Protocol

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Official Title of Study: Prospective Study to Assess Usage, Adherence, Effectiveness of Cabotegravir LA for Pre-Exposure Prophylaxis in the United States in the OPERA Cohort

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TITLE PAGE

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Title:	Prospective Study to Assess Usage, Adherence, Effectiveness of Cabotegravir LA for Pre-Exposure Prophylaxis in the United States in the OPERA Cohort

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1. LIST OF ABBREVIATIONS

ADAP	AIDS Drug Assistance Program
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ASCVD	Atherosclerotic Cardiovascular Disease
BAA	Business Associate Agreements
CAB	Cabotegravir
CD4	Cluster of Differentiation 4
CDC	Centers for Disease Control
CHORUS™	Clinical Health Outcomes Reporting and Utilization Service
CMS	Centers for Medicare & Medicaid Services
DTI	Direct to Injection
ECAB	Epidemiology & Clinical Advisory Board
EHR	Electronic Health Record
FTC	Emtricitabine
HBV	Hepatitis B Virus
HCP	Healthcare Provider
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HITECH	Health Information Technology for Economic and Clinical Health
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
INSTI	Integrase Strand Transfer Inhibitor
IQR	Interquartile Range
ISR	Injection Site Reaction
IRB	Institutional Review Board
LA	Long Acting
mL	Milliliter
MIPS	Merit-based Incentive Payment System
MSM	Men who have Sex with Men
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
OLI	Oral Lead In
OPERA®	Observational Pharmaco-Epidemiology Research and Analysis
PHI	Protected Health Information
PrEP	Pre-Exposure Prophylaxis
PWH	People with HIV
PWID	People Who Inject Drugs
QA	Quality Assurance
TAF	Tenofovir Alafenamide
TDF	Tenofovir Disproxil Fumarate
µL	Microliter
US	United States
VACS	Veterans Aging Cohort Study
VL	Viral Load
CAB	Cabotegravir

Trademark Information

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Apretude

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Truvada

2. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE

MARKETING AUTHORISATION HOLDER

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6/8/2023

Carolyn Brown
Primary Author/ Project officer

Date

PPD

6/8/2023

Vani Vannappagari
Global Head, Epidemiology and Real World Evidence

Date

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06-Feb-2024

Nassrin Payvandi
VP & Head, Safety and Pharmacovigilance

Date

PPD

08-Apr-2024

Jens-Ulrich Stegmann
ViiV QPPV

Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____Jennifer S. Fusco_____

PPD

PPD estigaPPD Signature

08 June 2023

Date

3. ABSTRACT

Rationale/Background

Clinical trials have demonstrated that preexposure prophylaxis (PrEP) with cabotegravir long-acting (CAB LA) (brand name: Apretude) had superior efficacy for HIV prevention compared to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC in transgender women, cisgender men who have sex with men, and cisgender women.[1, 2] CAB LA was approved for the prevention of HIV as PrEP by the FDA on December 20, 2021.[3] Apretude is given first as two initiation injections administered one month apart, and then every two months thereafter. Patients can either start their treatment with Apretude or take oral cabotegravir (brand name: Vocabria) as an oral lead in (OLI) for four weeks to assess how well they tolerate the drug. The CDC HIV PrEP Guidelines suggest that CAB LA-PrEP is especially appropriate in the context of significant renal disease or sub-optimal oral PrEP adherence.[4] To date, real-world evidence on CAB LA-PrEP use is very limited, and centers mainly on implementation and user experience. As more prescriptions are written and injections given for CAB LA, it is important to appreciate how many individuals are being prescribed the drug, how many are receiving injections, at which clinics, how providers are recording CAB LA-PrEP administrations, and viral suppression/failure among people who acquire HIV while on CAB LA for PrEP

Objectives

Analyses will be conducted cumulatively at three time points through this study. **Analysis 1** will include data through 30Jun2023, **Analysis 2** will include data through 31Dec2023, and **Analysis 3** will include data through 31Dec2024.

Primary Objectives:

1: To describe the baseline characteristics of oral PrEP users (TDF/FTC or TAF/FTC) and long-acting (LA) PrEP users (CAB, with or without OLI) at three time-points since market approval – **Analyses 1, 2, 3**

a) Demographic characteristics
b) Clinical characteristics
c) Sexual behavior and health
d) Factors for HIV acquisition
e) History of oral and LA-PrEP

2: To describe adherence and usage patterns of CAB OLI and/or LA-PrEP – **Analyses 1, 2, 3**

a) Describe the use of CAB OLI prior to initiating CAB LA-PrEP versus direct to injection (DTI)
b) Describe delayed and missed injections

c) Compare baseline demographic, behavioral, and clinical characteristics of individuals with vs. without any missed and/or delayed injections
d) Describe discontinuations of CAB (oral or LA) for PrEP
e) Compare baseline characteristics of individuals who did vs. did not discontinue oral and CAB LA-PrEP
f) Describe the use of oral (CAB, TDF/FTC or TAF/FTC) PrEP for oral bridging or switch

3: Monitor the incidence of HIV and STIs while on CAB OLI and/or LA PrEP – **Analysis 3**

a) Assess the incidence of HIV while on CAB (oral or LA) for PrEP
b) Compare baseline characteristics and adherence patterns of individuals who did vs. did not acquire HIV
c) Among individuals who acquire HIV, describe timing of HIV acquisition, and frequency and type of HIV testing
d) Assess the incidence of STIs while on CAB (oral or LA) for PrEP (gonorrhea, chlamydia, syphilis, HPV, HBV, HCV, primary HSV, trichomoniasis)

4: Evaluate HIV treatment and virologic suppression after HIV acquisition – **Analysis 3**

a) Describe the ART regimens initiated after acquiring HIV
b) Among individuals who initiated ART, assess the rate of viral suppression by INSTI-based vs. other ART regimens

Secondary Objective:

1: Describe incomplete initiation of CAB LA for PrEP (i.e., receipt of the loading dose only) – **Analyses 1, 2, 3**

a) Assess the number and proportion of individuals not fully initiating CAB LA for PrEP
b) Describe select demographic and clinical characteristics of individuals not fully initiating CAB LA for PrEP
c) Assess the number and proportion of individuals not fully initiating who experienced an injection site reaction (ISR)

Study Design

An observational study utilizing prospectively collected electronic health record (EHR) data obtained from the OPERA® clinical cohort will be used to address the study aims/objectives. For Primary Objective 1, the study population will consist of all HIV-negative adults and adolescents initiating a new PrEP formulation (oral or LA) in the eligibility window. For Primary Objectives 2- 3 and Secondary Objective 1, the study population will be further restricted to those initiating CAB LA for PrEP (oral lead in or

direct to injection). For Primary Objectives 1-3 and Secondary Objective 1, included individuals will be followed through the first of the following censoring events: discontinuation of PrEP formulation, HIV acquisition, death, loss to follow-up or study end. For Primary Objective 4, the study population will consist of PrEP users identified for Primary Objective 3 who acquire HIV between 21DEC2021 and 31DEC2023 while on PrEP with CAB. These will be followed from detection of HIV through the first of the following censoring events: change in ART regimen core agent, therapeutic gap, death, loss to follow-up or study end.

Analysis Methods

For Primary Objective 1, baseline characteristics will be described and statistical comparisons between PrEP type (CAB LA vs daily oral) will be conducted using chi-square tests for categorical variables and Wilcoxon-Mann-Whitney tests for continuous variables, as appropriate. For Primary Objective 2, adherence and usage pattern outcomes will be described among CAB PrEP users. For Primary Objective 3, incidence of STIs and HIV will be described as a frequency and an incidence rate among CAB PrEP users. For Primary Objective 4, follow-up care and virologic outcomes will be described as median (IQR) values for continuous data and relative frequencies for categorical data among individuals who acquired HIV while on CAB PrEP. For Secondary Objective 1, select baseline demographic and clinical characteristics and ISR will be assessed among individuals with only one injection (i.e., loading dose) who have sufficient follow-up after the loading dose to observe delayed or missed second doses.

Limitations

Data is collected for the medical management of patients and is not directly intended for research purposes, but rather for the care and management of individual patients and patient populations. Moreover, OPERA does not include pharmacy records. Daily oral PrEP use will be ascertained based on prescription records, not refills, which may lead to some misclassification. Follow-up time is relatively short to observe HIV incidence and subsequent HIV treatment outcomes.

4. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	February 6, 2024	Sponsor Signatory Pg	Update	Updated to ensure QPPV/CS&PV's review and approval with TSS and/or PASS studies per VQD-SOP-005925.
<2>	<Date>	<Text>	<Text>	<Text>
<n>	<Date>	<Text>	<Text>	<Text>

5. MILESTONES

Milestone	Planned date
Contract execution	4Q2022
Kickoff Meeting	4Q2022
Draft protocol	4Q2022
Final protocol	2Q2023
Analysis 1	
Database Set-up	4Q2022
Initiation of Analysis (Analysis 1)	2Q2023
Preliminary Tables	3Q2023
Final Deliverables	4Q2023
Analysis 2	
Database Set-up	1Q2024
Initiation of Analysis (Analysis 2)	1Q2024
Preliminary Tables	3Q2024
Final Deliverables	4Q2024
Analysis 3	
Database Set-up	1Q2025
Initiation of Analysis (Analysis 3)	1Q2025
Preliminary Tables	2Q2025
Final Deliverables	3Q2025

6. BACKGROUND AND RATIONALE

6.1. Background

Clinical trials have demonstrated that preexposure prophylaxis (PrEP) with cabotegravir long-acting injectable (CAB LAI) had superior efficacy for HIV prevention compared to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC). PrEP with CAB LA has been shown to be efficacious in transgender women, cisgender men who have sex with men, and cisgender women.[1, 2] CAB LA is generally well tolerated, and though injection site reactions were common, they infrequently led to discontinuation in a trial setting.[5] In addition, most trial participants reported a desire to continue received CAB

LA-PrEP.[6] When seroconversion did occur in the HPTN 083 and HPTN 084 trials, most occurred before enrollment, with no recent CAB exposure, or before CAB injection,

during the oral lead-in phase; some were associated with delayed injections.[1, 2] Among those who acquired HIV, PrEP CAB LA was associated with prolonged viral suppression and delayed antibody expression.[7, 8] A modelling study concluded that long-acting injectable PrEP has the potential to greatly reduce HIV transmission in men who have sex with men: at a coverage level of 35%, long-acting injectable PrEP led to a 44% reduction in new HIV infections.[9] Another modeling study found that if 50% of PrEP users in the US chose CAB LA-PrEP instead of daily oral PrEP, 4.3% of infections would be averted over 10 years, compared to all PrEP users being on daily oral PrEP.[10]

CAB LA for PrEP (brand name: Apretude) was approved for the prevention of HIV as PrEP by the FDA on December 20, 2021.[3] Apretude is initiated with a single 600 mg (3-mL) injection given one month apart for two consecutive months. After the second initiation injection, the recommended continuation injection dose is a single 600 mg (3-mL) injection given every two months. Individuals must test negative for HIV infection immediately prior to receiving Apretude at every administration. *Vocabria* (cabotegravir oral tablets) may be administered for approximately one month prior to initiating the first injection to assess the tolerability of the medicine (optional).[11] The CDC HIV PrEP Guidelines suggest that CAB LA-PrEP is especially appropriate in the context of significant renal disease or sub-optimal oral PrEP adherence.[4] PrEP with CAB LA may be a favorable strategy to counter difficulties with adherence to daily oral PrEP. In a meta-analysis of longitudinal studies, 38% (95% CI: 8, 67) of individuals on oral PrEP had suboptimal adherence within 6 months, 41% (95% CI: 19, 64) discontinued within 6 months, and among those who discontinued, 47% (95% CI: 32, 63) reinitiated PrEP within a year.[12] However, because CAB LA for PrEP is administered in the clinic, it has the potential to improve adherence. In the HPTN 083 trial, 92% of individuals in the CAB LA-PrEP arm received their injections within <2 weeks of the target, while only 72% of those in the TDF/FTC daily oral PrEP arm had drug concentrations consistent with ≥4 TDF/FTC doses per week in the preceding 1 or 2 months.[2]

To date, real-world evidence on CAB LA for PrEP use is very limited, and centers mainly on implementation and user experience.

6.2. Rationale

As more prescriptions are written and injections given for Apretude, it is important to appreciate how many individuals are being prescribed the medicine, how many are receiving injections, at which clinics, how providers are recording CAB LA-PrEP administrations, and viral suppression/failure among people who acquire HIV while on CAB for PrEP.

7. RESEARCH QUESTION AND OBJECTIVE(S)

Analyses will be conducted cumulatively at three time points through this study. **Analysis 1** will include data through 30Jun2023, **Analysis 2** will include data through 31Dec2023, and **Analysis 3** will include data through 31Dec2024.

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a) Demographic characteristics
b) Clinical characteristics
c) Sexual behavior and health
d) Factors for HIV acquisition
e) History of oral and LA-PrEP

2: To describe adherence and usage patterns of CAB OLI and/or LA-PrEP – **Analyses 1, 2, 3**

a) Describe the use of CAB OLI prior to initiating CAB LA-PrEP versus direct to injection (DTI)
b) Describe delayed and missed injections
c) Compare baseline demographic, behavioral, and clinical characteristics of individuals with vs. without any missed and/or delayed injections
d) Describe discontinuations of CAB for PrEP
e) Compare baseline characteristics of individuals who did vs. did not discontinue oral and CAB LA-PrEP
f) Describe the use of oral PrEP (CAB, TDF/FTC or TAF/FTC) for oral bridging or switch

3: Monitor incidence of HIV and STIs while on CAB OLI and/or LA PrEP – **Analysis 3**

a) Assess the incidence of HIV while on CAB (oral or LA) for PrEP
b) Compare baseline characteristics and adherence patterns of individuals who did vs. did not acquire HIV
c) Among individuals who acquire HIV, describe baseline characteristics, timing of HIV acquisition, and frequency and type of HIV testing
d) Assess the incidence of STIs while on CAB (oral or LA) for PrEP (gonorrhea, chlamydia, syphilis, HPV, HBV, HCV, primary HSV, trichomoniasis)

4: Evaluate HIV treatment and virologic suppression after HIV acquisition – **Analysis 3**

a) Describe the ART regimens initiated after acquiring HIV

b) Among individuals who initiated ART, assess the rate of viral suppression by INSTI-based vs. other ART regimens

Secondary Objectives:

1: Describe incomplete initiation of CAB LA for PrEP (i.e., receipt of the loading dose only) – **Analyses 1, 2, 3**

a) Assess the number and proportion of individuals not fully initiating CAB LA for PrEP
b) Describe select demographic and clinical characteristics of individuals not fully initiating CAB LA for PrEP
c) Assess the number and proportion of individuals not fully initiating who experienced an injection site reactions (ISR)

8. RESEARCH METHODS

8.1. Study Design

An observational study utilizing prospectively collected electronic health record (EHR) data over 18 to 36 months obtained from the OPERA® clinical cohort will be used to address the study aims/objectives.

Analyses will be conducted at three time points through this study, including data from 21Dec2021.

Analysis 1 will include data through 30Jun2023 and will assess Primary Objectives 1-2 & Secondary Objective 1.

Analysis 2 will include data through 31Dec2023 and will assess Primary Objectives 1-2 & Secondary Objective 1.

Analysis 3 will include data through 31Dec2024 and will assess Primary Objectives 1-4 & Secondary Objective 1.

For Primary Objective 1, the study population will consist of all HIV-negative adults and adolescents initiating a new PrEP formulation (TDF/FTC, TAF/FTC, CAB OLI or LA) in the eligibility window. For Primary Objectives 2-3 and Secondary Objective 1, the study population will the study population will be further restricted to those initiating PrEP with CAB (oral or LA). For Primary Objectives 1-3 and Secondary Objective 1, included individuals will be followed through the first of the following censoring events: discontinuation of PrEP formulation, HIV acquisition, death, loss to follow-up (i.e., 12 months since last clinical contact) or end of the follow-up period at three time points.

For Primary Objective 4, the study population will consist of individuals identified in Primary Objective 3 who acquired HIV between 21DEC2021 and 31DEC2023 while on PrEP with CAB. These will be followed from detection of HIV through the first of the following censoring events: change in ART regimen core agent, therapeutic gap, death, loss to follow-up or 31Dec2024.

8.2. Study Population and Setting

This study will include adults and adolescents initiating a new PrEP formulation: either as oral PrEP or LA-PrEP.

Population Inclusion:

- Primary Objective 1, **Analyses 1, 2, 3**
  - HIV negative
  - ≥ 12 years of age
  - Initiating PrEP with TDF/FTC, TAF/FTC, or CAB OLI or LA injectable, without any other ARV
    - Analysis 1: between 21Dec2021 and 31Dec2022
    - Analysis 2: between 21Dec2021 and 30Jun2023
    - Analysis 3: between 21Dec2021 and 30Jun2024

- Primary Objective 2 & Secondary Objective 1, **Analyses 1, 2, 3**
  - HIV negative
  - ≥ 12 years of age
  - Initiating PrEP with CAB OLI or LA injectable, without any other ARV
    - Analysis 1: between 21Dec2021 and 31Dec2022
    - Analysis 2: between 21Dec2021 and 30Jun2023
    - Analysis 3: between 21Dec2021 and 30Jun2024

- Primary Objective 3, **Analysis 3**
  - HIV negative
  - ≥ 12 years of age
  - Initiating PrEP with CAB OLI or LA injectable, without any other ARV between 21Dec2021 and 30Jun2024

- Primary Objective 4, **Analysis 3**
  - HIV negative at PrEP initiation
  - ≥ 12 years of age
  - Initiating PrEP with CAB OLI or LA injectable, without any other ARV between 21Dec2021 and 31DEC2023
  - Detection of HIV between 21DEC2021 and 31DEC2023 while on CAB OLI or LA PrEP

Censoring Events:

- Primary Objectives 1, 2, 3 & Secondary Objective 1

  - Study end (allows for up to six months of follow-up among individuals initiating PrEP at the end of the period of eligibility)
    - Analysis 1: 30Jun2023
    - Analysis 2: 31Dec2023
    - Analysis 3: 31Dec2024
  - Discontinuation of PrEP formulation
    - Oral PrEP: >45 consecutive days without an oral PrEP prescription
    - LA PrEP: 2 injection cycles (~127 consecutive days) in which no injections were administered without oral PrEP
  - Loss to follow-up (12 months after last clinical contact)
  - Death
  - HIV acquisition
- Primary Objective 4
  - Study end: 31Dec2024
  - Stop the core agent in the first ART regimen after HIV acquisition, or therapeutic gap >45 days
  - Loss to follow-up (12 months after last clinical contact)
  - Death

Index date (baseline):

- Primary Objectives 1, 2, 3 & Secondary Objective 1: start of a new PrEP formulation
- Primary Objective 4: date HIV detection, defined as the date of the first positive antigen/antibody or HIV RNA test

8.3. Variables

8.3.1. Exposure definitions

- Primary Objective 1: LA-PrEP (CAB) will be the exposure of interest. The comparator exposure will be oral PrEP (TDF/FTC or TAF/FTC).
- Primary Objectives 2-3 & Secondary Objective 1: CAB oral and CAB LA-PrEP will be the exposure of interest, without a comparator exposure.
- Primary Objective 4: INSTI-based ART regimen will be the exposure of interest. The comparator exposure will be non-INSTI-based ART regimen.

8.3.2. Measurements & outcome definitions

Baseline Characteristics (Primary Objective 1; Analyses 1, 2, 3)

The following characteristics will be described at baseline:

- Demographic characteristics
  - Age (years)

        - Continuous
        - Categorical (12-19, 20-29, 30-39, 40-49, 50-59, 60-69, ≥70)
    - Sex assigned at birth
    - Transgender or cisgender
    - Race (African American/Black, Asian, White, Other Race)
    - Ethnicity (Hispanic, non-Hispanic)
    - Geographic Region (Northeast, Midwest, South, West, US Territories)
    - Marital status
    - Payer type (Medicaid, Medicare, Commercial insurance, Cash)

- Clinical characteristics
    - Time since first OPERA® visit
    - Number of visits with OPERA® healthcare provider (HCP) within 12 months prior to baseline
    - Type of HIV tests received
    - Frequency of HIV testing
    - Weight(kg)
        - Test result available (yes/no)
        - Continuous
            - Categorical
    - BMI (kg/m^2)
        - Test result available (yes/no)
        - Continuous
        - Categorical
    - VACS Mortality Index score
        - Continuous
        - Categorical
    - Comorbid conditions
        - Cardiovascular disease
        - Invasive cancer
        - Endocrine disorders
        - Mental health conditions
        - Liver disease
        - Bone disorders
        - Renal disease
        - Hypertension
        - Autoimmune disorders
        - Substance abuse
    - Cardiovascular disease risk factors
        - Hypertension (systolic and diastolic)
        - Triglycerides
        - LDL
        - Index of Total Cholesterol /HDL Cholesterol
        - ASCVD risk
    - Markers of liver disease
        - Alanine aminotransferase (ALT) elevations (also called serum glutamic pyruvic transaminase (SGPT))

- Aspartate aminotransferase (AST) elevations (also called serum glutamic oxaloacetic transaminase (SGOT))
- Total bilirubin elevations(BILI)
- Alkaline phosphatase (ALP) elevations where available
- Albumin
- Prothrombin time (PT)/international normalized ratio (INR) where available
- Lipase levels where available
- Fib-4

- Sexual Behavior and Health
  - Syphilis ever
  - Gonorrhea ever
  - Chlamydia ever
  - HPV/genital warts ever
  - Hepatitis B virus (HBV) co-infection ever
  - Hepatitis C virus (HCV) co-infection ever
  - HSV infection ever
  - Trichomoniasis infection ever

- Factors for HIV acquisition
  - STI in the past 12 months (syphilis, gonorrhea, chlamydia, chancroid, lymphogranuloma venereum, mycoplasma genitalium, HCV, HBV, primary HSV, trichomoniasis)
  - Non-injection drug use in the past 12 months
  - Injection drug use in the past 12 months

- History of oral and LA-PrEP
  - Prior PrEP use (yes/no)
  - Prior oral PrEP use (yes/no)
  - Prior LA-PrEP use (yes/no)
  - Time since PrEP initiation (years)
  - Number of prior PrEP regimens
  - Type of prior PrEP regimens
  - Duration of prior PrEP usage(s)

CAB PrEP Adherence and Usage Patterns (Primary Objective 2; Analyses 1, 2, 3)

Based on the prescribing information (Tables 1 and 2),[13] an oral lead-in (pills) can be taken orally for 28 days prior to the initiation of CAB LA for PrEP or individuals can choose to start CAB for PrEP direct to injection. After the initiation injection, the second injection should be given one month later the same day of the month as the initiation

injection. All subsequent injections should be administered every 2 months within the target window. The CAB LA for PrEP treatment window is up to 7 days before or after the date of the scheduled monthly injection visit (i.e. +/-7 days).

Table 1. Recommended Dosing Schedule (with Oral Lead-in) for Pre-exposure Prophylaxis in Adults and Adolescents Weighing at Least 35 kg

Oral Lead-in (at Least 28 Days) (Month Prior to Starting Injections)	Intramuscular (Gluteal) Initiation Injection (Month 1 and Month 2)	Intramuscular (Gluteal) Continuation Injection (Month 4 and Every 2 Months Onwards)
Oral cabotegravir 30 mg by mouth once daily for 28 days	APRETUDE[a] 600 mg (3 mL)	APRETUDE[b] 600 mg (3 mL)

[a] Should be administered on the last day of oral lead-in or within 3 days thereafter.
[b] Individuals may be given APRETUDE up to 7 days before or after the date the individual is scheduled to receive the injections.

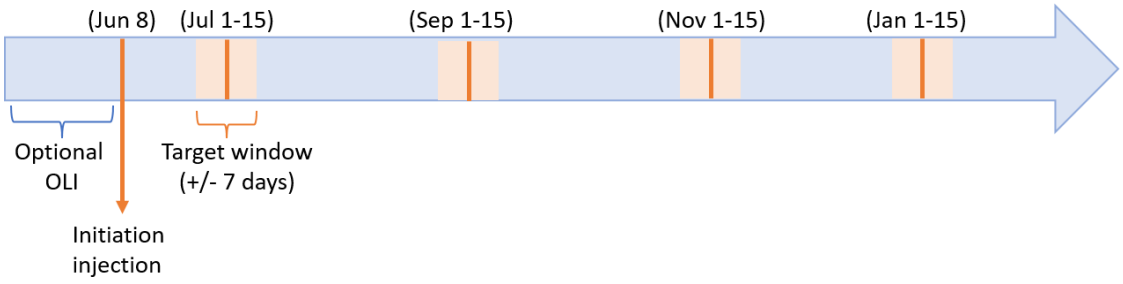
Table 2. Recommended Dosing Schedule (Direct to Injection) for Pre-exposure Prophylaxis in Adults and Adolescents Weighing at Least 35 kg

Intramuscular (Gluteal) Initiation Injection (Month 1 and Month 2)	Intramuscular (Gluteal) Continuation Injection (Month 4 and Every 2 Months Onwards)
APRETUDE[a] 600 mg (3 mL)	APRETUDE[a] 600 mg (3 mL)

[a] Individuals may be given APRETUDE up to 7 days before or after the date the individual is scheduled to receive the injections.

For example, someone who received their initiation injection on June 8th should receive their second injection between July 1st and July 15th and their third injection between September 1st and September 15th (Figure 1).

Figure 1. Illustration of Recommended CAB LA for PrEP Dosing Schedule

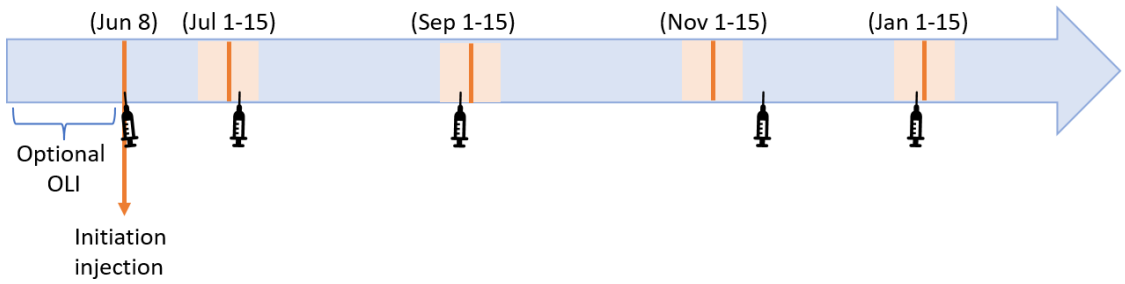


- CAB PrEP formulation at initiation: proportion with CAB oral lead-in (OLI) vs. direct to injection (DTI)

Non-adherence will be characterized as delayed injections or missed injections.

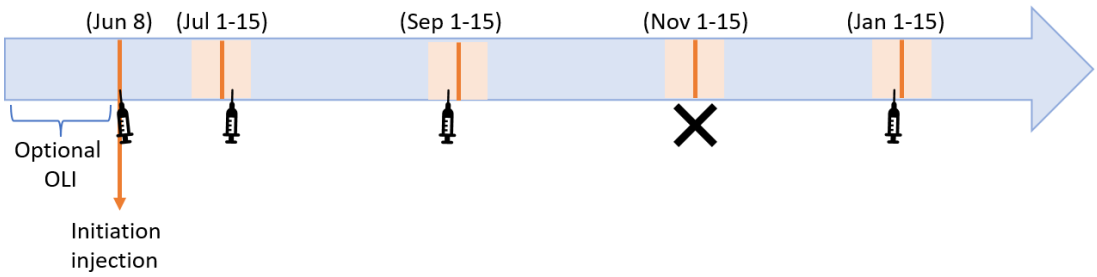
- Delayed injection
    - Definition: Injections received outside of the target window but before the next target window, without oral therapy for missed injection (Figure 2).
    - Measurements:
        - Number of individuals with delayed injection
        - Median duration of delayed injections

Figure 2. Illustration of CAB LA for PrEP Non-Adherence with Delayed Injection



- Missed injection
    - Definition**:** Absence of injections during the target window and during the interval between the target window and the next target window, **and** absence of oral therapy for missed injection during the target window, **and** presence of an injection within the subsequent target window (Figure 3).
    - Measurements:
        - Number of individuals who missed an injection
        - Total number of missed injections
        - Median number of injections missed per person

Figure 3. Illustration of CAB LA for PrEP Non-Adherence with Missed Injection



- Delayed and/or missed injections
  - Number of individuals with a missed and/or delayed injection
  - Baseline characteristics for the individuals with vs. without any missed/delayed injection

- Discontinuation
  - Definitions:
    - LA PrEP: 2 injection cycles (~127 consecutive days) in which no injections were administered without oral PrEP
    - Individuals who received only a loading dose and no maintenance doses will be considered not having fully initiated CAB LA for PrEP and discontinuation will not be assessed
    - Oral PrEP: >45 days without an oral PrEP prescription
  - Measurements:
    - Number of individuals who discontinued
    - Time from first injection to discontinuation
    - Baseline characteristics for the individuals who did vs. did not discontinue

- Oral bridging (if available)
  - If an individual plans to miss a scheduled every-2-month continuation injection visit by more than 7 days, daily oral cabotegravir can be taken for up to 2 months to replace 1 missed scheduled every-2-month injection. The first dose of oral PrEP should be taken approximately 2 months after the last injection. For oral PrEP durations greater than 2 months, an alternative oral regimen is recommended.
  - Measurements:
    - Number of individuals with oral bridging
    - Median days of oral bridging
    - Formulation of oral PrEP for bridging

- Switch to oral PrEP
  - When switching from CAB LA for PrEP to an oral regimen, a new oral PrEP regimen should start within the target window (±7 days of target day), in lieu of an injection. While prescriptions may be written earlier than that, switch will be assumed to start on the last day of the target window for analytical purposes.
  - Measurements:
    - Number of individuals switching to oral PrEP
    - Median days from first CAB LA injection to switch to oral PrEP
    - Formulation of oral PrEP after switch

Incomplete initiation of CAB LA PrEP (Secondary Objective 1; Analyses 1, 2, 3)

- Not fully initiated onto CAB LA for PrEP

- Definition: receipt of exactly one dose of CAB LA for PrEP (i.e., only the loading dose and no subsequent maintenance doses)
- Assessed among individuals with sufficient follow-up after the loading dose to observe delayed or missed second doses to avoid misclassification.
  Measurements:
  - Number of individuals not fully initiating
  - Proportion of individuals not fully initiating who experienced an ISR
  - Baseline demographic characteristics
    - Age (years)
    - Sex assigned at birth
    - Transgender or cisgender
    - Race (African American/Black, Asian, White, Other Race)
    - Ethnicity (Hispanic, non-Hispanic)
    - Geographic Region (Northeast, Midwest, South, West, US Territories)
    - Marital status
    - Payer type (Medicaid, Medicare, Commercial insurance, Cash)
  - Baseline clinical characteristics
    - Factors for HIV acquisition
    - History of oral and LA-PrEP
  -

Incident STIs & HIV (Primary Objective 3; Analysis 3)

- HIV acquisition
  - Definition: new HIV diagnosis after initiation of CAB PrEP, with ≥1 detectable HIV RNA viral load (with or without positive antigen or antigen/antibody lab result); date of HIV acquisition will be the date of the first positive antigen/antibody or HIV RNA test
  - Measurements:
    - Number of individuals who acquire HIV
    - HIV incidence rate
    - HIV acquisition detected during OLI vs. LA PrEP
    - Time from OLI or first injection to HIV acquisition
    - Time from last injection to HIV acquisition
    - Type of HIV testing performed when HIV was detected: antibody test, antigen/antibody test, nucleic acid test (NAT)
    - Frequency of HIV testing among individuals who acquire HIV
    - Baseline characteristics & adherence patterns for the individuals who did vs. did not acquire HIV

- STIs

- Definition: new diagnosis of either gonorrhea, chlamydia, syphilis, HPV, HBV, HCV, primary HSV, or trichomoniasis
- Measurements:
  - Number of individuals with any new STIs (overall and broken down by specific STI)
  - Incidence rate of any new STI

HIV treatment and virologic suppression after HIV acquisition (Primary Objective 4; Analysis 3)

- ART regimen following HIV acquisition
  - ART initiated during follow-up
  - Time from HIV acquisition to ART initiation
  - Core agent class in first ART regimen following HIV acquisition (INSTI, PI, NNRTI, Other, >1 core agent)
  - Most common core agents prescribed
  - 2-drug regimen vs. 3-drug regimen

- Virologic control while on the first ART regimen following HIV acquisition
  - Definition:
    - Undetectability: viral load <50 copies/mL
    - Suppression: viral load <200 copies/mL
  - Measurements
    - Number of individuals who achieved undetectability or suppression, overall and stratified by INSTI-based vs. non-INSTI-based regimen
    - Incidence rate of undetectability or suppression, overall and stratified by INSTI-based vs. non-INSTI-based regimen

8.3.3. Confounders and effect modifiers

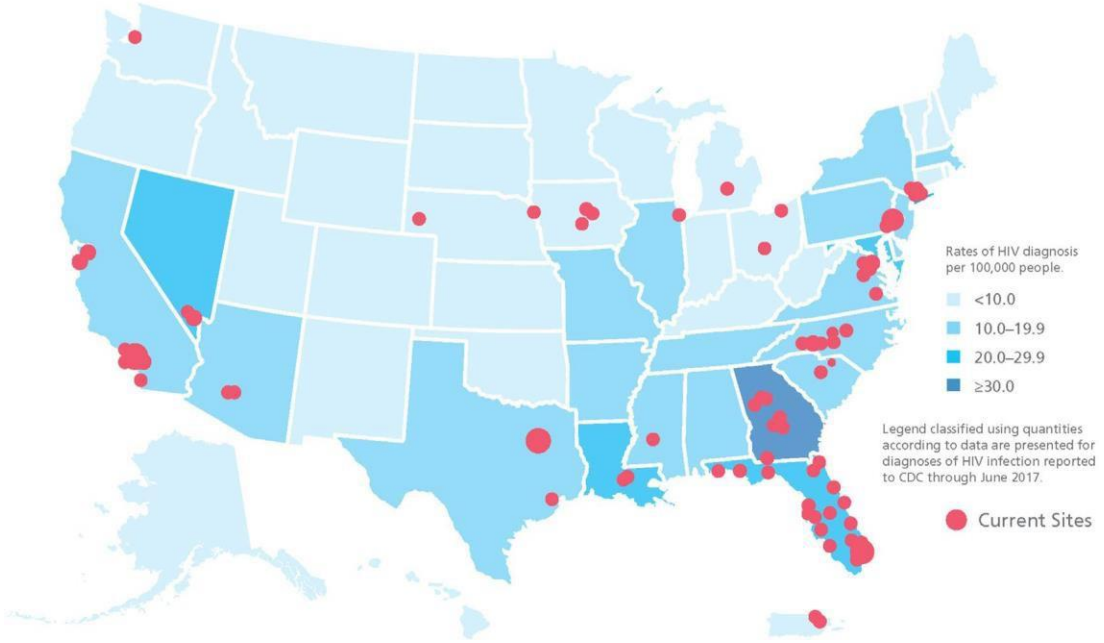
Not applicable, descriptive study.

8.4. Data sources

The OPERA® (Observational Pharmaco-Epidemiology Research & Analysis) database and research network is a multi-site observational database built from the complete patient health records managed in Electronic Health Record (EHR) systems from more than 400 participating caregivers at 142 separate locations throughout the U.S. (**Figure 4**). Through their membership in OPERA®, medical practices meet the Centers for Medicare & Medicaid Services (CMS) Merit-based Incentive Payment System (MIPS) Incentive Program for Integration with a Specialized Registry. OPERA®-participating physicians and ancillary healthcare providers have documented the care of over 1 million patients in their EHRs, including over 150,000 PWH of which approximately 20% are

women, representing 13% of all the PWH linked to care in the U.S. The OPERA® database is refreshed from these EHR systems at each clinic daily providing up-to-date data for both clinicians and researchers. In total, there are more than 13 million documented prospective visits in the EHR systems for PWH and 4.5 million prescriptions written for ART medications. The average years of follow-up (years of documenting patient visits prospectively in the EHR) for PWH in OPERA® is 5.6 years and there are over 30,000 PWH who have ten years or more of follow-up.

Figure 4. United States Map of OPERA HIV+ Population and CDC (2017) State-by-State Estimates



8.5. Study size

A total of 429 HIV-negative individuals received their first CAB LA-PrEP injection between 31DEC2021 and 12FEB2023. Oral PrEP prescriptions have been captured since 2012 in OPERA and has thousands of users.

This study is not a hypothesis testing study but is designed to assess usage of CAB LA for PrEP in real world clinical setting. The overall number of participants in the study will depend on uptake of CAB LA for PrEP and how widely it is used in the US during the study period. The study aims to include around 1000 participants. Table 3 below gives an indication of the likely precision of the estimates of the proportion with incident HIV infections, using Exact Clopper Pearson confidence limits under different scenarios. There is no formal hypothesis to be tested in these analyses.

Table 3. Precision Estimates

Confidence Level	Sample Size (N)	CI Width	Incident HIV infection rate (%)	Lower Limit	Upper Limit
0.95	1000	0.7568	0.25	0.0416	0.7984
0.95	1000	1.0004	0.5	0.1625	1.1629
0.95	1000	1.3507	1	0.4806	1.8313
0.95	1000	1.6201	1.5	0.8419	2.462
0.95	1000	1.8462	2	1.2258	3.072
0.95	1000	2.0442	2.5	1.6243	3.6685
0.95	2000	0.5012	0.25	0.0812	0.5824
0.95	2000	0.6776	0.5	0.24	0.9176
0.95	2000	0.9283	1	0.6119	1.5402
0.95	2000	1.1202	1.5	1.0143	2.1345
0.95	2000	1.281	2	1.4326	2.7136
0.95	2000	1.4217	2.5	1.8611	3.2828

8.6. Data management

8.6.1. Data handling conventions

The data used for this research study are not identifiable by the research staff. However, all data, even when stripped of identifiers, are handled and treated, in motion and at rest, as though the data could be identified. All data are managed according to regulations such as HIPAA and HITECH. These regulations and guidelines expand upon the ethical principles detailed in the 1964 Declaration of Helsinki.

8.6.2. Resourcing needs

Not applicable.

8.6.3. Timings of Assessment during follow-up

Analysis period	Objectives	Analysis period
1: 21Dec2021 through 30Jun2023	P1, P2, S1	2Q2023
2: 21Dec2021 through 31Dec2023	P1, P2, S1	3Q2024

3: 21Dec2021 through 31Dec2024	P1, P2, P3, P4, S1	2Q2025

8.7. Data analysis

8.7.1. Essential analysis

Primary Objective 1: Baseline Characteristics – Analyses 1, 2, 3

Baseline characteristics (see section 8.3.2) will be described by PrEP type (oral vs. CAB OLI and LA), using median (interquartile range [IQR]) values for continuous data and relative frequencies for categorical data. Statistical comparisons of baseline characteristics between PrEP type will be conducted using chi-square tests for categorical variables and Wilcoxon-Mann-Whitney tests for continuous variables.

Primary Objective 2: CAB PrEP Adherence and Usage Patterns – Analyses 1, 2, 3

Target day will be reset as the day of the previous injection (1 month later for the 2nd injection, 2 months later for ≥3rd injection).

Adherence and usage pattern outcomes (see section 8.3.2) will be described among CAB-PrEP users only, using median (interquartile range [IQR]) values for continuous data and relative frequencies for categorical data. The following information will be provided: CAB PrEP formulation at initiation, delayed injections (% of the population, median duration of delay), missed injections (% of the population, total number, median number per person), discontinuation (% of the population, median time from 1st injection), oral bridging (% of the population, median duration, formulation used), and switch to oral PrEP (% of the population, median time from 1st injection, formulation used).

Baseline characteristics of individuals with vs. without any delayed and/or missed injections will be compared, using t-test for continuous variables (Wilcoxon rank sum test for not normally distributed variables) or chi-square test for categorical variables.

Baseline characteristics of individuals who did vs. did not discontinue will be compared using t-test for continuous variables (Wilcoxon rank sum test for not normally distributed variables) or chi-square test for categorical variables. Regression modeling will be conducted to identify characteristics predictive of non-adherence (delayed or missed injections).

Primary Objective 3: Incident STIs & HIV – Analysis 3

Incident HIV and STIs will be described among oral and LA CAB for PrEP users (see section 8.3.2).

The primary effectiveness measure for Primary Objective 3 is the incidence proportion and rate of HIV incidence overall, and stratified by CAB formulation/timing (i.e., during OLI vs. during LA PrEP). The following will be described among individuals who acquire HIV: time from CAB PrEP initiation to HIV acquisition, time from last injection to HIV acquisition, type of HIV testing performed when HIV was detected, frequency of HIV testing.

Adherence patterns and baseline characteristics of individuals who did vs. did not acquire HIV will be compared, using t-test for continuous variables (Wilcoxon rank sum test for not normally distributed variables) or chi-square test for categorical variables.

Time to HIV acquisition (i.e., time from first CAB LA PrEP injection to the first positive HIV test) will be assessed using Kaplan-Meier curve.

Primary Objective 4 (Analysis 3):

The first ART regimen after HIV acquisition will be described among CAB PrEP users who acquire HIV (see section 8.3.2). will be described separately, during the follow up period. Among individuals who initiated ART during follow-up, achievement of, and time to, virologic undetectability or suppression (see section 8.3.2) will also be assessed and reported by ART regimen (INSTI-based vs. not).

Secondary Objective 1: Incomplete initiation of CAB LA PrEP – Analyses 1, 2, 3

Incomplete initiation of CAB LA PrEP will be assessed among individuals with only one injection (i.e., loading dose) who have sufficient follow-up after the loading dose to observe delayed or missed second doses. Baseline demographic characteristics and ISR at first injection will be described.

8.8. Quality control and Quality Assurance

Epividian has working practices & procedures governing the use of observational data, the development of analysis specifications and plans, the development of analytical programming, the analytical quality assurance process and the scientific review of reports as well as clinical advisory charters for the clinical review of output intended for public domain. Working practices for the development of analysis specifications include basic identifying information, background material, relevant definitions of key study variables, population definitions, baseline definitions, specific requirements for dataset creation, statistical requirements such as eligibility criteria, exposures, outcomes and model fitting. Working practices for programming include naming conventions, proper code documentation and commentary, content, appearance, efficiencies (i.e., use of macros), and organization of output, maintainability and generalizability. Working practices for programming quality assurance include self-reviews of observational counts, missing data values, many-to-many merges, variable formatting, numeric-character & character-numeric conversions, uninitialized variables, unresolved macro references, report completeness and report-to-specification correspondence, and system errors and logs.

The quality assurance team review may include small sample spot-checking, coding log reviews, complete coding review, selected observations from intermediary dataset reviews, and/or independent programming to reproduce the results. Documentation of non-public domain reports includes market, scientific, statistical, and clinical review. Documentation of scientific protocols, reports and manuscripts intended for public domain follows two sequential steps: an internal-to-Epividian epidemiological, statistical, and clinical review, followed by a clinical/epidemiological external advisory board review.

All analytical data, coding algorithms, quality assurance (QA) documentation, and report outputs will be retained per Epividian standard practices.

8.9. Limitations of the research methods

With approximately 13% of the HIV population that is linked to care in the OPERA® database (per the CDC estimates), OPERA® can provide detailed information on a large portion of the HIV population in the U.S. Even so, issues confronting population-level assessments include such aspects as differential medical care by practice size and specialty, academic and research orientation of the health care practitioner, ethnic-based & gender-based attitudes and geographic regional health care practices. OPERA® clinical data is collected at point-of-care and is subject to the record-keeping practices of each healthcare provider and the standards of each clinic or organization. Patients may see multiple physician practices for various conditions, which may result in incomplete case ascertainment. Data are collected for the medical management of patients and is not directly intended for research purposes, but rather for the care and management of individual patients and patient populations. Moreover, OPERA does not include pharmacy records. Daily oral PrEP use will be ascertained based on prescription records, not refills, which may lead to some misclassification. Follow-up time is relatively short to observe HIV incidence and subsequent HIV treatment outcomes.

8.9.1. Study closure/uninterpretability of results

Not applicable, descriptive study.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

Clinical information is originally compiled into separate CHORUS™ databases for each clinic. This protected health information (PHI) is used in the creation of the CHORUS™ analytics and reporting used by each practice and its providers as part of Quality Improvement activities in an effort to improve care of patients. The data collection occurs via a secure and encrypted connection as part of Epividian's privacy and security policies

and systems, which are routinely reviewed by a third-party privacy and security advisory organisation.

Subsequently, the clinical data in each CHORUS™ database is de-identified and aggregated into the OPERA® Database following the guidelines of the Health Insurance Portability and Accountability Act (HIPAA) and the Health Information Technology for Economic and Clinical Health Act (HITECH).

Business Associate Agreements (BAA) in place between Epividian and all medical practices govern, following the guidelines established in HIPAA and HITECH, the encryption, transportation, aggregation, de-identification and use of all clinical data in either the CHORUS™ reporting platform or the OPERA® Database. All medical practices are responsible for obtaining proper HIPAA consent for their patients. With BAAs in place and subsequent de-identification, a separate informed consent for each individual, non-interventional study is not required. Additionally, investigational review board (IRB) approval has been granted for the processes of data extraction, transmission, management, analysis and reporting of healthcare data from OPERA® by Advarra IRB.

9.2. Subject confidentiality

All clinical data in CHORUS™ is PHI and managed as such according to HIPAA, HITECH and relevant state regulations. The CHORUS™ portal, as a Quality Improvement activity, is accessed securely by clinic staff to view PHI for only those patients seen at the practice. All clinical data is subsequently de-identified as per HIPAA and HITECH in OPERA® with all reports submitted at the aggregated population level in OPERA®. No personally identifiable information is available in the OPERA® Database. The OPERA® Epidemiology & Clinical Advisory Board (ECAB) provides clinical and methodological review & oversight.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

There is no potential to collect individual level data on serious and non-serious adverse events (AE), pregnancy exposures, device deficiencies and device related events or incidents related to any ViiV Healthcare product during the conduct of this research, as the minimum criteria needed to report AEs, pregnancy exposures, device deficiencies and device related events and incidents are not collected. Specifically, the data are insufficient to establish attribution between a potential safety event and an individual using a ViiV Healthcare product as the study design is to analyse deidentified, secondary data collected from individual medical records. Therefore, a study specific pharmacovigilance plan will not be developed.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

The target audience for these data includes healthcare providers, health plan population-based decision-makers, and regulatory and health authorities.

11.2. Study reporting and publications

Results will be published via study reports. Study results will be presented at scientific conferences and published in peer reviewed journal publication.

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