NON-INTERVENTIONAL STUDY PROTOCOL

STUDY DETAILS

UNIQUE IDENTIFIER	219844
TITLE	Prospective Study to Assess Usage, Adherence, Effectiveness of Cabotegravir LA for Pre-Exposure Prophylaxis in the United States in the OPERA Cohort
STUDY ACCOUNTABLE PERSON	PPD
SCIENTIFIC LEAD	PPD, ViiV Healthcare
CONTRIBUTING AUTHORS	PPD, Epividian PPD, Epividian PPD Epividian PPD ViiV Healthcare PPD ViiV Healthcare PPD ViiV Healthcare
ASSET ID	GSK1265744
GSK or ViiV ASSET	Cabotegravir (Apretude)
EFFECTIVE DATE	Final: 8 June 2023 Amendment 1 Final: 6 February 2024 Amendment 2 Final: 24 November 2025 Amendment 3 Final: 30 April 2026
INDICATION	HIV pre-exposure prophylaxis
DATA COLLECTION TYPE	Secondary
SAFETY OBJECTIVE	No
ASSET INVOLVEMENT	Yes
TSS/PASS ASSESSMENT PERFORMED	Yes

STUDY CLASSIFICATION	Voluntary PASS/TSS
EVALUATING A PRODUCT **(TIER TYPE)**	Tier 1
REGULATORY COMMITMENT	No

TITLE PAGE

Division: ViiV, Global Medical Sciences, Epidemiology and Real World Evidence

Information Type: Non-Interventional Study Protocol

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

Effective Date: Final: 8 June 2023

Amendment 1 Final: 6 February 2024

Amendment 2 Final: 24 November 2025

Amendment 3 Final: 30 April 2026

Author(s):

PPD Epividian

PPD , Epividian

PPD , Epividian

PPD ViiV Healthcare

PPD ViiV Healthcare

PPD , ViiV Healthcare

STUDY INFORMATION

Title	Prospective Study to Assess Usage, Adherence, Effectiveness of Cabotegravir LA for Pre-Exposure Prophylaxis in the United States in the OPERA Cohort
Protocol version identifier	Amendment 3
Date of last version of protocol	24 November 2025
EU PAS (ENCEPP) register number	EUPAS1000000165
Active substance	Cabotegravir
Medicinal product	Apretude
Product reference	N/A
Procedure number	N/A
Marketing authorisation holder(s)	ViiV Healthcare
Research question and objectives	**Primary Objectives:** - Describe baseline characteristics of oral and LA-PrEP users (Analyses 1–5). - To describe adherence and usage patterns of CAB OLI and/or LA-PrEP (Analyses 1–5). - Monitor the incidence of HIV and STIs while on CAB OLI and/or LA PrEP (Analyses 3–5). - Evaluate HIV treatment and viral suppression after HIV acquisition (Analyses 3–5). - Describe HIV testing patterns among CAB LA PrEP users (Analyses 2-5). **Secondary Objective:** Describe incomplete initiation of CAB LA for PrEP and associated factors (Analyses 1–5).

Country(-ies) of study	United States of America
Authors	PPD

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	ViiV Healthcare
MAH contact person	N/A

REVISION CHRONOLOGY

Date	Version	Change(s) since last version
8 June 2023	Original	-
6 February 2024	Amendment 1	Updated to ensure QPPV/CS&PV's review and approval with TSS and/or PASS studies per VQD-SOP-005925.
24 November 2025	Amendment 2	• The study duration has been extended by 24 months, resulting in revised timelines for the inclusion and study period. The inclusion period has been updated from December 21, 2021–June 30, 2024, to December 21, 2021–June 30, 2026. Similarly, the overall study period has been extended from December 21, 2021–December 31, 2024, to December 21, 2021–December 31, 2026. • The population has been restricted to adults aged 18 years or older. • The evaluation of the proportion of missed CAB LA doses was removed. Instead, delays are categorized into two groups: short delays that do not require reinitiation and long delays that necessitate reinitiation. • The study will also determine the percentage of patients diagnosed with bacterial STIs, parasitic STIs, or genital herpes who receive an appropriate antimicrobial prescription within 14 days of their diagnosis. • With the FDA approval of injectable lenacapavir as a second long-acting option for HIV prevention in June 2025, the study will additionally evaluate the proportion of individuals who discontinue CAB-LA for PrEP and transition to injectable lenacapavir for PrEP.
30 April 2026	Amendment 3	• Added an objective to characterize HIV testing patterns among users of CAB LA for PrEP.

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LIST OF ABBREVIATIONS

ADAP	AIDS Drug Assistance Program
AIDS	Acquired Immunodeficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ART	Antiretroviral Therapy
ASCVD	Atherosclerotic Cardiovascular Disease
AST	Aspartate aminotransferase
BAA	Business Associate Agreements
BILI	Bilirubin
BMI	Body Mass Index
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
HCV	Hepatitis C Virus
HCP	Healthcare Provider
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HITECH	Health Information Technology for Economic and Clinical Health
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSV	Herpes Simplex Virus
INR	International Normalized Ratio
INSTI	Integrase Strand Transfer Inhibitor
IQR	Interquartile Range
ISR	Injection Site Reaction
IRB	Institutional Review Board
LA	Long Acting
LDL	Low-Density Lipoprotein
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
PT	Prothrombin time
PWH	People with HIV
PWID	People Who Inject Drugs
QA	Quality Assurance
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
STI	Sexually Transmitted Infection
TAF	Tenofovir Alafenamide
TDF	Tenofovir Disproxil Fumarate
µL	Microliter
US	United States
VACS	Veterans Aging Cohort Study
VL	Viral Load

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1. RESPONSIBLE PARTIES

MARKETING AUTHORISATION HOLDER

ViiV Healthcare Company

Sponsor Legal Registered Address:

ViiV Healthcare
Company 410
Blackwell Street,
Durham, NC 27701
USA

1.1. Sponsor signatory

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

Compound Number: GSK1265744

PPD

Adrienne Guignard
Primary Author/ NI Scientific Lead

14 April 2026
Date

PPD

Vani Vannappagari
Global Head, Epidemiology and Real World Evidence

30 April 2026
Date

PPD

Nassrin Payvandi
VP & Head, Safety and Pharmacovigilance

30-Apr-2026
Date

PPD

Jens Ulrich Stegmann
ViiV QP

30-Apr-2026
Date

1.2. 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

Investigator Signature

29 April 2026

Date

2. SYNOPSIS

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 five time points through this study. **Analysis 1** will include data through 30 June 2023, **Analysis 2** will include data through 31 Dec. 2023, **Analysis 3** will include data through 31 Dec. 2024, **Analysis 4** will include data through 31 Dec. 2025 and **Analysis 5** will include through 31 Dec. 2026.

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 five time-points since market approval – **Analyses 1, 2, 3, 4, 5**

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, 4, 5**

a) Describe the use of CAB OLI prior to initiating CAB LA-PrEP versus direct to injection (DTI)

b) Describe delayed injections
c) Compare baseline demographic, behavioral, and clinical characteristics of individuals with vs. without any 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 and the use of injectable lenacapavir for a switch after discontinuation of CAB LA for PrEP

3: Monitor the incidence of HIV and STIs while on CAB OLI and/or LA PrEP – **Analysis 3, 4, 5**

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)
e) Determine the percentage of patients diagnosed with bacterial STIs, parasitic STIs, or genital herpes who receive an appropriate antimicrobial prescription within 14 days of their diagnosis (**4, 5**)

4: Evaluate HIV treatment and virologic suppression after HIV acquisition – **Analysis 3, 4, 5**

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

5: Describe patterns of HIV testing among CAB LA PrEP users – **Analysis 2, 3, 4, 5**
a) HIV testing within ≤1 week before/at the first injection, among all CAB LA initiators with ≥1 CAB LA injection
b) Describe distribution of frequency of HIV testing within ≤1 week before/at follow-up injections, among CAB LA complete initiators
c) Incidence proportion and incidence rates of HIV testing between the 1st injection and 1st discontinuation (**Analysis 4, 5)**

Secondary Objective:

1: Describe incomplete initiation of CAB LA for PrEP (i.e., receipt of the loading dose only) – **Analyses 1, 2, 3, 4, 5**

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 initiating a new PrEP formulation (oral or LA) in the eligibility window. For Primary Objectives 2, 3, 5 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 21 Dec. 2021 and 31 Dec. 2026 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 Primary Objective 5, the number and proportion of HIV testing within ≤1 week before/at the first injection, will be described among all CAB LA initiators. The distribution of the frequency of HIV testing within ≤1 week before/at follow-up injections will be estimated among CAB LA complete initiators. The incidence proportion and incidence rate of HIV testing will be estimated between the 1st injection and 1st discontinuation.

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.

3. AMENDMENTS AND UPDATES

Amendment or update no	Date	Amendment or update	Section of study protocol	Reason
Amendment 1	6 Feb. 2024	Added signatory page for QPPV/CS&PV's	Signatory page	Updated to ensure QPPV/CS&PV's review and approval with TSS and/or PASS studies per VQD-SOP-005925.
Amendment 2	24 Nov. 2025	Added abbreviations	Abbreviation	Add missing abbreviations.
		Additional milestones	4. Milestones	Add milestones corresponding to study extension.
		Updated analysis timing to reflect extension. Added analysis of STI treatment. Included description of CAB LA discontinuers transitioning to injectable lenacapavir.	7. Research Methods 7.2 Study population and setting	Specify the analysis timepoints linked to the extension. Licensing of a new injectable PrEP drug in the US in June 2025.
		Updated the age eligibility (adults only)	7.2.1.1. Inclusion Criteria	Correct the age eligibility criterion (≥18 years old) to reflect the OPERA IRB.
		Updates to reflect changes described above; replaced "missing doses" terminology by "short delay" and "long delay"	6.2 Objectives 7.3 Variables	Improve characterization of adherence.
		Updated to reflect study size changes following extension of the study period	7.5 Study size	Align study size with projection associated with extension.
		Updated analysis timing to reflect extension	7.6.3 Timings of assessment 7.7.1 Essential analysis	Section alignment following study extension.
		Revised wording in accordance with template requirements	9. Legal basis 10. Management and reporting of AE/AR	Alignment with protocol template Doc ID: TMF-15706807

Amendment 3	30 April 2026	Added objective 5 on patterns of HIV testing among CAB LA PrEP users	6.2 Objective 7. Research method	Assess compliance with HIV testing recommendation

4. MILESTONES

Milestone	Planned date
Contract execution	4Q2022
Kickoff Meeting	4Q2022
Draft protocol	4Q2022
Final protocol	2Q2023
Protocol amendment 1	1Q2024
Protocol amendment 2	4Q2025
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
Analysis 4	
Database Set-up	1Q2026
Initiation of Analysis (Analysis 4)	1Q2026
Preliminary Tables	2Q2026
Final Deliverables	3Q2026
Analysis 5	
Database Set-up	1Q2027
Initiation of Analysis (Analysis 4)	1Q2027
Preliminary Tables	2Q2027
Final Deliverables	3Q2027

5. BACKGROUND AND RATIONALE

5.1. Background

Clinical trials have demonstrated that preexposure prophylaxis (PrEP) with cabotegravir long-acting (CAB LA) injectable 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.

5.2. 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.

6. RESEARCH QUESTION AND OBJECTIVE(S)

6.1. Research questions

This study aims at assessing the number and characteristics of individuals being prescribed oral PrEP and CAB LA for PrEP, the adherence to CAB LA injections as well as viral suppression/failure among people who may acquire HIV while on CAB LA for PrEP.

Analyses will be conducted cumulatively at five time points through this study. **Analysis 1** will include data through 30 June 2023, **Analysis 2** will include data through 31 Dec. 2023, and **Analysis 3** will include data through 31 Dec. 2024, **Analysis 4** will include data through 31 Dec. 2025 and **Analysis 5** will include through 31 Dec. 2026.

6.2. Objectives

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 five time-points since market approval – **Analyses 1, 2, 3, 4, 5**

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, 4, 5**

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

c) Compare baseline demographic, behavioral, and clinical characteristics of individuals with vs. without any 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 and the use of injectable lenacapavir for a switch after discontinuation of CAB LA PrEP

3: Monitor incidence of HIV and STIs while on CAB OLI and/or LA PrEP – **Analysis 3, 4, 5**

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)
e) Determine the percentage of patients diagnosed with bacterial STIs, parasitic STIs, or genital herpes who receive an appropriate antimicrobial prescription within 14 days of their diagnosis (4, 5)

4: Evaluate HIV treatment and virologic suppression after HIV acquisition – **Analysis 3, 4, 5**

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

5: Describe patterns of HIV testing among CAB LA PrEP users – **Analysis 2, 3, 4, 5**

a) HIV testing within ≤1 week before/at the first injection, among all CAB LA initiators with ≥1 CAB LA injection
b) Describe distribution of frequency of HIV testing within ≤1 week before/at follow-up injections, among CAB LA complete initiators
c) Incidence proportion and incidence rates of HIV testing between the 1st injection and 1st discontinuation (**Analysis 4, 5)**

Secondary Objectives:

1: Describe incomplete initiation of CAB LA for PrEP (i.e., receipt of the loading dose only) – **Analyses 1, 2, 3, 4, 5**

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)

7. RESEARCH METHODS

7.1. Study Design

An observational study utilizing prospectively collected electronic health record (EHR) data over 18 to 60 months obtained from the OPERA® clinical cohort will be used to address the study aims/objectives.

Analyses will be conducted at five time points through this study, including data from 21 Dec. 2021.

Analysis 1 will include data through 30 June 2023 and will assess Primary Objectives 1-2 & Secondary Objective 1.

Analysis 2 will include data through 31 Dec. 2023 and will assess Primary Objectives 1-2 & Secondary Objective 1.

Analysis 3 will include data through 31 Dec. 2024 and will assess Primary Objectives 1-4 & Secondary Objective 1.

Analysis 4 will include data through 31 Dec. 2025 and will assess Primary Objectives 1-4 & Secondary Objective 1.

Analysis 5 will include data through 31 Dec 2026 and will assess Primary Objectives 1-4 & Secondary Objective 1.

For Primary Objective 1, the study population will consist of all HIV-negative adults initiating a new PrEP formulation (TDF/FTC, TAF/FTC, CAB OLI or LA) in the eligibility window. For Primary Objectives 2, 3, 5 and Secondary Objective 1, 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 five time points.

For Primary Objective 4, the study population will consist of individuals identified in Primary Objective 3 who acquired HIV between 21 Dec. 2021 and 31 Dec. 2024, 2025 or 2026 (as per the relevant analysis period) 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 31 Dec. 2026.

7.2. Study Population and Setting

7.2.1. Eligibility Criteria

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

7.2.1.1. Inclusion Criteria

Population Inclusion:

- Primary Objective 1, **Analyses 1, 2, 3, 4, 5**
  - HIV negative
  - ≥ 18 years of age
  - Initiating PrEP with TDF/FTC, TAF/FTC, or CAB OLI or LA injectable, without any other ARV
    - Analysis 1: between 21 Dec. 2021 and 31 Dec. 2022
    - Analysis 2: between 21 Dec. 2021 and 30 June 2023
    - Analysis 3: between 21 Dec. 2021 and 30 June 2024
    - Analysis 4: between 21 Dec. 2021 and 30 June 2025
    - Analysis 5: between 21 Dec. 2021 and 30 June 2026

- Primary Objective 2 & Secondary Objective 1, **Analyses 1, 2, 3, 4, 5**
  - HIV negative
  - ≥ 18 years of age
  - Initiating PrEP with CAB OLI or LA injectable, without any other ARV
    - Analysis 1: between 21 Dec. 2021 and 31 Dec. 2022
    - Analysis 2: between 21 Dec. 2021 and 30 June 2023
    - Analysis 3: between 21 Dec. 2021 and 30 June 2024
    - Analysis 4: between 21 Dec. 2021 and 30 June 2025
    - Analysis 5: between 21 Dec. 2021 and 30 June 2026

- Primary Objective 3 and 5, **Analysis 3, 4, 5**
  - HIV negative
  - ≥ 18 years of age
  - Initiating PrEP with CAB OLI or LA injectable, without any other ARV between 21 Dec 2021 and 30 June 2024, 2025 or 2026, as applicable

- Primary Objective 4, **Analysis 3, 4, 5**
  - HIV negative at PrEP initiation
  - ≥ 18 years of age
  - Initiating PrEP with CAB OLI or LA injectable, without any other ARV between 21 Dec. 2021 and 30 June 2024, 2025 or 2026, as applicable
  - Detection of HIV between 21 Dec. 2021 and 31 Dec. 2024 (analysis 3), 2025 (analysis 4) or 2026 (analysis 5) while on CAB OLI or LA PrEP

Censoring Events:

- Primary Objectives 1, 2, 3, 5 & 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: 30 June 2023
    - Analysis 2: 31 Dec. 2023
    - Analysis 3: 31 Dec. 2024
    - Analysis 4: 31 Dec. 2025
    - Analysis 5: 31 Dec. 2026
  - 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 CAB LA injections were administered without oral PrEP
  - Loss to follow-up (12 months after last clinical contact)
  - Death
  - HIV acquisition
- Primary Objective 4
  - Study end: 31 Dec. 2024 (analysis 3), 2025 (analysis 4), 2026 (analysis 5)
  - 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, 5 & 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

7.2.1.2. Exclusion Criteria

None

7.3. Variables

7.3.1. 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, 5 & 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.

7.3.2. Measurements & outcome definitions

Baseline Characteristics (Primary Objective 1; Analyses 1, 2, 3, 4, 5)

The following characteristics will be described at baseline:

- Demographic characteristics
  - Age (years)
    - Continuous
    - Categorical (18-29, 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, 4, 5)

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 Weighting 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 Weighting 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.

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

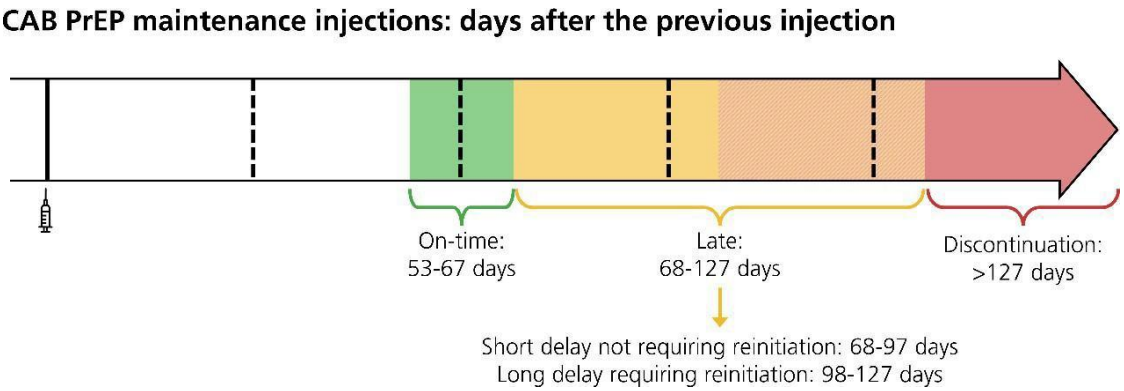
Non-adherence will be characterized as delayed injections.

- Delayed injection
  - Definition: Injections received outside of the target window but before the end of the next target window, without oral therapy for missed injection (Figure 1).
  - Determined based on the time between initiation injections (see Table 3)
    - All on-time maintenance injections
    - Any late maintenance injection (short delays not requiring reinitiation, long delays requiring reinitiation)
  - Measurements:
    - Number of individuals with delayed injection
    - Median duration of delayed injections
    - Baseline characteristics for the individuals with vs. without any delayed injection

Table 3: Timing of CAB LA PrEP maintenance injections, among complete initiators with ≥1 maintenance injection

Dosing pattern	**Timing of maintenance injections (following previous injection)**
On-time	53-67 days
Late	68-127 days
Short delay not requiring reinitiation	68-97 days
Long delay requiring reinitiation	98-127 days
Discontinuation	>127 days without injection

Figure 1: Illustration of Timing of Maintenance CAB LA PrEP Injection for Adherence Assessment



- 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

- Switch to injectable lenacapavir among individuals discontinuing CAB LA for PrEP
  - Number of individuals discontinuing CAB LA for PrEP who resume PrEP with injectable lenacapavir
  - Median number of days between last CAB LA injection and first lenacapavir injection

Patterns of HIV testing among CAB LA PrEP users (Primary Objective 5; Analyses 2, 3, 4, 5)

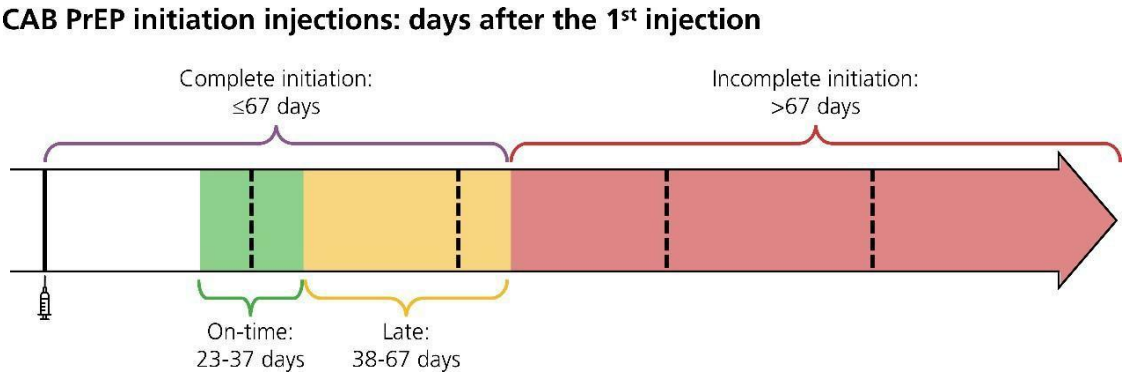
- HIV testing (Ag/Ab, RNA, Ag/Ab & RNA) within ≤1 week before/at the first injection, among all CAB LA initiators with ≥1 CAB LA injection
- Distribution of frequency of HIV testing within ≤1 week before/at follow-up injections, among CAB LA complete initiators
- Incidence proportion and incidence rates of HIV testing between the 1st injection and 1st discontinuation (**Analysis 4, 5)**

Incomplete initiation of CAB LA PrEP (Secondary Objective 1; Analyses 1, 2, 3, 4, 5)

- 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; Figure 2)
  - 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

Figure 2: Illustration of Timing of Initiation CAB LA PrEP Injections for Incomplete Initiation Assessment



Incident STIs & HIV (Primary Objective 3; Analysis 3, 4, 5)

- 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
    - Proportion of STI diagnoses with a prescription for an appropriate antimicrobial prescription within 14 days after the diagnosis

- Bacterial STI
  - Syphilis: benzathine penicillin G, aqueous crystalline penicillin G, procaine penicillin G + probenecid, doxycycline
  - Gonorrhoea: ceftriaxone, ceftriaxone + doxycycline, gentamicin + azithromycin, cefixime, cefotaxime
  - Chlamydia: doxycycline, azithromycin, levofloxacin, amoxicillin
- Parasitic STI
  - Trichomoniasis: metronidazole, tinidazole
- Genital herpes
  - HSV-2: acyclovir, famciclovir, valacyclovir

HIV treatment and virologic suppression after HIV acquisition (Primary Objective 4; Analysis 3, 4, 5)

- 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

7.3.3. Confounders and effect modifiers

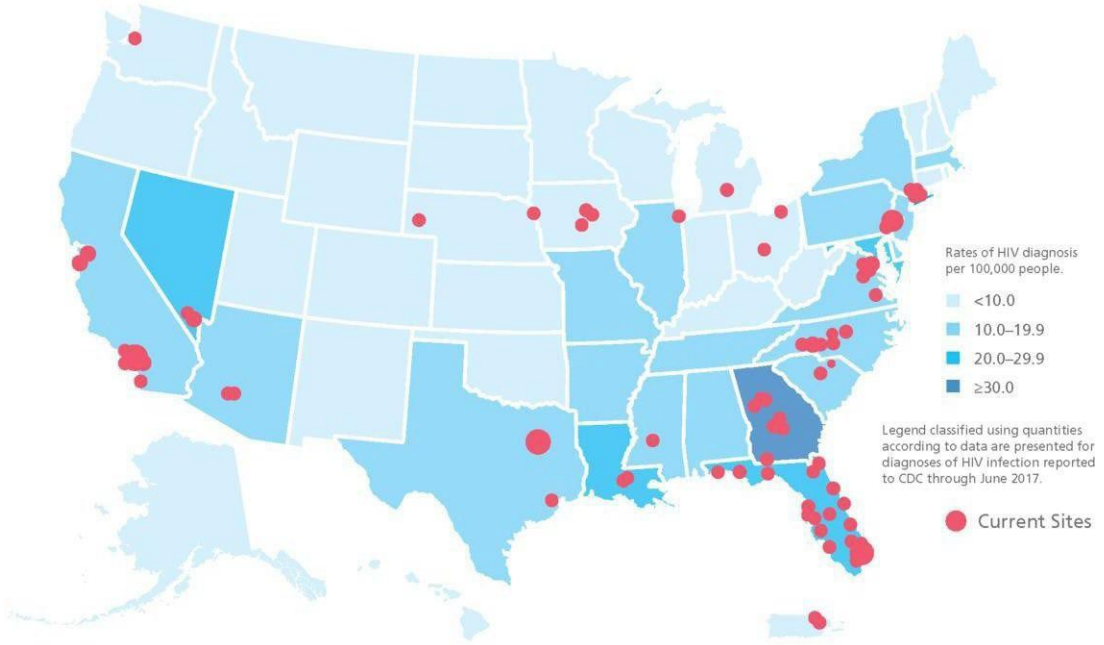
Not applicable, descriptive study.

7.4. 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 3).

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 3: United States Map of OPERA HIV+ Population and CDC (2017) State-by-State Estimates



7.5. Study size

A total of 429 HIV-negative individuals received their first CAB LA-PrEP injection between 31 Dec. 2021 and 12 Feb. 2023. Oral PrEP prescriptions have been captured since 2012 in OPERA and has thousands of users.

This study is observational and aims to assess usage of CAB LA for PrEP in real world clinical setting rather than testing a specific hypothesis. The initial phase, covering initiations between December 21, 2021, and June 30, 2024, aimed to enroll around 1,000 CAB LA PrEP users but ultimately included 1,748 initiators—1,547 complete initiators and 1,411 individuals with at least one continuation injection. Based on this, it is estimated that the total number of CAB LA initiators could range between 2,000 and

3,000 during the extended study period (December 21, 2021–June 30, 2026).

Table 4 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 4: 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
0.95	3000	0.3988	0.25	0.1044	0.5032
0.95	3000	0.5448	0.5	0.2798	0.8247
0.95	3000	0.7529	1	0.6747	1.4276
0.95	3000	0.9130	1.5	1.0941	2.0071
0.95	3000	1.0482	2	1.5262	2.5744
0.95	3000	1.1674	2.5	1.9664	3.1338

7.6. Data management

7.6.1. 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.

7.6.2. Resourcing needs

Not applicable.

7.6.3. Timings of Assessment during follow-up

Analysis period	Objectives	Analysis period
1: 21 Dec. 2021 through 30 June 2023	P1, P2, S1	2Q2023
2: 21 Dec. 2021 through 31 Dec. 2023	P1, P2, S1	2Q2023
3: 21 Dec. 2021 through 31 Dec. 2024	P1, P2, P3, P4, S1	2Q2025
4: 21 Dec. 2021 through 31 Dec. 2025	P1, P2, P3, P4, S1	2Q2026
5: 21 Dec. 2021 through 31 Dec. 2026	P1, P2, P3, P4, S1	2Q2027

7.7. Data analysis

7.7.1. Essential analysis

Primary Objective 1: Baseline Characteristics – Analyses 1, 2, 3, 4, 5

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, 4, 5

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), discontinuation (% of the population, median time from 1st injection), oral bridging (% of the population, median duration, formulation used), and switch to oral PrEP or lenacapavir long-acting for PrEP (% of the population, median time from 1st injection, formulation used).

Baseline characteristics of individuals with vs. without any delayed 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 injections).

Primary Objective 3: Incident STIs & HIV – Analysis 3, 4, 5

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, 4, 5):

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).

Primary Objective 5 (Analysis 2, 3, 4, 5):
The number and proportion of HIV testing within ≤1 week before/at the first injection will be described among all CAB LA initiators. The distribution of the frequency of HIV testing within ≤1 week before/at follow-up injections will be estimated among CAB LA complete initiators. Incidence rates and confidence intervals for HIV testing will be calculated using univariate Poisson regression (Analysis 4, 5).

Secondary Objective 1: Incomplete initiation of CAB LA PrEP – Analyses 1, 2, 3, 4, 5
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.

7.8. 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.

7.9. 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.

7.9.1. Study closure/uninterpretability of results

Not applicable, descriptive study.

8. PROTECTION OF HUMAN SUBJECTS

8.1. 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.

8.2. 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.

9. LEGAL BASIS FOR PROCESSING INDIVIDUAL HUMAN DATA

The authors confirm that study data is Individual Human Data (IHD) not owned by GSK/ViiV, but that the proposed use of the IHD aligns with the 'purpose of use' outlined in the source contract and/or the terms and conditions of use of the data source and it will comply with any specified prohibitions of use.

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.

This study does not have safety objectives. Safety collection and reporting will correspond to the following study type:

Study type 4: Secondary data collection studies based on structured data or unstructured data without human review without safety objectives. Structured data includes de-identified/anonymised healthcare data or health data are converted to a structured forms using automated/computer algorithms e.g., natural language processing. Unstructured data without human review, includes use of an automated algorithm and/or natural language processing for data extraction.	*These studies will not identify safety events as per study objective and cannot identify spontaneous events*

Collection of adverse events/reactions (Solicited Events)

The study outcomes are endpoints unrelated to safety that will not be collected and reported as solicited safety events.

Reporting of adverse events/reactions (Spontaneous Events)

There is no potential to collect serious and non-serious AEs, pregnancy exposures, or incidents related to any GSK/ViiV product during the conduct of this research, as the minimum criteria of identifiable patient, reporter, exposure and event, needed to collect and report individual case safety reports are not present in the data source. The study is based on secondary anonymised healthcare data which lack an identifiable patient and reporter and are insufficient to establish attribution between a potential safety event and an individual patient using a GSK/ViiV product.

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.

12. REFERENCES

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13. ANNEXES

13.1. Annex 1: Amendments to the protocol

AMENDMENT 2

- **Amendment 2**:

Change of protocol template: Protocol for Non-Interventional Studies PASS Studies and Non-PASS Studies (5.0) Apr 2025- Template Doc ID: TMF-15706807

- **Contributing authors**

Author(s):	PPD ~~ViiV Healthcare~~
	PPD ~~, ViiV Healthcare~~
	PPD ***ViiV Healthcare***

- **List of abbreviations**

ALP	***Alkaline Phosphatase***
ALT	***Alanine aminotransferase***
AST	***Aspartate aminotransferase***
BILI	***Bilirubin***
BMI	***Body Mass Index***
HCV	***Hepatitis C Virus***
HDL	***High-Density Lipoprotein***
HSV	***Herpes Simplex Virus***
INR	***International Normalized Ratio***
LDL	***Low-Density Lipoprotein***
PT	***Prothrombin time***
SGOT	***Serum glutamic-oxaloacetic transaminase***
SGPT	***Serum Glutamic Pyruvic Transaminase***
STI	***Sexually Transmitted Infection***

- **Milestones**

Milestone	**Planned date**
Contract execution	4Q2022
Kickoff Meeting	4Q2022
Draft protocol	4Q2022
Final protocol	2Q2023
Protocol amendment 1	***1Q2024***
Protocol amendment 2	***4Q2025***
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
Analysis 4	
Database Set-up	***1Q2026***
Initiation of Analysis (Analysis 4)	***1Q2026***
Preliminary Tables	***2Q2026***
Final Deliverables	***3Q2026***
Analysis 5	
Database Set-up	***1Q2027***
Initiation of Analysis (Analysis 4)	***1Q2027***
Preliminary Tables	***2Q2027***
Final Deliverables	***3Q2027***

- **Research questions**

This study aims at assessing the number and characteristics of individuals being prescribed oral PrEP and CAB LA for PrEP, the adherence to CAB LA injections as well as viral suppression/failure among people who may acquire HIV while on CAB LA for PrEP.

- **Objectives**

Analyses will be conducted cumulatively at ~~three~~ ***five*** time points through this study. Analysis 1 will include data through 30 June 2023, Analysis 2 will include data through 31 Dec. 2023, Analysis 3 will include data through 31Dec2024, ***Analysis 4 will include data through 31 Dec. 2025, and Analysis 5 will include through 31 Dec. 2026.***

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 five time-points since market approval – Analyses 1, 2, 3***, 4, 5***

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***, 4, 5***

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 ***and the use of injectable lenacapavir for a switch after discontinuation of CAB LA PrEP***

3: Monitor the incidence of HIV and STIs while on CAB OLI and/or LA PrEP – Analysis 3***, 4, 5***

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)
e) Determine the percentage of patients diagnosed with bacterial STIs, parasitic STIs, or genital herpes who receive an appropriate antimicrobial prescription within 14 days of their diagnosis (4, 5)

4: Evaluate HIV treatment and virologic suppression after HIV acquisition – Analysis 3*, **4, 5***

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) – Analysis 1, 2, 3***, 4, 5***

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**

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.

An observational study utilizing prospectively collected electronic health record (EHR) data over 18 to ~~36~~ ***60*** months obtained from the OPERA® clinical cohort will be used to address the study aims/objectives.

Analyses will be conducted at ~~three~~ ***five*** time points through this study, including data from 21 Dec. 2021

Analysis 4 will include data through 31 Dec. 2025 and will assess Primary Objectives 1-4 & Secondary Objective 1.

Analysis 5 will include data through 31 Dec 2026 and will assess Primary Objectives 1-4 & Secondary Objective 1.

For Primary Objective 4, the study population will consist of individuals identified in Primary Objective 3 who acquired HIV between 21 Dec. 2021 and ***31 Dec. 2024, 2025 or 2026 (as per the relevant analysis period)*** 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 31 Dec. ***2026***.

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~~ ***five*** time points.

- **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, ***4, 5***
  - HIV negative
  - ≥ ***18*** ~~12~~ years of age
  - Initiating PrEP with TDF/FTC, TAF/FTC, or CAB OLI or LA injectable, without any other ARV
    - Analysis 1: between 21 Dec. 2021 and 31 Dec. 2022
    - Analysis 2: between 21 Dec. 2021 and 30 June 2023
    - Analysis 3: between 21 Dec. 2021 and 30 June 2024
    - ***Analysis 4: between 21 Dec. 2021 and 30 June 2025***
    - ***Analysis 5: between 21 Dec. 2021 and 30 June 2026***

- Primary Objective 2 & Secondary Objective 1, Analyses 1, 2, 3, ***4, 5***
  - HIV negative
  - ≥ ***18*** ~~12~~ years of age
  - Initiating PrEP with CAB OLI or LA injectable, without any other ARV
    - ***Analysis 1: between 21 Dec. 2021 and 31 Dec. 2022***
    - ***Analysis 2: between 21 Dec. 2021 and 30 June 2023***
    - ***Analysis 3: between 21 Dec. 2021 and 30 June 2024***
    - ***Analysis 4: between 21 Dec. 2021 and 30 June 2025***
    - ***Analysis 5: between 21 Dec. 2021 and 30 June 2026***

- Primary Objective 3, Analysis 3, ***4, 5***
  - HIV negative
  - ≥ ***18*** ~~12~~ years of age
  - Initiating PrEP with CAB OLI or LA injectable, without any other ARV between 21 Dec. 2021 and 30 June 2024***, 2025 or 2026, as applicable***

- Primary Objective 4, Analysis 3, ***4, 5***
  - HIV negative at PrEP initiation
  - ≥ ***18*** ~~12~~ years of age
  - Initiating PrEP with CAB OLI or LA injectable, without any other ARV between 21 Dec. 2021 and ~~31DEC2023~~ ***30 June 2024, 2025 or 2026, as applicable***
  - Detection of HIV between 21 Dec. 2021 and ***31 Dec. ~~2023~~2024 (analysis 3), 2025 (analysis 4) or 2026 (analysis 5)*** 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: 30 June 2023
    - Analysis 2: 31 Dec. 2023
    - Analysis 3: 31 Dec. 2024
    - ***Analysis 4: 31 Dec. 2025***
    - ***Analysis 5: 31 Dec. 2026***
  - 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 ***CAB LA*** injections were administered without oral PrEP
  - Loss to follow-up (12 months after last clinical contact)
  - Death
  - HIV acquisition
- Primary Objective 4
  - Study end: 31 Dec. 2024 ***(analysis 3), 2025 (analysis 4), 2026 (analysis 5)***
  - 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

- **Measurements & outcome definitions**
- **Baseline Characteristics (Primary Objective 1; Analyses 1, 2, 3, *4, 5)***

  - Demographic characteristics
    - Age (years)
      - Continuous
      - Categorical (~~12-19~~, ~~20~~***18***-29, 30-39, 40-49, 50-59, 60-69, ≥70)

CAB PrEP Adherence and Usage Patterns (Primary Objective 2; Analyses 1, 2, 3, ***4, 5)***

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 **1** ~~2~~).
  - ***Determined based on the time between initiation injections (see Table 1)***
    - ***All on-time maintenance injections***
    - ***Any late maintenance injection (short delays not requiring reinitiation, long delays requiring reinitiation)***
  - Measurements:
    - Number of individuals with delayed injection
    - Median duration of delayed injections

Table 3: Timing of CAB LA PrEP maintenance injections, among complete initiators with ≥1 maintenance injection

Dosing pattern	***Timing of maintenance injections (following previous injection)***
On-time	***53-67 days***
Late	***68-127 days***
Short delay not requiring reinitiation	***68-97 days***
Long delay requiring reinitiation	***98-127 days***
Discontinuation	***>127 days without injection***

Figures: Figure 1 and 2 were updated. Figure 3 from the previous protocol version was removed.

Figure 1: Illustration of Timing of Maintenance CAB LA PrEP Injection for Adherence Assessment

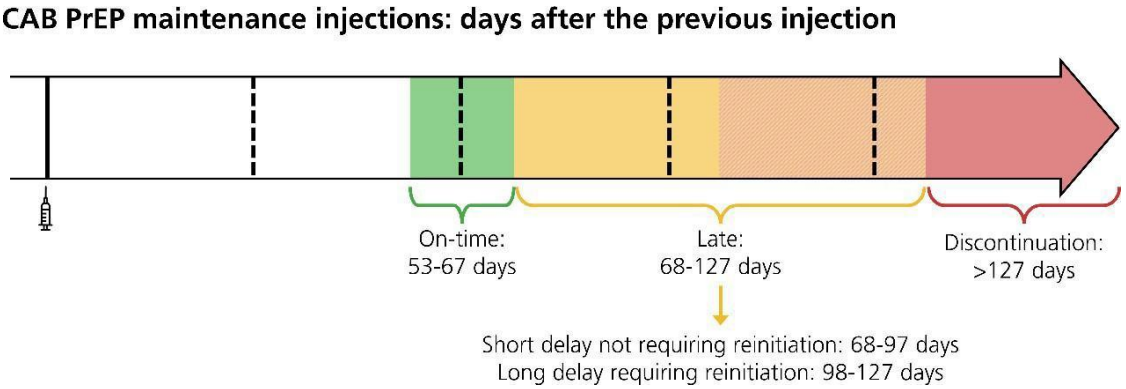
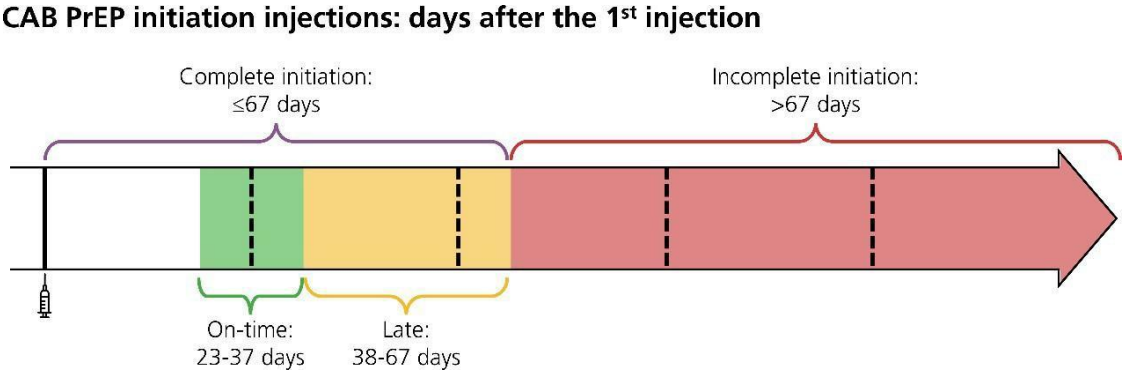


Figure 2: Illustration of Timing of Initiation CAB LA PrEP Injections for Incomplete Initiation Assessment



~~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~~

- ***Switch to injectable lenacapavir among individuals discontinuing CAB LA for PrEP***
  - ***Number of individuals discontinuing CAB LA for PrEP who resume PrEP with injectable lenacapavir***
  - ***Median number of days between last CAB LA injection and first lenacapavir injection***

- Incomplete initiation of CAB LA PrEP (Secondary Objective 1; Analyses 1, 2, 3, ***4, 5)***

- Incident STIs & HIV (Primary Objective 3; Analysis 3, ***4, 5)***

- HIV treatment and virologic suppression after HIV acquisition (Primary Objective 4; Analysis 3, ***4, 5)***

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
  - ***Proportion of STI diagnoses with a prescription for an appropriate antimicrobial prescription within 14 days after the diagnosis***
    - ***Bacterial STI***
      - ***Syphilis: benzathine penicillin G, aqueous crystalline penicillin G, procaine penicillin G + probenecid, doxycycline***
      - ***Gonorrhoea: ceftriaxone, ceftriaxone + doxycycline, gentamicin + azithromycin, cefixime, cefotaxime***
      - ***Chlamydia: doxycycline, azithromycin, levofloxacin, amoxicillin***
      - ***Chancroid: azithromycin, ceftriaxone, ciprofloxacin, erythromycin base***
      - ***Lymphogranuloma venereum: doxycycline, azithromycin, erythromycin base***
      - ***Mycoplasma genitalium: doxycycline + azithromycin, doxycycline + moxifloxacin***
    - ***Parasitic STI***
      - ***Trichomoniasis: metronidazole, tinidazole***
    - ***Genital herpes***
      - ***HSV-2: acyclovir, famciclovir, valacyclovir***

- **Study size**

~~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.~~

This study ***is observational and aims*** to assess usage of CAB LA for PrEP in real world clinical ***setting rather than testing a specific hypothesis. The initial phase, covering initiations between December 21, 2021, and June 30, 2024, aimed to enroll around 1,000 CAB LA PrEP users but ultimately included 1,748 initiators—1,547 complete initiators and 1,411 individuals with at least one continuation injection. Based on this, it is estimated that the total number of CAB LA initiators could range between 2,000 and 3,000 during the extended study period (December 21, 2021–June 30, 2026).***

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
0.95	***3000***	***0.3988***	***0.25***	***0.1044***	***0.5032***
0.95	***3000***	***0.5448***	***0.5***	***0.2798***	***0.8247***
0.95	***3000***	***0.7529***	***1***	***0.6747***	***1.4276***
0.95	***3000***	***0.9130***	***1.5***	***1.0941***	***2.0071***
0.95	***3000***	***1.0482***	***2***	***1.5262***	***2.5744***
0.95	***3000***	***1.1674***	***2.5***	***1.9664***	***3.1338***

- **Timings of Assessment during follow-up**

Analysis period	Objectives	Analysis period
1: 21 Dec. 2021 through 30 June 2023	P1, P2, S1	2Q2023
2: 21 Dec. 2021 through 31 Dec. 2023	P1, P2, S1	2Q2023
3: 21 Dec. 2021 through 31 Dec. 2024	P1, P2, P3, P4, S1	2Q2025
4: 21 Dec. 2021 through 31 Dec. 2025	***P1, P2, P3, P4, S1***	***2Q2026***
5: 21 Dec. 2021 through 31 Dec. 2026	***P1, P2, P3, P4, S1***	***2Q2027***

- **Data analysis**

Primary Objective 1: Baseline Characteristics – Analyses 1, 2, 3, ***4, 5)***

Primary Objective 2: CAB PrEP Adherence and Usage Patterns – Analyses 1, 2, 3, ***4, 5)***

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 ***or lenacapavir long-acting for PrEP*** (% of the population, median time from 1st injection, formulation used).

Primary Objective 3: Incident STIs & HIV – Analysis 3, ***4, 5)***

Primary Objective 4 (Analysis 3, ***4, 5)***

Secondary Objective 1: Incomplete initiation of CAB LA PrEP – Analyses 1, 2, 3, ***4, 5)***

- ***Legal basis for processing individual human data***

The authors confirm that study data is Individual Human Data (IHD) not owned by GSK/ViiV, but that the proposed use of the IHD aligns with the 'purpose of use' outlined in the source contract and/or the terms and conditions of use of the data source and it will comply with any specified prohibitions of use.

- **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.~~

This study does not have safety objectives. Safety collection and reporting will correspond to the following study type:

Study type 4: Secondary data collection studies based on structured data or unstructured data without human review without safety objectives. Structured data includes de-identified/anonymised healthcare data or health data are converted to a structured forms using	***These studies will not identify safety events as per study objective and cannot identify spontaneous events***

automated/computer algorithms e.g., natural language processing. ***Unstructured data without human review, includes use of an automated algorithm and/or natural language processing for data extraction.***	

Collection of adverse events/reactions (Solicited Events)

The study outcomes are endpoints unrelated to safety that will not be collected and reported as solicited safety events.

Reporting of adverse events/reactions (Spontaneous Events)

There is no potential to collect serious and non-serious AEs, pregnancy exposures, or incidents related to any GSK/ViiV product during the conduct of this research, as the minimum criteria of identifiable patient, reporter, exposure and event, needed to collect and report individual case safety reports are not present in the data source. The study is based on secondary anonymised healthcare data which lack an identifiable patient and reporter and are insufficient to establish attribution between a potential safety event and an individual patient using a GSK/ViiV product.

AMENDMENT 3

- **Objectives**

5: Describe patterns of HIV testing among CAB LA PrEP users
Analysis 2, 3, 4, 5

- ***HIV testing within ≤1 week before/at the first injection, among all CAB LA initiators with ≥1 CAB LA injection***
- ***Describe distribution of frequency of HIV testing within ≤1 week before/at follow-up injections, among CAB LA complete initiators***
- ***Incidence proportion and incidence rates of HIV testing between the 1st injection and 1st discontinuation (Analysis 4, 5)***

- **Study design**

Population Inclusion

- Primary Objective 3 ***and 5***, **Analysis 2, 3, 4, 5**

Censoring Events

- Primary Objectives 1, 2, 3***, 5*** & Secondary Objective 1

Index date (baseline):

- Primary Objectives 1, 2, 3***, 5*** & Secondary Objective 1: start of a new PrEP formulation

Variables

Exposure definitions

Primary Objectives 5: CAB LA-PrEP will be the exposure of interest, without a comparator exposure.

Measurements & outcome definitions

Patterns of HIV testing among CAB LA PrEP users (Primary Objective 5; Analyses 2, 3, 4, 5)

- ***HIV testing (Ag/Ab, RNA, Ag/Ab & RNA) within ≤1 week before/at the first injection, among all CAB LA initiators with ≥1 CAB LA injection Incidence proportion and incidence rates of HIV testing between the 1st injection and 1st discontinuation***
- ***Distribution of frequency of HIV testing within ≤1 week before/at follow-up injections, among CAB LA complete initiators***
- ***Incidence proportion and incidence rates of HIV testing between the 1st injection and 1st discontinuation (Analysis 4, 5)***

- **Data analysis**

Essential analysis

Primary Objective 5 (Analysis 2, 3, 4, 5):
The number and proportion of HIV testing within ≤1 week before/at the first injection, will be described among all CAB LA initiators. The distribution of the frequency of HIV testing within ≤1 week before/at follow-up injections will be estimated among CAB LA complete initiators. Incidence rates and confidence intervals for HIV testing will be calculated using univariate Poisson regression (Analysis 4, 5).