/TDF/FTC Relative-risk Confidence Bound, i.e., when true relative efficacy of TDF/FTC vs Cabotegravir is equal to the non-inferiority margin. (This is the worst-case-scenario expected based on a clinical trial that just concludes non-inferiority, i.e., the upper confidence bound equals the NI margin.) Background HIV incidence rate without PrEP assumed to be 5/100 PY.

TDF/FTC Adherence	Implied TDF/FTC Efficacy*	Implied HIV Incidence On TDF/FTC	HIV Incidence on CAB if true CAB/TDF/FTC efficacy equals the NI Margin ("Worst Case Scenario")**								
			NI Margin								
			1.01	1.08	1.14	1.2	1.23	1.26	1.32	1.37	1.43
0.4	21%	4.0%	4.0%	4.3%	4.5%	4.7%	4.9%	5.0%	5.2%	5.4%	5.6%
0.45	30%	3.5%	3.5%	3.8%	4.0%	4.2%	4.3%	4.4%	4.6%	4.8%	5.0%
0.5	38%	3.1%	3.1%	3.3%	3.5%	3.7%	3.8%	3.9%	4.1%	4.2%	4.4%
0.55	45%	2.8%	2.8%	3.0%	3.1%	3.3%	3.4%	3.5%	3.6%	3.8%	3.9%
0.575	48%	2.6%	2.6%	2.8%	3.0%	3.1%	3.2%	3.3%	3.4%	3.6%	3.7%
0.6	51%	2.5%	2.5%	2.6%	2.8%	2.9%	3.0%	3.1%	3.2%	3.4%	3.5%
0.65	57%	2.2%	2.2%	2.3%	2.5%	2.6%	2.6%	2.7%	2.8%	2.9%	3.1%
0.7	61%	2.0%	2.0%	2.1%	2.2%	2.3%	2.4%	2.5%	2.6%	2.7%	2.8%
0.75	66%	1.7%	1.7%	1.8%	1.9%	2.0%	2.1%	2.1%	2.2%	2.3%	2.4%

* Based on meta analysis of five major TDF/FTC PrEP trials, TDF/FTC efficacy is predicted based on adherence.
** For the level of TDF/FTC efficacy listed in each row, the column header of the highlighted cell contains the corresponding M2 non-inferiority margin.

7.5 Endpoints

7.5.1 Primary Endpoint

- Number of documented incident HIV infections in Steps 1 and 2
- Grade 2 or higher clinical and laboratory adverse events

7.5.2 Secondary Endpoints

- Number of documented incident HIV infections in Step 2
- Number of documented incident HIV infections in Steps 1, 2, and 3
- Number of documented incident HIV infections in Step 3
- Number of documented incident HIV infections in Step 2 and 3
- Kidney function as measured by: changes from baseline in creatinine and creatinine clearance

- Liver function as measured by: changes from baseline and Grade 3 or 4 liver-related AEs (laboratory assessment of ALT, AST, TBili, CPK or clinical assessment of jaundice/icterus).
- Bone mineral density (DXA subset) as measured by: Changes in Z-score from baseline and DXA criteria for osteopenia and osteoporosis
- Resistance mutations to study products (including but not limited to K65R, M184V/I, Q148R) among seroconverters
- Acceptability scale assessments

7.5.3 Tertiary Endpoints

- Adherence to study product during step 2: For CAB-LA/Placebo CAB-LA scheduled injections received; for TDF/FTC/Placebo TDF/FTC pill dispensing, pill counts
- Plasma and/or DBS levels of TDF in participants randomized to TDF/FTC
- Number of sexual partners (primary and non-primary), number of coital acts, number of non-condom protected anal intercourse acts (insertive and receptive)
- STIs (rectal and urinary GC/CT, syphilis [adjudicated])
- Resource utilization: Clinical visits, acuity visits (related to toxicity) hospital days (related to toxicity), standard laboratory monitoring, laboratory/radiography events (related to toxicity
- Cost-effectiveness: 1-5 year budgetary impact, lifetime expectancy, lifetime costs projections and incremental cost-effectiveness, stratified by country

7.6 Sample Size and Interim Monitoring

Assuming CAB LA is 25% more effective than TDF/FTC, approximately 174 observed HIV-infections will provide 90% power to rule out a non-inferiority margin of HR=1.23, with type-I error alpha = 0.025 (see Figure 7 below). This non-inferiority margin is an M2 margin based on an inverse-variance weighted meta-analysis of three randomized controlled trials of TDF/FTC versus placebo in MSM: iPrex, iPERGAY, and PROUD[4, 35-36]. The M2 margin is defined as the reduced bound that is designed to preserve a clinically acceptable amount of the benefit provided by the active control (TDF/FTC). Setting M2 to be 50% of M1 (on the log scale in the case of hazard ratios) is considered to be conservative. M1 is defined as the lower limit of the 95% confidence interval around the placebo versus active-control HR estimate (1.39, based on the meta-analysis). Once the stated number of HIV-infections have been observed, non-inferiority will be established if the estimated CAB LA versus TDF/FTC hazard ratio point estimate is approximately 0.90 or less (indicating a 10% or better advantage of CAB LA over TDF/FTC), and superiority will be established if the hazard ratio point estimate is approximately 0.68 or less (indicating a 32% or better advantage of CAB LA over TDF/FTC). The power to detect superiority is 47%.

The number of enrolled participants needed to observe the target number of HIV-infections depends on the background HIV incidence in the study populations, the efficacy of CAB LA and TDF/FTC in these populations, the dropout rate, and the study duration. Assuming (a) annual HIV incidence for the TDF/FTC arm is 2.0% (similar to the 1.8% incidence observed in the iPrex OLE study); (b) CAB LA is 25% more protective than TDF/FTC; and (c) the annual dropout rate is 7.5%, then approximately 4500 individuals will be needed to enroll and be followed for an average of 2.5 years. See Figure 8 below.

Interim monitoring will be conducted by an independent DSMB on a regular schedule, with safety review approximately every 6 months, and at least annually. Formal interim analyses will be planned approximately 4 times during the study, using the Lan-DeMets modification of the O'Brien-Fleming stopping bounds to control alpha spending. Superiority bounds will be used for early stopping for favorable risk-to-benefit ratio for CAB LA; non-inferiority bounds will be used for early stopping for unfavorable risk-to-benefit ratio. Thus the study will continue if non-inferiority is established but superiority remains plausible, however the study may end early if non-inferiority is ruled implausible or if inferiority is established.

As this is the first large-scale phase 2b/3 study of IM administration of a biomedical intervention for prevention of sexual HIV transmission, an early feasibility check will be employed whereby after approximately 250 participants have completed 3 injections (Week 29), a treatment-blinded analysis of injection feasibility will be conducted and reported to the SMC and DSMB. Enrollment of the remaining study participants will be deemed feasible if $\geq$ 75% of those 250 participants remain engaged in the trial and have not declined further injections. Enrollment will not be paused for this feasibility assessment, with the condition that no more than approximately 25% of the planned full study population will be enrolled prior to completion of the assessment.

The trial will be terminated at the first occurrence of any of the following: 1) The accrual of 172 incident HIV endpoints; 2) completion of 11,800 person-years of follow-up; or 3) reaching a stopping boundary.

Details of the interim monitoring approach and stopping rules will be further described in the Interim Monitoring Plan.

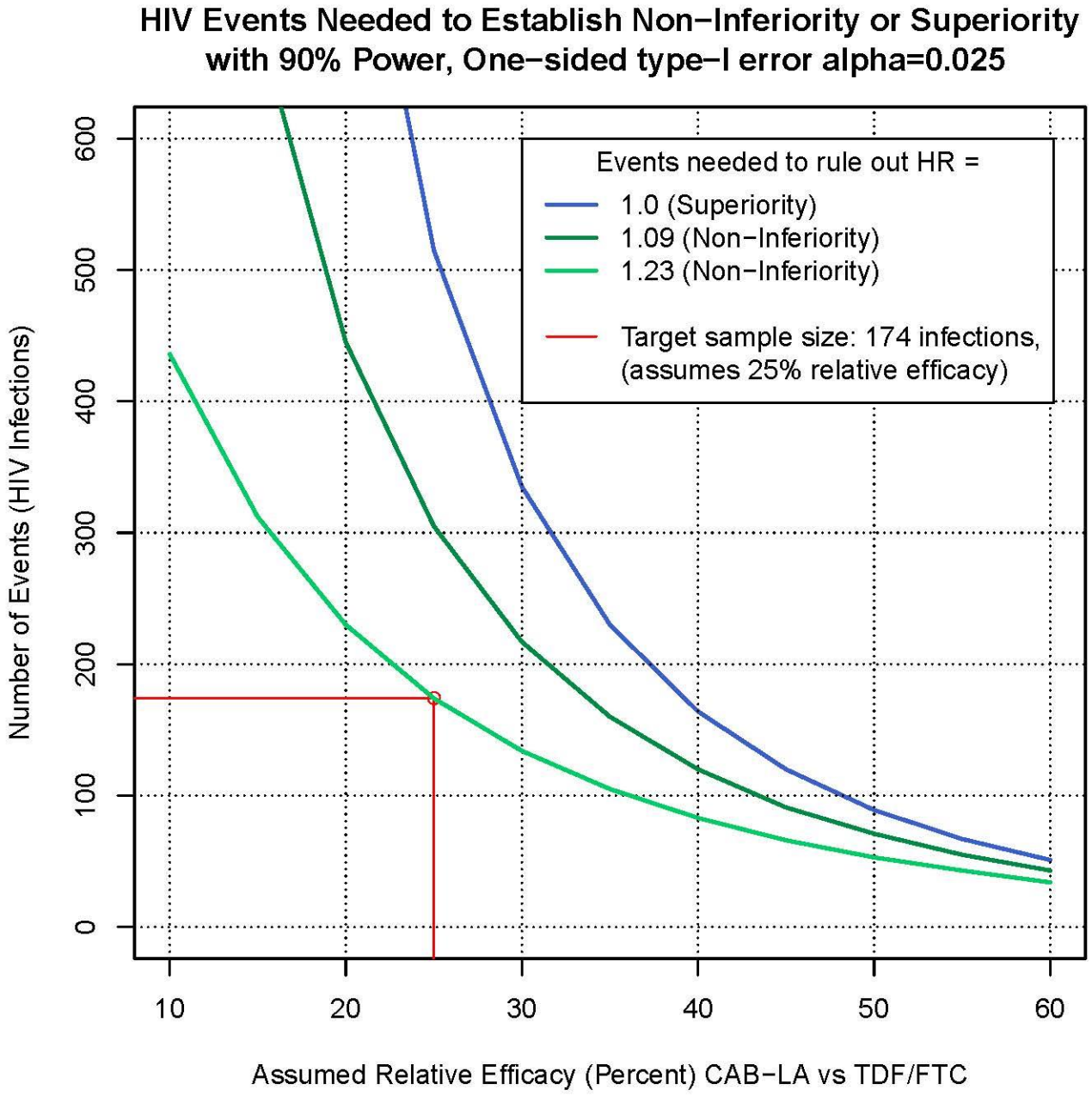


Figure 7: Indicates the number of observed HIV infections required to achieve 90% power for superiority and non-inferiority (NI) designs with NI margins of 1.09 and 1.23. The X-axis shows the relative efficacy of CAB LA vs TDF/FTC, the quantity that this trial is designed to estimate.

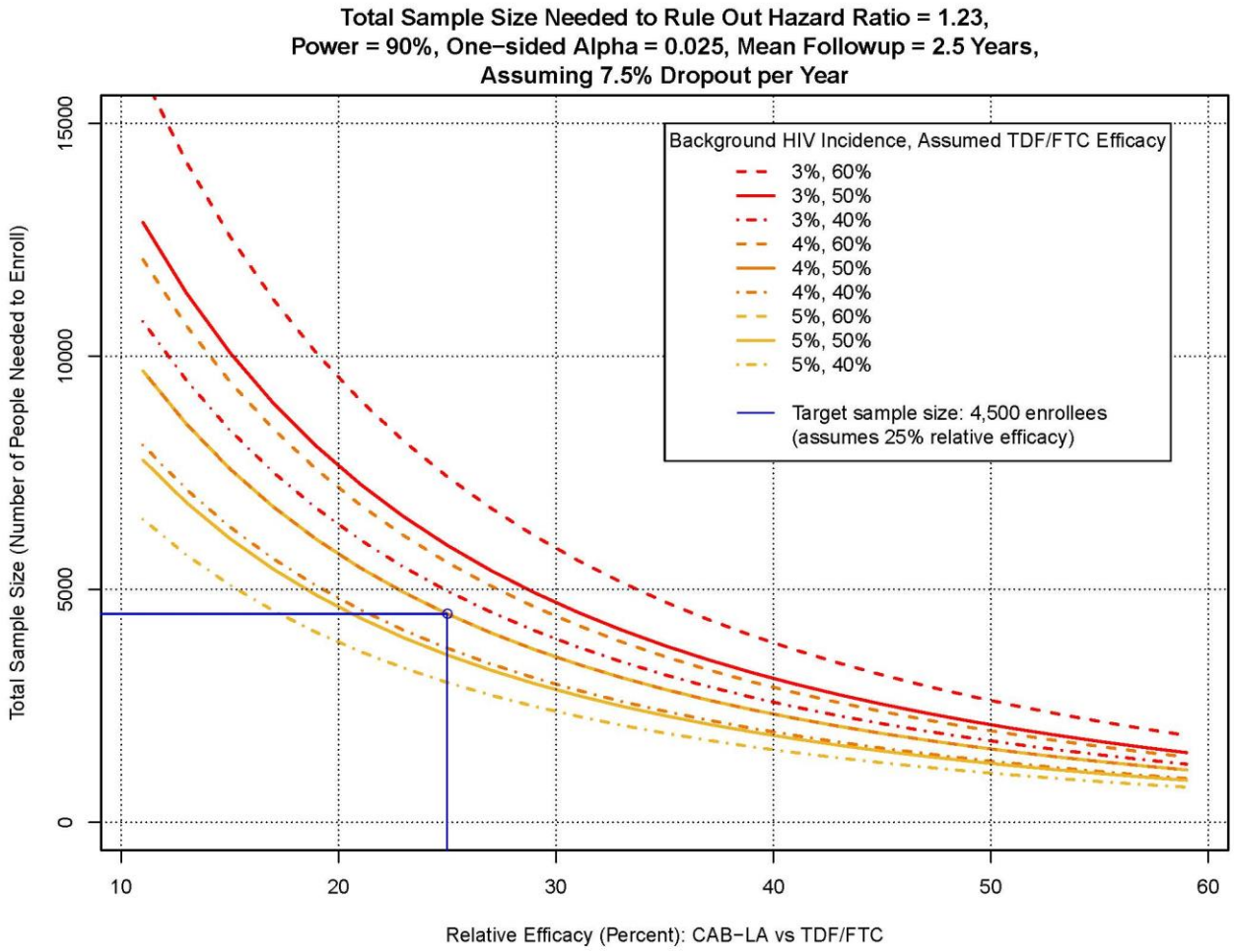


Figure 8: Indicates the total number of people needed to achieve the number of events required for a non-inferiority design (rule out HR of 1.23) under different assumptions of background incidence (i.e. HIV incidence without blinded use of TDF/FTC) and different TDF/FTC efficacy. The X-axis shows the relative efficacy of CAB LA vs TDF/FTC, the quantity that this trial is designed to estimate.

7.7 Accrual and Retention

A total of 4500 participants will be enrolled in approximately 30 months and followed for an average of 2.5 years. An average annual retention rate of at least 92.5% percent will be targeted.

7.8 Random Assignment

Enrolled participants will be randomized to one of two study arms in a 1:1 ratio. Randomization will be stratified by study site, race, and ethnicity, 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.

7.9 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 in to Step 2 completes approximately 60 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 5.13.2, 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 primary health care provider 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.

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

NIAID Data and Safety Monitoring Board oversight is planned for this study. Monitoring guidance will be detailed in a separate Interim Monitoring Plan. In addition, approximately every 6 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 MOP.

7.11 Statistical Analysis

This section briefly describes the final study analyses, unblinded as to treatment arm assignment. Detailed technical specifications of the statistical analyses will be described in a separate Statistical Analysis Plan.

7.11.1 Analyses of Primary Efficacy Objective

- To compare HIV incidence among participants randomized to oral CAB/CAB LA (oral lead in and injections) vs. oral TDF/FTC (Steps 1 and 2)

MITT: A modified intent-to-treat will be used as the primary assessment for the efficacy comparison, thus all participants who receive at least one dose of oral study product will contribute to the primary analyses. Any participant determined to be HIV infected prior to receiving study product will be omitted from the analysis.

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 based on Poisson distribution assumptions.

Treatment efficacy will be estimated as TE= 1 - HR. The Hazard Ratio comparing CAB-LA vs TDF/FTC and 95% confidence intervals will be estimated using Cox proportional hazards with treatment arm as the only covariate, stratified by site.

Per protocol: A per protocol estimate of treatment efficacy will be conducted as a secondary analysis in the non-inferiority context of active control, as a verification that a similar HR estimate is obtained in the compliant population. Compliance will be defined as: Adherent by administration and plasma TDF concentrations: In CAB LA arm, from the time of receipt of the injection the participant is considered adherent for 8 weeks. In the TDF/FTC arms, from time of dispensing pills the participant is considered adherent if plasma TDF concentrations are detectable at 8 weeks. Each HIV testing interval (time period between determining HIV status through study testing) will be defined as compliant if participant has TDF levels consistent with 4 or more doses per week by appropriate pharmacokinetic laboratory assays.

Estimates will be computed as follows:

- Time varying compliance: Compliance will be a time-dependent covariate, and the HR for efficacy CAB-LA vs TDF/FTC during periods of compliance will be estimated using Cox proportional hazards with an interaction term between study arm and compliance. The estimate of efficacy will be the HR for CAB-LA vs TDF/FTC in the compliant periods.
- Estimate in the compliant cohort: The compliant cohort is defined as those participants who were adherent >80% of their time on study. The same methods as detailed for the primary analysis will be used for estimating effectiveness on the compliant cohort. Evidence of confounding in this cohort will result in an analysis that is adjusted for additional baseline risk covariates.

7.11.2 Analyses of Primary Safety Objective

- To compare the safety of oral CAB/CAB LA vs. oral TDF/FTC

Local reactions

The number and percentage of participants experiencing local reactions to the injections will be tabulated by severity and treatment arm and the percentages displayed graphically by 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. Kruskal-Wallis tests will be used to test for differences in severity between arms.

AEs and 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. Formal statistical testing comparing arms is not planned since interpretation of differences must rely heavily upon clinical judgment.

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.

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 (values outside the box plot) will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

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

7.11.3 Analyses of Secondary Objectives

- To compare HIV incidence among participants receiving CAB LA vs. oral TDF/FTC (each step independently and all steps in aggregate).

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

The same methods as detailed for the primary analysis will be used for estimating effectiveness for these secondary objectives. For step 2 only, during the double blind phase, persons who do not initiate Step 2 and infections that occur in Step 1 will be omitted from the assessment of relative efficacy. For comparison across all three steps, all infections observed on trial will be included in the estimate of efficacy.

- To compare HIV incidence among participants randomized to CAB LA injections vs. oral TDF/FTC while taking open label TDF/FTC (Step 3 only, descriptive)

HIV incidence rates will be compared between arms for all participants after initiating open label FTC/TDF. Only events occurring during Step 3 will be included in the comparison.

- To compare the change in risk of HIV acquisition between CAB and oral TDF/FTC strategies (Arm A and Arm B) as participants progress from Step 2 to Step 3

Change in HIV incidence rates will be compared between arms during Step 2 and Step 3. In addition the change in HIV incidence rates in each arm will be compared as the study participant's transition from the double blind to open label phases of the study intervention.

- To compare HIV incidence among the following subgroups of participants receiving oral CAB/CAB LA vs. oral TDF/FTC; region, age, race, ethnicity, and baseline risk

The same methods as detailed for the primary analysis will be used for estimating effectiveness in each of the subgroups defined by the stated baseline characteristics. A test for significant interaction between intervention arm and subgroup will be conducted as a test of effect modification.

- To compare changes in renal function, liver function, and bone mineral density (BMD) among participants receiving oral CAB/CAB LA vs. oral TDF/FTC.

Global test of association: The number of participants by highest graded AE recorded for each renal and liver endpoint will be compared between arms using a Chi-squared test (or Fisher exact, if expected cell frequency is < 5).

Dose dependent association: The number of renal and liver function AEs within weeks 1-4 after injection will be compared with the number in weeks 5-8 in the CAB LA arm using a Chi-squared test.

Cumulative Exposure: To assess the risk of increasing severity in renal, liver and bone mineral density with increased exposure, summary statistics will be presented by treatment arm and time point, as well as changes from baseline for post-enrollment values.

- To evaluate and compare 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 will be reported by arm for all HIV seroconverters, separately for each Step of the trial. No formal statistical test will be performed.

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

Descriptive statistics will be used to summarize acceptability measures and preferences over the course of the study. Acceptability scores for each product will be compared between the arms (i.e. for CAB LA vs. Placebo CAB LA and TDF/FTC vs. Placebo TDF/FTC) using linear mixed effects model with study arm as a fixed effect.

7.11.4 Analyses of Tertiary Objectives

- To examine the association between levels of adherence and HIV incidence

HIV incidence and 95% CI will be estimated within periods defined by levels of adherence, and cohorts of adherers.

- To compare and describe the rates, patterns, and correlates of adherence to CAB LA vs oral TDF/FTC, in aggregate and by psychosocial/demographic variables.

Adherence rates will be calculated for the active drug using proportion injections received for CAB LA, and proportion of study time within 8 weeks of injection; and for TDF/FTC using proportion of visits where TDF pharmacokinetic laboratory assessment categorizes the participant as having taken at least 4 doses per week, and proportion of study time where pills were taken according to pill counts. Descriptive statistics will be used.

Adherence rates will be calculated for each blinded study group using proportion of injections received for CAB LA/Placebo CAB LA and proportion of study time where pills were taken according to pill counts for TDF/FTC. Statistical comparisons between the arms will use logistic regression with GEE methods to account for repeated assessments.

Detailed description of the patterns and psychosocial and demographic variables to be assessed as correlates will be described in the Statistical Analysis Plan.

- To estimate changes in sexual-risk behavior as measured by self-report and rates of incident gonorrhea, chlamydia, and syphilis in the study population.

Each sexual risk behavior will be assessed using a repeated measure approach to estimate effect of randomization arm on sexual behavior post-randomization. If statistically significant imbalance is observed at baseline, the model will be adjusted for the respective baseline covariate. Sexual behavior will additionally be assessed by perceived randomization assignment, as well as by actual randomization assignment using appropriate random effects regression models. For count outcomes, a Poisson-type regression model will be used to assess differences in rate; for binomial outcomes and logistic-type regression will be used.

Incident rates of STIs will be compared between arms using a HR estimated by Cox proportional hazards, with an Anderson-Gill approach for repeated events, assuming STIs are treated and resolve at each study visit.

- To compare the resource utilization and programmatic costs of long-acting injectable PrEP vs. daily oral PrEP vs. no PrEP for HIV uninfected MSM and TGW in the US, Brazil, South Africa and India

For each study arm, a standardized data collection instrument will be used which asks about resource utilization retrospectively since the prior visit including queries regarding additional outpatient, emergency department or inpatient visits (with duration), and laboratory/radiology visits. Resource utilization can be ascribed to be related to study (e.g., drug toxicity) or unrelated (e.g., trauma-related fracture). If different by study arm (or by country), resource utilization will be multiplied by country-specific unit costs to provide country-specific unit costs for differences in resources used. Country specific unit costs will also be applied to generate overall programmatic costs (e.g., personnel, baseline laboratory resources, space).

- To use mathematical simulation to project the short- and long-term clinical impact, cost projections, budgetary impact, and incremental cost-effectiveness of long-acting injectable PrEP vs. daily oral PrEP vs. no PrEP for HIV uninfected MSM and TGW in the US, Brazil, South Africa and India

The Cost-effectiveness of Preventing AIDS Complication-US and International models (CEPAC I), will be used and populated with data specific for each of the countries -- US, Brazil, South Africa and India. The model will be updated, specified, programmed and debugged for simulations specific to this protocol. It will further be parameterized with efficacy and resource utilization data obtained from the trial. We will use total cohort data where there is not statistically significant differences between country-level data. We will use country-specific data where those difference occur. For each country, the model will have the capacity to generate outcomes including: 1-, 5-, 10-year survival, life expectancy, per person lifetime costs (and a breakdown of where those costs occurred), 1- and 5- year budgetary impact, as well as incremental cost-effectiveness. This will allow for comparison of cost-effectiveness outcomes across regions of analysis with differences in baseline incidence, costing structures and gross domestic products (willingness/ability to pay).

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 and DAIDS Prevention Science Review Committee 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, 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 US FDA, OHRP, other government and regulatory authorities, and/or site IRBs.

For sites located in the US, the HPTN will obtain a Certificate of Confidentiality from the US Department of Health and Human Services that will be applicable for this study. Sites may register under the Certificate through the HPTN LOC once they have obtained local IRB approvals for the study. This Certificate protects study staff from being compelled to disclose study-related information by any Federal, State or local civil, criminal, administrative, legislative, or other body.

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 pharmaceutical sponsors, the US FDA, other government or regulatory authorities (OHRP), or site IRBs.

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

Laboratory procedures are described below, in Appendices I a-c and Section 5.0. Additional tests to be performed at subsequent visits for participants who have a reactive or positive HIV test result are described in Appendix II.

9.1 Local Laboratory Specimens

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

- HIV testing (see SSP Manual)
- HBV and HCV testing to include HBsAg, HBsAb, HBcAb, HCV antibody tests
- CBC with differential and platelets
- Chemistry testing (BUN/urea, creatinine, CPK, glucose, calcium, phosphorous, amylase, lipase
- LFTs (AST, ALT, total bilirubin, alkaline phosphatase)
- Fasting lipid profile (total cholesterol, high-density lipoprotein (HDL), triglycerides, low-density lipoprotein (LDL) – calculated or measured
- 25-OH-Vitamin D
- Syphilis serologic testing
- Urinalysis (protein and glucose)
- Urine for GC/CT NAAT testing
- Rectal swabs for GC/CT NAAT testing; for sites that cannot perform this testing, arrangements may be made for testing at another laboratory (see SSP Manual)
- Plasma storage
- DBS storage
- Whole blood storage for pharmacogenomic testing (sites may choose to opt out of this testing if is not acceptable to local regulatory bodies or for other reasons approved by the protocol team)
- HIV viral load (if HIV infected)
- CD4 cell count (if HIV infected)
- Real-time resistance testing for clinical management (if HIV infected)

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

Each study site will adhere to standards of good laboratory practice, the HPTN MOP, the SSP Manual and local standard operating procedures (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. In addition, whole blood samples will be stored at the Enrollment visit at sites that agree to store such samples for pharmacogenomic testing. A subset of the stored samples will be shipped to the HPTN LC (located in the US) for Quality Assurance (QA) and other assessments. As indicated below, testing on stored samples will be performed by the HPTN LC or another laboratory designated by the HPTN LC.

9.2.1 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.

9.2.2 Pharmacology

Plasma and DBS samples for drug levels 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 sites or 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 substances.

9.2.3 Pharmacogenomics

Blood samples collected for pharmacogenomics testing will be analyzed for genetic polymorphisms associated with study drug exposure. Assays will 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.

9.2.4 GC/CT Rectal Swab Storage (Non US Sites Only)

Rectal swab testing for GC/CT NAAT will occur throughout the study at 6-month intervals at sites that have this capacity. If the site does not have a validated NAAT assay, arrangements may be made for testing at another laboratory (see SSP Manual).

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, or other QA methods as deemed appropriate by the HPTN LC. 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

Before performing HIV diagnostic testing, all sites must validate their HIV testing procedures, and the validation studies must be approved by the HPTN LC. Local laboratories will perform testing for HIV diagnosis at Screening, Enrollment, and all 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 Schedule of Procedures and Evaluations. 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. US sites should send these tests to CLIA-certified laboratories and must participate in 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. US sites must use CLIA-certified laboratories; participation in the IQA program is recommended.

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. US sites must use CLIA-certified laboratories; participant in the VQA program is recommended.

9.4 Specimen Storage and Possible Future Research Testing

Study sites will store specimens collected in this study at least through the end of the study. 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 if participant does not enroll utilizing sample lists provided by the HPTN SDMC in consultation with the HPTN LC.

9.5 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).

10.0 ADMINISTRATIVE PROCEDURES

10.1 Protocol Registration

Initial Registration of the protocol by the DAIDS Protocol Registration Office (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) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (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 Regulatory Support Center (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 informed consent forms (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 by DAIDS and ViiV Healthcare, and DAIDS 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 Adverse Events 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 case report forms 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, case report forms), 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, ViiV Healthcare, Gilead Sciences, Inc., site IRBs/ECs, and US regulatory authorities (OHRP and US FDA). 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 Regulatory Support Center (RSC) prior to implementing the amendment.

10.6 Investigator's Records

The Investigator 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 Investigator 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. 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. 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, case report forms, 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, DAIDS, ViiV Healthcare, Gilead Sciences, Inc. for review prior to submission.

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APPENDICES I - IV

Appendix Ia: Schedule of Procedures and Evaluations – Screening; Step 1 – Blinded Daily Oral Pills

	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 counseling	X	X	X	X
Offer condoms and lubricant	X	X	X	X
Baseline acceptability assessment		X		
Baseline behavioral assessment		X		
Adherence counseling/pill count (Pill count Week 2 and 4 only)		X	X	X
CLINICAL EVALUATIONS & PROCEDURES				
History (including bleeding history at Screening), con meds, physical exam	X	X	X	X
ECG (screening ECG can serve as baseline value)	X			
DXA (BMD subset only, 175 per arm), to include dietary calcium and Vitamin D assessment		X		
Blood collection	X	X	X	X
Urine collection for urinalysis		X		
Urine collection for urinalysis GC/CT testing		X		
Rectal swab for GC/CT testing[1]		X		
Dispense Pills (enough for 5 weeks)		X		
LOCAL LABORATORY EVALUATIONS & PROCEDURES				
HIV testing[2]	X	X	X	X
HBV and HCV testing[3]	X	X		
CBC with differential	X	X	X	X
Chemistry testing[4]	X	X	X	X
Liver function tests[5]	X	X	X	X
Fasting lipid profile[6]		X		
Syphilis serologic testing		X		
BMD subset only: 25-OH-Vitamin D		X		
Urine GC/CT testing		X		
Rectal swab GC/CT testing[1]		X		
Urinalysis (protein and glucose)		X		
Plasma storage	X	X	X	X
DBS storage				X
Whole blood storage		X		

FOOTNOTES FOR APPENDIX Ia

[1] If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

[2] The HIV testing algorithm is provided in the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.

[3] HBsAg and HCV antibody testing are required at Screening. At Enrollment, HBsAb and HBcAb required; no HCV testing required at Enrollment.

[4] Creatinine required at screening; at and after enrollment, BUN/Urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase are required.

[5] ALT and bilirubin required at screening; at and after enrollment, AST, ALT, total bilirubin, and alkaline phosphatase are required.

[6] 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.

Appendix Ib: Schedule of Procedures and Evaluations - Step 2 – Blinded Injections + Blinded Daily Oral Pills

WEEKS (shaded column = injection/ dispense pills visit)	5	6	9	10	17	19	25	27	33	35	41	43	49	51	57	59	65	67	73	75	81	83	89	91	97	99	105	107	113	115	121	123	129	131	137	139	145	147	153	155	161	163	169	171	177	179	185	187
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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV 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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Condoms and lubricant	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	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	
Adherence 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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CLINICAL EVALUATIONS & PROCEDURES																																															
History, concomitant medications, 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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG															X												X												X									
DXA (subset only, 175 per arm)[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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine collection for urinalysis testing															X												X												X									
Urine collection for GC/CT testing									X						X						X						X						X						X						X			
Rectal swab for GC/CT testing[2]									X						X						X						X						X						X						X			
Injection/Dispense pills	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		X		X		X		X		X		X		X		X		X		X		X		X		X		X		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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV testing[4]															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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry testing[5]		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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver function tests[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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting lipid profile[7]															X												X																					
Syphilis serologic testing									X						X						X						X						X						X						X			
Urine GC/CT testing									X						X						X						X						X						X						X			
Rectal swab GC/CT									X						X						X						X						X						X						X			
Urinalysis															X												X												X									
Plasma storage	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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DBS storage			X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	

FOOTNOTES FOR APPENDIX Ib

[1] To include dietary calcium and Vitamin D assessment

[2] If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

[3] The HIV testing algorithm is provided in the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.

[4] Testing does not need to be repeated if infection was documented at a prior visit. HCV Ab testing is required.

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

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

[7] Required for lipid profile: 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.

Appendix Ic: Schedule of Procedures and Evaluations - Step 3 – Open Label Daily Oral TDF/FTC Post-Last Injection

Procedures	Day0*	Week 12	Week 24	Week 36	Week 48
ADMINISTRATIVE, BEHAVIORAL, REGULATORY					
Locator Information	X	X	X	X	X
HIV Counseling	X	X	X	X	X
Offer Condoms and lubricant	X	X	X	X	X
Acceptability Assessment[2]	X				
Behavioral Assessment (if done in last 4 weeks, skip D0 and start at W12)	X		X		X
Adherence Counseling	X	X	X	X	
CLINICAL EVALUATIONS & PROCEDURES					
History, concomitant medications, physical exam	X	X	X	X	X
Blood Collection	X	X	X	X	X
Urine collection for GC/CT testing	X[1]		X		X
Rectal swab for GC/CT testing[3]	X[1]		X		X
Dispense pills	X	X	X	X	
LOCAL LABORATORY EVALUATIONS & PROCEDURES					
HIV testing[4]	X	X	X	X	X
Chemistry testing[5]			X		X
Liver function tests[6]			X		X
Syphilis serologic testing	X[1]		X		X
Urine GC/CT testing	X[1]		X		X
Rectal swab GC/CT testing	X[1]		X		X
Plasma storage	X	X	X	X	X

FOOTNOTES FOR APPENDIX Ic

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

[2]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

[3] If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

[4] 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.

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

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

Appendix II: Schedule for Additional Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result (including HIV confirmatory visit)

Note 1: The procedures listed for the HIV Confirmation Visit apply to participants who become infected at any time during the study. The procedures listed for Weeks 12, 24, 36, and 48 apply only to participants with confirmed HIV infection during Step 2 of the study. Participants with confirmed HIV infection in Step 3 of the study may undergo similar procedures as listed in Weeks 12, 24, 26, and 48, and will be determined by the CMC.

	HIV Confirmation Visit	Week 12	Week 24	Week 36	Week 48[6]
ADMININISTRATIVE, BEHAVIORAL, REGULATORY					
Locator information	X	X	X	X	X
Offer condoms and lubricant	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

[1] The HIV confirmation testing algorithm is to be performed on a different day from the initial reactive/positive sample. The specifics 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.

[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 at the HPTN LC and for other assessments described in Section 9.0. Assessments will be performed retrospectively; results will not be returned to study sites or participants, except as noted in Section 9.0.

[6] The Week 48 visit should be timed as closely as possible to 52 weeks after the participant received their 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 Clinical Management Committee (CMC) will be 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. Investigators also should consult the CMC for further guidance in restarting study product or progressing to permanent discontinuation. Revealing a participant's blinded status will occur only for individuals who become HIV infected and choose to initiate antiretroviral therapy.

The following general guidance refers to all AEs except for AST/ALT. Refer to the section below "Specific Guidance on Transitioning from Oral to Injectable Phase", as well as 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 in the Table below may continue use of the study product per protocol. See an exception to this under "Specific Guidance on Transitioning from Oral to Injectable Phase".

Grade 3

Participants who develop a Grade 3 AE or toxicity that is not specifically addressed in the Table below and is judged to be related to study product by the Investigator, study product use should be temporarily discontinued in consultation with the CMC. In general, and unless otherwise decided in consultation with the CMC, the investigator should re-evaluate the participant until resolution of the toxicity. For Grade 3 AEs deemed related to study product, the study product should be permanently discontinued if improvement to severity ≤ Grade 2 cannot be documented within 4 weeks of receipt of the initial result. If study product is resumed and the same Grade 3 AE recurs at any time, the Investigator must consult the CMC for further guidance on holding of study product, frequency of reevaluation or progression to permanent discontinuation of the study product. 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 below (regardless of relationship to study product) should have the study product temporarily discontinued. The Investigator 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 products for any reason at any time. Investigators 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. Investigators 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 hepatitis B virus (HBV) infection

Participants in Step 2 who prematurely and permanently discontinue study product should be asked to continue to be followed according to the applicable Schedule of Evaluations and Procedures of Step 3.

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 he/she is no longer taking the prohibited medication, provided other reasons for temporary study product hold/permanent discontinuation do not apply. The CMC should be consulted in all cases where a participant reports taking a prohibited product during the course of the study.
- The participant is unable or unwilling to comply with required study procedures such as HIV testing and routine laboratory assessments, or otherwise might be put at undue risk to their safety and well-being by continuing study product use, according to the judgment of the IoR. The IoR must consult the CMC on all temporary study product holds

instituted for this reason for further guidance on resuming study product use, continuing the temporary hold, or progressing to permanent discontinuation.

- The participant has one or more reactive HIV test results, or expresses a concern about having acute HIV infection. Criteria for resuming use of study product in these circumstances are defined in the protocol and SSP Manual.

Participants who temporarily or permanently discontinue study product during the oral phase will be instructed to return all study products as soon as possible.

Note the following for cases of exercise-induced CK abnormalities: Cases of CK abnormality, presumed to be exercise induced, at the Grade 3 or higher level accompanied by ALT abnormalities of Grade 3 or lower up to and including Grade 3 should be brought to the attention of the CMC for adjudication of further management and further administration of study product. Grade 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:

Nausea, Vomiting, and Diarrhea

CONDITION AND SEVERITY[1]	IMMEDIATE ACTION	FOLLOW-UP AND MANAGEMENT[2]
Nausea, Vomiting, and Diarrhea		
Grade 1 and 2	Continue study product (reminder to take study product with food)	Treat symptomatically with hydration, oral antiemetic therapies or antiemetic suppositories at the discretion of the Investigator. The Investigator should order any clinically relevant laboratory analyses (per judgment of the Investigator).
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 Investigator 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

CONDITION AND SEVERITY[1]	STUDY PRODUCT USE	FOLLOW-UP AND MANAGEMENT[2]
ELEVATIONS in ALT		
Grade 2 and higher		**Oral phase:** A Grade 2 ALT abnormality reported at Week 2 or Week 4, regardless of relatedness to the study product, should be confirmed within one week. Oral study drug may continue until the confirmatory results are available; no injections should be administered until confirmatory results are available during consideration of the Week 4 ALT value. If the repeat value is ≤ Grade 2 at Week 2, study drug may continue to Week 4. If the repeat value is < Grade 2 at Week 4, the participant may proceed to Step 2 injection phase. If the repeat value is Grade 2 or higher at Week 4, study product should be stopped, and the participant will be followed annually for HIV testing only. All such cases must be reported to the CMC. In addition, participants will be followed with weekly ALT assessments until they return to ≤ Grade 1. A Grade 3 or higher ALT abnormality reported at Week 2 or Week 4, regardless of relatedness to the study product, will prohibit a participant from entering the injection phase of the study, and the participant will be followed annually for HIV testing only until the conclusion of Step 2 of the study. All such cases must be reported to the CMC. In addition, participants will be followed with weekly ALT assessments until they return to ≤ Grade 1. Excluding ALT, any grade 3 clinical or laboratory AE observed prior to Week 5 will prompt consultation with the CMC prior to any injectable dosing. Grade 3 adverse events deemed related to study product, or a Grade 3 ALT, or any Grade 4 adverse event will lead to permanent study product discontinuation, and the participant will be followed annually for HIV testing only until the conclusion of Step 2 of the study. AEs will be followed until resolution (≤ grade 1) in consultation with the CMC. Note the following for cases of exercise-induced CK abnormalities: Cases of CK abnormality, presumed to be exercise induced, at the Grade 3 or higher level accompanied by ALT abnormalities of Grade 3 or lower up to and including Grade 3 should be brought to the attention of the CMC for adjudication of further management and further administration of study product. Grade 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[1]	STUDY PRODUCT USE	FOLLOW-UP AND MANAGEMENT[2]
ELEVATIONS in ALT		
Grade 2 and higher		**Injection phase**: The CMC should be notified as soon as possible. For a Grade 2 ALT, the CMC will determine whether further injections may be given in cases where levels are ≤ Grade 2 prior to the next scheduled injection. Unless otherwise specified by the CMC, for Grade 2 ALT, repeat testing should be performed weekly until levels are ≤ Grade 1. For Grade 3 and higher ALT, study product will be permanently discontinued.* For Grade 3 and 4 ALT, repeat testing should be performed as soon as possible, and participants should be followed weekly until levels are ≤ Grade 1. Participants who are permanently discontinued from study product should continue to be followed on study/off study product, following the Step 3 Schedule of Evaluations for Arm A. Note the following for cases of exercise-induced CK abnormalities: Cases of CK abnormality, presumed to be exercise induced, at the Grade 3 or higher level accompanied by ALT abnormalities of Grade 3 or lower up to and including Grade 3 should be brought to the attention of the CMC for adjudication of further management and further administration of study product. Grade 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:

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 referred for 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.

Guidance on Toxicity Management for Specified Toxicities:

Creatinine Clearance

CONDITION AND SEVERITY	STUDY PRODUCT USE	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 study product must be permanently discontinued and the CMC notified. 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 Investigator must consult the CMC for further guidance on resuming study product use, continuing the hold temporarily, or progressing to permanent discontinuation. If the investigator 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 (CK or CPK)

CONDITION AND SEVERITY[\]	STUDY PRODUCT USE	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:

QTc – Criteria for Permanent Discontinuation of Study Product

A participant that meets either criterion below will have study product stopped, but will remain in study follow-up. The QT correction formula used to determine study product discontinuation should be the same one used throughout the study.

- QTcB > 550 msec, OR
- Change from baseline: QTcB >60 msec

Study product discontinuation decisions are to be determined by the Investigator of Record or designee in consultation with the CMC. A decision to permanently discontinue study product will be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain two more ECGs within one hour, and then use the averaged QTc values of the three ECGs to determine whether the participant should permanently discontinue study product.

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 083

A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men

Version 1.0
02/02/2016
DAIDS Document ID: 20725

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.

PRINCIPAL INVESTIGATOR: *[Insert Name*]

PHONE: [Insert Number]

GENERAL OVERVIEW

You are being asked to take part in an investigational research study related to the Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immunodeficiency Syndrome, or AIDS.

This study is being offered to 4500 HIV-uninfected men who have sex with men (MSM) and transgender women (TGW) that have sex with men in Asia, North and South America, and South Africa. Before you decide whether to join the study, we would like to explain the purpose of the study, the risks and benefits to you, and what is expected of you.

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.

There may be no direct benefits for you if you participate in this study. There also may be some risks with taking part in the study. Before you can make an informed decision about whether to take part in this study, you should understand the possible risks and potential benefits of being in this study. This informed consent form gives information about the study that will be discussed with you. Once you understand the study, and if you agree to take part, you will be asked to sign your name on this form.

Your participation is voluntary

This consent form gives information about the study that will be discussed with you. Once you understand the study, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep.

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

- Your participation is voluntary. You do not have to take part in any of the tests or procedures in the study.
- You may decide not to take part in the study, or you may decide to leave the study at any time. [You will continue to receive the same services that you can get at [insert clinic name]].
- If you decide not to take part in the study, you can still join another study at a later time if there is one available and you qualify.
- You cannot join this study if you are taking part in another study of drugs 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.

BACKGROUND AND PURPOSE OF THE STUDY

You are being asked to participate in this study because you are at risk of getting infected with HIV. Ideally, as part of routine medical care, ways to decrease your risk of getting infected with HIV would be discussed with you. *[Sites to include next sentence if Truvada is locally available*]: A treatment you might be offered to decrease your risk of getting HIV is a pill call Truvada (TDF/FTC). It is one pill that contains two drugs, one called emtricitibine [FTC] and the other called tenofovir disoproxil fumarate [TDF]). It is approved by the U.S. Food and Drug Administration (FDA) for the treatment of HIV and also to prevent people from getting HIV. *[Non-US sites to fill in the current status of approval of TDF/FTC here]*. The US FDA is the regulatory group that oversees the approval of all drugs in the US. The approval of TDF/FTC for the prevention of HIV is based in part on a previous study in men who have sex with men (MSM) and transgender women (TGW) who have sex with men, called iPrEX. The iPrEX trial enrolled close to 2,500 HIV-uninfected MSM and TGW who were at risk for getting HIV, to see whether TDF/FTC would lower their chances of getting HIV. The study showed that it did. The study also showed that people that took the drugs more regularly were more likely to not get HIV than those who did not take the drugs regularly. TDF/FTC is supposed to be taken every day in order to provide the highest chance of not getting HIV.

The main purpose of this study is to try to find out if a new drug, called cabotegravir (CAB), is as safe and will work as well as TDF/FTC in protecting you from getting HIV. CAB is available in the form of a pill and as an injection (shot). Researchers do not yet know if this injectable drug will work to protect people from getting HIV. This is why we are doing this study. In this study, you will take pills every day, and you will be get a shot every 8 weeks, after first getting two shots given one month apart.

STUDY GROUPS

If you decide to be in this study, you will be placed in to 1 of 2 groups. Each group will have 2250 people in it. We do not know exactly how long this study will last because the length of the study is determined by when you join the study and how well people do on the study. Your participation in the study could last up to 4 years and a half years, and include up to 57 visits to this clinic over that time. As the study goes on, we will let you know about the study progress and plans for how long it will be.

Each person in each group will get injections and a daily pill. 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. The pill should be taken every day.

The first group will get the real CAB drug in a pill and injections, and the second group will get the real TDF/FTC drug in a pill and an injection with no study drug in it. 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. In order to do this, each group will also get placebos of the injections and the pills. Placebos look and feel like the real drug, but they do not contain any of the active ("real") drug or any other medicines. The placebo for the CAB injection is a nutrition infusion called Intralipid. The placebo for the pills will look, feel and taste the same as the real pills.

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 one of the two groups. Both groups are very important to the study. In this study, you and the study researchers will NOT know which group you are in until the study is over.

No matter what group you are in, you must remember that we do not know if CAB works to protect you from getting HIV. We do know that taking TDF/FTC on a daily basis can be more than 90% protective against getting HIV infection. It is important to remember neither daily TDF/FTC nor CAB will protect you from getting sexually transmitted infections, like gonorrhea, chlamydia, syphilis, warts, or herpes. One of the best things you can do to protect yourself from getting HIV during sex is to us a condom every time you have sex.

The groups look like this, and each group moves through 3 Steps in the study [*sites may show a graphic to depict the groups and the steps*] like this:

Group A – this group gets real CAB pills and injections:

- Step 1: Real CAB pill AND placebo pill for TDF/FTC (2 pills total) every day for 5 weeks
- Step 2: Real CAB injections given as one shot, then another shot a month later, and then every 2 months after that AND placebo pill for TDF/FTC every day up to four and half years
- Step 3: Real TDF/FTC pill every day for about a year, then move to local HIV prevention services

Group B – this group gets real TDF/FTC pills:

- Step 1: Real TDF/FTC pill AND placebo pill for CAB (2 pills total) every day for 5 weeks
- Step 2: Placebo CAB injection AND real TDF/FTC pill everyday up to four and a half years
- Step 3: Real TDF/FTC pill every day for about a year, then move to local HIV prevention services

In Step 1, everyone starts the study by taking pills for 5 weeks. This is to see if you have any serious side effects to the study drugs before you starting getting the shots.

In Step 2, everyone takes pills and gets shots. This step will last up to four and a half years, depending on when you started in the study.

In Step 3, everyone gets the real TDF/FTC every day for about a year, then your participation in the study will end and we will refer you to local HIV prevention services. There are no current plans for the study to offer the injectable CAB drug to study participants after the completion of the study.

If the results of this study show that CAB works to prevent HIV, we will tell you that and let you know if it may become available in your local area. Often times it can take a long while for a new drug to become available to the public once it has been shown that it works in a study like this.

STUDY PROCEDURES

Screening Visit

Your screening visit may occur after you read, discuss, understand, and sign this form, or will we schedule it for you at another time. We will help you understand the form and answer your questions before you sign this form. 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.

At this 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 and lubricant.
- Have an electrocardiogram (ECG) scan, which is a test to monitor your heart.
- 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.
- [*Sites participating in the DXA substudy to include this:*] We may ask you to be a part of a group that gets a bone mineral density-energy x-ray absorptimetry (DXA) scan. A DXA

scan is a special kind of x-ray using a small amount of radiation, allowing the doctor to see parts of the body better than a regular x-ray. The scan will be done at the Enrollment visit (this visit), and 2 other times during the study (Weeks 57 and 105).

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.

Confirmation of Eligibility:

Once all the results of the screening tests are known, the following will happen within 45 days after screening:

- You will be told your test results and what they mean.
- If you have a positive HIV, hepatitis B or C test you will not be eligible for the study, and you will be referred for the appropriate medical care (*sites to add specifics about this here as necessary*).
- If you are negative for HIV but the results from the other blood or urine tests show that you might have some health problems, you may not be eligible for the study. Study staff will refer you to available sources of medical care and other services you may need. Later, if these problems resolve, you may be able to come back to find out if you are eligible at that time.

Step 1: Enrollment Visit (Week 0)

If you are eligible for this study and decide to take part in the study, you will be asked to return for the enrollment visit. This visit will last about xx hours. 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, and ask you about any other medicines you are taking.
- Collect a urine sample to see if there is sugar or protein in your urine.
- Collect ~XX mL (about x teaspoons) of blood for: HIV testing, Hepatitis B testing, syphilis, 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 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.

- Ask you questions about your sexual behavior.
- Ask you questions about your opinions about taking pills and getting injections.
- Perform a swab of your rectum and collect urine for gonorrhea and chlamydia.
- [*Sites participating in DXA substudy to include this*: If you agreed to be part of the DXA substudy, you will undergo a DXA scan [*Note to sites participating in the DXA substudy - the first DXA may occur 30 days before the Enrollment visit or 7 days after in order to allow for flexibility in scheduling.*]
- We may ask you to be a part of a group that gets a bone mineral density-energy x-ray absorptimetry (DXA) scan. A DXA scan is a special kind of x-ray using a small amount of radiation, allowing the doctor to see parts of the body better than a regular x-ray. The scan will be done at the Enrollment visit (this visit), and 2 other times during the study (Weeks 57 and 105). [*Sites that do not participate in the DXA subset to delete this*]. If you are in this group, we will also check your blood to see how much Vitamin D is in it.
- Randomize you into one of the two study groups.
- Give you your study pills, and explain how to take them, and 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 and lubricants.

Step 1: Weeks 2 and 4 Visits

These visits will last about XX. 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.
- Count your pills, and talk with you about ways to help you take your pills.
- 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 liver and kidneys, and for storage.
- Have a discussion to help work through any challenges of taking a pill every day; 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 the results of your blood tests when they are available.
- Offer you condoms and lubricant.

Step 2: Week 5 Visit – Visit for first injection

This visit will last up X hours. During this visit, the study staff will:

- Confirm where you live and how to contact you.
- Give you a brief physical exam, ask you if you have experienced any side effects from the study drugs, an ask you about any other medicines you are taking.
- Talk with you about HIV and ways to protect yourself from getting it.
- Collect ~XX mL (about x teaspoons) of blood for HIV testing and for storage.
- Ask you to answer questions about your sexual behavior.
- Give you your study pills, and explain how to take them, and any side effects they may cause.
- Administer the first shot in your buttock
- Have a discussion to help work through any challenges of taking a pill every day; 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 the results of your blood test when they are available.
- Offer you condoms and lubricant.

Step 2: All other visits where injections occurs: Week 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 137, 145, 153, 161, 169, 177, 185

In this step of the study, there will be approximately 23 visits where you will receive a shot and study pills. Injections will be given approximately every 2 months (8 weeks) after the first two are given one month (4 weeks) apart. These visits will last up to XX hours. During these visits, the study staff will:

[*Note: Sites may remove Week numbers in the text below if easier to depict it in a table or refer to the Schedule of Procedures and Evaluations*].

- 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 experience any side effects from the shots you received, 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 liver, and for storage (every injection visit)
    - HCV 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 injection visit for about 2 years, and then every other injection visit for the rest of Step 2 (Weeks 5, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 121, 137, 153, 169, 185 only)
- 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).
- *[Sites to include only for those sites participating in DXA subset:]* If you had a DXA scan (x-ray) when you started the study, we will ask you to have two more, about a year apart from each other (Weeks 57 and 105 only). We will also ask you questions about what you eat and if you take any vitamins or other supplements.
- Ask you to have an ECG scan about every year for 3 years (Weeks 57, 105, and 153 only).
- Perform a swab of your rectum and collect urine for gonorrhea and chlamydia about every 6 months throughout Step 2 (Weeks 33, 57, 81, 105, 129, 153 and 177 only).
- Give you your study pills, and explain how to take them, and any side effects they may cause (at all injections visits).
- Give you a shot (at all injection visits).
- Give you the results of your blood tests when they are available (at all injection visits).
- Have a discussion to help work through any challenges of taking a pill every day; 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 (at all injection visits).
- Offer you condoms and lubricant (at all injection visits).

Step 2: Post-Injection Visits: Weeks 6, 10, 19, 27, 35, 43, 51, 59, 67, 75, 83, 91, 99, 107, 115, 123, 131, 139, 147, 155, 163, 171, 179, 187)

[*Note: Sites may remove Week numbers in the text below if easier to depict it in a table or refer to the Schedule of Procedures and Evaluations*].

There will be up to approxmiately 24 visits following each visit where you got a shot. These visits will last up to XX hours. During these visits, the study staff will:

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

- Give you a brief physical exam. Ask you if you have experience any side effects from the shots you received, 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 liver, the amount of the study drug that is in your blood, and for storage.
- Offer you condoms and lubricant.

Step 3: If you stopped getting injections early, you will go to Step 3. If you got all of your injections, you will go to Step 3. This step includes 5 visits over about a year (Week 0, 12, 24, 36, and 48).

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

- Confirm where you live and how to contact you.
- Talk with you about HIV and ways to protect yourself from getting it.
- Give you a brief physical exam.
- 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.
- Perform a swab of your rectum and collect urine for gonorrhea and chlamydia (Day 0, Week 24 and 48 only). If you have had this test within 3 months of joining this part of the study, you will only have this done at Week 24 and Week 48 only.
- Give you your study pills, and explain how to take them, and any side effects they may cause (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).
- Have a discussion to help work through any challenges of taking a pill every day; 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 condoms and lubricant.

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].

Procedures if you become infected with HIV during the study

If you get HIV during the Step 1 of the study, you will stop taking your 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 (while you are getting shots), you will stop taking the study drugs and getting

shots and 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. If you get HIV during Step 3 of the study, you will stop taking the TDF/FTC (Truvada), and 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.

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, either because you decide you do not want to any longer, you get HIV, or 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 longer get shots or take pills. 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, samples from all study participants will be used for other testing that is part of this study. 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. If you are taking sex hormones, your stored samples may also be used to study whether these medications interact with the anti-HIV medications used in this study. 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 transmitted through sex, 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.

RISKS AND/OR DISCOMFORTS

Study Medications

The side effects of cabotegravir include:

Headaches, diarrhea, and fatigue. With the CAB that you get as a shot, people in other studies have said they had pain, irritation, skin redness, bumps, swelling, itching, bruising where they got the shot. Other reported side effects include muscle aches, nausea, fever and dizziness.

There have been some people who were taking this medicine in other studies who have had liver side effects. Most of these people were HIV-infected (HIV positive) and they all had some damage to their liver before taking the CAB study medication. In those studies, 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 are 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 shots you receive in this study are long acting, meaning they stay in your body for a long time. One single shot can stay in your body for up to one year. If you develop a side effect to the study drug after the shot, there will be no way to remove the drug from your body. If you are in Group A, the group that gets the real CAB, we will monitor your health for a year after your last injection. If you get infected with HIV while on the real CAB, it is possible that real CAB and other HIV drugs that are like it may not work to fight the virus.

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.

Side effects of TDF/FTC include:

Lactic acidosis (elevated lactic acid levels in the blood) and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may result in liver failure, other complications or death have been reported with the use of antiretroviral nucleoside analogues alone or in combination. The liver complications and death have been seen more often in women on these drug regimens. Some nonspecific symptoms that might indicate lactic acidosis include: unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, cramps, muscle pain, weakness, dizziness and shortness of breath.

Other side effects include:

The following side effects have been associated with the use of tenofovir:

- Upset stomach (nausea), vomiting, gas, loose or watery stools
- Abdominal pain
- Generalized weakness
- Dizziness
- Depression
- Headache
- Shortness of breath
- Increased couth
- Runny nose
- Allergic reaction: symptoms may include fever, rash, itching, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness or a potentially serious swelling of the face, lips, and/or tongue.
- Skin darkening of the palms of hands and/or soles (bottom) of feet
- Bone pain and bone changes such as thinning and softening which may increase the risk of breakage
- Muscle pain and muscle weakness
- Sleeping problems; unusual dreams; tiredne
- Worsening or new kidney damage or failure
- Liver problems. If you are developing liver problems, you may have one or more of the following symptoms:
    - Abnormal liver function tests, which could mean liver damage
    - Yellowing of the skin or whites of your eyes,
    - Dark urine,
    - Pain on the right side of your stomach,
    - Loss of appetite, upset stomach or vomiting,
    - Pale colored stools,
    - Itchy skin.
- Increases in pancreatic enzyme (substances in the blood), which could mean a problem with the pancreas
- Increased triglycerides
- Increased creatine phosphokinase (CPK), which could mean muscle damage

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.

Rectal Swabs

You may experience pain or discomfort in your rectum from the swab. In some cases, you may have some bleeding.

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.

DXA Scan *[Only sites participating in the DXA subset to include this section]*

If you receive the scan, note the following: We are exposed to radiation on a daily basis both from natural (sun and earth) and man-made sources. The average radiation dose from these sources for those living in the United States is 363 millirem per year. Exposure of up to 5,000 millirem of radiation is allowed in individuals who use radiation in their work (such as Radiologic Technologists and radiologists). Also, there is no evidence that a dose up to 5,000 millirem per year is associated with any risk. The radiation dose that you will receive from the DXA scans done for this research is less than 1% of this annual limit for radiation workers (if you receive the scans). The scanning machines will not cause any physical discomfort other than from having to lie still on the table for the duration of the test.

ECG

ECG patches may cause a skin reaction such as redness or itching. You may also experience localized skin discomforts and/or hair loss associated with the placement of ECG leads.

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.

We also may also use your samples and information for more complete genetic testing. For example, researchers may do "genome-wide association studies," also known as GWAS. A genome is all of your genes in total. Genes are made of even smaller "building blocks" that are arranged in a specific order. Many diseases can result from changes to this order or "sequence." These changes may somewhat explain why some people get diseases like cancer or diabetes while others do not. These changes may partly explain the body's response to disease and treatment. We are interested in understanding if the way the study medication interacts with your body has anything to do with your particular genes.

We may find information as we do this study that raises important other questions as to the safety of the study medication - - this new information may require that we do additional testing of left-over study samples. We will let you know right away if we find any new information or any new concerns develop about the medication as the study continues.

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.

HIV Infection

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.

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.

BENEFITS

There may be no direct benefit for you if you participate in the study. TDF/FTC is known to protect against 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. Neither you nor we will know which real drug you are getting in this study.

We will test you for HIV, hepatitis B and hepatitis C during this study, and other sexually transmitted infections. We will refer you for Hepatitis B vaccination if it is indicated. The counseling you get during this study may help you to avoid HIV and other sexually transmitted infections. If you have or become infected with HIV, this counseling may help you to learn how to better care for yourself and avoid passing HIV to your sexual partners. If you become HIV infected, or have another sexually transmitted infection, we will refer you for care and/or treatment. During the study you will also have other tests to check on the health of your blood, and liver. If any health problems are found, you will be referred for care. At every visit you will be offered condoms and lubricant 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

[*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*].

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

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

Your records may be reviewed by:

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

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

RESEARCH-RELATED INJURY

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

PROBLEMS OR QUESTIONS

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

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

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

SIGNATURE PAGE

HPTN 083

A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men

Version 1.0

02/02/2016

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. Also, please indicate by providing your initials in the spaces below the additional sample collection, genetic testing, or long-term storage that you agree to.

_____ I agree to take part in this study.

_____ I agree to have samples of my blood stored and used for future testing.

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

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

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

_____ [*Sites that participating in the DXA substudy to add this*]: I agree to take part in the DXA substudy.

_____ [*Sites that are participating in the DXA substudy to add* this]: I do not agree to take part in the DXA substudy.

_____	_____
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