

**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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**A Study by the HIV Prevention Trials Network**

**Sponsored by:**

Division of AIDS, National Institute of Allergy and Infectious Diseases

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## 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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## PROTOCOL SIGNATURE PAGE

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**DAIDS Document ID # 20725**

**Version 5.0**

**April 28, 2022**

**I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.**

\_\_\_\_\_  
Name of Investigator of Record

\_\_\_\_\_  
Signature of Investigator of Record

\_\_\_\_\_  
Date

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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  |
| BMI              | body mass index   |
| 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        | creatinine phosphokinase  |
| CLIA             | Clinical Laboratory Improvement Amendments  |
| C <sub>max</sub> | maximum or “peak” concentration of a drug observed after its administration   |
| CMC              | Clinical Management Committee   |
| C <sub>min</sub> | minimum or “trough” concentration of a drug observed after its administration and just prior to the administration of a subsequent dose |
| CPQA             | Clinical Pharmacology Quality Assurance   |
| CPK              | creatinine phosphokinase  |
| CRF              | Case Report Form  |
| CRM              | Clinical Research Manager   |
| CRPMC            | Clinical Research Products Management Center  |
| CT               | Chlamydia trachomatis   |
| DAERS            | DAIDS Adverse Event Reporting System  |

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#### **LIST OF ABBREVIATIONS AND ACRONYMS**

|           |   |
|-----------|---|
| DAIDS     | Division of AIDS  |
| DAIDS-ES  | DAIDS Enterprise System   |
| DAIDS PRO | DAIDS Protocol Registration Office  |
| DAIDS RSC | DAIDS Regulatory Support Center   |
| 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 gonorrhea   |
| 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   |

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#### **LIST OF ABBREVIATIONS AND ACRONYMS**

|           |   |
|-----------|---|
| HR        | hazard ratio  |
| HSV       | herpes simplex virus  |
| 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      | nucleoside reverse transcriptase inhibitor  |
| OHRP      | Office for Human Research Protections   |
| OLE       | open label extension  |
| 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  |



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#### **LIST OF ABBREVIATIONS AND ACRONYMS**

|         |   |
|---------|---|
| Pgp     | permeability glycoprotein   |
| PK      | Pharmacokinetic   |
| PO      | by mouth/orally   |
| 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  |

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### **LIST OF ABBREVIATIONS AND ACRONYMS**

|     |                           |
|-----|---------------------------|
| WHO | World Health Organization |
|-----|---------------------------|

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## 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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## HPTN 083

### TERMINOLOGY FOR CABOTEGRAVIR AND TDF/FTC FORMULATIONS

| Compound Name or Abbreviation                                | Comments   |
|--|--|
| <b>Cabotegravir or CAB</b>                                   | 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.   |
| <b>Oral CAB</b>  | When written as shown, this refers to the oral tablet formulation of cabotegravir.   |
| <b>CAB LA</b>  | When written as shown, this refers to the long-acting injectable formulation of cabotegravir.  |
| <b>TDF/FTC (tenofovir disoproxil fumarate/emtricitabine)</b> | When written as shown, this refers to the antiretroviral drug tenofovir/emtricitabine (trade name: Truvada <sup>®</sup> ), manufactured by Gilead Sciences, Inc.   |
| <b>TFV (tenofovir)</b>                                       | 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.   |
| <b>TFV-DP (tenofovir diphosphate)</b>                        | 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 |
| <b>FTC-TP (emtricitabine triphosphate)</b>                   | 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).   |



## HPTN 083

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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 disoproxil 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 5000, 2500 per arm.

#### Study

- Duration:** Due to staggered timelines of study activation at the participating sites, the overall study duration is approximately 7.5 years.

Individual participants will be followed on blinded study products for three years from the date of enrollment during Steps 1 and 2. After completion of blinded study products, participants will then receive 48 weeks of open label TDF/FTC during Step 3 – for a total of four years of follow-up for any individual participant.

In Step 1, participants will receive blinded daily 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 until Week 153, which is approximately three years from the date of the Enrollment visit.

All participants will all be simultaneously unblinded after the last participant concludes their participation in Step 2.

In Step 3, participants will receive study-provided open-label daily oral TDF/FTC for 48 weeks. The timeline for the 48 weeks of open label TDF/FTC for Step 3 begins 8 weeks from the last administered injection of Step 2, *irrespective of actual date of TDF/FTC initiation*.

#### Study

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

## 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 to Week 153

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) to Week 153

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** will start at Week 153 (last day of Step 2) /Day 0 (first day of Step 3) and continue for 48 weeks.

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, or if they transition to annual visits in Step 1 or Step 2, or if at the discretion of the primary care physician, they transition to Step 3 on study but off study-provided TDF/FTC.

A participant with confirmed HIV infection during Step 3 will be placed on ART and followed at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by the members of the 083HIV@hptn.org group.

## **HPTN 083**

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#### **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
- To compare changes in weight, blood pressure, pulse, fasting glucose, and fasting lipids among participants receiving oral CAB/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, and South Africa
- 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, and South Africa

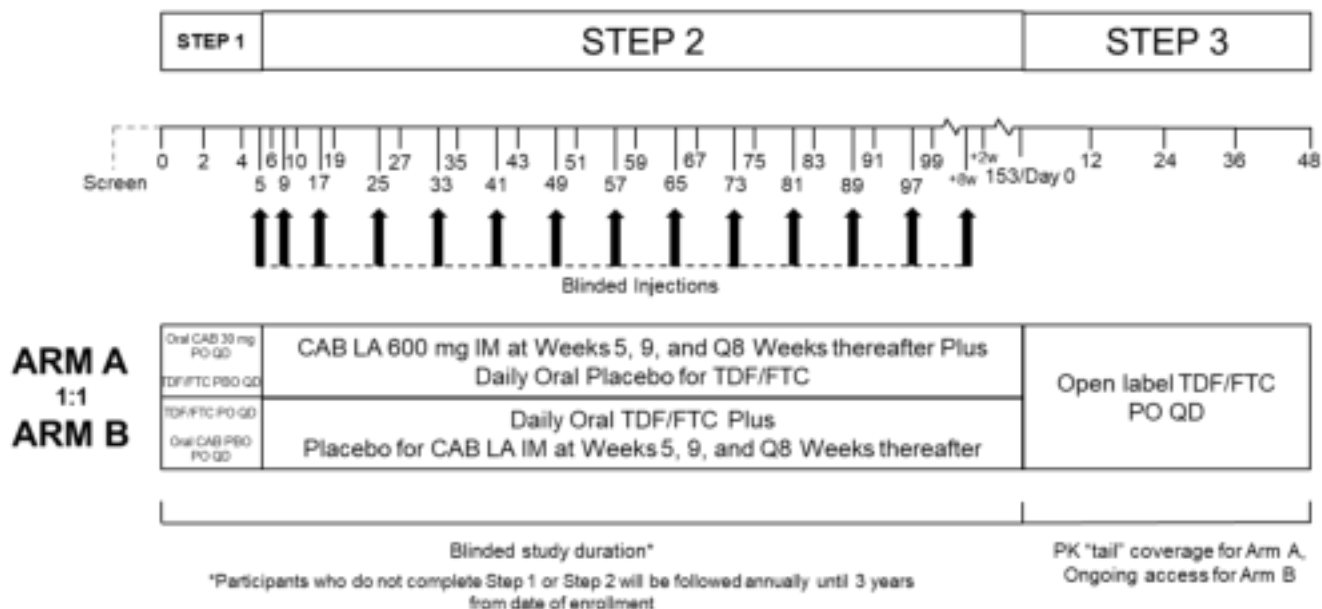
**Exploratory Objectives:**

- To perform secondary laboratory assessments that may include evaluation of factors related to HIV infection, hepatitis infection, or other infections; 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.<sup>1-9</sup> 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.<sup>10,11</sup> In healthy HIV-uninfected and HIV –infected individuals, sustaining adherence over time becomes increasingly challenging.<sup>12</sup> 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.<sup>13-16</sup> 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.<sup>1,4,17</sup> Resistance appears to emerge less frequently in individuals who acquire HIV infection after initiating a PrEP regimen,<sup>1,4,9,17-21</sup> however, recent studies using more sensitive drug resistance tests have revealed the presence of minority variants with resistance mutations in some individuals.<sup>17,18</sup> 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.<sup>18</sup>

Despite tremendous therapeutic advances in HIV treatment and prevention, the HIV epidemic persists worldwide.<sup>22</sup> 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.<sup>23,24</sup> The safety and efficacy of TDF/FTC in combination with other ARV drugs for ART,<sup>25-29</sup> and results from TDF/FTC PrEP studies in a rhesus macaque simian-HIV (SHIV) exposure model,<sup>30,31</sup> supported the development and evaluation of TDF/FTC for PrEP. Five randomized clinical trials (RCTs) have evaluated oral TDF or TDF/FTC as PrEP.<sup>1,4,8,20,21</sup> These five trials differ in several ways, but suboptimal adherence,<sup>32,33</sup> 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;<sup>34</sup> 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.<sup>35</sup> 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.<sup>36</sup> 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;<sup>4</sup> 2) TDF/FTC has been associated with increased creatinine levels and decreased bone density;<sup>37-39</sup> and 3) TDF/FTC is a key component of many first-line ART regimens;<sup>40</sup> 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.<sup>41</sup> 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.<sup>42</sup> Data from Brazil show that 64% of injectable contraception users discontinued use in the first 12 months, 27% related to side effects.<sup>43</sup> Increased choice in type and method of delivery of contraceptive methods has increased acceptability.<sup>44</sup> 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)**

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<sup>45</sup>. 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]<sub>50</sub>) 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<sub>50</sub>) were evaluated. The percent of challenges resulting in infection was calculated relative to the plasma cabotegravir protein-adjusted inhibitory concentration (PA-IC<sub>90</sub>) value. None of 59 challenges resulted in infection when plasma levels were greater than 3 times the PA-IC<sub>90</sub>, compared with 1 out of 22 challenges resulting in infection when plasma levels were between 1 to 3 times the PA-IC<sub>90</sub>, and 11 out of 43 challenges resulting in infection when plasma levels were less than 1 times the PA-IC<sub>90</sub>. Twelve out of 26 challenges resulted in infection in control animals; rectal tissue levels of cabotegravir were approximately 20% of plasma levels.<sup>45</sup> Additionally, a penile SHIV infection model in rhesus macaques demonstrated 93% protective efficacy of CAB LA against penile exposures to SHIV.<sup>46</sup>

### 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<sub>0-24</sub>) and C<sub>max</sub> of 547 µg·h/mL and 34.6 µg/h/mL, respectively). The results of the multiple dose rat subcutaneous (SC) and IM toxicity study, along with data from the oral toxicity program, support the careful conduct of clinical studies with CAB LA up to the mean C<sub>max</sub> plasma concentration observed at the NOAEL in the 39-week monkey oral CAB toxicity study (34.6 µg/mL) or the mean AUC<sub>1,440-2,160h</sub> 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  $\mu\text{g/mL}$ , 3.4-fold above the PA-IC<sub>90</sub> value, and was associated with a mean Day 11 HIV ribonucleic acid (RNA) change from a baseline of -2.2  $\log_{10}$  c/mL.<sup>47,48</sup> In LAI116482 (LATTE), the Phase 2b study in HIV-infected, ART-naïve adult participants,<sup>49</sup> 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  $\mu\text{g/mL}$ , 8-fold above PA-IC<sub>90</sub>, and 4.2 $\mu\text{g/mL}$ , 25-fold above PA-IC<sub>90</sub>, 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 7.5 $\mu\text{g/mL}$  (28%), which provides adequate safety coverage for the predicted median (90%PI) peak concentrations following CAB LA of 4.0 $\mu\text{g/mL}$  (1.8, 8.9 $\mu\text{g/mL}$ ). Therefore, CAB 30mg once daily has been selected for the oral 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. Data from the ECLAIR study (which administered three serial injections of 800 mg CAB LA IM every 12 weeks [as 2 x 400 mg IM at each injection]) have shown that in some individuals (14 out of 83, 17%), CAB was detectable in plasma at 52 weeks post last injection.<sup>50</sup> The CAB concentrations in these study participants ranged from 29-105 ng/ml; these values fall between the lower limit of quantitation (LOQ) of 25 ng/ml and 1 x PA-IC<sub>90</sub> (166 ng/ml).

Additional data through 76 weeks post last injection (an additional 24 weeks longer than the current follow-up of 52-weeks post last injection) in HPTN 077 (which administers CAB LA 800 mg IM every 12 weeks in Cohort 1 and CAB LA 600 mg IM every 8 weeks after two initial injections four weeks apart in Cohort 2) suggests that the median time from the last injection to CAB levels falling below the limits of quantitation (25 ng/mL) were 43.7 (range 20-4-152.5) weeks for males and 67.3 (range 17.7-225.5) weeks for females.

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<sub>90</sub> 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<sub>tau</sub> (C<sub>τ</sub>) of 1.11 µg/mL (139%), approximately 6.7-fold above the PA-IC<sub>90</sub> 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<sub>90</sub>. The overall range of predicted CAB C<sub>τ</sub> 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<sub>τ</sub> values were ≥4-fold PA-IC<sub>90</sub> following each of the three quarterly injections while 15 to 31% were below the PA-IC<sub>90</sub>. 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 C<sub>τ</sub> of 1.53µg/mL (median 1.45 µg/mL) at Week 32 (Figure 2), above the geometric mean C<sub>τ</sub> 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 ( $4.54 \times 10^{-4} \text{ hr}^{-1}$  to  $9.19 \times 10^{-4} \text{ hr}^{-1}$ ; i.e., more rapid absorption) and resulted in higher peak to trough ratios than previously observed.

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

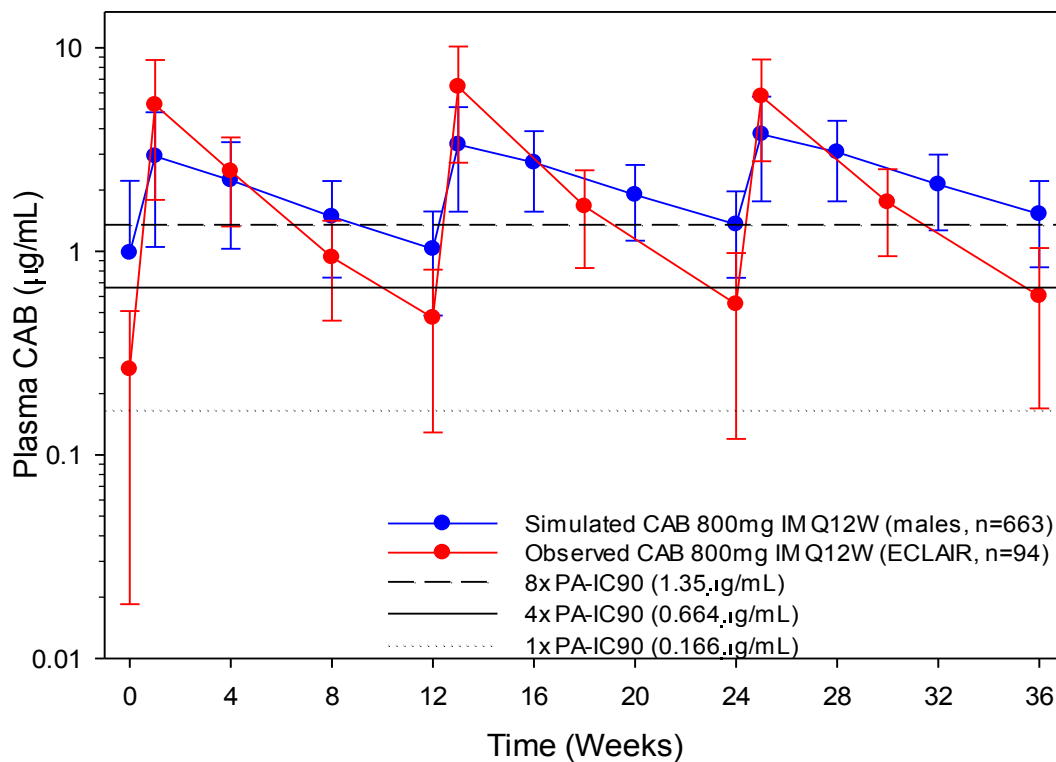
dosing regimen is predicted to yield a median steady-state  $C_{\tau}$  in males of approximately 1.35  $\mu\text{g/mL}$ , which is approximately 8-fold above PA-IC<sub>90</sub> (Figure 3), with  $C_{\tau}$  above the PA-IC<sub>90</sub> for 95% of participants, and 4-fold above PA-IC<sub>90</sub> for 80% of participants (Figure 4). A one-week delay in dosing of 600mg IM at steady state resulted in a drop in the median  $C_{\tau}$  to 1.08 $\mu\text{g/mL}$ , and the 5th percentile to 0.10 $\mu\text{g/mL}$ , with 92% of  $C_{\tau}$  values remaining above the PA-IC<sub>90</sub> (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. Additionally, pharmacokinetic analyses from HPTN 077, evaluating the 600mg IM dose of CAB LA at 8-week intervals after an initial 4-week interval between the first two injections, also support the choice of that dose for the Phase 3 studies of CAB LA for HIV prevention.<sup>51</sup>

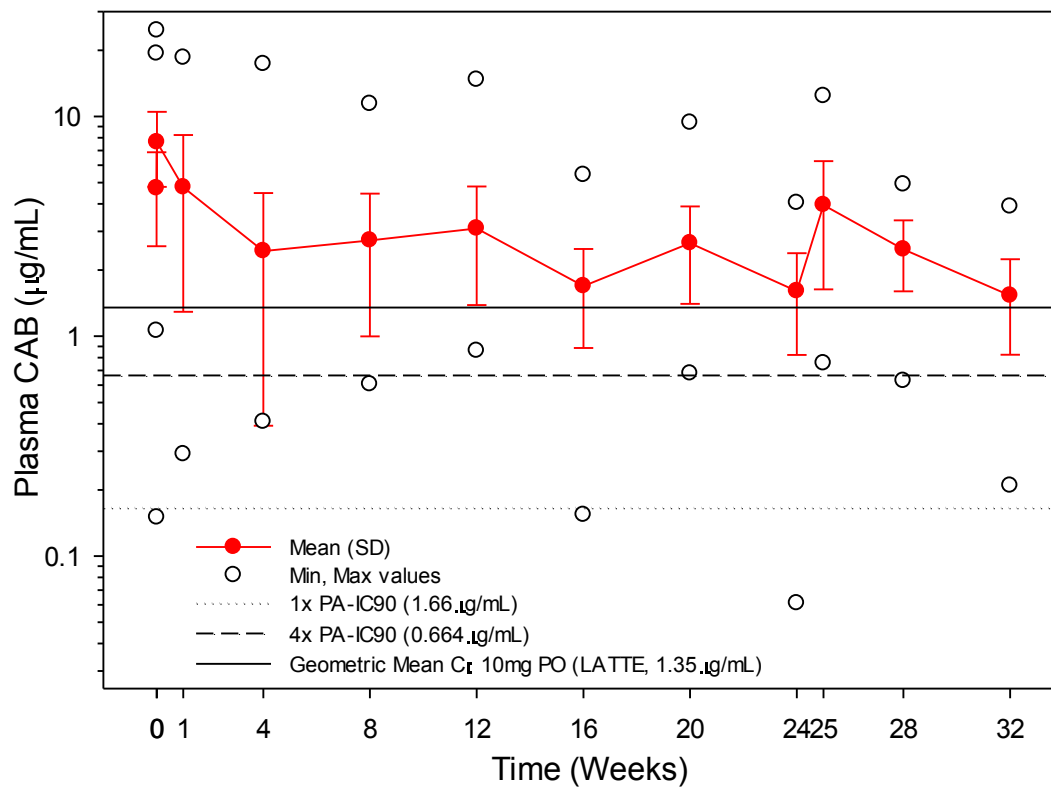
**Table 1: Summary of Cabotegravir Pharmacokinetic Parameters Following Oral and LA (IM) Administration and Pharmacokinetic Simulations in Healthy and HIV-Infected Participants**

| Route<br>Study<br>Population<br>N  | Cabotegravir<br>Regimen  | Cabotegravir PK Parameter                   |   |                        |   |
|--|--|---|---|------------------------|---|
|  |  | C <sub>τ</sub> or C <sub>0</sub><br>(μg/mL) | C <sub>max</sub><br>(μg/mL)               | AUC (0-τ)<br>(μg•h/mL) | Geomean IQ<br>C <sub>0</sub> or C <sub>τ</sub> /PA-<br>IC-90 <sup>b</sup> |
| Oral Data  |  |   |   |                        |   |
| Ph2a - ITZ112929<br>HIV infected<br>N=7  | 5 mg oral once<br>daily x10 d<br>monotherapy   | 0.57<br>[33%]                               | 1.02<br>[25%]                             | 17.7<br>[31%]          | 3.4   |
| Ph2b - LAI116482<br>(LATTE)<br>HIV infected<br>N=14  | 10 mg oral once<br>daily with<br>2NRTIs  | 1.35<br>[45%]<br>(n=57)                     | 2.77<br>[33%]                             | 45.7<br>[32%]          | 8.1   |
| Ph2b - LAI116482<br>(LATTE)<br>HIV infected<br>N=12  | 30 mg oral once<br>daily with 2<br>NRTIs   | 4.20<br>[40%]<br>(n=53)                     | 7.49<br>[28%]                             | 134<br>[32%]           | 25  |
| LA Data  |  |   |   |                        |   |
| Ph1 - LAI115428<br>HVs<br>N=9  | 800 mg IM every<br>12weeks x 2<br>(2nd dose<br>interval)   | 1.11<br>[139%]                              | 3.35<br>[56%]                             | 4417<br>[53%]          | 6.7   |
| Ph2a - 201120<br>(ECLAIR)<br>HVs <sup>c</sup>  | 800 mg IM every<br>12 weeks x 3<br>(third dose)<br>(n=85)  | 0.387<br>[150%]<br>(n=66)                   | 4.91<br>[67%]                             | 4021<br>[36%]          | 2.3   |
| Ph2b – 200056 Q4W<br>(LATTE-2 <sup>a</sup> )<br>HIV infected<br>(N=115)  | 800mg IM Day 1,<br>400mg IM W4,<br>then Q4W<br>following 30 mg<br>PO QD with 2<br>NRTIs lead-in  | 2.30<br>(0.85 – 5.0)<br>(W32,<br>n=85)      | 3.40<br>(1.64-<br>9.05)<br>(W25,<br>n=86) | ND <sup>c</sup>        | 13.9  |
| Ph2b – 200056 Q8W<br>(LATTE-2 <sup>a</sup> )<br>HIV infected(n=115)  | 800mg IM LD,<br>600mg IM W4,<br>W8, then Q8W<br>following 30 mg<br>PO QD with 2<br>NRTIs lead-in | 1.45<br>(0.21 – 3.<br>9)<br>(W32,<br>n=84)  | 3.36<br>(0.75-<br>12.4)<br>(W25,<br>n=87) | ND <sup>d</sup>        | 8.7   |
| Modeling and Simulation  |  |   |   |                        |   |
| PopPK simulation<br>(Initial PopPK<br>model) (N=1000)  | 800 mg IM every<br>12 weeks x 5<br>(last dose)   | 1.57<br>[56%]                               | ND <sup>d</sup>                           | ND <sup>d</sup>        | 9.5   |
| PopPK simulation <sup>a</sup><br>(Current PopPK<br>model) (N=10000)  | 600 mg IM Day1,<br>600 mg IM W4,<br>then Q8W   | 1.3<br>(0.18, 2.84)                         | 4.0<br>(1.8, 8.9)                         | ND <sup>d</sup>        | 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  |  |   |   |                        |   |

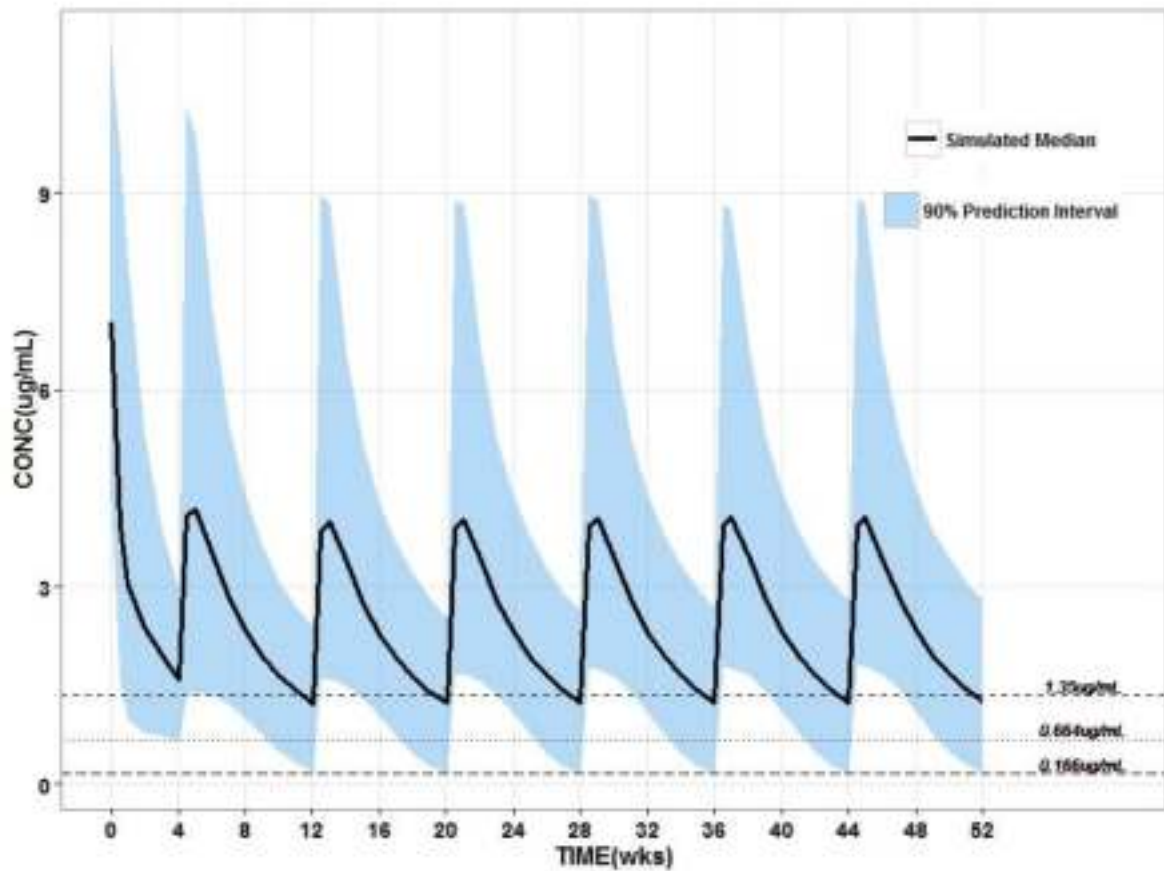
**Figure 1: Mean (SD) Plasma CAB Concentration-Time Profile following CAB LA 800mg IM Q12W in ÉCLAIR and Original Simulated Phase 2 Dose Rationale Model Predictions (Sparse Time Points)**



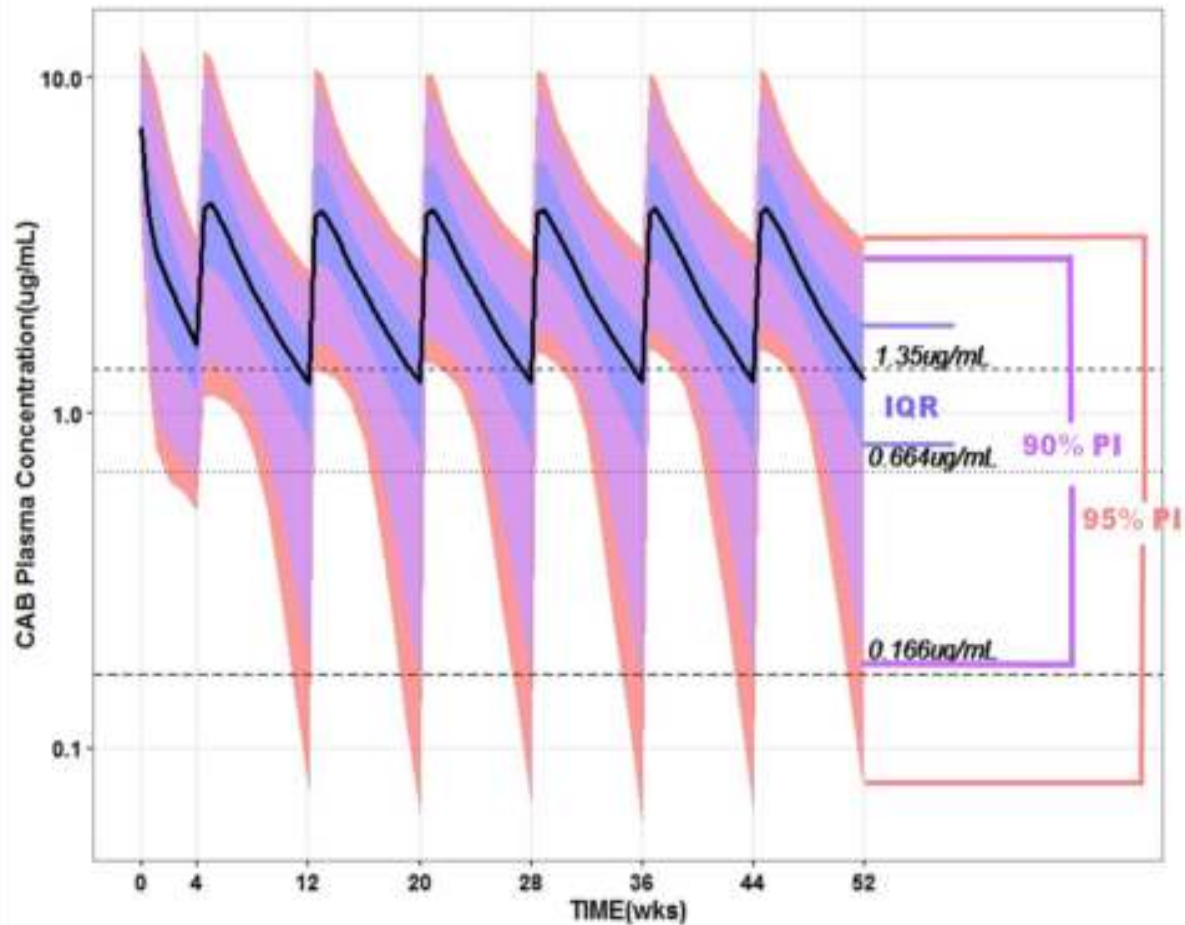
**Figure 2: Mean (SD) Plasma CAB Concentration-Time Profile following CAB LA Q8W Regimen (800mg IM Loading Dose, 600mg IM W4, W8, then Q8W) in 200056 (LATTE-2)**



**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)**

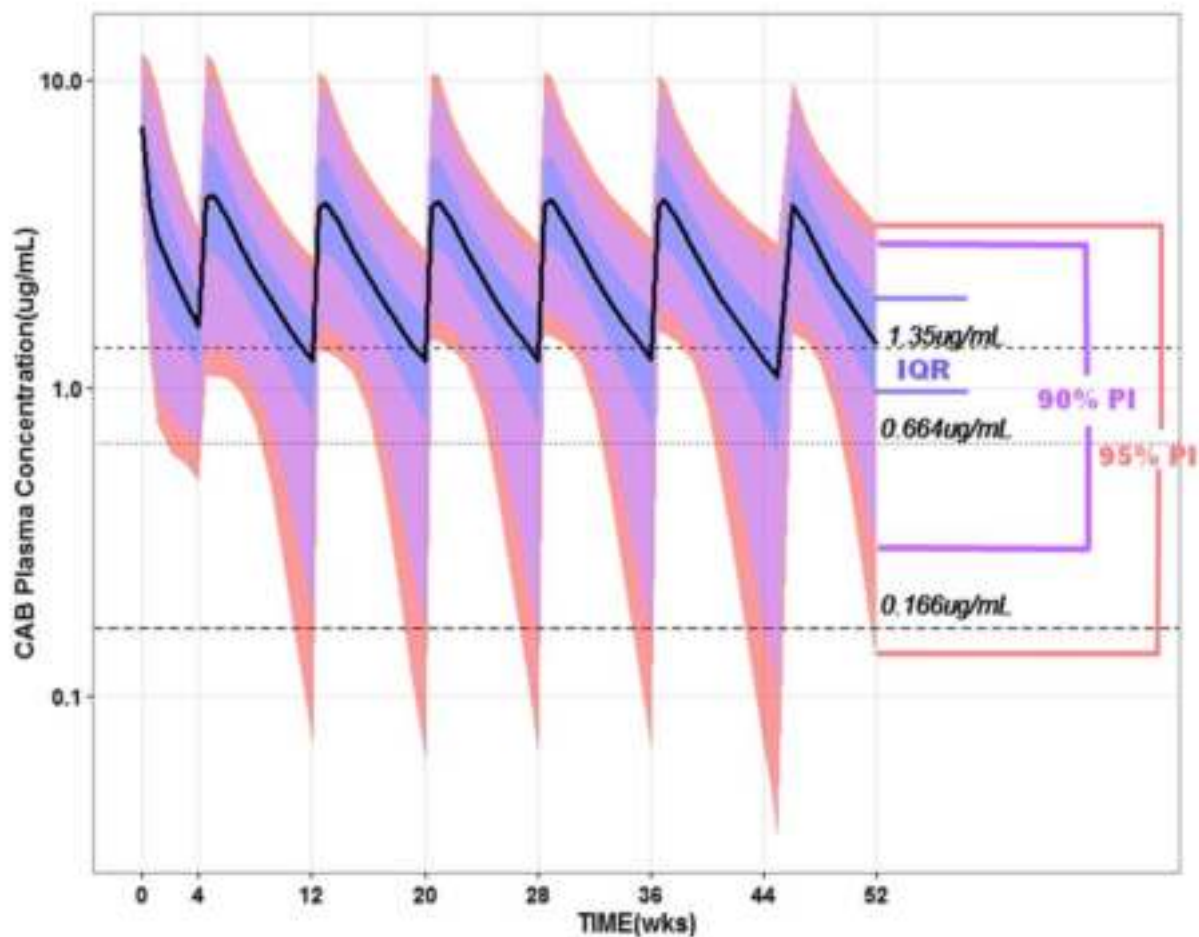


**Figure 4: Simulated Plasma CAB Concentration-Time Profile for the Proposed Regimen (600mg IM Day 1, W4 and Q8W) in Males based on Updated Population PK Model (semilog scale)**





**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.<sup>52</sup> 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).<sup>52</sup> ISRs related to CAB LA injection were common but generally mild (IM: 86%, SC: 99%) with no Grade 3 ISR AEs in Phase 1 studies. The most frequent ISRs for IM dosing were pain (71%), erythema (9%) and nodules (7%). Median IM ISR durations were approximately 5 days for pain and erythema, and approximately 22 days for nodules.<sup>52</sup>

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.<sup>48</sup> (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 rilpivirine 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.<sup>49</sup>

Safety results through week 144 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 (LATTE-2) is ongoing, 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 3/4 liver 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 CAB, through October 2018, are shown in Table 2.

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

| Treatment Population/<br>Dose                      | Duration                   | Completed        | Ongoing/<br>Concluded <sup>a</sup> | Total       |
|--|----------------------------|------------------|------------------------------------|-------------|
| <i>Healthy Volunteers/HIV-Uninfected</i>           |                            |                  |                                    |             |
| 5 to 150 mg oral                                   | Single dose                | 208              | 0                                  | 208         |
| 10 to 30 mg once daily oral                        | 10 to 28 days              | 293              | 1694                               | 1987        |
| 150 mg every 12 hours oral                         | 3 doses                    | 40               | 0                                  | 40          |
| 100 – 800 mg IM/SC LA                              | Max 763 days <sup>g</sup>  | 230 <sup>b</sup> | 1377 <sup>c</sup>                  | 1607        |
| <b>Any dose</b>                                    |                            | <b>599</b>       | <b>1694</b>                        | <b>2293</b> |
| <i>HIV-infected patients</i>                       |                            |                  |                                    |             |
| 5 to 30 mg once daily oral (Ph 2a)                 | 10 days                    | 15               | 0                                  | 15          |
| 10 to 60 mg once daily oral (Ph 2b)                | Max 2247 days <sup>h</sup> | 0                | 181                                | 181         |
| 30 mg once daily oral (Ph 2b)                      |                            | 0                | 1739                               | 1739        |
| Up to 800 mg IM LA <sup>d</sup>                    | Max 1477 days <sup>g</sup> | 0                | 1745 <sup>e</sup>                  | 1745        |
| <b>Any dose</b>                                    |                            | <b>15</b>        | <b>1928</b>                        | <b>1943</b> |
| <i>All participants</i>                            |                            |                  |                                    |             |
| Single dose oral (5 to 150 mg)                     |                            | 208              | 0                                  | 208         |
| Repeat dose once daily oral (5 to 60 mg)           |                            | 308              | 3614                               | 3922        |
| 150 mg oral every 12 hours x 3                     |                            | 40               | 0                                  | 40          |
| Single or repeat dose LA injection (100 to 800 mg) |                            | 230 <sup>b</sup> | 3122 <sup>f</sup>                  | 3352        |
| <b>Any dose</b>                                    |                            | <b>614</b>       | <b>3622</b>                        | <b>4236</b> |

a. Concluded studies: study completed through follow-up; and/or clinical study report is in preparation

b. 172 participants received both oral and LA dosing

c. All participants received both oral and LA dosing

d. Includes 400 mg Q4W and 600 mg Q8W dosing

e. 1736 participants received both oral and LA dosing

f. 3113 participants received both oral and LA dosing

g. Detectable CAB concentrations can remain for up to 72 weeks following the last CAB injection

h. As of 28 Dec 2014, all participants had transitioned to CAB 30 mg in the Open-Label phase of study LAI116482 (LATTE-1), therefore, the longer durations apply to the 30 mg dose only

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

As described above, two Phase 2b clinical trials are ongoing (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).<sup>49</sup> 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.<sup>49</sup> 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).<sup>53</sup> Two phase 3 trials of CAB LA + RPV LA administered at 4-week intervals for maintenance of virologic suppression in HIV-infected individuals have been presented (ATLAS, FLAIR), wherein CAB LA + RPV LA was found to be non-inferior to oral ART in both naïve treatment settings (after ABC/3TC/DTG induction to suppression) and as non-failure switch from stably suppressive ART; an additional phase 3b trial of CAB LA + RPV LA administered at 8-week intervals for maintenance of virologic suppression in HIV infected individuals is ongoing (ATLAS-2M).

### 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%).<sup>54</sup> 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 2a HPTN 077, Phase 2b LATTE and LATTE-2), some participants developed transaminase elevations, which were clinically asymptomatic and resolved rapidly with cessation of study product.

In a single-dose study, a healthy male volunteer with a history of prior seizure activity (one episode 14 years prior), on no anti-epileptic medication, experienced an unwitnessed seizure

event 270 days after a single injection of CAB LA 400 mg IM. Plasma levels of CAB were undetectable for 4 months prior to the seizure event. The event occurred in the context of consumption of approximately 10 cans of beer, and 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 did not receive 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”.<sup>4</sup> 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.<sup>1</sup> 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.<sup>8</sup> 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% ( $P=0.01$ ).<sup>9</sup> 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.”<sup>55</sup>

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;<sup>56</sup> 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.<sup>34</sup>

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.<sup>57,58</sup>

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%,<sup>1,4,9,17-21</sup> 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.<sup>59,60</sup> 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.<sup>1,9,20,21,61</sup> 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.<sup>37,62,63</sup> 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<sup>4,35,36</sup> 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.<sup>64</sup> 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.<sup>65</sup> 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, bone mineral density (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 subset. DXA evaluations will be conducted for subset participants at Enrollment and Weeks 57 and 105. An additional informed consent will be required for subset participation. The subset will be competitively enrolled until 350 baseline DXA scans are obtained.

## **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.<sup>66</sup> 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”<sup>67</sup> 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.<sup>68</sup> Previous studies in the region have found that this population has a high willingness and acceptability for the use of PrEP.<sup>69</sup> 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).<sup>70</sup> MSM and TGW in Brazil have a very high willingness to use PrEP to prevent HIV.<sup>71</sup>

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).<sup>72</sup> 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.<sup>73</sup> 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.<sup>74</sup> 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.<sup>60</sup> 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.<sup>75-79</sup>

### **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 at two time points 4 weeks apart followed by every 8 weeks thereafter. 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 a year or more after an injection (see Section 1.3.2). 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.<sup>34</sup> 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.<sup>80</sup> 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.

### **1.14 Rationale For Web-Based Sexual Health Promotion Score During Screening**

SexPro is a web-based tool that provides participants with a sexual health promotion score. The SexPro score was developed to estimate short-term HIV acquisition risk using data from several large cohorts of MSM in the United States and South America.<sup>81-85</sup> Different models were developed for North and South America, based on data from these two populations. In particular,

these models reflect differences in demographic and substance use effects on HIV acquisition and required tradeoffs between goodness of fit and delivering interpretable risk information. From this, two separate SexPro interfaces were created: one for North American MSM (available in English and Spanish), and one for South American MSM (in Spanish and Portuguese). Participants answer a brief questionnaire including age, race/ethnicity (US only), behavioral risk factors, substance use, and history of sexually transmitted diseases (gonorrhea, chlamydia, and syphilis) which are used to calculate their personalized HIV risk score reflecting their likelihood of HIV acquisition at six months. Scores range from 1 (highest risk) to 20 (lowest risk) based upon a positive sexual health promotion framing. The SexPro score for the North American model has been subsequently validated in two contemporary longitudinal cohorts of MSM – HPTN 061 and HVTN 505 – and shows good model fit, especially among Black MSM in HPTN 061.<sup>86</sup> A SexPro score of 16 or lower showed good sensitivity (75.4%) and specificity (51.8%) in HVTN 505. All HIV seroconversions in HPTN 061 occurred below this value; this cut-off was chosen to identify MSM at high risk for HIV infection, and to maximize sensitivity of the tool for Black MSM in the US. The SexPro score, using a score cut-off of 16 or lower, will be used in addition to the current behavioral risk inclusion criteria for the US-based cohort; participants who do not qualify on the basis of the current behavioral risk will be eligible with a risk score of 16 or lower. This recognizes that young men of color in the US are at risk of acquiring HIV with less self-reported risk than older white men. SexPro will also be administered to MSM outside of US but will not be used as part of the inclusion criteria, as this has not yet been validated in separate cohorts.

### **1.15 Rationale For Collecting and Analyzing Metabolic Parameters**

Data increasingly support the association of integrase inhibitors with weight gain in the setting of HIV infection.<sup>87,88</sup> The precise mechanism is unknown, is noted to be greater in Black participants, in women, and in those with lower CD4 cell counts, and appear to be additionally contributed to by the choice of nucleoside analogue reverse transcriptase inhibitors (NRTIs) used as part of the treatment regimen. The contribution of the HIV-associated inflammatory milieu is also unknown. HPTN 077 did not find a difference between CAB and placebo arms for weight gain for any population.<sup>89</sup> The HPTN 083 study will capture participant data for weight in a standardized way to evaluate changes between study product arms. Per FDA guidance, additional metabolic parameters (including but not limited to weight, pulse, blood pressure and fasting glucose/lipids) will also be analyzed for changes between study arms.<sup>90</sup>

## **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
- To compare changes in weight, blood pressure, pulse, fasting glucose, and fasting lipids among participants receiving oral CAB/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, and South Africa
- 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, and South Africa

## **2.4 Exploratory Objectives:**

- To perform secondary laboratory assessments that may include evaluation of factors related to HIV infection, hepatitis infection, or other infections; 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. Approximately 5000 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. Participants in Step 1 who do not transition to Step 2 for any reason other than HIV infection will remain blinded to their study assignment and be asked to attend annual visits until they each individually complete 3 years of follow-up from the time of Enrollment.

### 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 three years of follow-up, to Week 153, for each participant, with the last injection provided and the last blinded oral study product dispensed at Week 145. Participants who prematurely discontinue blinded study products during Step 2 (having received at least one injection) for any reason other than HIV infection will transition to Step 3 and receive 48 weeks of study-provided open label TDF/FTC, followed by annual follow-up until three years from the date of Enrollment. For these participants, the timepoint at which they transition to Step 3 will determine whether they will be asked to attend annual visits following the completion of Step 3; if the completion of Step 3 post-dates three years from the date of Enrollment, annual follow-up is not required.

All participants will also be simultaneously unblinded after the last participant concludes their participation in Step 2.

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 48 weeks in order to test for safety parameters, as well as CD4 cell count and HIV viral load.

### **Step 3:**

Participants who complete the full three years of follow-up in Step 2 at the Week 153 visit will ideally begin Step 3 on the same day, which will be considered Day 0 of Step 3. On this day, participants will begin study-provided open-label daily oral TDF/FTC for 48 weeks (for Arm A, to “cover the tail”). For participants who prematurely transition to Step 3 before completing three years of follow-up in Step 2, Step 3 will start 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, including services for PrEP, if available, when their participation in the study ends, or if they transition to annual visits in Step 1 or Step 2, or if at the discretion of the primary care physician, they transition to Step 3 on study but off study-provided TDF/FTC.

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 083HIV@hptn.org group.

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 7.5 years total, with individual participants being followed for approximately 4.0 years total. Accrual will require approximately 3.5 years.

### 3.0 STUDY POPULATION

Approximately five thousand (5000) 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 on 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
  - SexPro score of  $\leq 16$  (US sites only)
- 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<sup>3</sup>
  - Platelet count  $\geq 100,000$ /mm<sup>3</sup>
  - Calculated creatinine clearance  $\geq 60$  mL/minute using the Cockcroft-Gault equation (use sex at birth for calculation)
    - Although not protocol exclusionary, sites should carefully consider the advisability of enrolling participants with calculated creatinine clearance between 60-70 mL/min, as limited changes in creatinine clearance during study conduct



will lead to protocol-mandated product holds and may alter the risk-benefit considerations of study participation

- Alanine aminotransferase (ALT) < 2 times the upper limit of normal (ULN)
- Total bilirubin  $\leq$  2.5 times ULN
- Hepatitis B virus (HBV) surface antigen (HBsAg) negative
- HCV Ab negative
- No Grade 3 or higher laboratory abnormalities on any laboratory tests obtained at screening, including tests obtained as part of a panel of tests ordered to obtain the protocol-required laboratory test results.

\*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 provision of study product 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). **Note: Past participation in a monoclonal antibody study is not exclusionary, effective as of Version 1.0 of HPTN 083.**
- 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), including egg or soy products (egg and soy products are contained in Intralipid)
- Surgically-placed or injected buttock implants or fillers, per self-report. Contact the CMC for guidance regarding questions about individual cases.
- 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
- QTc interval (B or F) > 500 msec

### 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 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.

### 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. In general, participants should not be withdrawn from the study during the blinded, randomized portion of the study except in the case of a) withdrawal of consent; b) death; c) extreme/unusual circumstances to protect participant safety; or d) if they are unwilling or unable to comply with required study procedures. Any such safety-related participant terminations should only be implemented 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.

### 3.6.1 Premature Termination Visits

In general, for participants who withdraw consent from the study prematurely during a study visit, the requirements for that visit should be completed to the extent possible **except for provision of study product** and will be considered their final visit. When possible, a plan should be made to provide final laboratory results to the participant. For participants who inform the site in between visits that they wish to withdraw consent from the study, sites should make every effort to have the participant return any unused study product.

## 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, one tablet orally daily for five weeks, with or without food AND placebo for TDF/FTC tablets, one tablet orally daily for 5 weeks, with or without food
- Arm B: TDF/FTC 300 mg/200 mg fixed dose combination tablet, one tablet orally daily for five weeks, with or without food AND placebo for oral CAB tablet, orally 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) intramuscular IM injection in the gluteal muscle at two time points 4 weeks apart and every 8 weeks thereafter, AND placebo for TDF/FTC tablet, one tablet orally daily with or without food
- Arm B: TDF/FTC 300 mg/200 mg fixed dose combination tablet, one tablet orally daily, with or without food AND placebo for CAB LA (Intralipid 20% fat emulsion infusion) administered as one 3mL intramuscular (IM) injection in the gluteal muscle as two time points 4 weeks apart and every 8 weeks thereafter

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

### 4.2 Study Product Formulations

#### 4.2.1 Oral Products

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

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

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

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

TDF 300 mg/FTC 200 mg tablets (open-label) are capsule-shaped, film-coated blue tablets that must be stored in the original container. Each bottle contains a silica gel desiccant canister to protect the product from humidity. The bottles are to be stored at 25°C (77°F). Excursions are permitted between 15° to 30°C (59 to 86°F). The TDF/FTC fixed dose combination tablet containing 300 mg of TDF and 200 mg of FTC is available as Truvada® and is approved by the U.S. FDA for treatment and prevention of HIV-1 infection. Further information on Truvada® is available in the current package insert.<sup>91</sup>

#### **4.2.2 Injectable Suspension**

The CAB study product (oral and LA injectable) being tested in this study is investigational and not yet approved by the US FDA for the treatment or prevention of HIV-1 infection. Further information on the study product is available in the Investigator's Brochure (IB), which will be provided by the DAIDS Regulatory Support Center (RSC).

CAB LA is formulated as a sterile white to slightly pink colored suspension containing 200 mg/mL of CAB LA for administration by IM. The product is packaged in a 2 mL or 3 mL glass vial. Each vial is for single use containing 2 mL (400 mg) or 3 mL (600 mg) and does not require dilution prior to administration. CAB LA injectable suspension is to be stored up to 30°C (86°F), do not freeze.

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

### **4.3 Study Product Preparation**

#### **4.3.1 Preparation of the Oral Study Product**

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

Prior to dispensing, the un-blinded portion of the tear-off label must be removed and attached to the participant specific pharmacy record such as participant prescription or participant specific

study product accountability record. The permanently affixed section of the label will remain on the original container.

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

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

#### **4.3.2 Preparation of Injectable Study Product**

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

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

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

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

1. One CAB LA 600 mg/3 mL vial or two CAB LA 400 mg/2 mL vials
2. Becton Dickinson (BD) 3-mL syringe, Leur-Lok Tip, Product No.: 309657 or equivalent
3. Becton Dickinson (BD) 5-mL Syringe, Luer-Lok Tip, Product No.: 309646 or equivalent
4. Needle for aspiration: BD general use sterile hypodermic needle, 21G x 1½ inch (e.g. PrecisionGlide Needle, Product No.: 305165 or equivalent)
5. Needle for intramuscular injection: BD IM sterile hypodermic needle, 23G x 1½ inch (e.g. PrecisionGlide Needle, Product No.: 305194 or equivalent). Refer to the HPTN 083 SSP for further details on appropriate needle gauge size and length to use for IM administration.

##### **Preparation Steps:**

1. Remove two vials of CAB LA (400 mg/2 mL per vial) or one vial of CAB LA (600 mg/3 mL per vial) from storage. If the vials are stored in the refrigerator (2°C to 8°C), remove vial(s) from the refrigerator and wait at least 15 minutes to equilibrate to room temperature.
2. Vigorously shake the vial(s) for a full 10 seconds by shaking the vial(s) with long arm movements.
3. Invert the vial(s) and inspect to ensure uniform suspension. If solid remains undispersed, repeat Steps 2-3 until all material is uniformly suspended.

NOTE: It is normal to see small air bubbles at the end of shaking the vial for re-suspension.

4. Using aseptic technique under a pharmacy BSC/isolator, flip off the plastic cap from the vial. Wipe the top of the vial with an alcohol pad (isopropyl alcohol 70% or similar) and allow to dry. Do not touch the rubber stopper at any time.
5. Remove a 3 mL or 5 mL size syringe and 21G x 1½ inch (or equivalent) needle for aspiration. Attach the needle to the Luer connection of the syringe.
6. With the needle sheath on, pull the syringe plunger rod to allow approximately 1 mL of air into the syringe. Remove the needle sheath.
7. With the vial in the inverted position and the syringe with the needle in the upright position, push the needle through the vial stopper and inject approximately 1 mL of air into the vial.
8. While keeping the syringe with the needle in the upright position, withdraw needed volume of CAB LA suspension from the vial(s) into the syringe
  - Withdraw total of 3 mL (600 mg) of CAB LA suspension from the vial(s) into a syringe.
    - If using two CAB LA 400 mg/2 mL vials to prepare the dose, a second new aspiration needle should be used to withdraw suspension from the second vial. Remove the first needle that was used to withdraw the suspension out of the first vial and discard properly. Attach the new 21G x 1½ inch needle (or equivalent) to the syringe already containing suspension per instructions in Step 5 and repeat Steps 6 and 7 to withdraw the remaining needed volume from the second vial.

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

9. Remove the needle that was used to withdraw the suspension out of the vial and discard the needle properly.
10. Place an overlay around the prepared syringe to maintain the blind.
11. Attach a 23G x 1½ inch (or equivalent) needle to the Luer connection of the prepared CAB LA syringe for IM injection for the participant. Alternatively, the site pharmacist can attach a syringe cap to the prepared syringe. The study staff can then attach the appropriate needle for administration to the prepared syringe in the clinic before administration.

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

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



12. Record the time that the suspension was withdrawn from the vial and into the syringe in the participant's pharmacy log. This is the time of preparation.
13. Label the prepared syringe containing 3 mL (600 mg) of CAB-LA in a blinded fashion as "CAB LA 600 mg or Placebo for CAB LA", including the volume (3 mL), route (IM), participant's PTID, date and time of preparation, and date and time of expiration. Follow the DAIDS Pharmacy guidelines and local regulations for preparing the participant specific label.

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

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

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

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

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

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

1. One 100 mL IV bag of intralipid 20% fat emulsion
2. Becton Dickinson (BD) 3-mL syringe, Leur-Lok Tip, Product No.: 309657 or equivalent
3. Becton Dickinson (BD) 5-mL Syringe, Luer-Lok Tip, Product No.: 309646 or equivalent
4. Needle for aspiration: BD general use sterile hypodermic needle, 21G x 1½ inch (e.g. PrecisionGlide Needle, Product No.: 305165 or equivalent)
5. Needle for intramuscular injection: BD IM sterile hypodermic needle, 23G x 1½ inch (e.g. PrecisionGlide Needle, Product No.: 305194 or equivalent)

#### **Preparation Steps:**

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

2. Using aseptic technique under a pharmacy BSC/ Isolator, wipe the additive port of the infusion bag with an alcohol pad (isopropyl alcohol 70% or similar) and allow to dry.
3. Remove a 3 mL or 5 mL size syringe and 21G x 1½ inch (or equivalent) needle for aspiration. Attach the needle to the Luer connection of the syringe.
4. Remove the needle sheath.
5. Push the needle through the additive port of the infusion bag and withdraw 3mL of Intralipid 20% into the syringe.
6. Since the suspension can still contain some air, withdraw enough suspension from the Intralipid 20% IV bag in order to be able to de-aerate the syringe properly.
7. Remove the needle that was used to withdraw the suspension out of the Intralipid IV bag and discard the needle properly.
8. Place an overlay around the dosing syringe to maintain the blind.
9. Attach a 23G x 1½ inch (or equivalent) needle to the Luer connection of the prepared Intralipid 20% (placebo) syringe for IM injection for the participant. Alternatively, the site pharmacist can attach a syringe cap to the prepared syringe. The study staff can then attach the appropriate needle for administration to the prepared syringe in the clinic before administration.

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

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

10. Record the time the suspension was withdrawn from the Intralipid 20% IV bag into the syringe in the participant's pharmacy log. This is the time of preparation.
11. Label the prepared syringe containing 3 mL of Intralipid 20% suspension in a blinded fashion as "CAB LA 600 mg or Placebo for CAB LA", including the volume (3 mL), route (IM), participant's PTID, date and time of preparation, and date and time of expiration. Follow the DAIDS Pharmacy guidelines and local regulations for preparing the participant specific label.
12. Any entered IV bag or expired filled syringes should be disposed of in accordance with institutional or pharmacy policy.

After withdrawal of the Intralipid 20% suspension from the IV bag into a syringe, it is recommended to inject the suspension immediately. Do not exceed 2 hours between withdrawing from the IV bag into a syringe (Step 5) and administration to the study participant. The prepared Placebo for CAB LA study product in a syringe must be stored at controlled room temperature between 20° C to 25° C (68° F-77° F) from the time it is withdrawn into a syringe to the time it is administered.

#### **4.4 Study Product Acquisition and Accountability**

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

##### **4.4.1 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.

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

#### **4.5 Toxicity Management**

Toxicity management guidelines can be found in Appendix III.

#### **4.6 Concomitant, Prohibited, and Precautionary Medications**

As noted in the SSP Manual Section 9, a variety of medications including rifampicin, rifapentine and rifabutin are contraindicated for concurrent use with cabotegravir. If treatment for any condition requiring the use of a prohibited medication (including but not limited to TB or LTBI) is planned, blinded study product should be held. Depending on which step the participant is in, the participant will be offered study-provided open label TDF/FTC during the course of prohibited medication use and may return to blinded study product once the prohibited medication use is completed. This is also applicable to any participant who stopped blinded

study product prior to all relevant national and local approvals of Version 3.0 of the protocol. Sites must contact the CMC for clinical guidance on implementation of this blinded study product hold, concurrence on the appropriateness of planned resumption of blinded study products upon prohibited medication completion, and resumption of blinded study products when/if appropriate. Section 9 of the SSP provides guidance regarding the visit schedule during the use of study-provided open label TDF/FTC while using a prohibited medication.

As also outlined in the SSP Manual Section 9, non-study provided TDF/FTC or TAF/FTC for PrEP is not permitted during any portion of HPTN 083. Exceptions to this include that non-study provided PrEP may be used per primary care physician discretion during annual follow-up (when participants are off study-provided product per protocol) and during Step 3 *in circumstances in which a participant is not on study-provided open label TDF/FTC per protocol* (e.g., in the case of an AE).

The precautionary and prohibited medications are:

Cabotegravir:

- Not to be administered concurrently:
  - Cytotoxic chemotherapy or radiation therapy
  - Systemically administered immunomodulators
    - NOTE: Stable physiologic glucocorticoid doses (defined as prednisone  $\leq 15$  mg/day or equivalent as a stable or tapering dose) are not prohibited. Use of corticosteroids for an acute condition such as asthma exacerbation, or receiving a short course (defined as  $\leq 2$  weeks of pharmacologic glucocorticoid therapy) is also not prohibited
  - barbiturates
  - carbamazepine
  - oxcarbazepine
  - phenytoin
  - pheonobarbital
  - rifabutin
  - rifampin
  - rifapentine
  - St. John's wort
- Prohibited within 7 days before and 7 days after an injection
  - high dose aspirin ( $>325$  mg per day)
  - anagrelide
  - apixaban
  - argatroban
  - bivalirudin
  - clopidogrel

- dabigatran
- dalteparin
- enoxaparin
- fondaparinux
- heparin
- lepirudin
- prasugrel
- rivaroxaban
- ticagrelor
- ticlopidine
- warfarin
- Oral formulation precautions
  - Antacid products containing divalent cations (e.g., aluminum, calcium, and magnesium) must be taken at least 2 hours before or at least 4-6 hours after the oral CAB administration

Truvada:

- Medications containing the following ingredients should not be administered concurrently:
  - emtricitabine or tenofovir disoproxil fumarate (e.g. ATRIPLA®, COMPLERA®, EMTRIVA, GENVOYA®, ODEFSEY®, STRIBILD®, or VIREAD, Descory).
  - lamivudine (e.g. Combivir, Dutrebis, Epivir, Epivir-HBV, Epivir A/F, Epzicom, Triumeq, or Trizivir)
  - adefovir (e.g. HEPSERA®)
  - tenofovir alafenamide (e.g. Vemlidy)
  - didanosine (e.g. Videx EC)
  - atazanavir (e.g. Reyataz, Evotaz (atazanari/cobicistat))
  - ledipasvir/sofosbuvir (e.g. HARVONI®)
  - darunavir (e.g. Prezista)
  - lopinavir/ritonavir (e.g. Kaletra)
  - orlistat (e.g. Alli, Xenical)

Intralipid 20% fat emulsion: There are no precautionary/prohibited medications in the current package insert for Intralipid 20% fat emulsion.

Additional information regarding recommended, prohibited, and precautionary concomitant medications can be found in the cabotegravir IB and the Truvada® PI.

The precautionary and prohibited medications listed above are also included in Section 9 of the SSP Manual; refer to that section for other information.

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).

#### **4.7 Other Study Product Dispensing Considerations**

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

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

## 5.0 STUDY PROCEDURES

Overviews of the study visit and procedures schedules are presented in Appendix IA, Appendix IB, Appendix IC, and Appendix ID, and Appendix II in the event of suspected and confirmed HIV infection. Appendix IE, Appendix IF, and Appendix IG include the required HIV testing algorithm for screening, enrollment and follow-up, respectively (these are also included in the SSP). 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
- Administer SexPro assessment (US only for inclusion purposes; South American sites only for data collection purposes currently)
- 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 eligibility criteria for the study and will be referred for appropriate medical care, if necessary.

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

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, per section 9 of the SSP Manual, including concomitant medications, as well as height, weight, blood pressure, and pulse data entry into Medidata Rave (the complete medical history and complete physical exam may be performed during screening at the discretion of the Investigator of Record or their designee). Note: The collection of height is a one-time data entry into Medidata Rave.
- For BMD Subset only: DXA scan, and dietary calcium and Vitamin D assessment. The scan may be performed -30 days/+7 days of enrollment.
- Blood collection (collect prior to administration of study product)
- Urine collection for urinalysis
- Urine collection for Neisseria gonorrhea (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 after 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 and fasting glucose (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.

**NOTE 2:** Throughout this section, the CASI and interviewer-administered assessments are referred to as “behavioral” and “acceptability” assessments. Refer to the SSP Manual Schedule of Forms for the schedule of CASI and interviewer-administered assessments.

### 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, as well as weight, blood pressure, and pulse data entry to Medidata Rave
- Blood collection

#### Laboratory Evaluations

- HIV testing (see SSP Manual)
- CBC with differential
- Chemistry testing (see Appendix IA)
- Liver function testing (see Appendix IA)
- 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 repeated value is Grade 2 or higher at Week 4, study product should be stopped, and the participant will be followed annually until three years from the date of Enrollment. 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. If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up.

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 until three years from the date of Enrollment. 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. If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up.

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 until three years from the date of Enrollment. AEs will be followed until resolution ( $\leq$  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 until three years from the date of Enrollment. All such cases must be reported to the CMC.

The Week 4 visit must take place within 120 days of study enrollment. Participants with pill counts resulting in less than 50% adherence as assessed by pill count at the Week 4 visit will not be allowed to transition to Step 2. These participants will be asked to report for annual visits until three years from the date of Enrollment. Refer to Section 5 of the SSP for instructions regarding participants who forget to bring their pill bottles to the Week 4 visit.

For participants who do not transition to Step 2 as outlined above, the following procedures will take place (see also Appendix ID)

- Review/update locator information
- Targeted medical history and targeted physical exam, with concomitant medications update
- HIV pre and post-test counseling
- HIV testing, plasma storage, DBS storage
- Offer condoms and lubricant

## 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, as well as weight, blood pressure, and pulse data entry into Medidata Rave
- Blood collection
- Administer injection
- Dispense pills

### Laboratory Evaluations

- HIV testing (see SSP Manual)
- Plasma storage

**NOTE 1:** 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.

**NOTE 2:** Refer to Section 5 of the SSP regarding instructions for **split visits** where the injection was not administered during the first half of the split visit, and for **merged visits** where in unforeseen circumstances, a safety visit and an injection visit occur on the same day.

## 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 IB)
- Liver function testing (see Appendix IB)
- 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**

## 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)
- Acceptability assessment (only at Weeks 17, 41, 65, 89, 137)
- Adherence counseling

## Clinical Procedures

- Targeted medical history and targeted physical exam, including concomitant medications, as well as weight, blood pressure, and pulse data entry to Medidata Rave
- ECG (only at Weeks 57, 105)
- BMD Subset only (only at Weeks 57 and 105): DXA scan, and dietary calcium and Vitamin D assessment. These scans may be performed  $\pm$  8 weeks of each visit).

Note: If a participant in the BMD subset prematurely transitions out of Step 2 to Step 3 or annual visits, and the transition occurs close to the Week 57 or Week 105 DXA timepoints, the CMC may authorize that a DXA be performed

- Blood collection
- Urine collection for urinalysis (only at Weeks 57, 105)

- Urine collection for GC/CT testing (only at Weeks 33, 57, 81, 105, 129)
- Rectal swab for GC/CT testing (only at Weeks 33, 57, 81, 105, 129)
- Administer injection
- Dispense pills

#### Laboratory Evaluations

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

**NOTE 1:** 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.

**NOTE 2:** Refer to Section 5 of the SSP regarding instructions for **split visits** where the injection was not administered during the first half of the split visit, and for **merged visits** where in unforeseen circumstances, a safety visit and an injection visit occur on the same day.

#### **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**

#### 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 IB)
- Liver function testing (see Appendix IB)
- Plasma storage

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

### **5.8 Week 153, Last Visit of Step 2/ Day 0, First Visit of Step 3**

The final visit of Step 2 will take place at Week 153, which is also Day 0 of Step 3. An injection will not be administered at this visit and blinded oral study product will not be dispensed at this visit. All other procedures required for Week 153/Day 0 will be performed. Any remaining blinded oral study product will be collected from the participant as part of the conclusion of Step 2. Open-label oral product will be dispensed at this visit as part of Day 0 of Step 3. The procedures required at Week 153 (except for administration of the injection) and results of testing from Week 153 will also apply to Day 0 of Step 3 unless otherwise noted below and otherwise directed by the CMC. Additionally, if the Week 153 visit is missed or has already occurred or passed at the time Version 3.0 of the protocol is approved and implemented at a site, the final visit of Step 2/first visit of Step 3 will take place at the next visit the participant attends; the CMC may be contacted if additional guidance is required in these cases, though this is not required.

#### 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 as well as weight, blood pressure, and pulse data entry to Medidata Rave
- ECG
- Blood collection
- Urine collection for urinalysis
- Urine collection for GC/CT testing
- Rectal swab for GC/CT testing
- Collect any unused blinded oral study product
- Dispense OPEN-LABEL oral TDF/FTC pills

## Laboratory Evaluations

- HIV testing (see SSP Manual)
- HCV testing
- CBC with differential
- Chemistry testing (see Appendix IB)
- Liver function testing (see Appendix IB)
- Syphilis serologic testing
- Urinalysis
- Urine GC/CT testing
- Rectal swab GC/CT testing
- Plasma storage
- DBS storage

NOTE: If a participant in Step 2 transitions prematurely to Step 3 or misses the Week 153 visit for any reason, or if the Week 153 visit already occurred under Version 2.0 of the protocol and the participant now needs to move to Step 3 under Version 3.0 of the protocol, the procedures listed above will be performed as part of the last visit of Step 2 (whenever that occurs)/Day 0 of Step 3 to the extent possible. All assessments are identical to Week 153/Day 0 listed above with the following exceptions:

- Behavioral assessment – do not administer if done within the last month before entering Step 3. Refer to SSP Sections 6 and 13 and SSP Appendix III – Schedule of Forms.
- Acceptability assessment (not listed above) – this should be administered at this visit if it was not done in the last 6 months before entering Step 3. Refer to SSP Sections 6 and 13 and SSP Appendix III – Schedule of Forms.



- Urine collection and testing for GC/CT – do not collect/do not perform test if testing occurred within 3 months prior to entering Step 3
- Rectal swab collection and testing for GC/CT – do not collect/do not perform test if testing occurred within 3 months prior to entering Step 3
- Syphilis testing – do not perform test if testing occurred within 3 months prior to entering Step 3
- ECG – do not perform procedure if done within 3 months prior to entering Step 3
- Urine collection for urinalysis – do not collect/do not perform test if testing occurred within 3 months prior to entering Step 3
- HCV – do not perform test if testing occurred within 3 months prior to entering Step 3

As mentioned above, any scenarios that do not fit into these exceptions or any other questions about the requirements for the last day of Step 2/first day of Step 3 (Week 153/Day 0), whenever that visit may occur, should be directed to the CMC.

## **5.9 Step 3: Open-label TDF/FTC**

**(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
- Behavioral assessment (only Weeks 24 and 48; if conducted within the last month before entering Step 3, conduct at Weeks 12, 24, and 48).
- Adherence counseling (Weeks 12, 24, and 36)

### **Clinical Procedures**

- Targeted medical history and targeted physical exam, including concomitant medications, as well as weight, blood pressure, and pulse data entry to Medidata Rave
- Blood collection
- Urine collection for GC/CT testing (Weeks 24, 48)
- Rectal swab collection for GC/CT testing (Weeks 24, 48)
- Dispense pills (Weeks 12, 24, 36)

### **Laboratory Evaluations**

- HIV testing (see SSP Manual)

- Chemistry testing (only at Weeks 24 and 48) (see Appendix IC)
- Liver function testing (only at Weeks 24 and 48) (see Appendix IC)
- Syphilis testing (only at Weeks 24, 48)
- Urine GC/CT testing (only at Weeks 24, 48)
- Rectal swab GC/CT testing (only at Weeks 24, 48)
- 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.

## **5.10 Visit Windows**

The target visit windows for all visits, including injection visits, are outlined in the SSP Manual. In brief, the target visit window for injection visits for the Week 5 and 9 injections is +/- 3 days, and is +/- 7 days for all other injections visits. Visits conducted outside of the target visit windows are allowable without restriction and are also defined in the SSP Manual for scheduling guidance. Each study visit, including the injection visit, should ideally be conducted within the target date range. When that is not possible, visits outside of the target dates may be completed. Additionally, and as already outlined above, the windows for the DXA subset are -30/+ 7 days for Enrollment, and +/- 8 weeks for Weeks 57 and 105.

It is not required to contact the CMC for out of target visit window injection visits provided that they are a minimum of 6 weeks from the last injection and a maximum of 15 weeks from the prior injection, and for the Week 9 injection, when it is a minimum of 3 weeks from the Week 5 injection and a maximum of 11 weeks from the Week 5 injection. It is required to contact the CMC for guidance in cases outside of these parameters.

It is not required to contact the CMC for out of target window safety visits no matter when they occur; however, an injection visit may never be completed without a preceding safety visit being completed and all the assessments being resulted and protocol-allowable.

## **5.11 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.

## **5.12 Procedures for Participants Who Do Not Complete the Full Course of Injections**

Participants in Step 1 of the study who are unable to transition to Step 2 of the study for any reason other than HIV infection will be asked to attend annual visits until three years from the

date of Enrollment. These participants will remain blinded to their original randomized assignment until all participants complete Step 2 of the study. Participants with confirmed HIV infection during Step 1 of the study will not transition to Step 2 of the study but will be referred for care and will be terminated from the study.

Participants in Step 2 of the study that prematurely stop receiving injections due to any reason other than HIV infection will be asked to transition to Step 3 of the study and receive 48 weeks of open label TDF/FTC, (or may be transitioned to Step 3 off study product for safety reasons due to an AE or condition where open label TDF/FTC is contraindicated), followed by annual follow-up until three years from the date of Enrollment (see note below). The timepoint during Step 2 that a participant transitions to Step 3 will determine whether they will be asked to attend annual visits following the completion of Step 3. If the completion of open label TDF/FTC for Step 3 post-dates three years from the date of Enrollment, no further annual follow-up is required. Once a participant has completed three years of follow-up, they will then be transitioned to local prevention services. These participants will remain blinded to their original randomized assignment until all participants complete Step 2 of the study. Participants in Step 2 of the study with confirmed HIV infection will be followed according to Appendix II.

Note: Participants who wish to prematurely discontinue injections in Step 2 due to an injection site reaction AE must follow procedures detailed in Appendix III, Guidance for Injection Site Reactions (**ISRs**) prior to discontinuation of Step 2 procedures.

Sites should contact **083HIV@hptn.org** for guidance regarding study visit procedures for participants that become HIV-infected during Step 3 of the study.

For participants that transition to annual visits as outlined above, the following procedures will take place (see also Appendix ID):

- Review/update locator information
- Targeted medical history and targeted physical exam, with concomitant medications update
- HIV pre and post-test counseling
- Blood collection
- HIV testing, plasma storage, DBS storage
- Offer condoms and lubricant

### **5.13 Planned Unblinding of Study Participants**

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.

#### **5.13.1 Emergency Unblinding for Medical Reasons**

If, in the judgment of the site investigator of record (IoR), or in the judgment of the participant's medical provider and the site IoR, a medical event is of sufficient extreme

severity that it requires the immediate unblinding of a participant, the site IoR may proceed with unblinding a participant per the instructions in Appendix VI of the SSP (Unblinding Medical Emergency) and any separate applicable instructions provided by the HPTN SDMC. Emergency unblinding is expected to be extremely rare. It should only occur in the setting of a potentially life-threatening clinical event, and if knowing the participant's treatment assignment would affect decisions regarding the participant's immediate medical management. Both conditions must be satisfied.

## **5.14 Participants with Suspected or Confirmed HIV Infection, at Screening, Enrollment, or Follow-Up**

### **5.14.1 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 the Screening or Enrollment visit are not eligible to participate in this study. Furthermore, at the Screening and Enrollment visit (at Enrollment, prior to randomization; and for sites that do split enrollment visits due to physical location constraints, prior to administration of study product), 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.

### **5.14.2 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 a 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, and will also follow the toxicity management guidelines in Appendix III. An Investigator can request unblinding from the HPTN SDMC directly to a participant's primary care provider in the event a participant becomes infected with HIV during the study; the randomized assignment will not be provided to the site where the participant was enrolled and followed. See Section 7.9 and 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 083HIV@hptn.org group.

It should be noted that all reactive/positive HIV test results will be reviewed by an independent HIV Endpoint Adjudication Committee whose responsibility is to determine whether the test results meet the primary endpoint of the study of HIV infection.

## **5.15 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 performed at a site's discretion and costs associated may come out of each site's respective per participant study reimbursements.

Any positive/reactive laboratory test results for syphilis from the time of study enrollment and any positive/reactive test during the study must be referred to the CMC for adjudication accompanied by any prior testing and treatment results. The communication with the CMC should occur prior to the subsequent study visit at which the positive/reactive testing is resulted. Cases of syphilis discovered prior to study participation should be documented as a pre-existing condition.

Sites will report STIs into the study database on the Adverse Event e-CRF as well as the STI e-CRF. Further instructions regarding reporting STIs into the database are included in Section 9 of the SSP.

## **5.16 Hepatitis B and Hepatitis C**

Testing for HBV and HCV will be performed at Screening (HBsAg and HCAb). Persons whose screening tests results are not negative will be excluded from study participation 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.

## **5.17 Interim Contacts and Visits and Missed 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.

In general, when a visit is missed altogether and a participant reports to the site for the next scheduled visit, the procedures from the missed visit that are not also required for the current visit should be performed.

Refer to the SSP Manual for further details regarding management of such visits.

## **5.18 Criteria for Early Termination of Study Participation**

Refer to Section 3.6 of the protocol.

## **5.19 Pharmacokinetic Monitoring**

Plasma and DBS will be collected throughout the study for pharmacokinetic assessments. 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.

## **5.20 Other Considerations for Premature Transition from Step 2 to Step 3**

In other circumstances prompting premature transition from Step 2 to Step 3, if a return to Step 2 blinded study products is feasible and desirable, contact the CMC for guidance on the permissibility and operationalization of such a resumption of blinded study products. For example, a participant may transition prematurely to Step 3 due to relocation to an area where there is no HPTN 083 clinical site; if this participant were to relocate again to an area where there is an HPTN 083 clinical site (including back to the original location), he or she could be considered for a return to Step 2, with resumption of blinded study products, in consultation with the CMC. Protocol-mandated premature transitions to Step 3 for adverse clinical or laboratory events are not eligible for return to Step 2 blinded study products, even if the adverse event has resolved.

## **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 e-CRF AEs (Grade 1 and higher clinical AEs, as well as Grade 2 and higher laboratory AEs, and any AE (clinical or laboratory) that leads to a study product hold (temporary or permanent) will be captured on AE e-CRFs) reported by or observed in enrolled (defined as after randomization has occurred) 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 2.1 corrected, July 2017. STIs will be dually reported on the AE e-CRF as well as the STI e-CRF (see Section 9 of the SSP for further details related to STI reporting into the study database).

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 <https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids>.

#### 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. This form is available on the DAIDS RSC website at <https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting>. For questions about DAERS, please contact CRMSSupport@niaid.nih.gov. Site queries may also be sent with the DAERS application itself.

For questions about EAE reporting, please contact the RSC at [DAIDSRSCSafetyOffice@tech-res.com](mailto: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:

- ALT $\geq$ 3xULN AND total bilirubin $\geq$ 2xULN (must be both in order to require expedited reporting)
- Any seizure event

These reporting requirements are required for each study participant from enrollment until their follow-up in the study ends. After this time, sites must report to DAIDS serious, unexpected, clinical suspected adverse drug reactions, as defined in Version 2.0 of the DAIDS EAE manual, 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 1 and higher AEs will be included in reports to the US FDA, and other government and regulatory authorities as applicable. Site staff will report information regarding AEs to their IRB in accordance with all applicable regulations and local IRB requirements.

#### **6.4.3 Grading Severity of Events**

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, will be used for determining and reporting the severity of adverse events. The DAIDS grading table is available on the DAIDS RSC website at <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables>.

### **6.5 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 for a total of 3 years. In Step 3, all participants will receive open-label daily oral TDF/FTC for up to 48 weeks. Participants will therefore be followed for 3 years on blinded study product and 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 Section 7.3.2).

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%<sup>1</sup>). 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-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

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

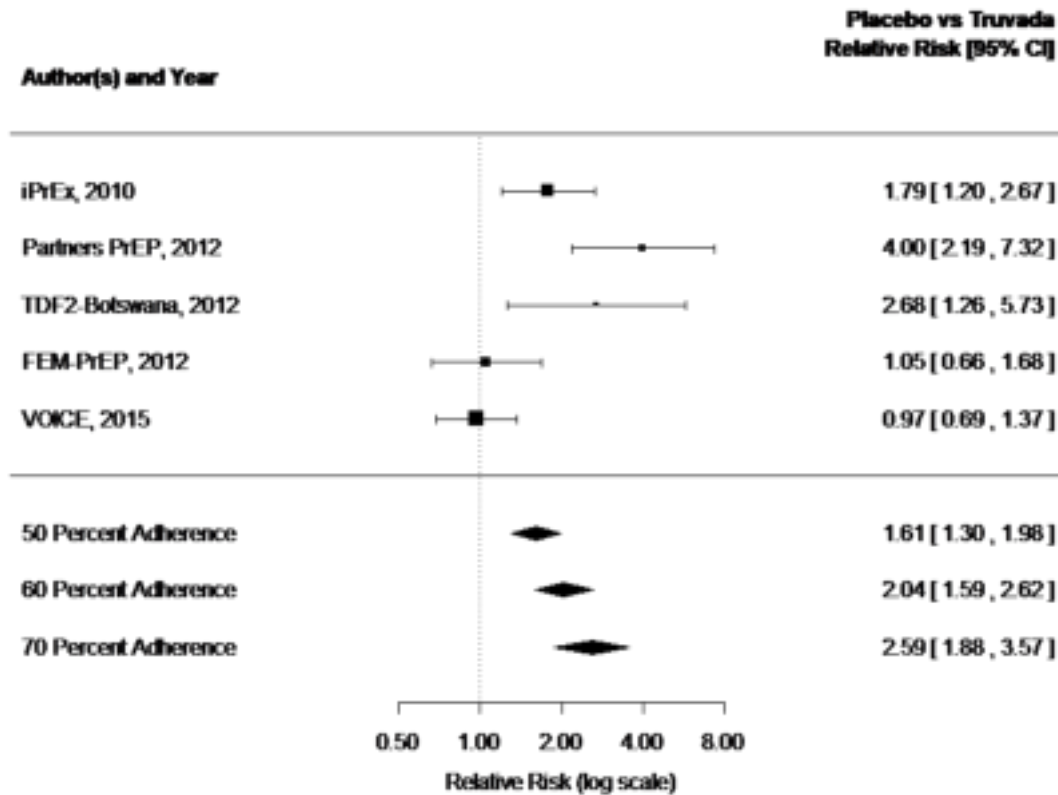
makes it possible to estimate efficacy at moderate (e.g., 55%) or moderately high (e.g., 75%) levels of adherence without extrapolating beyond the range of observed data<sup>2</sup>. Incorporating results from all five major trials should provide a more robust, precise estimate of TDF/FTC efficacy than 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.<sup>92</sup> 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.

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<sup>2</sup> 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 <sup>2</sup>   | 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 than 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 <sup>†</sup> CAB Infections         | Observed TDF/FTC Infections | Additional CAB Infections per 10,000 pyrs implied <i>at the NI margin</i> <sup>§</sup> |                   |
|                   |           |                            |  |                             | 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                |

<sup>†</sup> 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.

<sup>§</sup> 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
- Weight, blood pressure, pulse, fasting glucose, and fasting lipids

### 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
- 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<sup>4, 35-36</sup>. 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 0.74 or less (indicating a 26 % 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 5000 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. Non-inferiority bounds will be used for early stopping for favorable risk-to-benefit ratio for CAB LA compared to TDF/FTC. Stopping will also be advised if there is early evidence that CAB LA is clearly not as effective as TDF/FTC (i.e., early evidence that  $HR > 1.0$ ).

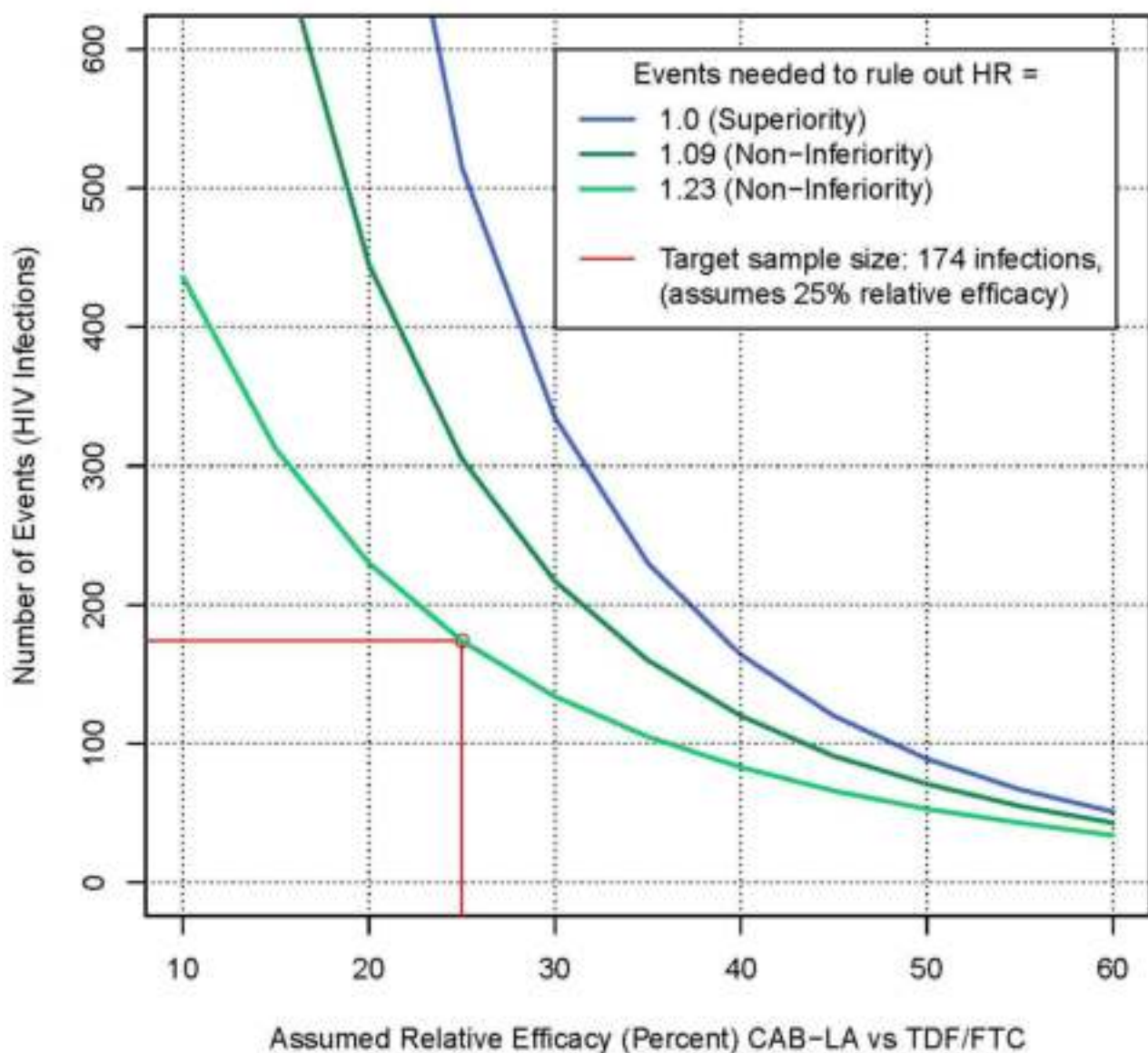
As this is the first large-scale phase 2b/3 study of IM administration of a biomedical intervention for prevention of sexual HIV transmission, an early feasibility check will be employed whereby after approximately 250 participants have completed 3 injections (Week 29), a treatment-blinded analysis of 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.

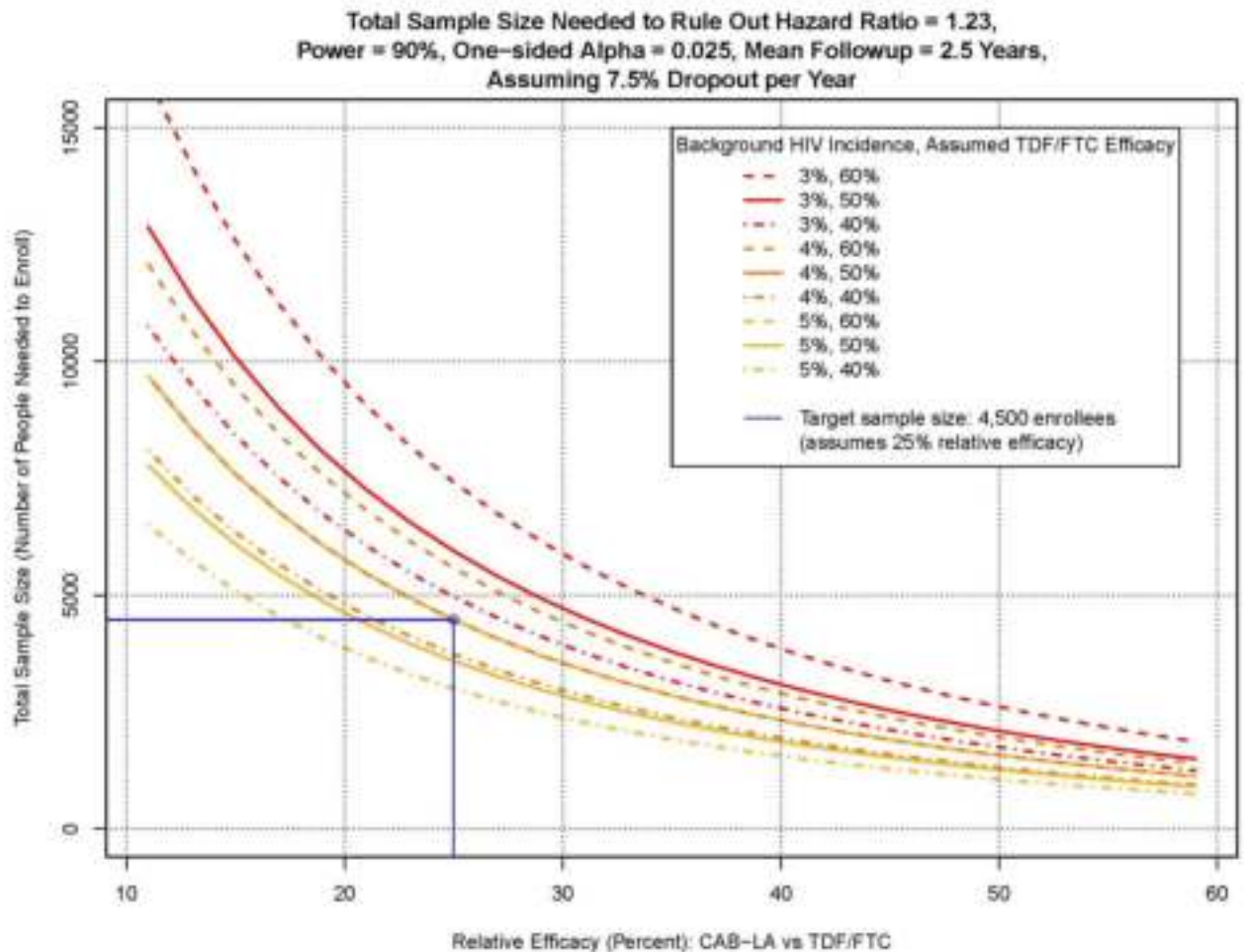
The trial will be terminated at the first occurrence of any of the following: 1) The accrual of 172 incident HIV endpoints; 2) completion of 11,800 person-years of follow-up; or 3) reaching a stopping boundary.

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

# HIV Events Needed to Establish Non-Inferiority or Superiority with 90% Power, One-sided type-I error $\alpha=0.025$



**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

Approximately 5000 participants will be enrolled in approximately 3.5 years and followed for a maximum of 3.0 years on blinded study product, followed by 1 year on open-label study product, for a total of a maximum of 4.0 years of follow-up. 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, 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 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 5.14.2, 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 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.

**On blinded study product:** An on blinded study product 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 participants who are HIV-uninfected at the time of the first injection, while participants are compliant to the injection schedule. Compliance will be defined as: receiving the second injection within 6 weeks of the first injection and all subsequent injections within 10 weeks of the prior injection. Per Protocol: A per protocol estimate of treatment efficacy, excluding participants with major protocol violations, or participant time after a major protocol violation, will be conducted as a secondary analysis in the non-inferiority context of an active control, as a verification that a similar HR estimate is obtained.

### 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.

- To compare changes in weight, blood pressure, pulse, fasting glucose, and fasting lipids among participants receiving oral CAB/CAB LA vs. oral TDF/FTC

Change from baseline (enrollment) for weight, blood pressure, pulse, fasting glucose, and fasting lipids will be computed at each follow-up visit where these measures are collected. The mean changes will be plotted over time by treatment arm for visits where participants remained on blinded, protocol-specified treatment. (Per-protocol analysis). A linear mixed model will be fit with categorical intervals for time in study, treatment and time by treatment interaction to evaluate time trends in each arm and the association between treatment and biological measures. Categorical models will also be used to assess changes over time in BMI category, proportion of participants with 5% or more weight change, and occurrence of new diabetes diagnoses. Differences in time trends and treatment effects will be explored for demographic and clinical subgroups, including race/ethnicity, age, baseline smoking status, baseline BMI, and baseline weight.

#### **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 and South Africa

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, and South Africa

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, and South Africa. 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 are 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 U.S., local and international regulatory entities, 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/ECs.



## 9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

Laboratory procedures are described below, in Appendix IA, Appendix IB, Appendix IC: 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 periodically during the study. Results of this testing will not be returned to study sites. Because real-time resistance testing may be needed for clinical management in the event of HIV infection, each site will have an SOP as to how they will accomplish real-time local or regional resistance testing to assist with clinical decision making; separate specimens should be collected for that testing.

### **9.2.2 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 <https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration>.

### **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.

Electronic 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 MediData Rave electronic 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 other US, local, and international regulatory authorities. 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 and at least three years after the completion of research. 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.

Completion of a clinical research study occurs when the following activities have been completed:

- All research-related interventions or interactions with human subjects (e.g. when all subjects are off study);
- All protocol-required data collection of identifiable private information described in the IRB/EC-approved research plan;
- All analysis of identifiable private information described in the IRB/EC-approved research plan;
- Primary analysis of either identifiable private or de-identified information.

## 10.7 Use of Information and Publications

Publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be submitted by the Investigator to the HPTN Manuscript Review Committee, DAIDS, ViiV Healthcare, Gilead Sciences, Inc. for review prior to submission.

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## **APPENDICES I – V**

## 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         |                  |        |        |
| SexPro assessment (US sites only for inclusion; South American sites only for data collection) | 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      |
| Height <sup>7</sup> , weight, blood pressure, pulse data entry to Medidata Rave                |           | 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 <sup>1</sup>   |           | X                |        |        |
| Dispense Pills (enough for 5 weeks)  |           | X                |        |        |
| LOCAL LABORATORY EVALUATIONS & PROCEDURES  |           |                  |        |        |
| HIV testing <sup>2</sup>   | X         | X                | X      | X      |
| HBV and HCV testing <sup>3</sup>   | X         | X                |        |        |
| CBC with differential  | X         | X                | X      | X      |
| Chemistry testing <sup>4</sup>   | X         | X                | X      | X      |
| Liver function tests <sup>5</sup>  | X         | X                | X      | X      |
| Fasting glucose and fasting lipid profile <sup>6</sup>   |           | X                |        |        |



|  | Screening | Step 1           |        |        |
|--|-----------|------------------|--------|--------|
|  |           | DAY 0/Enrollment | WEEK 2 | WEEK 4 |
| <b>Syphilis serologic testing</b>            |           | X                |        |        |
| <b>BMD subset only: 25-OH-Vitamin D</b>      |           | X                |        |        |
| <b>Urine GC/CT testing</b>                   |           | X                |        |        |
| <b>Rectal swab GC/CT testing<sup>1</sup></b> |           | X                |        |        |
| <b>Urinalysis (protein and glucose)</b>      |           | X                |        |        |
| <b>Plasma storage</b>                        | X         | X                | X      | X      |
| <b>DBS storage</b>                           |           |                  |        | X      |
| <b>Whole blood storage</b>                   |           | X                |        |        |

FOOTNOTES FOR APPENDIX IA

<sup>1</sup> If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

<sup>2</sup> The HIV testing algorithm is provided in Appendices IE-G and the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.

<sup>3</sup> HBsAg and HCV antibody testing are required at Screening. At Enrollment, HBsAb and HBcAb required; no HCV testing required at Enrollment.

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

<sup>5</sup> ALT and bilirubin required at screening; at and after enrollment, AST, ALT, total bilirubin, and alkaline phosphatase are required.

<sup>6</sup> 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.

<sup>7</sup> Height is a one-time measurement required to be captured in the source documents at enrollment as part of the complete physical exam. The height measurement should be entered into MediData Rave when the database is updated to capture the measurement.

# 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 | Week 153/<br>Day 0* |   |   |   |    |    |                |
|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---------------------|---|---|---|----|----|----------------|
| 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 |   |    |    |                |
| 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 |    |    |                |
| 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 |    |    |                |
| Acceptability Assessment*                                 |   |   |   |    | X  |    |    |    |    |    | X  |    |    |    |    |    | X  |    |    |    |    |    | X  |    |    |    |     |     |     |     |     |     |     |     | X   |     |     |     |                     |   |   |   |    |    |                |
| Behavioral Assessment                                     | 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  |                |
| 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  |                |
| Weight, blood pressure, pulse data entry to Medidata Rave | 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) <sup>1</sup>               |   |   |   |    |    |    |    |    |    |    |    |    |    |    | 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              |
| Urine collection for urinalysis testing                   |   |   |   |    |    |    |    |    |    |    |    |    |    |    | X  |    |    |    |    |    |    |    |    |    |    |    |     | X   |     |     |     |     |     |     |     |     |     |     |                     |   |   |   |    | X* |                |
| Urine collection for GC/CT testing                        |   |   |   |    |    |    |    |    |    | X  |    |    |    |    | X  |    |    |    |    |    |    | X  |    |    |    |    |     | X   |     |     |     |     |     | X   |     |     |     |     |                     |   |   |   | X* |    |                |
| Rectal swab for GC/CT testing <sup>2</sup>                |   |   |   |    |    |    |    |    |    | 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 <sup>8</sup> |
| ISR evaluation  |   | X |   | X  |    | X  |    | X  |    | X  |    | X  |    | X  |    | X  |    | X  |    | X  |    | X  |    | X  |    | X  |     | X   |     | X   |     | X   |     | X   |     | X   |     | X   |                     | X |   | X |    |    |                |

| 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 | Week 153/<br>Day 0* |   |    |    |    |
|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---------------------|---|----|----|----|
| LOCAL LABORATORY EVALUATIONS & PROCEDURES               |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |                     |   |    |    |    |
| HIV testing <sup>3</sup>                                | X | X | X | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | 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 <sup>4</sup>                                |   |   |   |    |    |    |    |    |    |    |    |    |    |    | 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  |    |    |
| Chemistry testing <sup>5</sup>                          |   | X | X | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | 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 <sup>6</sup>                       |   | X | X | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | 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 glucose and fasting lipid profile <sup>7</sup>  |   |   |   |    |    |    |    |    |    |    |    |    |    |    | X  |    |    |    |    |    |    |    |    |    |    |    |     | X   |     |     |     |     |     |     |     |     |     |     |                     |   |    |    |    |
| Syphilis serologic testing                              |   |   |   |    |    |    |    |    |    | X  |    |    |    |    | X  |    |    |    |    |    |    | X  |    |    |    |    |     | X   |     |     |     |     |     |     | X   |     |     |     |                     |   |    | X* |    |
| Urine GC/CT testing                                     |   |   |   |    |    |    |    |    |    | X  |    |    |    |    | X  |    |    |    |    |    |    | X  |    |    |    |    |     | X   |     |     |     |     |     |     | X   |     |     |     |                     |   |    | X* |    |
| Rectal swab GC/CT                                       |   |   |   |    |    |    |    |    |    | 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  |    |
| DBS storage   |   |   | 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

\* For participants who transition to Step 3 at Week 153, the first day of Step 3 begins at Week 153 and is also considered Day 0 of Step 3. The timeline for Step 3 continues whether or not a participant attends the Week 153/Day 0 visit or any subsequent visits.

For participants who are already beyond Week 153 of Step 2 in their follow-up schedule, the timeline for Step 3 begins 8 weeks following their last injection and continues whether or not a participant attends the Day 0 visit or subsequent visits.

For participants who transition to Step 3 prematurely, the timeline for Day 0 begins 8 weeks after that participant's last injection, even if the participant does not report to the Day 0 visit (or the Week 12 visit, etc.). Sites may contact the CMC for questions regarding participants who transition to Step 3 prematurely who are then subsequently missing, though it is not required to do so.

Per Section 5.8 of the protocol, note the following:

- Do not perform the following tests/procedures if they occurred within the last three months prior to either prematurely transitioning to Step 3, or the Week 153/Day 0 visit was missed for any reason, or if the Week 153 visit already occurred under Version 2.0 of the protocol and the participant now needs to move to Step 3 under Version 3.0 of the protocol: ECG; urine collection for urinalysis and GC/CT testing; rectal swab for GC/CT testing; HCV testing; and syphilis testing, and perform these requirements only at Weeks 24 and 48 (except for HCV testing, which is not required at Weeks 24 and 48). Refer to Appendix IC.
- For participants who either prematurely transition to Step 3, or the Week 153/Day 0 visit was missed for any reason, or if the Week 153 visit already occurred under Version 2.0 of the protocol and the participant now needs to move to Step 3 under Version 3.0 of the protocol, administer the acceptability assessment at the Week 153/Day 0 visit (whenever it occurs) as the final assessment if not done in the previous 6 months prior to transitioning, to include a brief preference assessment.
- Regarding the behavioral assessment, for participants who either prematurely transition to Step 3, or the Week 153/Day 0 visit was missed for any reason, or if the Week 153 visit already occurred under Version 2.0 of the protocol and the participant now needs to move to Step 3 under Version 3.0 of the protocol, do not administer at Week 153 and instead administer the behavioral assessment at Week 12 if it was done within the last month prior to transitioning, (see Appendix IC).

<sup>1</sup> To include dietary calcium and Vitamin D assessment

<sup>2</sup> If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

<sup>3</sup> The HIV testing algorithm is provided in Appendices IE-G and the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.

<sup>4</sup> Testing does not need to be repeated if infection was documented at a prior visit. HCV Ab testing is required.

<sup>5</sup> Required chemistry testing: BUN/Urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.

<sup>6</sup> Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.

<sup>7</sup> 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.

<sup>8</sup> Per Section 5.8 of Protocol V3.0 and Appendix IB, the last injection in Step 2 will occur at the Week 145 visit. An injection will not be administered at the Step 2 Week 153/Step 3 Day 0 visit; any remaining blinded oral study product will be collected from the participant, and open-label TDF/FTC will be dispensed.

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

| Procedures*   |  | Week 12 | Week 24 | Week 36 | Week 48 |
|---|--|---------|---------|---------|---------|
| <b>ADMINISTRATIVE, BEHAVIORAL, REGULATORY</b>             |  |         |         |         |         |
| Locator Information                                       |  | X       | X       | X       | X       |
| HIV Counseling  |  | X       | X       | X       | X       |
| Offer Condoms and lubricant                               |  | X       | X       | X       | X       |
| Behavioral Assessment*                                    |  |         | X       |         | X       |
| Adherence Counseling                                      |  | X       | X       | X       |         |
| <b>CLINICAL EVALUATIONS &amp; PROCEDURES</b>              |  |         |         |         |         |
| History, concomitant medications, physical exam           |  | X       | X       | X       | X       |
| Weight, blood pressure, pulse data entry to Medidata Rave |  | X       | X       | X       | X       |
| Blood Collection  |  | X       | X       | X       | X       |
| Urine collection for GC/CT testing                        |  |         | X       |         | X       |
| Rectal swab for GC/CT testing <sup>1</sup>                |  |         | X       |         | X       |
| Dispense pills  |  | X       | X       | X       |         |
| <b>LOCAL LABORATORY EVALUATIONS &amp; PROCEDURES</b>      |  |         |         |         |         |
| HIV testing <sup>2</sup>                                  |  | X       | X       | X       | X       |
| Chemistry testing <sup>3</sup>                            |  |         | X       |         | X       |
| Liver function tests <sup>4</sup>                         |  |         | X       |         | X       |
| Syphilis serologic testing                                |  |         | X       |         | X       |
| Urine GC/CT testing                                       |  |         | X       |         | X       |
| Rectal swab GC/CT testing                                 |  |         | X       |         | X       |
| Plasma storage  |  | X       | X       | X       | X       |

#### FOOTNOTES FOR APPENDIX IC

\*\*See Week 153/Day 0 of Appendix IB for Step 3 Day 0 procedures. If the behavioral assessment was not done at Day 0, administer at Week 12.

<sup>1</sup> If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

<sup>2</sup> The HIV testing algorithm is provided in Appendices IE-G and the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.

<sup>3</sup> Required chemistry testing: BUN/Urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.

<sup>4</sup> Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.

## Appendix ID: Schedule of Procedures and Evaluations for Annual Visits

The procedures listed below are for the following participants:

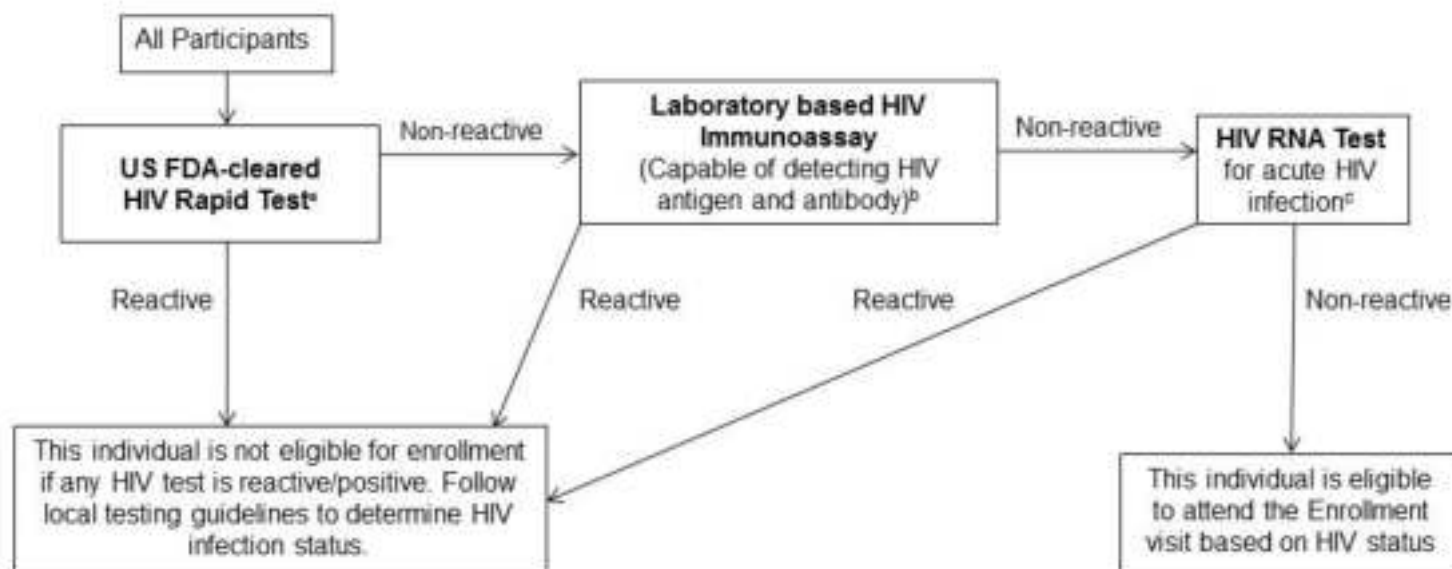
- Participants in Step 1 who do not transition to Step 2 for any reason other than HIV infection will be asked to attend annual visits until three years from the date of Enrollment.
- Participants in Step 2 who prematurely stop receiving injections for any reason other than HIV infection will transition to Step 3, complete the required 48 weeks of follow-up in Step 3, and will then be asked to attend annual visits until three years from the date of Enrollment. The timepoint during Step 2 that a participant transitions to Step 3 will determine whether they will be asked to attend annual visits following the completion of Step 3. If the completion of open label TDF/FTC for Step 3 post-dates three years from the date of Enrollment, no further annual follow-up is required.

In both cases above, these participants will remain blinded to their original randomized assignment until all participants complete Step 2 of the study.

| Procedure                                 | Annual Visit |
|---|--------------|
| Locator information                       | X            |
| Offer condoms and lubricant               | X            |
| HIV counseling (pre- and post-test)       | X            |
| Targeted history, con meds, physical exam | X            |
| Blood collection                          | X            |
| HIV testing                               | X            |
| Plasma storage                            | X            |
| DBS storage                               | X            |

## Appendix IE: HIV Testing Algorithm at the Screening Visit:

### HIV Testing Algorithm at Screening\*



#### NOTES:

\* Site-specific HIV testing plans must be approved by the HPTN LC before the study opens.

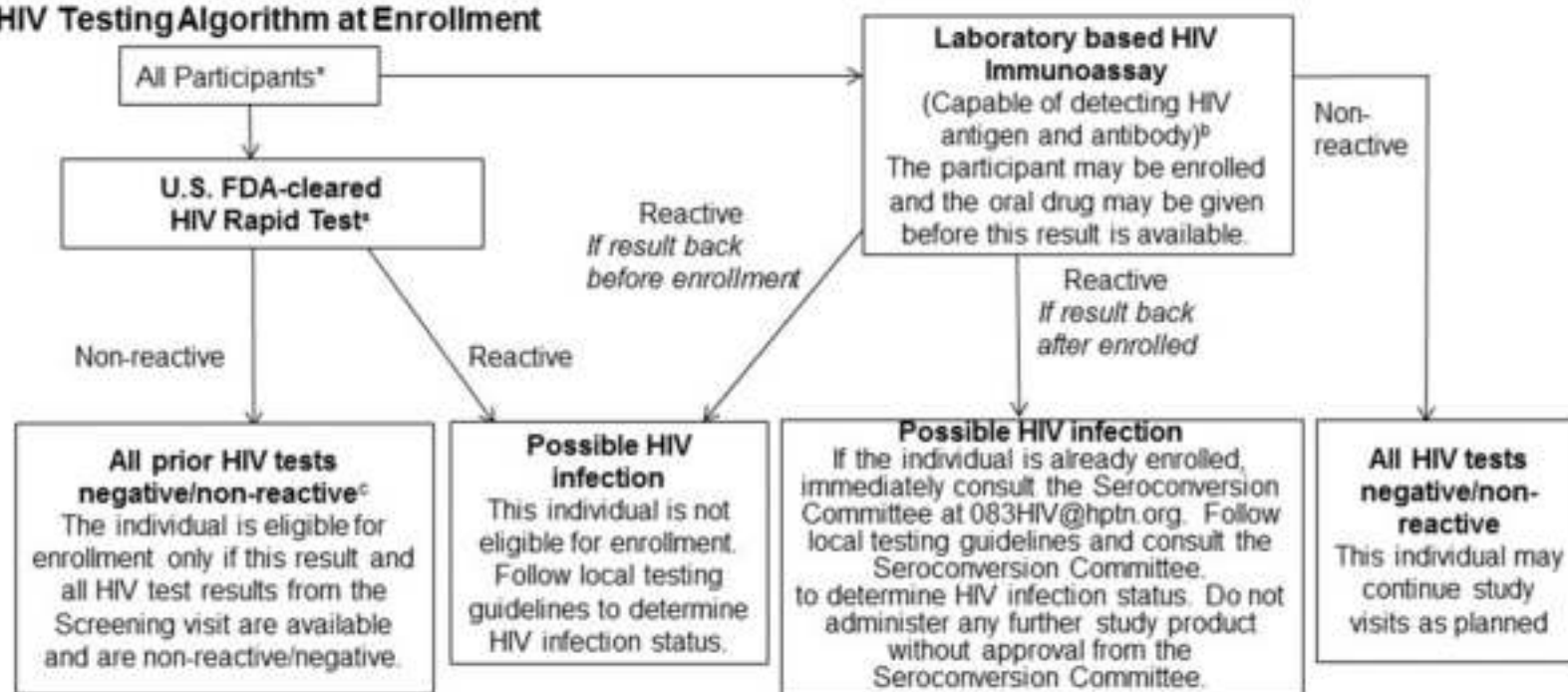
\* Sites that are not able to obtain HIV rapid test kits that are cleared by the US FDA may seek approval from the HPTN LC to use an alternate kit.

<sup>b</sup> This testing must be performed using a laboratory based, non-rapid HIV immunoassay that detects both HIV antigen and HIV antibody (either a 4<sup>th</sup> generation or 5<sup>th</sup> generation assay).

<sup>c</sup> Screening for acute infection should be performed using an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should use an assay that is FDA-cleared for this testing, such as the APTIMA HIV-1 RNA Qualitative Assay. RNA test results must be obtained from a specimen collected within 14 days prior to enrollment.

## Appendix IF: HIV Testing Algorithm at the Enrollment Visit:

### HIV Testing Algorithm at Enrollment



#### NOTES:

<sup>a</sup> If acute HIV infection is suspected, do not enroll the participant or administer study product at this time. In addition to following the algorithm above, the site should send a sample for an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should use an assay that is FDA-cleared for early HIV diagnosis, such as the APTIMA HIV-1 RNA Qualitative Assay. The site should contact the Seroconversion Committee (083HIV@hptn.org) for additional guidance once all of the test results from this visit (including the HIV RNA test) are available.

<sup>a</sup> Sites that are not able to obtain HIV rapid test kits that are cleared by the US FDA may seek approval from the HPTN LC to use an alternate kit.

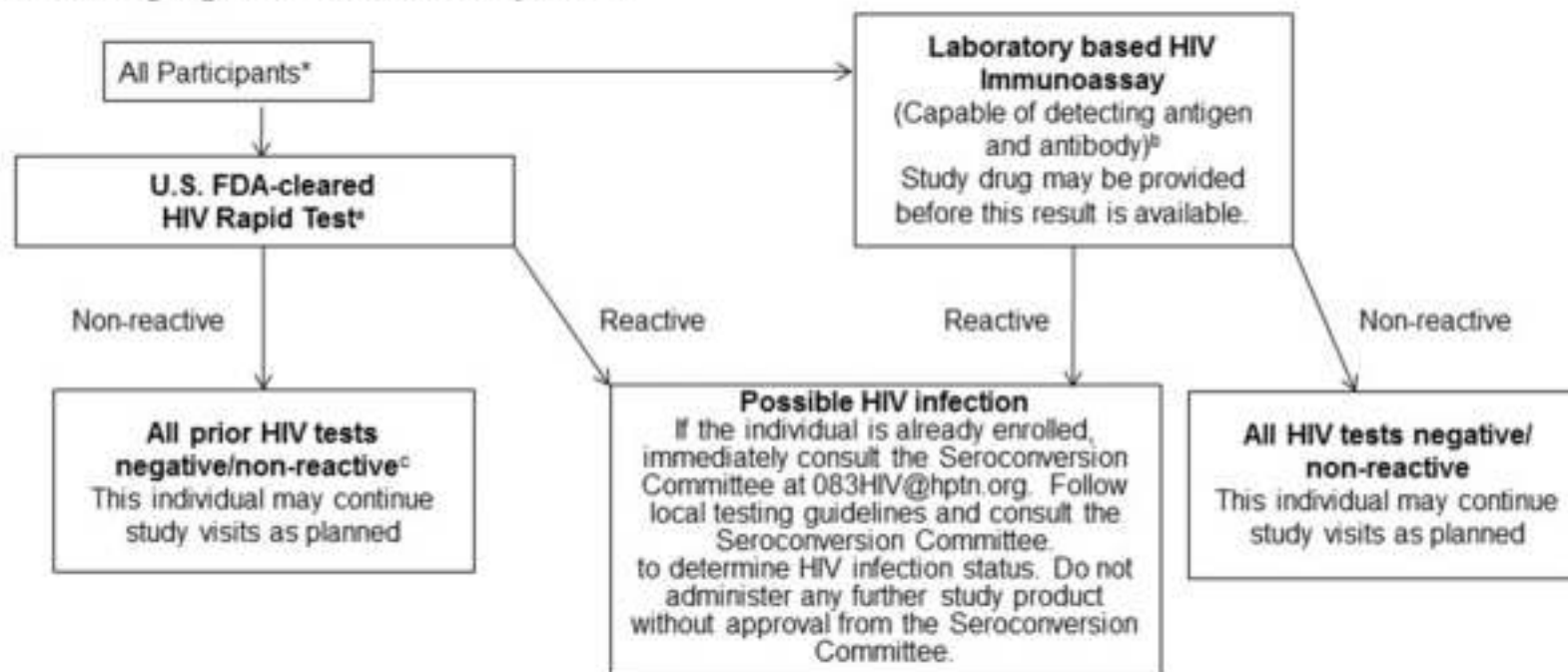
<sup>b</sup> This testing must be performed using a laboratory based, non-rapid HIV immunoassay that detects both HIV antigen and HIV antibody (either a 4<sup>th</sup> generation or 5<sup>th</sup> generation assay).

<sup>c</sup> Before providing study drug, the site must ensure that the HIV rapid test from the Enrollment visit, and all HIV results from the Screening visit are available and are negative or non-reactive.



## Appendix IG: HIV Testing Algorithm at Follow-up Visit:

### HIV Testing Algorithm for Follow up Visits



#### NOTES:

<sup>a</sup> If acute HIV infection is suspected, do not administer any further study product. Immediately consult the Seroconversion Committee. In addition to following the algorithm above, the site should send a sample for an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should use an assay that is FDA-cleared for early HIV diagnosis, such as the APTIMA HIV-1 RNA Qualitative Assay. The site should contact the Seroconversion Committee (083HIV@hptn.org) for additional guidance once all of the test results from this visit (including the HIV RNA test) are available.

<sup>\*</sup> Sites that are not able to obtain HIV rapid test kits that are cleared by the US FDA may seek approval from the HPTN LC to use an alternate kit.

<sup>b</sup> This testing must be performed using a laboratory-based, non-rapid HIV immunoassay that detects both HIV antigen and HIV antibody (either a 4<sup>th</sup> generation or 5<sup>th</sup> generation assay).

<sup>c</sup> At any visit where study product will be given, the site must ensure that the HIV rapid test from this visit, and all HIV results from prior study visits are negative or non-reactive.

## 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, 36, and 48, and will be determined by the members of 083HIV@hptn.org.

**Note 2:** Procedures for discordant or discrepant HIV test results are outlined in the SSP.

|   | HIV<br>Confirmation<br>Visit | Week 12 | Week 24 | Week 36 | Week 48 <sup>6</sup> |
|---|------------------------------|---------|---------|---------|----------------------|
| <b>ADMINISTRATIVE, BEHAVIORAL, REGULATORY</b> |                              |         |         |         |                      |
| Locator information                           | X                            | X       | X       | X       | X                    |
| Offer condoms and lubricant                   | X                            | X       | X       | X       | X                    |
| HIV counseling                                | X                            |         |         |         |                      |
| <b>CLINICAL EVALUATIONS AND PROCEDURES</b>    |                              |         |         |         |                      |
| History, con meds, physical exam              | X                            | X       | X       | X       | X                    |
| Blood collection                              | X                            | X       | X       | X       | X                    |
| <b>LOCAL LABORATORY EVALUATIONS</b>           |                              |         |         |         |                      |
| HIV testing <sup>1</sup>                      | X                            |         |         |         |                      |
| CD4 cell count                                | X                            |         | X       |         | X                    |
| HIV viral load testing                        | X                            |         | X       |         | X                    |
| HIV resistance testing <sup>2</sup>           | X                            |         |         |         |                      |
| Chemistry testing <sup>3</sup>                |                              | X       | X       | X       | X                    |
| Liver function testing <sup>4</sup>           |                              | X       | X       | X       | X                    |
| Plasma storage <sup>5</sup>                   | X                            | X       | X       | X       | X                    |
| DBS storage                                   | X                            |         |         |         |                      |

<sup>1</sup> 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.

<sup>2</sup> Sites will collect specimens for resistance testing at a local laboratory to assist with clinical management; results from resistance testing performed at local laboratories will not be reported to the SDMC. Stored plasma will not be used for real-time/local resistance testing.

<sup>3</sup> Required chemistry testing: BUN/Urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.

<sup>4</sup> Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.

<sup>5</sup> 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.

<sup>6</sup> 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, or in the case of a medical management decision (as approved by DAIDS), or as outlined in Section 5.13.1 of the protocol and Appendix VI of the SSP regarding unblinding in the event of an immediate medical emergency.

The following general guidance refers to all AEs except for ALT, creatinine clearance (absolute and change from baseline), and CPK. Refer to the tables below for specific guidance about these laboratory abnormalities.

#### Grade 1 or 2

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

#### Grade 3

Any grade 3 or higher clinical or laboratory AE observed prior to Week 5 will prompt consultation with the CMC prior to any injectable dosing. 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  $\leq$  Grade 2 cannot be documented within 4 weeks of receipt of the initial result. If study product is resumed and the same Grade 3 AE recurs at any time, the 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. Additionally, for Grade 3 or higher abnormalities at Week 0 (study enrollment), consult the CMC for guidance regarding follow up and ongoing study product administration.

## Grade 4

Any grade 4 or higher clinical or laboratory AE observed prior to Week 5 will prompt consultation with the CMC prior to any injectable dosing. 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 until three years from the date of Enrollment. All such cases must be reported to the CMC.

## Guidance on Toxicity Management for Specified Toxicities:

### Nausea, Vomiting, and Diarrhea

| CONDITION AND SEVERITY                | IMMEDIATE ACTION  | FOLLOW-UP AND MANAGEMENT <sup>2</sup>   |
|---------------------------------------|---|---|
| <b>Nausea, Vomiting, and Diarrhea</b> |   |   |
| 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 $\geq 3$                        | Discontinue study product temporarily                             | Participants with Grade $\geq 3$ 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 $\leq 2$ 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   | STUDY PRODUCT USE | FOLLOW-UP AND MANAGEMENT <sup>2</sup>  |
|--------------------------|-------------------|--|
| <b>ELEVATIONS in ALT</b> |                   |  |
| Grade 2 and higher       |                   | <p><b>Oral phase (Step 1):</b> 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 <math>\leq</math> Grade 2 at Week 2, study drug may continue to Week 4. If the repeat value is <math>&lt;</math> 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 until three years from the date of Enrollment. All such cases must be reported to the CMC. In addition, participants will be followed with weekly ALT assessments until they return to <math>\leq</math> Grade 1. If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up.</p> <p>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 until three years from the date of Enrollment. All such cases must be reported to the CMC. In addition, participants will be followed with weekly ALT assessments until they return to <math>\leq</math> Grade 1. If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up.</p> <p>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 until three years from the date of Enrollment. All such cases must be reported to the CMC.</p> |

| CONDITION AND SEVERITY   | STUDY PRODUCT USE | FOLLOW-UP AND MANAGEMENT <sup>2</sup>   |
|--------------------------|-------------------|---|
| <b>ELEVATIONS in ALT</b> |                   |   |
| Grade 2 and higher       |                   | <p><b><u>Injection phase (Step 2):</u></b> 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 <math>\leq</math> 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 <math>\leq</math> 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 <math>\leq</math> Grade 1. If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up.</p> <p>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.</p> <p>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.</p> <p><b><u>Open-label phase (Step 3):</u></b> Participants outlined above who transition to Step 3 will be followed per the Schedule of Procedures and Evaluations for Step 3 except for provision of study product.</p> <p>When Step 3 concludes in these cases, the participant will be followed annually until three years from the date of Enrollment. The timepoint during Step 2 that a participant transitions to Step 3 will determine whether they will be asked to attend annual visits following the completion of Step 3. If the completion of open label TDF/FTC for Step 3 post-dates three years from the date of Enrollment, no further annual follow-up is required. All such cases must be reported to the CMC.</p> |



### **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

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

| CONDITION AND SEVERITY          | STUDY PRODUCT USE                     | FOLLOW-UP AND MANAGEMENT   |
|---------------------------------|---------------------------------------|--|
| <b>CREATININE CLEARANCE</b>     |                                       |  |
| Estimated CrCl < 60 mL/min      | Discontinue study product temporarily | If the calculated creatinine clearance is <60mL/min, it should be confirmed within 1 week of the receipt of the results, and the CMC should be consulted for adjudication and recommendation for further testing and follow-up.  |
| Confirmed CrCl < 60 mL/min      | Permanently discontinue study product | If the calculated creatinine clearance is confirmed to be <60 mL/min, the 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.<br>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  |
|-------------------------------|--|---|
| <b>Creatine Phosphokinase</b> |  |   |
| Grade 1 and 2                 | Continue study product   | A Grade 2 or lower elevation does not warrant retesting or changes to study product use.  |
| 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 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. If after retesting, a Grade 3 elevation persists, consult the CMC for guidance.   |
| Grade 4                       | Continue study product until repeat test results are available | Grade 4 elevations in CPK should have a repeat assessment within 2 weeks at least 24 hours after the subject has abstained from exercise. For persistent Grade 4 CPK elevations that are symptomatic (myalgias, muscle pain, dark urine, or clinically significant changes in creatinine clearance, defined in consultation with the CMC) should have study product discontinued. Otherwise, the CMC will provide guidance on frequency of additional CPK monitoring and ongoing study product use. |

## **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 (QTc) correction formula used to determine study product discontinuation should be the same one used throughout the study. For example, either Bazett's (QTcB) or Fridericia (QTcF) correction formula may be used, as long as the same formula is used throughout for a given participant.

- QTc > 550 msec, OR
- Change from baseline: QTc > 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. Starting at the point of when Version 3.0 is implemented at an individual site, sites should document all interventions that have been attempted to mitigate injection site reactions, which should include at a minimum:

1. Pre-treatment (prior to injection administration) warm compresses
2. Topical or oral pre-treatment with NSAID preparations, unless contraindicated
3. Immediate post-injection massage to injection location
4. Post-treatment warm or cold compresses
5. Post-treatment NSAID or other analgesic preparations, topically or orally

Such interventions and their outcome should be documented in the source documents and the CMC consulted prior to discontinuation of Step 2 follow-up. A proactive and comprehensive approach to mitigating ISRs should be undertaken, with premature transition from Step 2 to Step 3 being reserved for refractory cases in extreme circumstances.

### **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  $\geq 3$  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 5.0

April 28, 2022

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 approximately 5000 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 clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. 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 called 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 approximately 2500 people in it. You will be followed for approximately four years, and include up to approximately 47 visits to this clinic over that time.

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 use 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 three years after enrollment
- 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 three years after enrollment
- 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 start getting the shots.

In Step 2, everyone takes pills and gets shots. This step will continue until three years after enrollment.

In Step 3, which starts on the same day as the last day of Step 2, 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. [Sites in US to add this here: We will ask you to answer some additional questions about sexual practices using an assessment called SexPro, which may provide additional information about your HIV risk, and whether this study is appropriate for you.] [Sites in South America to add this here: We will ask you to answer some additional questions about sexual practices using an assessment called SexPro, which may provide additional information about your HIV risk.]
- 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. We know that TDF/FTC may cause thinning or softening of bones in some people. We want to see whether there are changes to your bones during the study, and the DXA scan lets us evaluate your bones. We want to see if this is different between the TDF/FTC and CAB treatments. 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 DXA scans will be given to you at the end of the study.

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 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, blood pressure, pulse, 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 subset, 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 absorptiometry (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 subset will include 350 participants. The scan will be done at the Enrollment visit and 2 other times during the study (Weeks 57 and 105). If you are in this group, we will also check your blood to see how much Vitamin D is in it, and will ask you about your diet to see if you are eating foods with calcium in it. We will tell you if the DXA subset is no longer available to participate in. *[Sites that do not participate in the DXA subset to delete this entire bullet item].*
- 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, to include measuring your weight, blood pressure, pulse, and 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.

If you have a side effect from the pills, or if you do not take enough of your pills, you may not be able to get the shots. If this happens, we will ask you to attend a visit once a year for three years from the time you enrolled in the study. The procedures for those visits are outlined later in this consent form document [*sites may also list the procedures here*].

## **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, to include measuring your weight, blood pressure, pulse, ask you if you have experienced any side effects from the study drugs, and 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 (an injection is not given at Week 153 but is a study visit),**

In this step of the study, there will be approximately 19 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, to include measuring your weight, blood pressure, pulse. 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 and 153 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)
- 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 and 137).
- *[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, and 153 only).

- Give you your study pills, and explain how to take them, and any side effects they may cause (at all injections visits).
- At Week 153 only or if you move to Step 3 early, collect any unused blinded oral study product
- Give you a shot (at all injection visits except for Week 153).
- 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**

*[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 approximately 19 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 at Week 153 of Step 2, which is the same visit as Day 0 of Step 3. This step includes 4 more visits over about a year (Week 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, to include measuring your weight, blood pressure, pulse, and ask you about any other medicines you are taking
- Collect ~XX mL (about x teaspoons) of blood for HIV testing, syphilis testing, to check your general health, the health of your liver, the amount of the study drug in your blood,

and for storage. Note: Blood will be collected for syphilis testing at Day 0 (which is the same as Step 2 Week 153), and Weeks 24 and 48. However, if you have had syphilis testing within 3 months of joining this part of the study, you will only have this done at Week 24 and Week 48.

- Perform a swab of your rectum and collect urine for gonorrhea and chlamydia (Day 0 (same as Step 2 Week 153), 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.

If you move into Step 3 prematurely, some of the procedures above may not have to be performed, which will depend on when during the study you moved into Step 3. The procedures that may not have to be performed are: asking you about questions about your sexual behavior, urine collection and testing for GC/CT, and rectal swab collection and testing for GC/CT and syphilis testing.

It may be necessary for additional visit(s) and procedures in the event of unforeseen or unanticipated events or results; for example, you may have a side effect that requires repeat testing on your blood to ensure that the study drugs continue to be safe for you to use. Or, sometimes the results of some tests are not clear and additional testing is needed in order to confirm a test result. There also may be difficulties in sample shipping, processing, or testing; and/or if you are experiencing any symptoms or changes in your physical condition. There also may be a time that you are not able to complete all of the procedures in a visit and you have to come back the next day or another day, and additional blood may be needed when you come back in order to complete the requirements of the visit. In the event of any of these unforeseen or unanticipated results, we will explain to you what will happen and what procedures will need to be done.

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].

### **Annual Visits**

Procedures for HIV testing every year if you do not get shots or have completed or been in Step 3:

As we mentioned, the study begins with taking pills only for five weeks before you can start with the shots. During this time, you may get a side effect that would result in not moving to the part of the study where the shots are given. Or, you may not have taken enough of the pills. If any of this happens, you would not get shots, and we would ask you to attend a visit once a year until three years from your date of Enrollment in order to test you for HIV.

If you do get shots but stop getting them early, you will move to Step 3 of the study where you will get real TDF/FTC for approximately a year and come in for visits every three months for approximately a year. After that time, we will help you find prevention services in the local area, and we will ask you to attend a visit once a year until three years from your date of Enrollment in order to test you for HIV.

The procedures for these visits every year while Step 2 of the study is still ongoing are:

- Confirm where you live and how to contact you.
- Talk with you about HIV and ways to protect yourself from getting it.
- Give you a brief physical exam, and ask you about any medicines you are taking.
- Collect ~XX mL (about x teaspoons) of blood for HIV testing, the amount of the study drug in your blood, and for storage.
- Give you condoms and lubricant.

As we mentioned at the beginning of the consent form, you can decide to not participate in the study at any time during the study. If you decide this during a study visit, that study visit may be your last study visit. If you decide this in between visits, we will ask you to return any unused study pills.

### **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:

- Headache
- Diarrhea
- Fatigue
- Muscle aches
- Nausea
- Fever
- Dizziness

- Runny nose
- Sore throat
- Upper respiratory tract infection
- Vomiting (being sick)
- Difficulty sleeping
- Abnormal dreams/nightmares
- Depression
- Flatulence (gas or wind)
- Increase in the level of enzymes in the muscles (creatine phosphokinase)
- With the CAB that you get as a shot, some people in other studies have said they had pain, irritation, skin redness, bumps, swelling, itching, bruising in the area where they got the shot, some of which lasted a few weeks before resolving.

There have been some people who were taking this medicine who have had liver side effects. Some of these people were HIV-infected (HIV positive) and some had damage to their liver before taking the CAB study medication. While taking the study medication, their blood tests showed that their liver was irritated, although they felt well. The medications were stopped, and the liver blood tests returned to normal. In this study, anyone with HIV-infection, Hepatitis C (or B), or any liver irritation will not be allowed to be in the study.

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

The shots you receive in this study are long acting, meaning they stay in your body for a long time – as long as a year or more. 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:

- Upset stomach (nausea), vomiting, gas, loose or watery stools
- Abdominal pain
- Generalized weakness
- Dizziness
- Depression
- Headache
- Shortness of breath
- Increased cough
- 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 (this side effect goes away after stopping TDF/FTC)
- Muscle pain and muscle weakness
- Sleeping problems; unusual dreams; tiredness
- 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

Side effects of Intralipid when used as an intramuscular injection placebo include headache, anxiety, insomnia, vomiting, nausea, constipation, extremity pain, agitation, diarrhea, sedation, nasopharyngitis, upper respiratory infection, cough, urinary tract infection, decreased weight, and increased muscle tone.

When Intralipid is given as an intravenous infusion (into a vein directly) for nutrition, the following side effects have been reported (note that these side effects have not been reported when Intralipid is administered through an intramuscular injection):

Immediate or early adverse reactions, each of which has been reported to occur in clinical trials less than 1% of the time: trouble breathing, blue appearance to the skin at where the injection was given, allergic reactions, elevated levels of fat in your blood, increased chances of getting blood clots, nausea, vomiting, headache, flushing, increase in temperature, sweating, sleepiness, pain in the chest and back, slight pressure over the eyes, dizziness, and irritation at the site of the infusion,

Delayed adverse reactions such as: large liver, yellowing of the skin and eyes, large spleen, low blood cell counts, increases in liver function tests, and overloading syndrome (seizures, fever, increase in white blood count, large liver, large spleen, and shock).

### **Possible Injection Side Effects:**

The injections will be given in the muscles of your buttocks (bottom “cheeks”). The injection could be given too deeply or not deeply enough, missing the muscle and entering your skin, blood, or a nerve. The risk of this is unknown but may result in higher levels of the injected medication in your system. Getting injections could also cause some people to feel lightheaded or feel like they might pass out, or ‘faint’. This reaction, called a ‘vasovagal reaction’, can occur with many medical procedures and resolves quickly.

### **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 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**

We told you earlier that we do not know if CAB works to protect you from getting HIV. If you are in the group that gets the real CAB, you still may be at risk of getting HIV. We do know that taking TDF/FTC every day can be very effective at preventing HIV infection. If it is not taken every day, you may not be well protected. Because of these risks, it is very important that you use condoms every time you have sex, no matter what group you are in.

Because the study medication is itself being studied to be an HIV treatment medication, if you become HIV infected while taking the study medication, there is a chance that other drugs used to treat HIV infection might not work. This is called drug resistance.

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 Health and Human Services (DHHS), Office of Human Research Protection (OHRP)
- *[insert names of applicable IRBs/ECs/other local review bodies as applicable]*



- Study staff
- Study monitors
- Companies that makes the study drug (ViiV Healthcare and Gilead Sciences, Inc.)
- Other U.S., local, and international regulatory entities may also review study records

[*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 5.0**

**April 28, 2022**

### 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 subset to add this]: I agree to take part in the DXA subset.

\_\_\_\_\_ [Sites that are participating in the DXA subset to add this]: I do not agree to take part in the DXA subset.

\_\_\_\_\_ [Sites that are participating in the DXA subset to add this]: I have been told that the DXA subset is no longer available for participation.

\_\_\_\_\_  
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

NO LONGER IN USE

## **APPENDIX V: PROCEDURES FOR THE OPEN LABEL EXTENSION OF CABOTEGRAVIR**

### **A. Background, Purpose and Implementation, Description of Steps**

#### **1. Background**

The majority of the HPTN 083 sites initiated the open-label extension (OLE) part of HPTN 083 under Appendix V of Version 4.0. Some sites have not, due to regulatory reasons, and will initiate the procedures of Appendix V under Version 5.0.

Since the time that Version 4.0 of the protocol was finalized in February 2021, the US FDA approved the use of CAB LA for PrEP in December 2021. At the time this protocol amendment (Version 5.0) was finalized, ViiV Healthcare, the pharmaceutical manufacturer of cabotegravir products, had also applied for regulatory approval for CAB LA for PrEP in several other countries where HPTN 083 is being conducted. As such, it is anticipated that local CAB LA will become available outside of the study over time in other countries where HPTN 083 is taking place.

Further data have been analyzed and presented or published since Version 4.0 as follows (for ease of reference, refer also to the Summary of Changes document that accompanies this full protocol amendment to see the updates):

In the randomized blinded portion of the HPTN 083 study, among 4570 participants enrolled, the primary pre-specified analysis found 13 incident cases of HIV in the CAB arm, and 39 incident cases in the TDF/FTC arm. Two CAB arm and three TDF/FTC arm participants were also found to have HIV prior to administration of any study products (prevalent). An HIV incidence rate of 0.41 per 100 person years (PY) was observed for participants randomized to CAB in the primary results. Post-hoc testing revised these metrics slightly. In post-hoc testing initially 12, and in the final analysis 14 incident cases of HIV were in the CAB arm, and initially 39, and in the final analysis 41 incident cases in the TDF/FTC arm. In addition, four CAB arm and three TDF/FTC arm participants were found to have HIV prior to administration of any study products (prevalent). The CAB arm incidence rate in this revised post-hoc analysis was 0.44 per 100 PY; an HIV incidence rate of 1.29 per 100 PY was observed for participants randomized to TDF/FTC, demonstrating a consistent result of superior 66% (in both the primary and post-hoc analyses), reduction in incident HIV infections in participants randomized to CAB compared to TDF/FTC. Genotypic resistance testing has been completed for the original 12 incident HIV infections in the CAB arm; six were found to have integrase strand transfer inhibitor (INSTI) resistance-associated mutations (RAMs); in addition, one of the four prevalent CAB-group HIV infections was found to have such mutations. These mutations were Q148R or Q148K in combination with additional INSTI RAMs, N155H, or R263K; these mutations would be expected to confer variable levels of resistance to DTG and BIC. Additionally, detection of HIV infection at study sites was delayed in CAB participants in all four prevalent cases and in 7 of the 12 incident infections, by a median 62 days (range 28-72) for the prevalent cases and 79 days (range 35-185 days) for incident cases. In most of these cases, infection would have been detected at the first HIV-positive visit using a sensitive viral load assay. These observations prompted the updating of the HIV testing algorithm in Version 4.0 to include a viral load assay with a limit of detection of 50 c/mL or lower as part of the testing performed at all study visits. Participants who are receiving CAB LA or are in the CAB LA tail

period (e.g., 48 months since their last injection) with RNA (viral load) evidence of HIV infection should be initiated on fully suppressive ART as rapidly as possible to avoid emergence of INSTI resistance. The sample informed consent for Version 5.0 has been updated to include this information to assist participants in making a fully informed decision about the risks and benefits of each PrEP option.

In the randomized, blinded portion of the study, no safety signal for hypersensitivity or other concerns were identified; therefore, these observations in combination with recently presented data from the CAB-LA/RPV-LA treatment program which did not include the oral lead-in phase without safety or efficacy concerns have allowed relaxation of the requirement for an oral lead-in period in this next part of HPTN 083. The oral lead-in may still be employed at the discretion of local IRBs/ECs, investigators of record or participants.

## **2. Purpose and Implementation**

To avoid confusion, sites will herein be divided into two categories – Category A and Category B – as described below:

### **Category A Sites: Implemented OLE procedures under Version 4.0 (majority of the sites)**

The primary purpose of this updated Appendix V at Category A sites is to allow for continued access to CAB LA while participants transition to local CAB LA or other available clinical PrEP prevention services by adding up to an additional 48-weeks (Weeks 56 up to 96) of CAB LA as a new Step 6. Step 6 is the continuation of Step 4c, beyond Week 48.

For sites in Category A, the HPTN Leadership and Operations Center (HPTN LOC) already provided official notification to each site to implement the OLE under Version 4.0. Similar official notification from the HPTN LOC for the continued implementation of Appendix V under Version 5.0 will NOT be issued for this amendment. Sites in this category should implement Version 5.0 immediately upon obtaining IRB/EC/other regulatory entity approvals (and submit for but not wait for DAIDS Protocol Registration Office approval). Sites in this category are also responsible for ensuring that adequate study product supply is available for participants who will continue study product under Version 5.0.

### **Category B Sites: Implementing OLE procedures for the first time under Version 5.0**

The primary purpose of this updated Appendix V at Category B sites is to allow participants to make their initial choice regarding whether to continue to receive CAB LA or TDF/FTC through Steps 4a-c and 5 as initially described in Version 4.0 and below. Given the extended time it has taken to implement the OLE at Category B sites, Step 6 may also be utilized for participants if necessary.

For sites in Category B, the following is required for implementation: 1) all required IRB/EC/other regulatory entity approvals for Version 5.0 are in place; 2) the site receives notification from the DAIDS Protocol Registration Office that the site-specific informed consent addendum is approved and indicates successful completion of the Version 5.0 amendment protocol registration process; 3) confirmation that adequate **supply of study products are in place at the site**; and 4) the site has confirmed that training of all active personnel for Version 5.0 has been completed. **The HPTN Leadership and Operations**

**Center (LOC) will issue an approval notice to begin implementation of Version 5.0 upon confirmation that all items outlined above are in place; a Category B site cannot implement Version 5.0 until this notice is issued.**

For both categories of sites, Appendix V under Version 5.0 of the protocol includes an updated Protocol Signature Page (in the main body of the protocol) and updated procedures including new Step 6 (Weeks 56 – 96). Two sample addendum consent forms are also included – one for Category A sites and one for Category B sites.

### **3. Description of Steps 4a-c, 5, and 6**

Sites will discuss with participants their options for ongoing study participation as outlined in the Steps below. Two addendums to the main informed consent form are included for continuation in the study, based on which category of site (A or B) and the status of each participant still in follow-up. In either case, a site may opt to conduct informed consent discussions via telephone or telemedicine at the discretion of the IoR and in accordance with all relevant IRB/ECs/other regulatory entities. If the consent discussion occurs off-site and the participant chooses to continue in the study, once the participant reports to the study site, product dispensation can only occur after signature of the applicable addendum informed consent form. Contact the CMC for guidance if there are other consent-related scenarios not outlined here.

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

Participants originally randomized to TDF/FTC who have passed three years from the date of enrollment will not be permitted to make the choice of entering Step 5 (open-label TDF/FTC), per the original study design and informed consent; such participants will be referred to local standard of care for prevention services. These participants will still be consented so that they may receive the new information about cabotegravir contained in the addendum consent form and to document that they will not take part in the OLE. Additionally, participants who are otherwise not eligible to join the OLE or who do not wish to participate in the OLE will also be consented so that they may receive the new information about cabotegravir contained in the addendum consent form, and to document that they will not take part in the OLE. Participants who already left the study prior to Version 5.0 because they were ineligible to continue in the OLE, or did not wish to participate in the OLE, or were lost to follow up beyond six months of initial OLE implementation at their site, will not be allowed to be reconsented to Version 5.0. As outlined in the consent form, participants who continue in the OLE but then leave the study before their last scheduled study visit will be asked to complete a final visit based on the OLE schedule if available to do so. Participants who do not participate in the OLE will be told that this will be considered their final study visit and will be asked to complete the procedures listed for participants who are not continuing under the OLE.

Participants who have not initiated any procedures under Appendix V in either Version 4.0 or Version 5.0 who wish to continue study participation under the OLE must be consented within six months of

HPTN LOC notification to the site to begin OLE implementation. Participants will not be allowed to transition to the OLE beyond six months from date of HPTN LOC notification to implement. This includes participants who have indicated that they need time to decide whether they want to participate in the OLE. If a participant returns to a site more than six months after LOC notification to implement the OLE, the participant will be provided the new information in the informed consent form and will mark that they are not eligible to participate on the consent signature page.

NOTE: Participants in the first 48 weeks of the OLE who have been on TDF/FTC throughout the study and choose to stay on it, or participants who have been on CAB and choose to switch to TDF/FTC, will be permitted to change their mind once up to 6 months after making their choice at their initial OLE visit and switch to CAB. **There will be no switches allowed during Step 6.**

Contact the CMC for guidance for other cases that do not fit the descriptions or criteria described above.

**a. Step 4a: Oral Cabotegravir Lead-In (Optional) for Participants Originally Randomized to TDF/FTC**

This step is optional and a decision as to whether to opt in and take daily oral cabotegravir for approximately 4 weeks prior to receiving injections will be made by the participant in consultation with the IoR (or designee). There also may be cases where the local IRB/EC/other review bodies require the participant to participate in the oral lead-in prior to receiving injections; either way, each site's local informed consent form will reflect the situation at the site.

This step - for participants who opt to participate in it (or if the IoR or the IRBs/ECs/other review bodies require it) - is only for those originally randomized to oral TDF/FTC who choose to initiate cabotegravir for the first time. If a participant participates in Step 4a, and since it is deemed optional from the central management standpoint of the study, it will be at the discretion of the site Investigator of Record (or designee) as to what level of adherence to daily oral cabotegravir (if any) will be required by self-report prior to receiving injections. There are no pill counts in this Step (that is, no Pill Count eCRF will be used); however, a site may choose to perform pill counts for documentation in the participant chart. **This Step is not to be used for any participant who has ever received CAB LA injections in the past.**

Contact the CMC for guidance regarding cases or situations not outlined here.

See [Table 7](#) for the schedule of procedures and evaluations for Step 4a.

**b. Step 4b: Loading Dose Visit for Injectable Cabotegravir for Participants Initiating or Restarting CAB Injections**

This is a one-visit step for participants who are initiating cabotegravir for the first time (and have either completed Step 4a or not) or for participants who have been on cabotegravir during the study but have had a long absence of visits (> 15 weeks since prior injection) and require a reload of cabotegravir injections (two injections, 4 weeks apart). The first of these two injections is considered Step 4b. The participant will then transition to Step 4c four weeks later.

Contact the CMC for guidance regarding cases or situations not outlined here.

See [Table 8](#) for the schedule of procedures and evaluations for Step 4b.

### c. Step 4c: Cabotegravir Injections

This Step is for participants originally randomized to cabotegravir who choose to continue it and do not need a reloading dose, or for participants transitioning from Step 4b. This Step includes cabotegravir injections every eight weeks and will last for approximately one year. Participants who are transitioning from Step 4b will have their first Step 4c visit conducted approximately four weeks following the Step 4b visit.

Participants who have had at least one injection in Step 4b or Step 4c who then choose not to or cannot continue receiving cabotegravir injections before Week 48 of Step 4 occurs will move to Step 5.

Participants who complete Week 48 of Step 4c and live in a country where CAB LA is approved for PrEP will be prioritized to transition to local CAB LA as soon as possible instead of moving to Step 5. If necessary, and if Version 5.0 approval is in place, these participants may continue CAB LA injections through the study up to Week 96 in Step 6 while this transition occurs. **Priority must be given to transitioning these participants to local CAB LA once they complete Step 4c and wish to remain on CAB LA.**

If Version 5.0 approval is not in place by the time the next injection (Week 56) is scheduled AND local CAB LA is not available, these participants will move to Step 5 until Version 5.0 approval is obtained; such participants will be allowed to enter Step 6 when Version 5.0 approvals and applicable implementation requirements are in place.

Note: Cases of significant delay of approval of Version 5.0 that would otherwise result in a lapse in the PrEP coverage for the duration of Step 5 will be considered on a case-by-case basis by the CMC.

Contact the CMC for guidance regarding cases or situations not outlined here.

See [Table 9](#) for the schedule of procedures and evaluations for Step 4c.

### d. Step 5: Participants Who Choose to Remain On or Switch To Oral TDF/FTC

This Step is for:

- Participants who were originally randomized to oral TDF/FTC and choose to remain on oral TDF/FTC. They will complete the procedures of this Step until three years from the time of enrollment.
- Participants who were originally randomized to CAB LA and choose to switch to TDF/FTC. They will complete the procedures of this Step for approximately one year from the last



injection; that is, Step 5 Day 0 begins 8 weeks after that participant's last injection and is 48 weeks in duration.

- Participants in Step 4b or Step 4c who decide they no longer wish to receive CAB or experience an AE that no longer allows them to receive CAB. They will complete the procedures of this Step for approximately one year from the last injection; that is, Step 5 Day 0 begins 8 weeks after that participant's last injection and is 48 weeks in duration.
- Participants who complete Step 4c and wish to continue receiving CAB LA and Version 5.0 is not approved yet and local CAB is not available. These participants will temporarily move to Step 5 until Version 5.0 approval is in place and then move to Step 6 while transitioning to local CAB.

If a participant completed Week 48 of Step 4c AND started Step 5 under Version 4.0, and then does not want to or cannot continue CAB injections in Step 6 when consenting to Version 5.0, they will complete the remaining visits of Step 5 under Version 5.0 and then be terminated from the study and referred to local PrEP services.

If a participant completes Week 48 of Step 4c under Version 5.0, and then does not want to or cannot continue CAB injections in Step 6, they will NOT enter Step 5 and will instead be terminated from the study and referred to local PrEP services.

Contact the CMC for guidance regarding cases in which Day 0 of Step 5 would occur beyond 48 weeks from the time the participant received their last injection, or for other cases or situations not outlined here.

See [Table 10](#) for the schedule of procedures and evaluations for Step 5.

See [Figure 9](#) below for a decision tree regarding the step sequences based on a participant's initial choice when first joining the OLE, which applies mainly to participants at Category B sites; that is, participants who have not yet been offered the **initial choice** of CAB or TDF/FTC. This decision tree applies only to a participant's initial choice when starting the OLE and therefore only includes Steps 4a, 4b, 4c and 5. Note that Step 6 is only to be used as a continuation of Step 4c.

#### **e. Step 6: Participants Transitioning to Local CAB LA (Week 56 to Week 96)**

Step 6 is a new Step under Version 5.0 and is only for participants who complete follow-up in Step 4c and who wish to continue CAB LA while awaiting transition to local CAB LA. The provision of CAB LA in Step 6 is for up to an additional 48 weeks (Weeks 56 – 96); **however, the priority should be given to transition participants to local CAB LA as soon as possible after a participant completes Week 48 of Step 4c.**

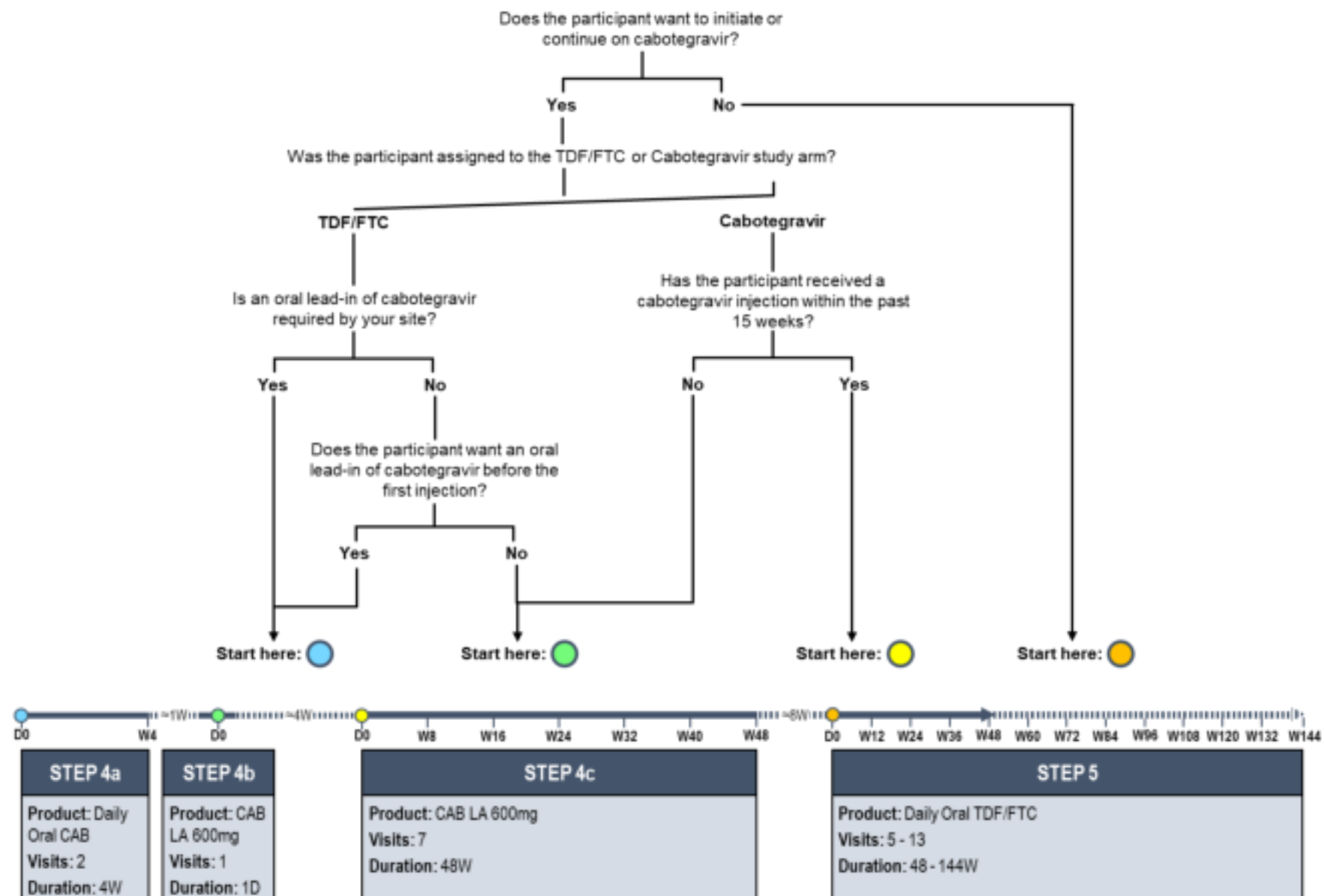
Participants on Step 6 who no longer want to receive injections or who can no longer receive injections due to an AE will be terminated from the study and referred to local prevention services. That is, these participants will not transition to Step 5 (TDF/FTC tail coverage) within the protocol.

Participants on Step 6 who become infected with HIV will complete the HIV confirmation visit in [Table 13](#), then be terminated from the study and referred to HIV treatment services.

NOTE: As noted above, participants who completed Step 4c at a site that does not have Version 5.0 approved and who wish to remain on CAB LA but have not completed the transition to local CAB LA will move to Step 5. Once Version 5.0 is approved (and the participant has still not transitioned to CAB LA) the participant may move to Step 6 until they are able to transition to local CAB LA access or other prevention services.

See [Table 11](#) for the schedule of procedures and evaluations for Step 6.

Figure 9: Decision Tree



#### 4. Open-Label Extension Objectives/Endpoints/Statistical Analysis

Note: The OLE objectives, endpoints, and statistical analysis refer to participants in the first 48 weeks of the OLE only and will not include any data collected on participants during Step 6, Weeks 56 – 96. Step 6 is in place only as a transitional mechanism to allow time to access local CAB LA.

##### Objectives

1. To estimate HIV incidence in participants who receive CAB during the unblinded and OLE periods, both separately and in aggregate; compare these outcomes to HIV incidence in the CAB-LA arm during the blinded period.
2. Evaluate the safety of CAB during the unblinded and OLE periods; compare these outcomes to safety during the blinded period.
3. Estimate HIV incidence in participants who choose to receive TDF/FTC during the OLE period, separately and in combination with incidence during the unblinded period among those randomized to TDF/FTC. Compare with HIV incidence during the blinded period in those randomized to TDF/FTC.
4. Evaluate safety and HIV incidence among participants randomized to CAB-LA who receive TDF/FTC dosing during temporary discontinuation of CAB injections (e.g. due to lack of access during COVID, or between the end of randomized dosing and restart of CAB-LA during OLE).
5. Summarize PrEP choice at entry into OLE according to randomized study arm and most recent study product, including the number/proportion of participants who fall into each of the following (a) CAB-arm: continue on CAB, (b) CAB-arm: switch from CAB to TDF/FTC at entry into OLE, (c) CAB-arm: switch back from TDF/FTC to CAB at entry into OLE, (d) CAB-arm: stay on TDF/FTC, (e) TDF/FTC-arm: switch to CAB, and (f) TDF/FTC-arm: remain on TDF/FTC. And, among those initially assigned to TDF/FTC who choose to initiate CAB during the OLE, how many elect oral lead in and how many choose direct to inject.
6. Assess CAB continuation, adherence, and acceptability during the OLE and unblinded periods compared to the blinded period.
7. Assess tail-phase HIV incidence rates amongst those who discontinue CAB-LA injections.
8. Characterize HIV infections, including drug resistance, drug concentrations, viral load, and results from HIV diagnostic tests.
9. Evaluate weight changes over time among participants who transition from TDF/FTC to CAB during the OLE, and among participants who transition from CAB to TDF/FTC.
10. STI incidence rates to corroborate/contextualize HIV incidence rates as a biomarker of risk behavior.
11. Summarize reasons for choice/preferences for study product.
12. Provide on-going access to CAB LA to eligible participants as a bridge to local CAB LA.

## Exploratory Objectives

1. To perform secondary laboratory assessments that may include evaluation of factors related to HIV infection, hepatitis infection, or STIs; antiretroviral (ARV) drug use; pharmacogenomics; further characterization of HIV infections; and evaluation of laboratory assays related to the study objectives
2. To continue to explore possible drug-drug interactions between cross-sex hormone therapy (csHT) and cabotegravir and TDF/FTC in a subset of participants who self-identify as transgender women.
3. Consider extending the CAB case-control (concentration-response) analysis to include infections that occur in persons who received CAB-LA during the unblinded and/or OLE phase of the study.

## Endpoints

1. Number of incident HIV infections among participants who receive any CAB dosing, oral or injectable, during the unblinded stage and the OLE period, as well as infections that occurred during the 48-week CAB tail phase following CAB LA discontinuation.
2. Grade 2 and higher clinical or laboratory adverse events (AEs). Grade 2 and higher injection site reactions.
3. Number of incident HIV infections among participants who are initially randomized to TDF/FTC (blinded and unblinded) and any participants who choose to receive TDF/FTC during OLE follow-up.
4. Number of documented incident HIV infections, and grade 2 or higher AEs, among participants receiving temporary TDF/FTC during temporary discontinuations of CAB.
5. Treatment choice at entry into the OLE.
6. Time of CAB discontinuation during the OLE and unblinded stages.
7. Number of documented incident HIV infections between 8 and 56 weeks after the last CAB injection.
8. Genotypic resistance, drug concentrations, infection timing, and HIV testing results for all incident infections. Phenotypic INSTI resistance may also be evaluated in selected cases.
9. Weight and body mass index (BMI) among participants who transition to or from CAB.
10. Number of STIs detected among participants during the unblinded and OLE periods.
11. Self-reported reasons for choice/preferences for study products.
12. Number of participants transitioned to local CAB LA.

## Statistical Analysis

1. To estimate HIV incidence in participants who receive CAB during the unblinded and OLE periods, both separately and in aggregate. Compare against HIV incidence in the CAB-LA arm during the blinded period.
  - a. The first-positive date for incident HIV events will be determined by an independent Endpoint Adjudication Committee (EAC); the infection time will be calculated as the midpoint between the first HIV positive visit date and the last HIV negative visit date.
  - b. Overall incidence. Incident HIV events will be classified as having occurred in the blinded or OLE periods based on the infection time and participant-specific dates of unblinding and entry into the OLE. A “participant who received CAB” in blinded follow-up will be defined as being randomized to CAB-LA; in unblinded follow-up as having received at least one pill or injection; and in OLE follow-up as having received at least one pill or injection. Person time starting with last visit prior to May 14<sup>th</sup>, 2020 up through the first OLE visit will be classified as “unblinded” time; person time following entry into the OLE will be classified as “OLE” time. Incidence rates will be calculated as the number of incident events per 100 person years, with exact-Poisson based confidence intervals.
  - c. On Study Product (OSP) HIV incidence. Events, and person time will be classified as in (b) above, however the OSP analysis will define CAB exposure to include only injections and only events and person time that occur within 10 weeks of the last non-delayed injection (or within 6 weeks of the last injection if only one injected was given).
2. Evaluate the safety of CAB during unblinded follow-up, and in the OLE. Compare with the blinded period.

For CAB-LA safety, participants are excluded from the cohort if they never receive any CAB. Safety evaluation ends one year after the last injection. The blinded period will end on the first visit before May 14, 2020; the unblinded period will begin the day after the blinded period ends until the first OLE visit for each participant, and the OLE period will extend from the first OLE visit until the last study visit.

- a. Oral CAB step. For the blinded and OLE stages: Counts and proportions of participants reporting any Grade 2+ AEs occurring after the receipt of oral CAB, up to 2 weeks following the last planned oral dose, and prior to the first injection. Events will be tabulated by blinded and OLE stages, overall and by grade.
- b. Overall CAB safety. Counts and proportions of participants reporting any Grade 2+ AEs after receiving at least one dose of oral or injectable CAB, with onset date up to one year following the last injection. For blinded stage, all events up through May 14, 2020, are tabulated; for unblinded, all events up through the participant OLE visit; for OLE all events with onset date up to one year following the last injections. Events will be tabulated by blinded, unblinded and OLE, overall and by grade.
- c. Evaluating the OLI. Among participants assigned to the TDF/FTC arm who elect to initiate CAB, counts and proportions of participants reporting one or more Grade 2+ AEs or any event leading to product discontinuation within the first 12 weeks and within the first 48 weeks of initiating CAB injections comparing participants who received an oral

- lead in (OLI) to those who chose direct to inject. Events will be tabulated overall and by grade; for events of interest, rates of events may be computed to enable statistical comparison. ISRs will not be considered in the evaluation in this comparison.
- d. Injection site reactions. Counts and proportions of ISRs reported by all participants will be tabulated by blinded, unblinded and OLE amongst those receiving at least one CAB injection, overall, by injection number, and by severity.
3. Estimate HIV incidence in participants who choose to receive TDF/FTC during the OLE, separately and in combination with incidence amongst those assigned to TDF/FTC during the unblinded period. Compare with HIV incidence in those assigned to TDF/FTC during the blinded period.
    - a. As per section (1) above the timing of incident infections will be calculated based on the first-positive date determined by the EAC, and person time will be classified on an individual basis depending on OLE entry dates. In blinded and unblinded follow-up, all person time from participants assigned to TDF/FTC will be included. In OLE follow-up, Step 3 events (i.e., events occurring after a decision to stop CAB-LA injections and initiate TDF/FTC) will not be included. However, for participants initially assigned to CAB-LA who switch to TDF/FTC, and participants assigned to TDF/FTC who choose to continue TDF/FTC during the OLE, all events and person time will be included starting with the date TDF/FTC is initiated/continued in the OLE. Incidence rates and confidence intervals will be computed as above.
  4. Evaluate safety and HIV incidence among participants who receive TDF/FTC dosing during temporary discontinuation (e.g. due to lack of access during COVID) of CAB injections.
    - a. For participants who were assigned to CAB (oral or injectable) and temporarily switched to TDF/FTC, then return to CAB, tabulate the number and proportion who report grade 2 or higher AEs within 12 weeks (first two injection cycles) of the first post-TDF/FTC dose of CAB.
    - b. HIV incidence rates will be calculated during and following the CAB-discontinuation period, where the discontinuation period begins at the time of TDF/FTC initiation and ends at the first post-discontinuation CAB dose.
  5. Summarize PrEP choice at entry into OLE, including the number/proportion of participants who elect to (a) CAB-arm: continue on CAB, (b) CAB-arm: switch from CAB to TDF/FTC at entry into OLE, (c) CAB-arm: switch back from TDF/FTC to CAB at entry into OLE, (d) CAB-arm: stay on TDF/FTC, (e) TDF /FTC-arm: switch to CAB, and (f) TDF/FTC-arm: remain on TDF/FTC. And, among those initially assigned to TDF/FTC who choose to initiate CAB during the OLE, how many elect oral lead in and how many elect direct to inject.
    - a. Counts and proportions will be presented in tabular form by arm
  6. Assess CAB continuation and adherence (i.e. acceptability) during the OLE and unblinded stage compared to the blinded period.
    - a. Time from initiation of CAB injections to discontinuation, defined as not receiving an injection within 16 weeks of the prior injection, will be plotted using the product limit method, separately by period/arm (blinded, unblinded, and TDF/FTC-arm participants choosing CAB during the OLE), and aggregated across all periods.

- b. Proportion of injections that were given more than 8, 10, and 12 weeks from the prior injection compared between the blinded, unblinded, and OLE (participants choosing CAB-LA in both arms), (noting that potential COVID-related delays may need to be accounted for). Analyses may be tabulated by injection number.
7. Assess tail-phase HIV incidence rates amongst those who discontinue CAB-LA injections.
  - a. A “tail-phase” infection is defined as an event that occurred in a participant who has received an CAB-LA injection and whose first HIV positive visit (per completion of extended central laboratory testing) occurred between 9 and 56 weeks of the last CAB LA injection.
  - b. Tail-phase person time will start from the first HIV-negative visit at approximately 8 weeks after the last CAB LA injection and end at the last visit (with HIV testing) within 56 weeks of the last injection. For participants who re-start CAB in the OLE prior to 56 weeks from their last injection, person time will be truncated at the date of their first CAB dose in the OLE.
  - c. Tail phase events from blinded, unblinded, and OLE follow-up time will all be included, with incidence rates and confidence intervals computed as described in section (1) above.
8. Genotypic resistance, drug concentrations, infection timing, and HIV testing results for all incident infections. Phenotypic INSTI resistance may also be evaluated in selected cases.
  - a. Details of each confirmed incident HIV infection will be presented, including longitudinal CAB concentrations (tabular and plot), resistance mutations detected (tabular, by visit), and results of HIV testing performed at each visit (table).
9. Evaluate weight changes over time among participants who transition from TDF/FTC to CAB during the OLE, and among participants who transition from CAB to TDF/FTC.
  - a. Mean and median weight and BMI will be tabulated and plotted for the 12 months prior to the treatment transition point (TDF/FTC to CAB or CAB to TDF/FTC), and for 12 months after the treatment transition point. Changes over time will be computed and compared before and after the treatment transition using longitudinal random effects regression models with a term for time (years) and an interaction with an indicator for the post-transition time period.
  - b. Paired weight changes over a fixed time period (e.g. 4 months) will be assessed in the cohort of participants who
    - i. Were initially assigned to TDF/FTC and subsequently chose to initiate CAB-LA
    - ii. Were initially assigned to CAB-LA, or chose CAB during the OLE, and subsequently switched to TDF/FTC.

Each person in each of i) and ii) will contribute two weight changes (one when receiving each of the drugs). Weight changes for each person will be compared across the two drugs.
10. STI incidence rates to corroborate/contextualize HIV incidence rates as a biomarker of risk behavior



- a. Counts and incidence rates will be presented in tabular form for incident syphilis, gonorrhea (rectal and urethral), and chlamydia (rectal and urethral) for both the unblinded stage and the OLE period, separately and combined, using the same person time definitions for these time periods as described section (1) above. Repeat events within the same participant will be counted separately in the incidence calculations. Counts and rates will be presented by randomized arm for the blinded and unblinded stages, and by treatment choice for the OLE.
11. Summarize reasons for choice/preferences for study product.
  - a. A tabular summary of choices and preferences will be presented by arm for participants agreeing to participate in the OLE, and during the unblinded stage for participants who elected to stop randomized treatment at that time.
12. Describe number of participants who transitioned to local CAB LA.

## **B. Information in the Main Protocol that is Not Included in Appendix V**

The sections listed below from the main protocol are no longer applicable to the procedures described in this Appendix or they pertain to the original study design and therefore are not applicable to the Appendix. Information from sections not listed here are outlined under “C” below.

Information from the following sections of the protocol is **not** included in this Appendix:

- Front matter such as the protocol roster, table of contents, schema, etc. An updated Protocol Signature Page is included in the body of the main protocol and should be signed and dated by the Investigator of Record.
- Section 1.0 in full
- Section 2.0, in full
- Section 3.0; Section 3.1; Section 3.2, Section 3.3
- Section 4.1
- Section 5.0 - Section 5.9; Section 5.11; Section 5.13; Section 5.13.1; Section 5.14.1; Section 5.18; Section 5.20. To reduce inconsistencies, specific listings of Steps 4, 5, and 6 procedures and assessments are not repeated as was done for Steps 1, 2 and 3 in the main protocol, and appear in this Appendix in Tables only.
- Section 7.0 in full (analyses from endpoints outlined are completed or ongoing and pertain to the original study design and are not repeated in this Appendix)
- Section 9.0 in full (all relevant information from this section of the protocol is included in the updated SSP section pertaining to this Appendix – which is identified as Appendix VIII of the SSP)

## **C. Information in the Main Protocol that is Included Or Modified in Appendix V**

Several sections from the main protocol still apply in full or in part to the procedures outlined in this Appendix and are outlined below and updated where necessary:

1. **Co-Enrollment (from Section 3.4 of the main protocol, with modifications):** Participants may participate in COVID-19 vaccine or treatment studies provided that participant study burden and

American Red Cross-mandated limitations on per-unit-time phlebotomized blood volumes are not exceeded. There is no need to consult the CMC for participation in these studies. The CMC should be consulted for participation in other COVID or non-COVID related biomedical intervention studies.

2. **Participant Retention (from Section 3.5 of the main protocol with modifications):** Sites will continue to implement existing retention strategies; however, priority must be given to transitioning participants to local CAB LA for participants who have completed Step 4c and wish to continue receiving it.
3. **Participant Withdrawal (from Section 3.6 of the main protocol):** Participants may voluntarily withdraw from the study for any reason at any time. 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/ECs 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.
4. **Premature Termination Visits (from Section 3.6.1 of the main protocol, with modifications):** In general, for participants who withdraw consent from the study prematurely during a study visit, the requirements for that visit should be completed to the extent possible **except for provision of study product** and will be considered their final visit. When possible, a plan should be made to provide final laboratory results from site testing to the participant. For participants on oral TDF/FTC who inform the site in between visits that they wish to withdraw consent from the study, sites should make every effort to have the participant return any unused study product. It is at a site's discretion to terminate participants who have been lost to follow-up for a minimum of 6 months or who have relocated to an area where there is no HPTN 083 site. The timeline for the 6 months lost to follow-up or relocation begins at the participant's first missed visit (which may have occurred longer than 6 months ago by the time the OLE is in effect at the site).
5. **Study Product Considerations (from Section 4.0 of the main protocol, with modifications):** The CAB study product (oral and LA injectable) being tested in this study has been approved by the US FDA for the prevention of HIV-1 infection. Further information on the study product is available in the current prescribing information. An Investigator's Brochure (IB), dated January 12, 2022, is provided by the DAIDS Regulatory Support Center (RSC), for sites that require it for submission to IRBs/ECs/other regulatory entities.

#### Oral Study Products

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

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

### Injectable Study Product

Cabotegravir Long-Acting (CAB LA) is formulated as a sterile white to slightly pink colored suspension containing 200 mg/mL of CAB LA for administration by IM. The product is packaged in a 2 mL or 3 mL glass vial. Each vial is for single use containing 2 mL (400 mg) or 3 mL (600 mg) and does not require dilution prior to administration. CAB LA injectable suspension is to be stored up to 30°C (86°F), do not freeze.

### Prescription

A prescription for unblinded study product (oral active CAB, oral active TDF/FTC or injectable CAB-LA) signed by an authorized prescriber must be provided to the site pharmacist prior to preparation of study product. The prescription must include the Step number (4a, 4b, 4c, 5, or 6). For participants making their choice and initiating the OLE for the first time, the prescription should include a notation if the participant is switching between their original CAB arm or original TDF/FTC arm.

### Study Product Preparation:

The site pharmacist should consult the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations.

### **CAB 30 mg Oral Product**

- The pharmacist will take the following steps to prepare and dispense un-blinded active oral CAB to the participant:
  - 1) Retrieve oral active CAB 30mg tablet bottle with two part-label from Step 1 supply.
  - 2) Retain both the un-blinded part and the blinded part of the two-part label on the CAB bottle. Do not tear off the un-blinded part of the two-part label from the bottle.
  - 3) Place pharmacist-prepared participant- specific un-blinded label in such a way that the blinded part of the two-part label on the bottle is covered.
- The pharmacist prepared, participant-specific, un-blinded oral active CAB bottle will have the manufacturer's unblinded part of the two-part label and site pharmacist generated participant specific un-blinded label visible on the prepared bottle before dispensation.

The participant specific label must be in accordance with the local regulations and the DAIDS Pharmacy Guidelines manual.

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

### **TDF/FTC (300 mg/200mg) Oral Product**

- The pharmacist will take the following steps to prepare and dispense un-blinded active oral TDF/FTC to the participant:
  - 1) Retrieve oral active TDF 300 mg/FTC 200 mg (open-label) bottle from Step 3 supply.
  - 2) Place pharmacist prepared participant-specific un-blinded label in such a way that the manufacturer's unblinded label on the bottle is not covered.
- The pharmacist-prepared, participant-specific, un-blinded oral active TDF/FTC bottle will have the manufacturer's unblinded label and site pharmacist generated participant-specific un-blinded label visible on the prepared bottle before dispensation.

The participant specific label must be in accordance with the local regulations and the DAIDS Pharmacy Guidelines manual.

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

### **Injectable CAB LA 600 mg/3mL**

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

The site pharmacist will follow the steps below for preparation of active injectable study product, CAB LA injectable suspension. In Step 4b and 4c of the study, one syringe containing 3 mL (600 mg) of CAB-LA must be prepared using aseptic technique under a pharmacy BSC/Isolator.

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

- One CAB LA 600 mg/3 mL vial or two CAB LA 400 mg/2 mL vials
- Becton Dickenson (BD) 3-mL syringe, Luer-Lok Tip, Product No.: 309657 or equivalent
- Becton Dickinson (BD) 5-mL Syringe, Luer-Lok Tip, Product No.: 309646 or equivalent
- Needle for aspiration: BD general use sterile hypodermic needle, 21G x 1½ inch (e.g. PrecisionGlide Needle, Product No.: 305165 or equivalent)
- Needle for intramuscular injection: BD IM sterile hypodermic needle, 23G x 1½ inch (e.g. PrecisionGlide Needle, Product No.: 305194 or equivalent). Refer to the HPTN 083 SSP for further details on appropriate needle gauge size and length to use for IM administration.

### Preparation Steps:

- Remove two vials of CAB LA (400 mg/2 mL per vial) or one vial of CAB LA (600 mg/3 mL per vial) from storage. If the vials are stored in the refrigerator (2°C to 8°C), remove vial(s) from the refrigerator and wait at least 15 minutes to equilibrate to room temperature.
- Vigorously shake the vial(s) for a full 10 seconds by shaking the vial(s) with long arm movements.
- Invert the vial(s) and inspect to ensure uniform suspension. If solid remains undispersed, repeat vigorous shaking and inversion until all material is uniformly suspended.
  - NOTE: It is normal to see small air bubbles at the end of shaking the vial for re-suspension.
- Using aseptic technique under a pharmacy BSC/isolator, flip off the plastic cap from the vial. Wipe the top of the vial with an alcohol pad (isopropyl alcohol 70% or similar) and allow to dry. Do not touch the rubber stopper at any time.
- Remove a 3 mL or 5 mL size syringe and 21G x 1½ inch (or equivalent) needle for aspiration. Attach the needle to the Luer connection of the syringe.
- With the needle sheath on, pull the syringe plunger rod to allow approximately 1 mL of air into the syringe. Remove the needle sheath.
- With the vial in the inverted position and the syringe with the needle in the upright position, push the needle through the vial stopper and inject approximately 1 mL of air into the vial.
- While keeping the syringe with the needle in the upright position, withdraw needed volume of CAB LA suspension from the vial(s) into the syringe.
- Withdraw total of 3 mL (600 mg) of CAB LA suspension from the vial(s) into a syringe.
  - If using two CAB LA 400 mg/2 mL vials to prepare the dose, a second new aspiration needle should be used to withdraw suspension from the second vial. Remove the first needle that was used to withdraw the suspension out of the first vial and discard properly. Attach the new 21G x 1½ inch needle (or equivalent) to the syringe already containing suspension per instructions above to withdraw the remaining needed volume from the second vial.
  - Since the suspension can contain some air after having shaken the vial, withdraw enough suspension from the vial in order to be able to de-aerate the syringe properly.
- Remove the needle that was used to withdraw the suspension out of the vial and discard the needle properly.

- Attach a 23G x 1½ inch (or equivalent) needle to the Luer connection of the prepared CAB LA syringe for IM injection for the participant. Alternatively, the site pharmacist can attach a syringe cap to the prepared syringe. The study staff can then attach the appropriate needle for administration to the prepared syringe in the clinic before administration.
  - NOTE: The participant-specific prepared CAB LA in a syringe is to be de-aerated by administrator prior to injection so that the correct volume can be administered.
    - De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in an upright position until the first drop of suspension appears. Remove the excess suspension in order to administer the correct volume (3 mL). If needed, collect the excess suspension in a beaker to avoid spilling.
- Record the time that the suspension was withdrawn from the vial and into the syringe in the participant's pharmacy log. This is the time of preparation.
- Label the prepared syringe containing 3 mL (600 mg) of CAB-LA as "CAB LA 600 mg per 3 mL", including the volume (3 mL), route (IM), participant's PTID, date and time of preparation, and date and time of expiration. Follow the DAIDS Pharmacy guidelines and local regulations for preparing the participant specific label.

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

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

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

### Study Product Acquisition and Accountability

All study products 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.

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

Networks. The site pharmacist at non-US clinical research sites must follow the instructions in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks DAIDS Pharmaceutical Affairs for the destruction of unused study products.

### Concomitant, Prohibited, and Precautionary Medications

The precautionary and prohibited medications are:

#### Cabotegravir:

- Not to be administered concurrently:
  - Cytotoxic chemotherapy or radiation therapy
  - barbiturates
  - carbamazepine
  - oxcarbazepine
  - phenytoin
  - pheonobarbital
  - rifabutin
  - rifampin
  - rifapentine
  - St. John's wort

NOTE: Systematically administered immunomodulators is removed

- Prohibited within 7 days before and 7 days after an injection
  - high dose aspirin (>325 mg per day)
  - anagrelide
  - apixaban
  - argatroban
  - bivalirudin
  - clopidogrel
  - dabigatran
  - dalteparin
  - enoxaparin
  - fondaparinux
  - heparin
  - lepirudin
  - prasugrel
  - rivaroxaban
  - ticagrelor

- ticlopidine
- warfarin
- Oral formulation precautions
  - Antacid products containing divalent cations (e.g., aluminum, calcium, and magnesium) must be taken at least 2 hours before or at least 4-6 hours after the oral CAB administration

Truvada®:

- Medications containing the following ingredients should not be administered concurrently:
  - emtricitabine or tenofovir disoproxil fumarate (e.g. ATRIPLA®, COMPLERA®, EMTRIVA, GENVOYA®, ODEFSEY®, STRIBILD®, or VIREAD, Descovy).
  - lamivudine (e.g. Combivir, Dutrebis, Epivir, Epivir-HBV, Epivir A/F, Epzicom, Triumeq, or Trizivir)
  - adefovir (e.g. HEPSERA®)
  - tenofovir alafenamide (e.g. Vemlidy)
  - didanosine (e.g. Videx EC)
  - atazanavir (e.g. Reyataz, Evotaz (atazanari/cobicistat))
  - ledipasvir/sofosbuvir (e.g. HARVONI®)
  - darunavir (e.g. Prezista)
  - lopinavir/ritonavir (e.g. Kaletra)
  - orlistat (e.g. Alli, Xenical)

Additional information regarding recommended, prohibited, and precautionary concomitant medications can be found in the cabotegravir IB and the Truvada® PI.

All concomitant medications/preparations (prescription and non-prescription) including alternative/complementary medications/preparations (e.g., herbs, vitamins, etc.) will be collected in the study participant's chart and on study case report forms (CRFs). 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).

Refer to SSP Appendix VIII for NSAIDS and considerations for co-administration of precautionary and prohibited medications.

Other Study Product Dispensing Considerations

While it is not required, it is recommended that sites dispense an additional bottle of study product (TDF/FTC or CAB) to ensure an extra month supply between visits. For example, for participants initiating cabotegravir, sites should dispense two bottles of oral CAB to cover the 4- week period prior to the first injection. Participants should be advised to bring open bottles to appointments, finish an open bottle before opening a new one, and should not combine or transfer pills between open bottles. Formal pill counts will not occur under the procedures of this Appendix.



- 6. Procedures for Steps 4, 5, and 6 (originally Steps 1 – 3 from Section 5.0, with modifications):** Procedures and evaluations for Steps 4, 5, and 6 are outlined in Tables 7 – 11 and are not repeated here. [Table 12](#) details final procedures and evaluations for participants who receive the new study information but do not continue follow up under the OLE because they do not want to or are ineligible to do so. The HIV testing algorithm for follow-up visits is shown in [Figure 10](#).
- 7. Visit Windows (from Section 5.10 of the main protocol, with modifications):** Target windows for all visits are outlined in Appendix VIII of the SSP Manual.

For injections that are scheduled or intended to be 4 weeks apart: If the planned return visit is 12 or more weeks since the last injection, a 4-week interval should be used for the next injection after returning, and then 8-week intervals resumed.

For injections that are scheduled or intended to be 8 weeks apart: If the planned return visit is 16 or more weeks since the last injection, a 4-week interval should be used for the next injection after returning, and then 8-week intervals resumed.

**It is no longer required to contact the CMC regarding late injections.**

An injection visit or a study product dispensation visit may never be completed without preceding safety laboratory assessments being completed and all the assessments being result and protocol allowable.

- 8. Procedures for Participants Who Do Not Complete Step 4a (originally Step 1 from Section 5.12 of the main protocol, with modifications):** Participants in Step 4a of the study who are unable to transition to Steps 4b and 4c for any reason – including HIV infection - will be referred to local care and terminated from the study.

Participants in Step 4b or 4c of the study who prematurely stop receiving injections will be asked to transition to Step 5 of the study and receive 48 weeks of open label TDF/FTC unless the reason is HIV infection or an AE or condition where open label TDF/FTC is contraindicated. Participants with HIV infection during Step 4b or 4c will be asked to be followed per [Table 13](#) below.

Participants who prematurely stop receiving injections for an AE or condition where open label TDF/FTC is contraindicated during Step 4b or 4c will be asked to continue follow-up for 48 weeks off study product.

- 9. Procedures for Suspected or Confirmed HIV Infection (from Section 5.14.2 of the main protocol, with modifications):** Refer to the updated Appendix VIII of the SSP for guidance regarding suspected or confirmed HIV infection during Steps 4, 5, and 6.

Under this amendment, sites will continue to contact the [083HIV@hptn.org](mailto:083HIV@hptn.org) email alias any time a participant has a reactive HIV test result for guidance regarding clinical management or other questions.

Note: Participants who became infected with HIV under Version 3.0 or Version 4.0 of the protocol and are being followed on the HIV infection quarterly visit schedule when Version 5.0 is

implemented will complete their visits under Version 5.0. For example, if they completed Weeks 0, 12, and 24 under Version 3.0 or Version 4.0 and Version 5.0 is now approved at the site, the participant will complete Weeks 36 and 48 under Appendix V of Version 5.0 and then be terminated from the study.

Participants who are found to have a positive or reactive HIV test during consent to or participation in Steps 4b-c or Step 5 and have ever received an active CAB injection at any time during previous study conduct will be followed according to [Table 13](#) - Schedule for Additional Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result.

Participants who have a positive or reactive HIV test during Step 4a or Step 5 and have received only oral TDF/FTC and/or oral CAB but never an active CAB injection at any time during previous study conduct will be referred to local clinical care if HIV infection is confirmed based on testing performed at study sites; there will be no further study follow-up for these participants once HIV infection is confirmed.

Participants with suspected or confirmed HIV infection during Step 6 will be terminated from the study and referred to clinical care.

- 10. Sexually Transmitted Infections (from Section 5.15 of the main protocol):** Testing for GC/CT and syphilis will continue under this amendment. 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). Testing may be adjusted or prioritized at the discretion of the site investigator if there is a potential for shortage of supplies for collection and testing. Please see CDC recommendation September 8, 2020. <https://www.cdc.gov/std/general/DCL-Diagnostic-Test-Shortage.pdf>

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 performed at a site's discretion and costs associated may come out of each site's respective per participant study reimbursements.

Sites will determine if syphilis testing meets the criteria for incident infection and will mark accordingly on the appropriate eCRF. Refer to Appendix VIII in the SSP for guidance regarding syphilis titer adjudication. **The CMC no longer needs to be consulted regarding syphilis testing results. As has been the case in the study to date, syphilis infections deemed incident by the site IoR should continue to be reported into the study database via the STI and AE eCRFs.**

Upon initial entry into the OLE, any participant who has not had asymptomatic STI screening in the previous 6 months should have STI testing performed at that OLE initial visit.

Sites will continue to report STIs into the study database on the Adverse Event e-CRF as well as the STI e-CRF.

- 11. Hepatitis C (from Section 5.16 of the main protocol, with modifications):** Participants on Step 4c and Step 6 will have HCV antibody testing performed approximately annually. Incident HCV infection during follow-up will not mandate discontinuation of study product absent other requirements per [Part E, Toxicity Management](#).

**12. Interim Contacts and Visits and Missed Visits (from Section 5.17 of the main protocol, with modification):** Refer to SSP Appendix VIII for information.

**13. Pharmacokinetic Monitoring (from Section 5.19 of the main protocol, with modifications):**

Plasma will be collected for pharmacokinetic assessments during Steps 4a, 4b and 4c. Results of this testing will not be provided to study sites or participants. Plasma will be collected during Step 6 for confirmation of HIV infection; participants will be informed of their HIV testing results. Stored plasma may be used for future analyses.

**14. Adverse Event Reporting (from Section 6.0 of the main protocol, with modifications):**

**For participants in Step 4a-c, and Step 5:** Study site staff will document in source documents all AEs. Grade 2 and higher clinical and laboratory AEs (including SAEs), and any AE (clinical or laboratory) that leads to a study product hold (temporary or permanent) will be captured on AE e-CRFs reported by or observed in enrolled (defined as after randomization has occurred) 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 2.1 corrected, July 2017. STIs will be dually reported on the AE e-CRF as well as the STI e-CRF.

**For participants in Step 6:** Study site staff will document in source documents all AEs. Grade 3 and higher study drug related clinical and laboratory AEs, any AE related to study drug discontinuation (temporary or permanent), and any SAE will be captured on AE e-CRFs. These include AEs reported by or observed in enrolled (defined as after randomization has occurred) study participants. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.1 corrected, July 2017. STIs will be dually reported on the AE e-CRF as well as the STI e-CRF.

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.

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 <https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-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. This form is available on the DAIDS RSC website at <https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting>. For questions about DAERS, please contact [CRMSSupport@niaid.nih.gov](mailto:CRMSSupport@niaid.nih.gov). Site queries may also be sent with the DAERS application itself.

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, will be used for determining and reporting the severity of adverse events. The DAIDS grading table is available on the DAIDS RSC website at <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables>.

For questions about EAE reporting, please contact the RSC at DAIDSRSCSafetyOffice@tech-res.com.

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:

- ALT $\geq$ 3xULN AND total bilirubin $\geq$ 2xULN (must be both to require expedited reporting)
- Any seizure event

These reporting requirements are required for each study participant from enrollment until their follow-up in the study ends or as otherwise stated above. After this time, sites must report to DAIDS serious, unexpected, clinical suspected adverse drug reactions, as defined in Version 2.0 of the DAIDS EAE manual, if the study site becomes aware of the event on a passive basis, i.e., from publicly available information.

The study agents for the purposes of EAE reporting are: Oral CAB 30 mg oral tablet; CAB LA injectable suspension (200mg/mL); TDF/FTC fixed dose combination tablet containing 200 mg of FTC and 300 mg of TDF.

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 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.

Sites will continue “Social Impact” reporting for participants in Steps 4a-c and 5 only. “Social Impact” reporting will not take place for participants in Step 6. 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. If 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.

## **15. Human Subjects Considerations (from Section 8.0 of the main protocol, with modifications):**

The protocol, site-specific informed consent form, participant education and recruitment materials, and other requested documents — and any subsequent modifications — 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 must comply with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108b for promptly reporting the following: all unanticipated problems involving risks to human subjects or others; serious or continuing noncompliance with applicable regulations or the requirements or determinations of their IRBs/ECs; and any suspension or termination of IRB approval.

Study sites will follow all applicable local and national requirements for required reporting and continual renewal of the protocol. 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.

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 this Appendix that describes the purpose of the amendment, 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 per site SOPs (refer also to the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual). Site-specific reimbursement amounts will be specified in the study informed consent forms. All participants will be offered a copy of their informed consent form. If applicable, sites should follow all SOPs and institutional requirements for off-site consent discussions.

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 U.S., local and international regulatory entities, and/or site IRBs.

For sites located in the US, the HPTN has obtained a Certificate of Confidentiality from the US Department of Health and Human Services that is applicable for this 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.

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.

The study 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/ECs.

- 16. Administrative Procedures (from Section 10.0 of the main protocol, with modifications):** Full protocol amendments require submission of a protocol registration packet to the DAIDS Protocol Registration Office (PRO). Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

Category A sites are not required to wait for DAIDS PRO registration to implement Version 5.0.

For Category B sites only, site-specific ICF(s) WILL be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification from the DAIDS PRO that approves the site specific ICFs and indicates successful completion of the amendment protocol registration process. Receipt of DAIDS PRO approval and the HPTN LOC implementation memo is required prior to implementation of Version 5.0 of the protocol.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which can be found at <https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration>.

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.

Implementation of this amendment will be directed by Appendix V of this protocol as well as SSP Manual Appendix VIII. The SSP Manual includes links to the DAIDS SCORE Manual, Manual for Expedited Reporting of Adverse Events to DAIDS and the DAIDS Toxicity Tables.

Sites will continue to use the MediData Rave data management system. Quality control reports and queries routinely will be generated and distributed to the study sites for verification and resolution.

Study monitoring will continue to be performed as specified by and in accordance with DAIDS policies. Study monitors will:

- 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.

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID or other contractors. Remote monitoring visits may be performed in place of, or in addition to onsite visits to ensure the safety of study participants and data integrity.<sup>93</sup> The site will make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. Sites should consult with their DAIDS Office of Clinical Site Oversight Program Officer for acceptable platform options.

For on-site visits, site investigators will also 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, as applicable. 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 other US, local, and international regulatory authorities. A site visit log will be maintained at each study site to document all visits (including virtual visits).

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.

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 and at least three years after the completion of research. 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.

Completion of a clinical research study occurs when the following activities have been completed:

- All research-related interventions or interactions with human subjects (e.g., when all subjects are off study);

- All protocol-required data collection of identifiable private information described in the IRB/EC-approved research plan;
- All analysis of identifiable private information described in the IRB/EC-approved research plan;
- Primary analysis of either identifiable private or de-identified information.

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.

17. Appendices from the main body of the protocol have been modified accordingly to reflect this open label part of the study.

#### **D. Schedules of Procedures and Evaluations for the OLE and for Participants who are not Continuing under the OLE**

See Tables 7 – 12 for corresponding Schedules of Procedures and Evaluations for Steps 4 a-c, Step 5, Step 6, and for participants not continuing under the OLE, as well as [Table 13](#) for participants who become infected with HIV during Steps 4-6 or at a final visit if not continuing in the OLE. Refer to the Schedule of Forms (in SSP Appendix VIII) as well as instructions on the forms for whom and when to administer forms.



**Table 7: STEP 4a Schedule of Procedures and Evaluations – Daily Oral Cabotegravir – OPTIONAL for participants initiating CAB injections**

| Procedures  | DAY 0 | WEEK 4 |
|---|-------|--------|
| Informed consent/Product Choice discussion  | X     |        |
| Product choice assessment questionnaire (Interviewer-administered)                  | X     |        |
| Locator information   | X     | X      |
| HIV counseling  | X     | X      |
| Offer condoms and lubricant   | X     | X      |
| Interviewer-administered assessment (SMSQ) <sup>4</sup>                             | X     |        |
| CASI-administered assessment (behavioral assessment) <sup>4</sup>                   | X     |        |
| Adherence counseling  | X     | X      |
| Self-reported pill adherence  |       | X      |
| Directed history, con meds, directed physical exam                                  | X     | X      |
| Blood collection  | X     | X      |
| Urine collection for GC/CT testing <sup>5</sup>                                     | X     |        |
| Rectal swab collection for GC/CT testing <sup>5, 6</sup>                            | X     |        |
| Dispense pills (enough for 8 weeks)   | X     |        |
| HIV testing <sup>1</sup>  | X     | X      |
| Chemistry testing <sup>2</sup> (creatinine only)                                    | X     | X      |
| Liver function tests <sup>3</sup> (AST, ALT, total bilirubin, alkaline phosphatase) | X     | X      |
| Syphilis serologic testing <sup>5</sup>   | X     |        |
| Urine GC/CT testing <sup>5</sup>  | X     |        |
| Rectal swab GC/CT testing <sup>5</sup>  | X     |        |
| Plasma storage  | X     | X      |

**FOOTNOTES FOR TABLE 7:**

<sup>1</sup> The HIV testing algorithm is provided in [Figure 10](#) below and Appendix VIII of the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.

<sup>2</sup> The only chemistry required is creatinine. If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.

<sup>3</sup> Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase. If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.

<sup>4</sup> Refer to instructions in the interviewer-administered and CASI assessments as well as the Schedule of Forms for whom and when these assessments should be administered

<sup>5</sup> Perform testing at Day 0 if not done within the last 6 months

<sup>6</sup> If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

**Table 8: STEP 4b Schedule of Procedures and Evaluations – Loading Dose Cabotegravir Injection – for participants initiating or restarting CAB injections**

| Procedures*   | DAY 0 |
|---|-------|
| Informed consent/ Product Choice discussion <sup>1</sup>                            | X     |
| Interviewer-administered Product Choice assessment questionnaire <sup>1</sup>       | X     |
| Locator Information   | X     |
| HIV counseling  | X     |
| Condoms and lubricant   | X     |
| Interviewer-administered assessment (SMSQ) <sup>2</sup>                             | X     |
| CASI-administered assessment (behavioral assessment) <sup>2</sup>                   | X     |
| Adherence counseling  | X     |
| Directed history, concomitant medications, directed physical exam                   | X     |
| Blood collection  | X     |
| Urine collection for GC/CT testing <sup>7</sup>                                     | X     |
| Rectal swab collection for GC/CT testing <sup>7, 8</sup>                            | X     |
| Injection   | X     |
| ISR evaluation <sup>9</sup>   | X     |
| HIV testing <sup>3</sup>  | X     |
| Plasma storage <sup>4</sup>   | X     |
| Chemistry testing <sup>5</sup> (creatinine only)                                    | X     |
| Liver function tests <sup>6</sup> (AST, ALT, total bilirubin, alkaline phosphatase) | X     |
| Syphilis serologic testing <sup>7</sup>   | X     |
| Urine GC/CT testing <sup>7</sup>  | X     |
| Rectal swab GC/CT testing <sup>7</sup>  | X     |

FOOTNOTES FOR TABLE 8:

\*Participants who opted into Step 4a must complete Step 4b Day 0 and receive their first injection within 120 days of starting Day 0 of Step 4a.

<sup>1</sup> For participants who transition from Step 4a to Step 4b and completed this assessment as part of Step 4a, do not repeat upon entry to Step 4b.

<sup>2</sup> Refer to instructions in the interviewer-administered and CASI assessments as well as the Schedule of Forms for whom and when these assessments should be administered.

<sup>3</sup> The HIV testing algorithm is provided in [Figure 10](#) below and Appendix VIII of the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.

<sup>4</sup> Blood collected for plasma storage must be collected prior to the loading dose.

<sup>5</sup> The only chemistry required is creatinine. If it was performed during Step 4a, do not perform at Day 0 of Step 4b

<sup>6</sup> Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.

<sup>7</sup> Perform testing at Day 0 if not done within the last 6 months

<sup>8</sup> If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

<sup>9</sup> An ISR typically begins 24-48 hours after an injection. The “X” marked in this Day 0 box pertains to reporting an ISR if a participant experiences signs and symptoms of one (e.g., pain, redness, swelling, etc.) as a result of the injection that occurred at this visit at any point later that day and onward (as reported by the participant). A participant may follow-up with the site before their next visit to report that they have experienced an ISR or they may report it at their next visit. Sites need not

actively solicit this information from participants, either in-person or remotely. Should ISR symptoms be reported by the participant, it should be reported as an ISR for the injection that occurred at this visit. If an ISR is reported, use the Injection Site Reaction eCRF. As a reminder, symptoms experienced immediately at the time of an injection are NOT considered ISRs. No ISR assessment is required at the visit at which the injection is provided.

**Table 9: STEP 4c Schedule of Procedures and Evaluations – Cabotegravir Injections – Day 0 - Week 48**

| Procedures*   | DAY 0 | WEEK 8 | WEEK 16 | WEEK 24 | WEEK 32 | WEEK 40 | WEEK 48 |
|---|-------|--------|---------|---------|---------|---------|---------|
| Informed consent/ Product "Choice" discussion <sup>1</sup>                          | X     |        |         |         |         |         |         |
| Interviewer-administered Product Choice assessment <sup>1</sup>                     | X     |        |         |         |         |         |         |
| Locator Information   | X     | X      | X       | X       | X       | X       | X       |
| HIV counseling  | X     | X      | X       | X       | X       | X       | X       |
| Condoms and lubricant   | X     | X      | X       | X       | X       | X       | X       |
| Interviewer-administered assessment (SMSQ) <sup>8</sup>                             | X     |        | X       |         |         |         | X       |
| CASI-administered assessment (behavioral assessment) <sup>8</sup>                   | X     |        | X       |         |         |         | X       |
| Adherence counseling <sup>11</sup>  | X     | X      | X       | X       | X       | X       | X       |
| Directed history, concomitant medications, directed physical exam                   | X     | X      | X       | X       | X       | X       | X       |
| Weight data entry to Medidata Rave  |       |        | X       |         |         |         | X       |
| Blood collection  | X     | X      | X       | X       | X       | X       | X       |
| Urine collection for GC/CT testing <sup>9</sup>                                     | X     |        |         | X       |         |         | X       |
| Rectal swab collection for GC/CT testing <sup>2, 9</sup>                            | X     |        |         | X       |         |         | X       |
| Injection   | X     | X      | X       | X       | X       | X       | X       |
| ISR evaluation <sup>10</sup>  | X     | X      | X       | X       | X       | X       | X       |
| HIV testing <sup>3</sup>  | X     | X      | X       | X       | X       | X       | X       |
| HCV testing <sup>4</sup>  |       |        |         |         |         |         | X       |
| Chemistry testing <sup>5</sup> (creatinine only)                                    | X     |        |         | X       |         |         | X       |
| Liver function tests <sup>6</sup> (AST, ALT, total bilirubin, alkaline phosphatase) | X     |        |         | X       |         |         | X       |
| Syphilis serologic testing <sup>9</sup>   | X     |        |         | X       |         |         | X       |
| Urine GC/CT testing <sup>9</sup>  | X     |        |         | X       |         |         | X       |
| Rectal swab GC/CT testing <sup>9</sup>  | X     |        |         | X       |         |         | X       |
| Plasma storage <sup>7</sup>   | X     | X      | X       | X       | X       | X       | X       |

## FOOTNOTES FOR TABLE 9

\*Participants in Step 4c who no longer wish to continue receiving cabotegravir injections before Week 48 occurs will move to Step 5. The timeline for Step 5 Day 0 begins 8 weeks after a participant's last injection and continues whether a participant attends visits or not.

Participants who completed Step 4c under Version 4.0 and moved to Step 5 have the option under Version 5.0 to finish Step 5 or start Step 6 if CAB is not yet approved and locally available.

Participants who complete Step 4c under Version 5.0 and want to continue CAB will move from Step 4c to Step 6 if CAB is not yet approved and locally available.

Participants who complete Step 4c under Version 5.0 but do not want to or cannot continue CAB in Step 6 are not eligible to enter Step 5 and will be terminated from the study and referred to local PrEP services.

<sup>1</sup> For participants who transition from Step 4b or Step 5 and completed these procedures in Steps 4a, 4b, or 5 do not repeat upon entry to Step 4c.

<sup>2</sup> If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

<sup>3</sup> The HIV testing algorithm is provided in [Figure 10](#) below and Appendix VIII of the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.

<sup>4</sup> Testing does not need to be repeated if infection was documented at a prior visit. HCV Ab testing is required.

<sup>5</sup> The only required chemistry test is creatinine. If it was performed during Step 4a or 4b, do not perform at Day 0 of Step 4c.

<sup>6</sup> Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.

<sup>7</sup> Blood collected for plasma storage must be collected prior to injection.

<sup>8</sup> Refer to instructions in the interviewer-administered and CASI assessments as well as the Schedule of Forms for whom and when these assessments should be administered.

<sup>9</sup> Perform testing at Day 0 if not done within the last 6 months; perform testing at all other visits as noted

<sup>10</sup> An ISR typically begins 24-48 hours after an injection. The "X" marked in each visit box pertains to reporting an ISR if a participant experiences signs and symptoms of one (e.g., pain, redness, swelling, etc.) as a result of the injection that occurred at that visit at any point later that day and onward (as reported by the participant). A participant may follow-up with the site before their next visit to report that they have experienced an ISR or they may report it at their next visit. Sites need not actively solicit this information from participants, either in-person or remotely. Should ISR symptoms be reported by the participant, it should be reported as an ISR for the visit at which that injection occurred. If an ISR is reported, use the Injection Site Reaction eCRF. As a reminder, symptoms experienced immediately at the time of an injection are NOT considered ISRs. No ISR assessment is required at the visit at which the injection is provided.

<sup>11</sup> Adherence counseling at Week 48 should be tailored to each participant. A participant who wants to continue CAB injections either in Step 6 or through local PrEP services should be reminded of the importance of receiving their next injection within 8 weeks of Week 48. A participant who does not want to continue CAB injections should be told where they can go locally for other PrEP services and reminded of the importance of doing so within 8 weeks of Week 48.

**Table 10: STEP 5 Schedule of Procedures and Evaluations – Open Label Daily Oral TDF/FTC**

| Procedures*   | Day 0 | *Weeks 12, 36 (60, 84, 108, 132, if required) | *Week 24, 48 (72, 96, 120, 144, if required) |
|---|-------|---|--|
| Informed consent/ "Choice" discussion <sup>9</sup>                                  | X     |   |  |
| Interviewer-administered Product Choice assessment <sup>9</sup>                     | X     |   |  |
| Locator information   | X     | X   | X  |
| HIV counseling  | X     | X   | X  |
| Offer condoms and lubricant   | X     | X   | X  |
| Interviewer-administered assessment (SMSQ) <sup>8</sup>                             | X     |   | X  |
| CASI-administered assessment (behavioral assessment) <sup>8</sup>                   | X     |   | X  |
| Adherence counseling <sup>7</sup>   | X     | X   | X  |
| Directed history, concomitant medications, directed physical exam                   | X     | X   | X  |
| Weight for entry to Medidata Rave   | X     | X   | X  |
| Blood collection  | X     | X   | X  |
| Urine collection for GC/CT testing and urinalysis <sup>1</sup>                      | X     |   | X  |
| Rectal swab collection for GC/CT testing <sup>1, 2</sup>                            | X     |   | X  |
| Dispense pills  | X     | X   | X  |
| HIV testing <sup>3</sup>  | X     | X   | X  |
| Chemistry testing <sup>4</sup> (creatinine only)                                    | X     |   | X  |
| Liver function tests <sup>5</sup> (AST, ALT, total bilirubin, alkaline phosphatase) | X     |   | X  |
| Urinalysis  | X     |   | X  |
| Syphilis serologic testing <sup>1</sup>   | X     |   | X  |
| Urine GC/CT testing <sup>1</sup>  | X     |   | X  |
| Rectal swab GC/CT testing <sup>1</sup>  | X     |   | X  |
| HCV <sup>6</sup>  |       |   | X  |
| Plasma storage  | X     | X   | X  |
| DBS   | X     | X   | X  |

**FOOTNOTES FOR TABLE 10:**

\* Participants originally randomized to TDF/FTC who choose to continue TDF/FTC will be followed in this step for three years from the time of enrollment. Contact the CMC for guidance for participants originally randomized to TDF/FTC who have been missing to follow-up and wish to continue TDF/FTC on Step 5.

Participants originally randomized to CAB who choose to initiate TDF/FTC, as well as participants who no longer want to or cannot continue CAB injections before Week 48 of Step 4c occurs will be followed for approximately one year since their last injection. The timeline for Day 0 begins 8 weeks after a participant's last injection, even if the participant does not report to the Day 0 visit (or the Week 12 visit, etc.). The timeline for Step 5 continues whether a participant attends visits or not. Participants who completed Step 4c under Version 4.0 and moved to Step 5 have the option under Version 5.0 to finish Step 5 or start Step 6 if CAB is not yet approved and locally available.

Participants who complete Week 48 of Step 4c under Version 5.0 are not eligible to enter Step 5 and will either enter Step 6 to continue CAB or be terminated from the study and referred to local PrEP services.

<sup>1</sup> Perform testing at Day 0 if not done within the last 6 months: perform testing at all other visits as noted.

<sup>2</sup> If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

<sup>3</sup> The HIV testing algorithm is provided in [Figure 10](#) below and Appendix VIII of the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.

<sup>4</sup> The only required chemistry test is creatinine. If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.

<sup>5</sup> Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase. If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.

<sup>6</sup> Testing does not need to be repeated if infection was documented at a prior visit. HCV Ab testing is required.

<sup>7</sup> Adherence counseling is not conducted during a participant's final visit of Step 5

<sup>8</sup> Refer to instructions in the interviewer-administered and CASI assessments as well as the Schedule of Forms for whom and when these assessments should be administered.

<sup>9</sup> For participants who transition from Step 4 and completed these procedures in Step 4, do not repeat upon entry to Step 5.

**Table 11: STEP 6 Schedule of Procedures and Evaluations – Cabotegravir Injections – Weeks 56 - 96**

| Procedures  | WEEK 56 | WEEK 64 | WEEK 72 | WEEK 80 | WEEK 88 | WEEK 96 |
|---|---------|---------|---------|---------|---------|---------|
| <b>Informed consent<sup>1</sup></b>   | [X]     |         |         |         |         |         |
| <b>Locator Information</b>  | X       | X       | X       | X       | X       | X       |
| <b>HIV counseling</b>   | X       | X       | X       | X       | X       | X       |
| <b>Condoms and lubricant</b>  | X       | X       | X       | X       | X       | X       |
| <b>Adherence counseling<sup>11</sup></b>  | X       | X       | X       | X       | X       | X       |
| <b>Directed history, concomitant medications, directed physical exam</b>                  | X       | X       | X       | X       | X       | X       |
| <b>Weight data entry to Medidata Rave</b>   |         |         | X       |         |         | X       |
| <b>Blood collection</b>   | X       | X       | X       | X       | X       | X       |
| <b>Urine collection for GC/CT testing<sup>9</sup></b>                                     | X       |         | X       |         |         | X       |
| <b>Rectal swab collection for GC/CT testing<sup>2,9</sup></b>                             | X       |         | X       |         |         | X       |
| <b>Injection</b>  | X       | X       | X       | X       | X       | X       |
| <b>ISR evaluation<sup>10</sup></b>  | X       | X       | X       | X       | X       | X       |
| <b>HIV testing<sup>3</sup></b>  | X       | X       | X       | X       | X       | X       |
| <b>HCV testing<sup>4</sup></b>  |         |         |         |         |         | X       |
| <b>Chemistry testing<sup>5</sup> (creatinine only)</b>                                    |         |         |         |         |         | X       |
| <b>Liver function tests<sup>6</sup> (AST, ALT, total bilirubin, alkaline phosphatase)</b> |         |         | X       |         |         | X       |
| <b>Syphilis serologic testing<sup>9</sup></b>   | X       |         | X       |         |         | X       |
| <b>Urine GC/CT testing<sup>9</sup></b>  | X       |         | X       |         |         | X       |
| <b>Rectal swab GC/CT testing<sup>9</sup></b>  | X       |         | X       |         |         | X       |
| <b>Plasma storage<sup>7</sup></b>   | X       | X       | X       | X       | X       | X       |

**FOOTNOTES FOR TABLE 11**

<sup>1</sup>IMPORTANT NOTE: A participant should be consented to Version 5.0 at their next visit, and they should continue to be followed under the appropriate Steps contained in Appendix V. The “[X]” listed at Week 56 with a bracket is to signify that consenting to Version 5.0 may or may not occur at that visit but consent to Version 5.0 must occur before any procedures are undertaken for Step 6. If consent to Version 5.0 is obtained in a previous step before entering Step 6, do not repeat at entry to Step 6.

<sup>2</sup> If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

<sup>3</sup> The HIV testing algorithm is provided in [Figure 10](#) below and Appendix VIII of the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.

<sup>4</sup> Testing does not need to be repeated if infection was documented at a prior visit. HCV Ab testing is required.

<sup>5</sup> The only required chemistry test is creatinine.

<sup>6</sup> Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.

<sup>7</sup> Blood collected for plasma storage must be collected prior to injection.

<sup>9</sup> Perform testing at Week 56 if not done within the last 6 months; perform testing at all other visits as noted.

<sup>10</sup> Only report on an eCRF during Weeks 56 – 96 an ISR that meets the definition of an SAE (all others should still be documented in source documents). An ISR typically begins 24-48 hours after an injection. The “X” marked in each visit box pertains to reporting an ISR if a participant experiences signs and symptoms of one (e.g., pain, redness, swelling, etc.) as a result of the injection that occurred at that visit at any point later that day and onward (as reported by the participant). A



participant may follow-up with the site before their next visit to report that they have experienced an ISR or they may report it at their next visit. Sites need not actively solicit this information from participants, either in-person or remotely. Should ISR symptoms be reported by the participant, it should be reported as an ISR for the visit at which that injection occurred. If an ISR is reported, use the Injection Site Reaction eCRF. As a reminder, symptoms experienced immediately at the time of an injection are NOT considered ISRs. No ISR assessment is required at the visit at which the injection is provided.

<sup>11</sup> Adherence counseling at final visit of Step 6 should be tailored to each participant and include a reminder of the importance of receiving their next CAB injection or other PrEP through local services within 8 weeks of last injection. A participant's final visit in Step 6 may occur before Week 96 if CAB is approved and available locally, or if a participant does not want to or cannot continue receiving CAB injections.

**Table 12: Schedule of Procedures and Evaluations – For Participants Who Are Not Continuing Under the OLE**

| <b>Procedures</b>  | <b>DAY 0</b> |
|--|--------------|
| <b>Informed consent/ New information discussion</b>            | X            |
| <b>Locator Information</b>                                     | X            |
| <b>HIV counseling</b>  | X            |
| <b>Offer condoms and lubricant</b>                             | X            |
| <b>Blood collection</b>  | X            |
| <b>Urine collection for GC/CT testing<sup>1</sup></b>          | X            |
| <b>Rectal swab collection for GC/CT testing<sup>1, 2</sup></b> | X            |
| <b>HIV testing<sup>3</sup></b>                                 | X            |
| <b>Syphilis serologic testing<sup>1</sup></b>                  | X            |
| <b>Urine GC/CT testing<sup>1</sup></b>                         | X            |
| <b>Rectal swab GC/CT testing<sup>1</sup></b>                   | X            |
| <b>Plasma storage</b>  | X            |
| <b>DBS Storage</b>   | X            |

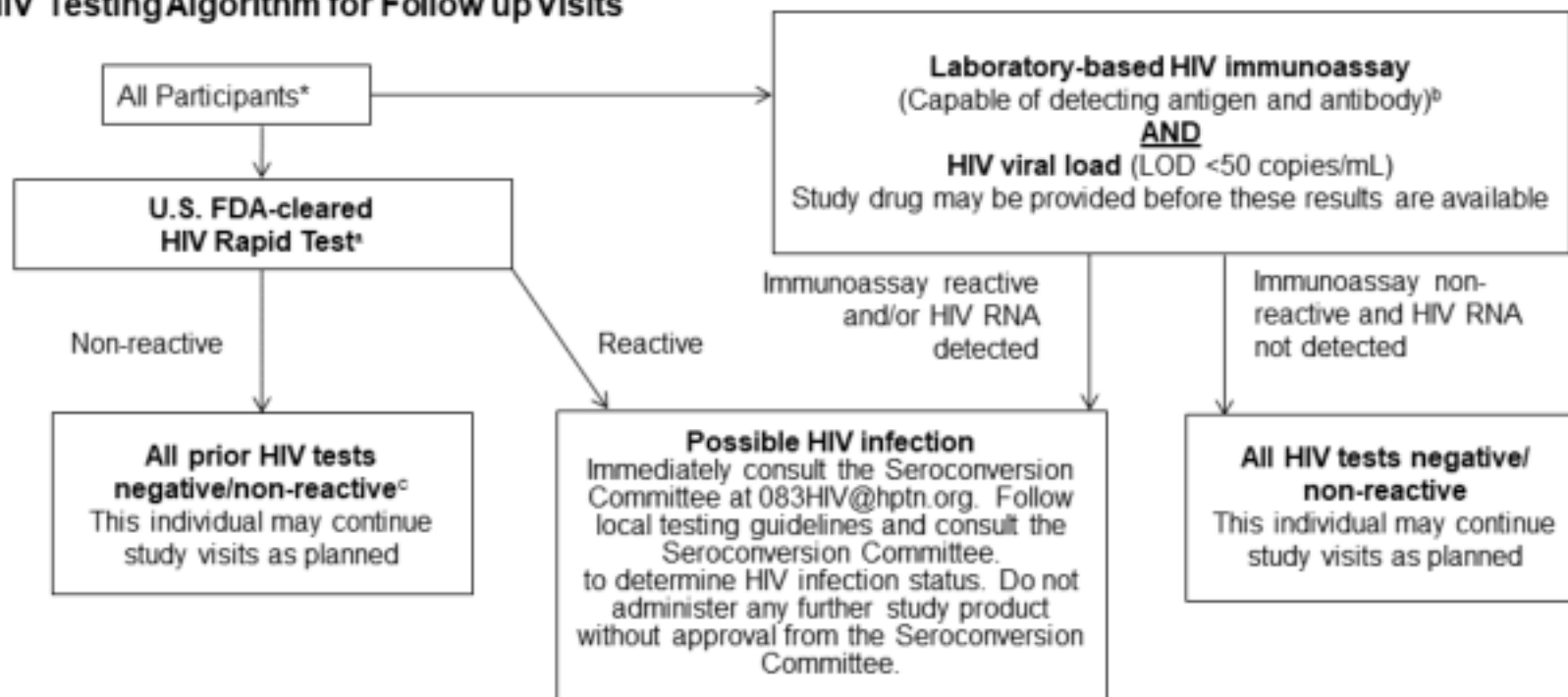
<sup>1</sup> Perform testing at Day 0 if not done within the last 6 months

<sup>2</sup> If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

<sup>3</sup> The HIV testing algorithm is provided in [Figure 10](#) below and Appendix VIII of the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.

Figure 10: HIV Testing Algorithm for Follow up Visits:

### HIV Testing Algorithm for Follow up Visits



#### NOTES:

<sup>a</sup> If acute HIV infection is suspected, do not administer any further study product. Immediately consult the Seroconversion Committee. In addition to following the algorithm above, the site should send a sample for an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should use an assay that is FDA-cleared for early HIV diagnosis, such as the APTIMA HIV-1 RNA Qualitative Assay. The site should contact the Seroconversion Committee (083HIV@hptn.org) for additional guidance once all of the test results from this visit (including the HIV RNA test) are available.

<sup>a</sup> Sites that are not able to obtain HIV rapid test kits that are cleared by the US FDA may seek approval from the HPTN LC to use an alternate kit.

<sup>b</sup> This testing must be performed using a laboratory based, non-rapid HIV immunoassay that detects both HIV antigen and HIV antibody (either a 4<sup>th</sup> generation or 5<sup>th</sup> generation assay).

<sup>c</sup> At any visit where study product will be given, the site must ensure that the HIV rapid test from this visit, and all HIV results from prior study visits are negative or non-reactive.

**Table 13: Schedule for Additional Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result (including HIV Confirmation Visit)**

Note 1: The procedures listed for the HIV Confirmation Visit apply to all participants who have a reactive or positive HIV test during Steps 4-6, or at their final study visit if not continuing participation under the OLE. Participants who have a positive or reactive HIV test during Steps 4b and 4c, Step 5, or at their final visit if not continuing in the OLE and have ever received an active CAB injection at any time during previous study conduct, will be followed according to Table 13 - Schedule for Additional Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result. Participants who have a positive or reactive HIV test during Step 4a, Step 5, or their final visit if not continuing in the OLE and have received only oral TDF/FTC and/or oral CAB but never an active CAB injection will be referred to local care. The procedures listed for Weeks 12, 24, 36, and 48 apply to participants with confirmed HIV infection during Steps 4b and 4c of the study. Participants with confirmed HIV infection in Step 5 of the study may undergo similar procedures as listed in Weeks 12, 24, 36, and 48, and will be determined by the members of 083CMC@hptn.org. Participants in Step 6 who have a reactive or positive HIV test will only undergo the procedures in the HIV Confirmation Visit. Participants with confirmed HIV infection in Step 4a and Step 6 will be terminated from the study and referred to local care.

Note 2: Procedures for discordant or discrepant HIV test results are outlined in the SSP.

|   | HIV Confirmation Visit | Week 12 | Week 24 | Week 36 | Week 48 <sup>7</sup> |
|---|------------------------|---------|---------|---------|----------------------|
| <b>ADMINISTRATIVE, BEHAVIORAL, REGULATORY</b> |                        |         |         |         |                      |
| Locator information                           | X                      | X       | X       | X       | X                    |
| Offer condoms and lubricant                   | X                      | X       | X       | X       | X                    |
| HIV counseling                                | X                      |         |         |         |                      |
| <b>CLINICAL EVALUATIONS AND PROCEDURES</b>    |                        |         |         |         |                      |
| History, con meds, physical exam              | X                      | X       | X       | X       | X                    |
| Blood collection                              | X                      | X       | X       | X       | X                    |
| <b>LOCAL LABORATORY EVALUATIONS</b>           |                        |         |         |         |                      |
| HIV testing <sup>1</sup>                      | X                      |         |         |         |                      |
| CD4 cell count                                | X                      |         | X       |         | X                    |
| HIV viral load testing                        | X                      |         | X       |         | X                    |
| HIV resistance testing <sup>2</sup>           | X                      |         |         |         |                      |
| Chemistry testing <sup>3</sup>                |                        |         | X       |         | X                    |
| Liver function testing <sup>4</sup>           |                        |         | X       |         | X                    |
| Plasma storage <sup>5</sup>                   | X                      | X       | X       | X       | X                    |
| DBS storage <sup>6</sup>                      | X                      |         |         |         |                      |

<sup>1</sup> The HIV confirmation visit procedures, sample collection, and testing are to be performed on a different day from day of sample collection where the participant had an initial reactive/positive HIV test result. Procedures for the HIV Confirmation Visit are 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.

<sup>2</sup> Sites will collect specimens for resistance testing at a local laboratory to assist with clinical management; results from resistance testing performed at local laboratories will not be reported to the SDMC. Stored plasma cannot be used for real-time/local resistance testing.

<sup>3</sup> The only required chemistry test is creatinine.

<sup>4</sup> Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.

<sup>5</sup> Stored plasma will be used for Quality Assurance testing at the HPTN LC and for other assessments described in the SSP. Assessments will be performed retrospectively; results will not be returned to study sites or participants.

<sup>6</sup> Stored DBS will be used for pharmacokinetic assessments. Assessments will be performed retrospectively; results will not be returned to study sites or participants.

<sup>7</sup> The Week 48 visit should be timed as closely as possible to 52 weeks after the participant received their last injection.

## E. 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. 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.

The following general guidance refers to all AEs except for ALT, creatinine clearance (absolute and change from baseline), and CPK. Refer to the tables below for specific guidance about these laboratory abnormalities.

### Grade 1 or 2

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

### Grade 3

Any grade 3 or higher clinical or laboratory AE observed prior to their first injection of active CAB (i.e. in STEP 4a) will prompt consultation with the CMC prior to any injectable dosing.

At any time, 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 general, 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  $\leq$  Grade 2 cannot be documented within 4 weeks of receipt of the initial result. If study product is resumed after holding for a Grade 3 AE and the same Grade 3 AE recurs without alternative explanation, study product should be permanently discontinued. For Grade 3 AEs deemed unrelated to study product, study product may continue with appropriate clinical management by the site, per local standards of care.

### Grade 4

Any grade 4 or higher clinical or laboratory AE observed prior to first injection (i.e. in STEP 4a) will prompt permanent study product discontinuation. Participants who develop a Grade 4 AE or toxicity that is not specifically addressed below (regardless of relationship to study product) should have the study product temporarily discontinued. Study product use will not be resumed (i.e. product hold will be permanent) if the Grade 4 AE is considered by the IoR to be related to study product use. If 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, unless an alternative explanation for the recurrence is clearly documented.

## 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

Participants in Step 4c 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 5.

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 and protocol. Study product use may resume 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 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 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 CAB oral phase (STEP 4a) will be instructed to return all study products as soon as possible.

## Guidance on Toxicity Management for Specified Toxicities:

### Nausea, Vomiting, and Diarrhea

| CONDITION AND SEVERITY                | IMMEDIATE ACTION  | FOLLOW-UP AND MANAGEMENT  |
|---------------------------------------|---|---|
| <b>Nausea, Vomiting, and Diarrhea</b> |   |   |
| 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 $\geq 3$                        | Discontinue study product temporarily                             | Participants with Grade $\geq 3$ 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 $\leq 2$ 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   | STUDY PRODUCT USE | FOLLOW-UP AND MANAGEMENT   |
|--------------------------|-------------------|--|
| <b>ELEVATIONS in ALT</b> |                   |  |
| Grade 3 and higher       |                   | <p><b><u>Oral CAB (Step 4a):</u></b> A Grade 3 or higher ALT abnormality reported at Week 4, regardless of relatedness to the study product, will prohibit a participant from entering the injection phase (Step 4b) of the study, and the participant will be permanently discontinued from the study. All such cases must be reported to the CMC. Prior to discontinuation, participants will be followed every two weeks for ALT assessments until they return to <math>\leq</math> Grade 1. If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up, or return to clinical care.</p>   |
| Grade 3 and higher       |                   | <p><b><u>Injectable CAB (Steps 4b, 4c, and Step 6):</u></b> For Grade 3 and higher ALT, study product will be permanently discontinued. Repeat testing should be performed as soon as possible, and participants should be followed every two weeks until levels are <math>\leq</math> Grade 1. <b>If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up, or in rare cases where alternative etiology has been identified and ALT has resolved to Grade 1 or lower, restart of study product.</b></p> <p>Participants who are permanently discontinued from study product will be transitioned to local clinical care for clinical management and local prevention services and terminated from the study per CMC direction.</p> <p><b><u>Open label TDF/FTC (Step 5):</u></b> Participants will be followed per the Schedule of Procedures and Evaluations for Step 5; for participants who have transitioned to Step 5 from Step 4c, the decision whether it is safe to provide oral TDF/FTC will be made with guidance from the CMC.</p> <p>When Step 5 concludes in these cases, the participant will be referred to local prevention services. Note that Step 5 concludes at Week 48 for all participants transitioning from Step 4c.</p> |

### **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, however incident HBV infection may occur and should be considered in cases of otherwise unexplained 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, as well as autoimmune and toxin-mediated conditions. A standardized work-up will be recommended by the CMC in such cases.

## Guidance on Toxicity Management for Specified Toxicities:

### Creatinine Clearance, only applicable to TDF/FTC recipients

**Changes in creatinine clearance, in CAB recipients should be managed per clinical standards of care, unless attributed by the IoR to SP, in which case the below toxicity management guidelines should apply.**

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

| CONDITION AND SEVERITY          | 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 for adjudication and recommendation for further testing and follow-up.   |
| Confirmed CrCl < 60 mL/min      | Permanently discontinue study product | If the calculated creatinine clearance is confirmed to be <60 mL/min, the 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:**

### **Guidance for Injection Site Reactions (ISRs)**

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. Recommended interventions include:

- Pre-treatment (prior to injection administration) warm compresses
- Topical or oral pre-treatment with NSAID preparations, unless contraindicated
- Immediate post-injection massage to injection location
- Post-treatment warm or cold compresses
- Post-treatment NSAID or other analgesic preparations, topically or orally

A proactive and comprehensive approach to mitigating ISRs should be undertaken, with premature transition from Step 4c to Step 5 being reserved for refractory cases in extreme circumstances. The CMC should be notified of such transitions.

During Step 6, only ISRs meeting the definition of an SAE or leading to discontinuation of study product will be entered into the database and such participants should be discontinued from the study. No need to contact the CMC in these cases. ISRs that are Grade 3 or higher that do not meet the above criteria do not need to be entered into the database.

### **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  $\geq 3$  allergic reactions that are considered 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.

**F1. Addendum to the Main Sample Informed Consent Form for Category A Sites (Sites That Have Implemented Version 4.0)**

**HPTN 083**

**Original Study Title: 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 5.0

April 28, 2022

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]*

You are currently taking part in the above-named research study.

You were offered to make a choice of being on CAB or TDF/FTC. As a reminder, you chose to do one of the following:

- Stay on CAB if you were already on it
- Stay on TDF/FTC if you were already on it
- Switch to getting CAB if you were on TDF/FTC and it was safe for you to do so
- Switch from CAB to TDF/FTC
- Receive CAB if you were on the annual visit schedule and it was safe for you to start CAB again or to start it for the first time
- If you are HIV infected and you had been coming to this clinic already for a visit every 3 months, completing the remainder of these visits for a total of a year.
- If there was another status that is not listed here, we will discuss it with you.

Since the time you made your choice, the United States Food and Drug Administration approved the use of CAB for prevention of HIV in December 2021. That means that participants in this study in the United States will soon be able to get CAB shots outside of this study and at a local provider.

ViiV Healthcare, the drug company that makes cabotegravir, has also applied for approval of CAB for HIV prevention in each country where this study is taking place. That means that CAB shots will also become available in [*non-US sites to insert name of country here*] outside of this study.

Since CAB shots are or will become available at local providers in these countries, we need to work on completing this study and moving you to local prevention or clinical care, which may include access to CAB.

Also, we previously told participants that they could change their mind and choose the other study medication (CAB or TDF/FTC) one time at any point during this part of the study. Now that CAB is or will soon be available outside of the study, we need to work on completing this study. Therefore, we will allow you to change your mind only during the first 6 months after you started on this part of the study. We will tell you if you are already beyond this point.

### **Your participation is voluntary**

This consent form gives information about the process for moving you off the study and into local prevention or clinical care, which may include access to CAB. We also provide some new information about CAB in this consent form.

Once you understand the process, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep. Your continued participation in this study is voluntary. If you decide not to take part, you will not lose any of the benefits to which you are otherwise entitled. You may decide to not take part in the next part of the study now or at any time without a loss of benefits to which you are otherwise entitled. [*Instruction to sites: Include in your site-specific consent form any update to the participant reimbursement or any other relevant site-specific updates*]

You may also participate in COVID-19 vaccine or treatment studies while on this part of the study.

### **Process for Transition Off of the Study**

#### **If you are getting CAB now in Step 4:**

- You will continue to get CAB pills (if you opted to) and shots until you complete the schedule for Steps 4a (if you opted to), 4b, and Step 4c. You also may have already completed the schedule of CAB shots in Step 4c. If so, you may have moved to TDF/FTC in Step 5 until you can get CAB shots again either through this study or at a local provider. These Steps have been explained to you before. Let us know if you want to go over them again.
- Once your current schedule of CAB shots ends or if it has already ended (Week 48 of Step 4c), we will work closely with you to move you off the study and to a local provider where you can keep getting CAB shots. While we do this, you can continue to get CAB shots every 8 weeks through this study for up to another year in a new Step 6. However, our priority will be to move you to a local provider as soon as possible.

- We told you before that if you stop getting shots after Step 4b or before the end of Step 4c for any reason other than getting HIV infection that you will move to Step 5. If you complete Week 48 of Step 4c, you will not move to Step 5 – you will have the option to continue CAB injections in Step 6 or be terminated from the study and referred to local PrEP services.
- We told you before that if you are in Step 4b or Step 4c and get HIV infection that you will stop getting CAB shots, be followed every three months for a year, and be referred for HIV clinical care.
- Step 6 is different: If you stop getting CAB shots in Step 6 for any reason, your participation in the study will end and we will refer you to local HIV prevention or clinical services. This is because Step 6 is being added only to allow participants who can continue CAB shots to do so while we move them off the study and to a local provider.
- We will continue to test you for sexually transmitted infections during Step 6.
- Step 6 has fewer procedures than Step 4c. We will review this with you.
- If you complete Week 48 of Step 4c and no longer wish to or cannot continue CAB shots, your participation in the study will end and we will refer you to local HIV prevention or clinical services. You will not have the option to enter Step 5.

**If you are on oral TDF/FTC in Step 5:**

- We told you before that at the time you made your choice to continue in the study and you chose to continue or switch to TDF/FTC, that you will complete your follow-up visits under Step 5 until three years from the time of enrollment. If you were originally randomized to TDF/FTC and have reached three years from enrollment, you cannot continue TDF/FTC in this part of the study. Then your participation in the study will end and we will refer you to local HIV prevention services.
- If you were getting CAB shots and chose to or had to switch to TDF/FTC before finishing Step 4c, you will be followed for one year since your last CAB injection. Once that happens, your participation in the study will end and we will refer you to local HIV prevention services.
- If you were getting CAB shots, have already finished Week 48 of Step 4c, and then moved to Step 5 before the time of this consent, you have the option to finish Step 5 or resume CAB shots in Step 6 if you are healthy and able to do so.
- We will explain the options you can choose and tell you when your time in the study will end.

**If you continue CAB injections in Step 6:**

This is a continuation of Step 4c and will last for up to an additional year of shots only if you wish to keep getting them (Weeks 56 up to 96) and CAB is not yet approved or available in your local area. The main reason for this Step is to allow time for you and the site staff to help you get shots at a local provider once CAB is approved for PrEP in your country or if approved, available in your area. You will no longer be in this study once you start getting shots at a local clinic, which may happen before Week

96. If you stop getting the shots while in this Step, you will be terminated from the study and told where you can go for other HIV prevention services.

#### REASONS YOU MAY HAVE TO STOP TAKING STUDY PRODUCT

There are some reasons you may have to stop taking study product:

- You experience a side effect and it is no longer safe for you to take it
- The doctor in charge of the study at this site determines that it is not safe for you to take it
- You complete the full course of taking the study product during this part of the study
- You get HIV infection

#### **Steps and Procedures**

We will review the Steps below with you and answer any questions you may have.

There may be special circumstances where your time in the study may be different (shorter or longer) from what is outlined in this consent form to ensure your safety. We will tell you if this happens and how long you will be followed.



*[Note to Category A sites: Sites where all participants are beyond their six-month window to change product choice may delete Step 4a]*

**STEP 4a: Schedule of Procedures and Evaluations – Daily Oral Cabotegravir – OPTIONAL if you start CAB for the first time**

| Procedures   | DAY 0 | WEEK 4 |
|--|-------|--------|
| Confirm where you live and how to contact you  | X     | X      |
| Talk with you about HIV and ways to protect yourself from getting it   | X     | X      |
| Offer you condoms and lubricant  | X     | X      |
| Ask you questions about your opinions of taking pills and getting injections   | X     |        |
| Ask you questions about your sexual behavior   | X     |        |
| Talk with you about ways to help you take your pills   | X     | X      |
| Ask you to count the total number of pills you took  |       | X      |
| Give you a brief physical exam, to include measuring your weight, blood pressure, pulse, and ask you if you have experienced any side effects from the study drugs, and ask you about any other medicines you are taking | X     | X      |
| Collect ~XX mL (about x teaspoons) of blood for HIV testing, syphilis testing (Day 0 only)*, to check your general health, the health of your liver and kidneys, and for storage   | X     | X      |
| Perform a swab of your rectum and collect urine for gonorrhea and chlamydia testing*   | X     |        |
| Give you study pills, explain how to take them and any side effects they may cause   | X     |        |

\* Syphilis, gonorrhea, and chlamydia testing will be done at Day 0 if you have not had this testing in the past 6 months of the study, or at any visit if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections.

*[Note to Category A sites: Sites where all participants are beyond their six-month window to change product choice may delete Step 4b]*

**STEP 4b: Schedule of Procedures and Evaluations – Loading Dose Cabotegravir Injection – If you are initiating or restarting CAB injections**

| Procedures  | DAY 0 |
|---|-------|
| Confirm where you live and how to contact you   | X     |
| Talk with you about HIV and ways to protect yourself from getting it  | X     |
| Offer you condoms and lubricant   | X     |
| Ask you questions about your opinions of taking pills and getting injections  | X     |
| Ask you to answer questions about your sexual behavior  | X     |
| Discuss with you any challenges of attending your injection visits and getting shots  | X     |
| Give you a brief physical exam, to include measuring your weight, blood pressure, pulse, and ask you if you have experienced any side effects from the study drug, and ask you about any other medicines you are taking | X     |
| Collect ~XX mL (about x teaspoons) of blood for HIV testing, syphilis testing*, to check your general health, the health of your liver and kidneys, and for storage   | X     |
| Perform a swab of your rectum and collect urine for gonorrhea and chlamydia testing*  | X     |
| Administer the first shot in your buttocks  | X     |

\* Syphilis, gonorrhea, and chlamydia testing will be done at Day 0 if you have not had this testing in the past 6 months of the study, or if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections.

#### STEP 4c: Schedule of Procedures and Evaluations – Cabotegravir Injections

| Procedures  | DAY 0 | WEEK 8 | WEEK 16 | WEEK 24 | WEEK 32 | WEEK 40 | WEEK 48 |
|---|-------|--------|---------|---------|---------|---------|---------|
| Confirm where you live and how to contact you   | X     | X      | X       | X       | X       | X       | X       |
| Talk with you about HIV and ways to protect yourself from getting it  | X     | X      | X       | X       | X       | X       | X       |
| Offer you condoms and lubricant   | X     | X      | X       | X       | X       | X       | X       |
| Ask you questions about how you feel about getting injections   | X     |        | X       |         |         |         | X       |
| Ask you to answer questions about your sexual behavior  | X     |        | X       |         |         |         | X       |
| Discuss with you any challenges of attending your injection visits and getting shots <sup>1</sup>   | X     | X      | X       | X       | X       | X       | X       |
| Give you a brief physical exam, to include measuring your weight, blood pressure, pulse. Ask you if you have experienced any side effects from the shots you received, and ask you about any other medicines you are taking   | X     | X      | X       | X       | X       | X       | X       |
| Collect ~XX mL (about x teaspoons) of blood for HIV testing (every visit); to check your general health and the health of your liver and kidneys (Week 0, 24 and 48 only); for storage (every visit); HCV testing (Week 48 only); and Syphilis testing (Day 0*, Weeks 24 and 48 only) | X     | X      | X       | X       | X       | X       | X       |
| Perform a swab of your rectum and collect urine to test for gonorrhea and chlamydia*  | X     |        |         | X       |         |         | X       |
| Give you a shot in the buttocks   | X     | X      | X       | X       | X       | X       | X       |

<sup>1</sup> We will talk with you about how important it is to stay on schedule for your PrEP appointments.

\* Syphilis, gonorrhea, and chlamydia testing will be done at Day 0 if you have not had this testing in the past 6 months of the study, or at any visit if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections.

**STEP 5: Schedule of Procedures and Evaluations – Open Label Daily Oral TDF/FTC - If you are staying on or switching to TDF/FTC**

| Procedures   | Day 0 | Weeks 12, 36 (60, 84, 108, 132, if required) | Week 24, 48 (72, 96, 120, 144, if required) |
|--|-------|--|---|
| Confirm where you live and how to contact you  | X     | X  | X   |
| Talk with you about HIV and ways to protect yourself from getting it   | X     | X  | X   |
| Offer you condoms and lubricant  | X     | X  | X   |
| Ask you questions about getting the injections and taking the study pills  | X     |  | X   |
| Ask you to answer questions about your sexual behavior   | X     |  | X   |
| Discuss with you any challenges of taking a pill every day (except at your final visit)  | X     | X  | X   |
| Give you a brief physical exam, to include measuring your weight, blood pressure, pulse, and ask you about any other medicines you are taking  | X     | X  | X   |
| Collect ~XX mL (about x teaspoons) of blood for HIV testing (every visit); syphilis testing (Day 0*, then every 6 months only); to check your general health and the health of your liver and kidneys (Day 0, then every 6 months only); the amount of the study drug in your blood, and for storage (every visit) | X     | X  | X   |
| Perform a swab of your rectum; collect urine for urinalysis and gonorrhea and chlamydia testing*   | X     |  | X   |
| Give you your study pills, and explain how to take them, and any side effects they may cause   | X     | X  | X   |

\* Syphilis, gonorrhea, and chlamydia testing will be done at Day 0 if you have not had this testing in the past 6 months of the study, or at any visit if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections.

## STEP 6: Schedule of Procedures and Evaluations – Cabotegravir Injections – Weeks 56 – 96

| Procedures  | WEEK 56 | WEEK 64 | WEEK 72 | WEEK 80 | WEEK 88 | WEEK 96 |
|---|---------|---------|---------|---------|---------|---------|
| Confirm where you live and how to contact you   | X       | X       | X       | X       | X       | X       |
| Talk with you about HIV and ways to protect yourself from getting it  | X       | X       | X       | X       | X       | X       |
| Offer you condoms and lubricant   | X       | X       | X       | X       | X       | X       |
| Discuss with you any challenges of attending your injection visits and getting shots <sup>1</sup>   | X       | X       | X       | X       | X       | X       |
| Give you a brief physical exam, to include measuring your weight, blood pressure, and pulse. Ask you if you have experienced any side effects from the shots you received, and ask you about any other medicines you are taking   | X       | X       | X       | X       | X       | X       |
| Collect ~XX mL (about x teaspoons) of blood for HIV testing (every visit); to check your general health and the health of your liver and kidneys (Week 72 and 96 for liver; Week 96 only for kidneys); for storage (every visit); HCV testing (Week 96 only); and Syphilis testing (Week 56*, Weeks 72 and 96 only) | X       | X       | X       | X       | X       | X       |
| Perform a swab of your rectum and collect urine to test for gonorrhea and chlamydia*  | X       |         | X       |         |         | X       |
| Give you a shot in the buttocks   | X       | X       | X       | X       | X       | X       |

<sup>1</sup> We will talk with you about how important it is to stay on schedule for your PrEP appointments.

\* Syphilis, gonorrhea, and chlamydia testing will be done at Weeks 72 and 96. It will also be done at Week 56 if you have not had this testing in the past 6 months before the Week 56 visit, or at any visit if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections.

**If you are not continuing in the study at the time of this consent, we will ask you to do these procedures as your final visit:**

| <b>Procedures</b>  | <b>Day 0</b> |
|--|--------------|
| <b>Confirm where you live and how to contact you</b>   | X            |
| <b>Talk with you about HIV and ways to protect yourself from getting it</b>                        | X            |
| <b>Offer you condoms and lubricant</b>   | X            |
| <b>Collect ~XX mL (about x teaspoons) of blood for HIV testing, syphilis testing*, and storage</b> | X            |
| <b>Perform a swab of your rectum and collect urine for gonorrhea and chlamydia testing*</b>        | X            |

\* Syphilis, gonorrhea, and chlamydia testing will be done at final visit (Day 0) if you have not had this testing in the past 6 months of the study, or if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections.

## IF YOU LEAVE THE STUDY BEFORE YOUR FINAL VISIT:

If you join this part of the study and then leave the study before the last visit of the study schedule, we will ask you to complete a final study visit if you are available to do so. The final study visit will include the requirements for the visit at which it is confirmed you are leaving the study, and you will not receive CAB or TDF/FTC study product at this visit. Also, if you are on TDF/FTC and leave the study prior to your final visit, we will ask you to return any unused study product.

### **New Information about CAB**

We went over the side effects of CAB and TDF/FTC with you when you joined the study. We can go over these again if you want to.

We also went over with you the results from the first part of this study where you did not know whether you were getting real CAB shots or real TDF/FTC.

CAB protected people in this study from getting HIV infection about 66% better than TDF/FTC. The reason for this is that TDF/FTC works best when taken daily. The participants in HPTN 083 for whom TDF/FTC did not work was mostly because it was not being taken as prescribed (that is, it was not being taken every day). Both PrEP regimens work very well to prevent a person from getting HIV if taken as prescribed. In the participants who got HIV while getting CAB, about half of them had some resistance to CAB and likely other drugs like CAB (called integrase inhibitors). Resistance means that the drug, and sometimes other drugs like it, would not work as part of a treatment regimen (“cocktail”) to control the HIV infection. If you get infected with HIV while on CAB, you might need a regimen (“cocktail”) that contains other drugs that are not like CAB to treat the HIV infection. Just over 15% of HIV infections that occurred in participants taking TDF/FTC had resistance to one or both drugs in TDF/FTC as well. Some HIV infections that occurred in participants taking TDF/FTC had resistance to one or both drugs in TDF/FTC as well. If you become HIV infected while taking PrEP it is important to make sure you tell your doctor or provider which PrEP drug you have been taking so that a treatment regimen can be given to you that will be able to control the HIV to undetectable levels.

### **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 5.0**

**April 28, 2022**

*[Insert signature blocks as required by the local IRB:]* If you have read this addendum to the main consent form, or had it read and explained to you, and you understand the information, please initial the one line that applies to you to note that you want to continue in the study, or you no longer want to continue in the study, or you are not eligible to continue in the study. Then sign your name or make your mark below.

\_\_\_\_\_ I voluntarily agree to continue to take part in this portion of the study.

\_\_\_\_\_ I do not agree to take part in this portion of the study, but I do agree to the procedures listed in the table for not continuing in this part of the study.

\_\_\_\_\_ I do not agree to take part in this portion of the study, and I do not agree to the procedures listed in the table for not continuing in this part of the study.

\_\_\_\_\_ I understand I am not eligible to take part in this portion of the study, and I do agree to the procedures listed in the table for not continuing in this part of the study.

\_\_\_\_\_ I understand I am not eligible to take part in this portion of the study, and I do not agree to the procedures listed in the table for not continuing in this part of the study.

\_\_\_\_\_  
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

**F2. Addendum to the Main Sample Informed Consent Form for Category B Sites (Sites That Have Not Implemented Version 4.0)**

**HPTN 083**

**Original Study Title: 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 5.0

April 28, 2022

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]*

You are currently taking part in the above-named research study. You were told about the results of the blinded part of the study after an independent committee determined that participants getting TDF/FTC pills had three times the number of HIV infections than participants getting long-acting cabotegravir shots (real CAB, also called CAB LA). As a reminder, both CAB and TDF/FTC were very good at preventing new HIV infections, and both were safe and well tolerated.

Since that time, the United States Food and Drug Administration approved the use of CAB LA shots for PrEP in December 2021. ViiV Healthcare, the drug company that makes cabotegravir, has asked for approval from all of the other countries where the HPTN 083 study is being done. That means that CAB LA shots will become available in your country outside of this study.

You have been told which medication you are on. We are now able to offer you the following choices if you wish to continue in the next part of the study:

- Stay on CAB if you are already on it
- Stay on TDF/FTC if you are already on it for up to three years from the time of enrollment
- Switch to getting CAB if you are on TDF/FTC and it is safe for you to do so
- Switch from CAB to TDF/FTC
- Receive CAB if you are on the annual visit schedule now and it is deemed safe for you to start CAB again or to start it for the first time

- If you are HIV infected and you have been coming to this clinic already for a visit every 3 months you will complete the remainder of these visits in this next part of the study.
- If there is a scenario that is not described here, we will discuss it with you.

Once you make your choice, you can change your mind once during the first 6 months after you start this part of the study. For example, if you are on TDF/FTC and you are within 3 years from the time of enrollment, you can change your mind and switch to CAB. If you are on CAB and choose to switch to TDF/FTC, then you change your mind and want to switch back to CAB, you may do so only once during the first 6 months after you start this part of the study.

We will tell you how long we will follow you in this part of the study, based on the choice you make. We are doing this part of the study in order to learn more about why people in the study choose CAB or TDF/FTC. For participants who choose CAB, we want to learn more about how it works to prevent getting HIV.

### **Your participation is voluntary**

This consent form gives information about the next part of this study that will be discussed with you. Once you understand the next part, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep. Your continued participation in this research is voluntary. If you decide not to take part, you will not lose any of the benefits to which you are otherwise entitled. You may decide to not take part in the next part of the study now or at any time without a loss of benefits to which you are otherwise entitled. We will also review the information in the main consent form that you already signed again with you, if you would like to do so, and will review with you any changes as related to this next part of the study [*Instruction to sites: Include in your site-specific consent form any update to the participant reimbursement or any other relevant site-specific updates*]

You may also participate in COVID-19 vaccine or treatment studies while on this part of the study.

### **New Steps of the Study**

If you decide to take part in the next part of the study, there are 5 new steps, and you will come in for visits similar to what you have already been doing throughout the study based on your choice of study medication.

#### **IF YOU CHOOSE TO START CAB FOR THE FIRST TIME:**

Step 4a: You will have the **option** of taking CAB pills for 30 days before starting to get shots of CAB. During the blinded part of the study, you may remember that you had to take pills before getting shots. This was because we did not have enough information then about CAB to know if it was safe to start getting shots right away. Based on what we learned in the blinded part of the study, we now know that it is safe. But you may feel more comfortable taking 30 days of CAB pills first to be sure. If you ever had a CAB shot during the blinded part of the study, you cannot restart CAB pills in Step 4a during this part of the study. We will talk with you about this and answer any questions that you have. [Note to

sites: If your IRB/EC requires this step, or if the IoR requires this step, then update this language to make it non-optional].

If you choose to take CAB pills before starting injections and for any reason do not move to Step 4b and 4c, your participation in the study will end and we will refer you to local HIV prevention services.

Step 4b: This is a one-time visit where you will get your first CAB shot.

#### IF YOU CHOOSE TO CONTINUE ON CAB:

Step 4b: If you have been on real CAB but have not been to the clinic in over 15 weeks since your last injection, this is a one-time visit where you will get a CAB shot to get you back on track with getting shots.

Step 4c: These are visits where you will continue to come to the clinic for approximately 1 year to get CAB shots every 8 weeks. The next shot you will get after the one you received in Step 4b will be 4 weeks later, followed by shots every 8 weeks.

Step 5: If you stop getting shots before the end of Step 4c, you will be offered to take TDF/FTC pills for one year in Step 5. If you complete the one year of CAB shots in Step 4c and don't want to continue shots in Step 6, you will not start Step 5 and will instead be referred to local PrEP services and terminated from the study.

Step 6: This is a continuation of Step 4c and will last for up to an additional year of shots (Weeks 56 up to 96) only if you wish to keep getting them and CAB is not yet approved or available in your local area. The main reason for this Step is to allow time for you and the staff at the site to help you get shots at a local provider once CAB is approved for PrEP in your country or if approved, available in your area. You will no longer be in this study once you start getting shots at a local clinic, which may happen before Week 96. If you stop getting the shots while in this Step, you will be terminated from the study and told where you can go for other HIV prevention services.

#### IF YOU CHOOSE TO STAY ON TDF/FTC OR START TDF/FTC:

Step 5: If you have been getting TDF/FTC pills and you choose to continue, or if you have been on CAB and choose to start TDF/FTC, you will come to the clinic for visits every 3 months for 3 years from the time that you enrolled in the study, or for one year since your last injection of CAB, whichever is longer. If you were originally randomized to TDF/FTC and have reached three years from enrollment, you cannot continue TDF/FTC in this part of the study. Then your participation in the study will end and we will refer you to local HIV prevention services. We will tell you when your time in the study will end.

#### IF YOU PREMATURELY STOP GETTING INJECTIONS

If you choose to continue or start receiving CAB shots and have to stop getting them because of a side effect or if you choose to stop getting them during Steps 4b or 4c, we will ask you to move to Step 5 of the study and receive 48 weeks of oral TDF/FTC. You may also experience a side effect that makes taking oral TDF/FTC not safe; if this is the case, you will be asked to move to Step 5 of the study but not receive TDF/FTC so that we can make sure you are healthy. If you stop getting shots in Step 6 for any reason, you will be terminated from the study.

## REASONS YOU MAY HAVE TO STOP TAKING STUDY PRODUCT

There are some reasons you may have to stop taking study product:

- As explained above, you experience a side effect and it is no longer safe for you to take it
- The doctor in charge of the study at this site determines that it is not safe for you to take it
- You complete the full course of taking the study product during this part of the study
- You get HIV infection, which is explained further below

## Steps and Procedures

No matter which new step you start in, we will review the information in this consent form with you and answer any questions you may have. We will discuss which study product you would like to choose and ask you questions about your decision. The new steps also include the procedures listed at each visit marked with an X in Steps 4a, 4b, 4c, 5, and 6 below.

There may be special circumstances where your time in this part of the study may be different (shorter or longer) from what is outlined in this consent form to ensure your safety. We will tell you if this happens and how long you will be followed.

**STEP 4a: Schedule of Procedures and Evaluations – Daily Oral Cabotegravir – OPTIONAL if you choose to start CAB for the first time**

| <b>Procedures</b>   | <b>DAY 0</b> | <b>WEEK 4</b> |
|---|--------------|---------------|
| <b>Confirm where you live and how to contact you</b>  | X            | X             |
| <b>Talk with you about HIV and ways to protect yourself from getting it</b>   | X            | X             |
| <b>Offer you condoms and lubricant</b>  | X            | X             |
| <b>Ask you questions about your opinions of taking pills and getting injections</b>   | X            |               |
| <b>Ask you questions about your sexual behavior</b>   | X            |               |
| <b>Talk with you about ways to help you take your pills</b>   | X            | X             |
| <b>Ask you to count the total number of pills you took</b>  |              | X             |
| <b>Give you a brief physical exam, to include measuring your weight, blood pressure, pulse, and ask you if you have experienced any side effects from the study drugs, and ask you about any other medicines you are taking</b> | X            | X             |
| <b>Collect ~XX mL (about x teaspoons) of blood for HIV testing, syphilis testing (Day 0 only)*, to check your general health, the health of your liver and kidneys, and for storage</b>   | X            | X             |
| <b>Perform a swab of your rectum and collect urine for gonorrhea and chlamydia testing*</b>   | X            |               |
| <b>Give you study pills, explain how to take them and any side effects they may cause</b>   | X            |               |

\* Syphilis, gonorrhea, and chlamydia testing will be done at Day 0 if you have not had this testing in the past 6 months of the study, or at any visit if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections

**STEP 4b: Schedule of Procedures and Evaluations – Loading Dose Cabotegravir Injection – If you are initiating or restarting CAB injections**

| <b>Procedures</b>  | <b>DAY 0</b> |
|--|--------------|
| <b>Confirm where you live and how to contact you</b>   | X            |
| <b>Talk with you about HIV and ways to protect yourself from getting it</b>  | X            |
| <b>Offer you condoms and lubricant</b>   | X            |
| <b>Ask you questions about your opinions of taking pills and getting injections</b>  | X            |
| <b>Ask you to answer questions about your sexual behavior</b>  | X            |
| <b>Discuss with you any challenges of attending your injection visits and getting shots</b>  | X            |
| <b>Give you a brief physical exam, to include measuring your weight, blood pressure, pulse, and ask you if you have experienced any side effects from the study drug, and ask you about any other medicines you are taking</b> | X            |
| <b>Collect ~XX mL (about x teaspoons) of blood for HIV testing, syphilis testing*, to check your general health, the health of your liver and kidneys, and for storage</b>   | X            |
| <b>Perform a swab of your rectum and collect urine for gonorrhea and chlamydia testing*</b>  | X            |
| <b>Administer the first shot in your buttocks</b>  | X            |

\* Syphilis, gonorrhea, and chlamydia testing will be done at Day 0 if you have not had this testing in the past 6 months of the study, or if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections

#### STEP 4c: Schedule of Procedures and Evaluations – Cabotegravir Injections - if you choose to continue CAB injections

| Procedures  | DAY 0 | WEEK 8 | WEEK 16 | WEEK 24 | WEEK 32 | WEEK 40 | WEEK 48 |
|---|-------|--------|---------|---------|---------|---------|---------|
| Confirm where you live and how to contact you   | X     | X      | X       | X       | X       | X       | X       |
| Talk with you about HIV and ways to protect yourself from getting it  | X     | X      | X       | X       | X       | X       | X       |
| Offer you condoms and lubricant   | X     | X      | X       | X       | X       | X       | X       |
| Ask you questions about how you feel about getting injections   | X     |        | X       |         |         |         | X       |
| Ask you to answer questions about your sexual behavior  | X     |        | X       |         |         |         | X       |
| Discuss with you any challenges of attending your injection visits and getting shots <sup>1</sup>   | X     | X      | X       | X       | X       | X       | X       |
| Give you a brief physical exam, to include measuring your weight, blood pressure, pulse. Ask you if you have experienced any side effects from the shots you received, and ask you about any other medicines you are taking   | X     | X      | X       | X       | X       | X       | X       |
| Collect ~XX mL (about x teaspoons) of blood for HIV testing (every visit); to check your general health and the health of your liver and kidneys (Week 0, 24 and 48 only); for storage (every visit); HCV testing (Week 48 only); and Syphilis testing (Day 0*, Weeks 24 and 48 only) | X     | X      | X       | X       | X       | X       | X       |
| Perform a swab of your rectum and collect urine to test for gonorrhea and chlamydia*  | X     |        |         | X       |         |         | X       |
| Give you a shot in the buttocks   | X     | X      | X       | X       | X       | X       | X       |

<sup>1</sup> We will talk with you about how important it is to stay on schedule for your PrEP appointments.

\* Syphilis, gonorrhea, and chlamydia testing will be done at Day 0 if you have not had this testing in the past 6 months of the study, or at any visit if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections.



**STEP 5: Schedule of Procedures and Evaluations – Open Label Daily Oral TDF/FTC - If you choose to stay on or switch to TDF/FTC, or after you complete Step 4c**

| Procedures   | Day 0 | Weeks 12, 36 (60, 84, 108, 132, if required) | Week 24, 48 (72, 96, 120, 144, if required) |
|--|-------|--|---|
| Confirm where you live and how to contact you  | X     | X  | X   |
| Talk with you about HIV and ways to protect yourself from getting it   | X     | X  | X   |
| Offer you condoms and lubricant  | X     | X  | X   |
| Ask you questions about getting the injections and taking the study pills  | X     |  | X   |
| Ask you to answer questions about your sexual behavior   | X     |  | X   |
| Discuss with you any challenges of taking a pill every day (except at your final visit)  | X     | X  | X   |
| Give you a brief physical exam, to include measuring your weight, blood pressure, pulse, and ask you about any other medicines you are taking  | X     | X  | X   |
| Collect ~XX mL (about x teaspoons) of blood for HIV testing (every visit); syphilis testing (Day 0*, then every 6 months only); to check your general health and the health of your liver and kidneys (Day 0, then every 6 months only); the amount of the study drug in your blood, and for storage (every visit) | X     | X  | X   |
| Perform a swab of your rectum; collect urine for urinalysis and gonorrhea and chlamydia testing*   | X     |  | X   |
| Give you your study pills, and explain how to take them, and any side effects they may cause   | X     | X  | X   |

\* Syphilis, gonorrhea, and chlamydia testing will be done at Day 0 if you have not had this testing in the past 6 months of the study, or at any visit if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections.

## STEP 6: Schedule of Procedures and Evaluations – Cabotegravir Injections – Weeks 56 – 96

| Procedures  | WEEK 56 | WEEK 64 | WEEK 72 | WEEK 80 | WEEK 88 | WEEK 96 |
|---|---------|---------|---------|---------|---------|---------|
| Confirm where you live and how to contact you   | X       | X       | X       | X       | X       | X       |
| Talk with you about HIV and ways to protect yourself from getting it  | X       | X       | X       | X       | X       | X       |
| Offer you condoms and lubricant   | X       | X       | X       | X       | X       | X       |
| Discuss with you any challenges of attending your injection visits and getting shots <sup>1</sup>   | X       | X       | X       | X       | X       | X       |
| Give you a brief physical exam, to include measuring your weight, blood pressure, and pulse. Ask you if you have experienced any side effects from the shots you received, and ask you about any other medicines you are taking   | X       | X       | X       | X       | X       | X       |
| Collect ~XX mL (about x teaspoons) of blood for HIV testing (every visit); to check your general health and the health of your liver and kidneys (Week 72 and 96 for liver; Week 96 only for kidneys); for storage (every visit); HCV testing (Week 96 only); and Syphilis testing (Week 56*, Weeks 72 and 96 only) | X       | X       | X       | X       | X       | X       |
| Perform a swab of your rectum and collect urine to test for gonorrhea and chlamydia*  | X       |         | X       |         |         | X       |
| Give you a shot in the buttocks   | X       | X       | X       | X       | X       | X       |

<sup>1</sup> We will talk with you about how important it is to stay on schedule for your PrEP appointments.

\* Syphilis, gonorrhea, and chlamydia testing will be done at Weeks 72 and 96. It will also be done at Week 56 if you have not had this testing in the past 6 months before the Week 56 visit, or at any visit if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections.

**If you are not continuing in the study at the time of this consent, we will ask you to do these procedures as your final visit:**

| <b>Procedures</b>  | <b>Day 0</b> |
|--|--------------|
| <b>Confirm where you live and how to contact you</b>   | X            |
| <b>Talk with you about HIV and ways to protect yourself from getting it</b>                        | X            |
| <b>Offer you condoms and lubricant</b>   | X            |
| <b>Collect ~XX mL (about x teaspoons) of blood for HIV testing, syphilis testing*, and storage</b> | X            |
| <b>Perform a swab of your rectum and collect urine for gonorrhea and chlamydia testing*</b>        | X            |

\* Syphilis, gonorrhea, and chlamydia testing will be done at final visit (Day 0) if you have not had this testing in the past 6 months of the study, or if you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections.

## IF YOU LEAVE THE STUDY BEFORE YOUR FINAL VISIT:

If you join this part of the study and then leave the study before the last visit of the study schedule, we will ask you to complete a final study visit if you are available to do so. The final study visit will include the requirements for the visit at which it is confirmed you are leaving the study, and you will not receive CAB or TDF/FTC study product at this visit. Also, if you are on TDF/FTC and leave the study prior to your final visit, we will ask you to return any unused study product.

## Other New Information about CAB

We went over the side effects of CAB and TDF/FTC with you when you joined the study. We can go over these again in the main consent form if you want. We do have some new information about CAB that we will share with you to help you make your choice about whether to continue CAB or start CAB for the first time.

CAB protected people in this study from getting HIV infection about 66% better than TDF/FTC. The reason for this is that TDF/FTC works best when taken daily. The participants in HPTN 083 for whom TDF/FTC did not work was mostly because it was not being taken as prescribed (that is, it was not being taken every day). Both PrEP regimens work very well to prevent a person from getting HIV if taken as prescribed. In the participants who got HIV while getting CAB, about half of them had some resistance to CAB and likely other drugs like CAB (called integrase inhibitors). Resistance means that the drug, and sometimes other drugs like it, would not work as part of a treatment regimen (“cocktail”) to control the HIV infection. If you get infected with HIV while on CAB, you might need a regimen (“cocktail”) that contains other drugs that are not like CAB to treat the HIV infection. Just over 15% of HIV infections that occurred in participants taking TDF/FTC had resistance to one or both drugs in TDF/FTC as well. Some HIV infections that occurred in participants taking TDF/FTC had resistance to one or both drugs in TDF/FTC as well. If you become HIV infected while taking PrEP it is important to make sure you tell your doctor or provider which PrEP drug you have been taking so that a treatment regimen can be given to you that will be able to control the HIV to undetectable levels.

## If you become infected with HIV during this part of the study

If you get HIV during Step 4a, you will stop taking the CAB 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 4b or 4c (while you are getting shots), you will stop getting any further shots and we will ask you to come back for a visit every 3 months for about a year.

If you get HIV during Step 5 of the study, you will stop taking the TDF/FTC pills and will be referred for local care and treatment of HIV. If you get HIV during Step 5 and you have ever had a CAB injection at any time during past study visits, we will ask you to come back for a visit every 3 months for about a year; if you did not receive any CAB injections during past study visits, you will be discontinued from the study.

If you get HIV during Step 6, your study participation will end, and you will be referred to local HIV clinical care.

## **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 5.0**

**April 28, 2022**

*[Insert signature blocks as required by the local IRB:]* If you have read this addendum to the main consent form, or had it read and explained to you, and you understand the information, please initial the one line that applies to you to note that you want to continue in the study, or you no longer want to continue in the study, or you are not eligible to continue in the study. Then sign your name or make your mark below.

\_\_\_\_\_ I voluntarily agree to continue to take part in this portion of the study.

\_\_\_\_\_ I do not agree to take part in this portion of the study, but I do agree to the procedures listed in the table for not continuing in this part of the study.

\_\_\_\_\_ I do not agree to take part in this portion of the study, and I do not agree to the procedures listed in the table for not continuing in this part of the study.

\_\_\_\_\_ I understand I am not eligible to take part in this portion of the study, and I do agree to the procedures listed in the table for not continuing in this part of the study.

\_\_\_\_\_ I understand I am not eligible to take part in this portion of the study, and I do not agree to the procedures listed in the table for not continuing in this part of the study.

\_\_\_\_\_  
Participant Name (print)

\_\_\_\_\_  
Participant Signature and Date

---

Study Staff Conducting  
Consent Discussion (print)

---

Study Staff Signature and Date

---

Witness Name (print)  
(As appropriate)

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Witness Signature and Date

## APPENDIX VI: OPERATIONAL GUIDANCE DURING THE COVID-19 PANDEMIC

The extent to which site operations may be disrupted by the COVID-19 pandemic may vary across sites and over time. **All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff.** Site investigators should continue to follow current protocol specifications for communication with the Protocol Team and/or Clinical Management Committee and should contact the protocol team leadership with any questions or concerns regarding management of study participants.

### PRIORITIZATION OF STUDY VISIT PROCEDURES

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

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

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

**NOTE: Steps 4b, 4c, and 6 injectable Cabotegravir cannot be provided at an off-site visit.**



## **GUIDANCE FOR STEP 4a, STEPs 4b, 4c, 5 and 6**

**For participants in Step 4a:** Continuation on daily oral Cabotegravir would be appropriate – meaning, for participants who cannot report for the Week 4 visit, study product would continue, and where possible, study product potentially shipped or couriered to participants directly from PAB DAIDS established site pharmacies. If this is not feasible, participants should be instructed to protect themselves against HIV infection and exposure by all means available to them until they can return to study participation, and participants should document as carefully as possible the dates of exhaustion of their Step 4a study product medication supplies. Investigators of Record should use their clinical judgement regarding ongoing dispensation of oral Cabotegravir in these extraordinary circumstances absent interim safety monitoring.

**For participants in Steps 4b, 4c, and 6:** The same advice above would apply - that participants should protect themselves against HIV infection and exposure by all means available to them until they can return to study participation or to local CAB LA if it is available.

All sites should emphasize multi-modal HIV prevention activities – including social distancing, HIV status discussion, condom use, PEP and PrEP clinical services, HIV and STI testing (and treatment), clean needle use (if applicable), and other locally available in-person and/or on-line HIV prevention resources.

### **If a site can no longer provide injectable Cabotegravir in Steps 4b, 4c, and 6:**

Sites that are able may provide PrEP services through NON-STUDY clinical services, or through referral to PrEP services as a bridging mechanism while study product injections are unable to be administered.

### **For sites that are not be able to provide PrEP services through NON-STUDY clinical services:**

Additional open-label TDF/FTC supply was provided by Gilead Sciences, Inc., for the purpose of a bridging mechanism while study injections are unable to be provided as a result of the global COVID-19 pandemic and is available for ordering through the DAIDS Clinical Research Product Management Center.

- Open-label Truvada for oral bridge therapy is available from the CRPMC now.
- The site team should communicate closely and notify the site pharmacist on which participants receiving CAB LA will need study provided open-label Truvada for oral bridge therapy.
- The site pharmacist should place an order into the CRPMC for appropriate quantity of open-label Truvada supply for applicable participants receiving CAB LA.
- The site pharmacist at US sites can place an order into the CRPMC for up to three-month supply of open-label Truvada for applicable participants receiving CAB LA.
- The site pharmacist at international sites can place an order into the CRPMC for up to six-month supply of open-label Truvada for applicable participants receiving CAB LA.

**For participants in Step 5:** Continuation on daily oral TDF/FTC would be appropriate; (if oral study product is ongoing for that participant) – meaning, for participants who cannot report for the quarterly visits, study product would continue, and where possible, study product potentially shipped or couriered to participants directly from PAB DAIDS established site pharmacies. If this is not feasible, participants should be instructed to protect themselves against HIV infection and exposure by all means available to them until they can return to study participation, and participants should document as carefully as possible the dates of exhaustion of their Step 5 study product medication supplies. Investigators of Record should use their clinical judgement regarding ongoing

dispensation of oral study product in these extraordinary circumstances absent interim safety monitoring, given known previous creatinine clearance and adherence reported trajectories.

It is acceptable to provide a 3-month supply plus 1 additional month for overage for each quarterly dispensation (again, provided quarterly only if the IoR determines ongoing dispensation is acceptable as stated above).

## STUDY PRODUCT CONSIDERATIONS

- For emergency cases, the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* permits shipment or courier of oral study product from the site directly to participants. The pharmacist should refer to the section on “Shipping Study Product to a Participant” in this manual for detailed procedures. If this method is to be implemented, each site pharmacist must develop appropriate procedures for the shipment or courier of oral study product to identified participant in accordance with these guidelines and must include appropriately documented chain of custody. This method should only be used if permissible per local institutional and IRB/EC policies.
- All questions related to study product management should be directed to Katie Shin – [kashin@niaid.nih.gov](mailto:kashin@niaid.nih.gov).

## DOCUMENTATION

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for HPTN 083.
- Participant-specific documentation should be entered in participant study charts in real-time to the extent possible.
- Specific guidance regarding coding visits and instructions has been provided from SCHARP in a separate communication to all sites (Data Communique #5 - Corrected, dated April 2, 2020).
- Sites will continue to document deviations related to study visits and procedures impacted by the global COVID-19 pandemic just as would be done in the absence of the pandemic.