NON-INTERVENTIONAL STUDY PROTOCOL

TITLE PAGE

Division: Global Medical

Information Type: Non-Interventional Study Protocol Amendment

Title: Patient Characteristics, Adherence and Clinical Outcomes among People Living with HIV (PLWH) Initiating Cabotegravir + Rilpivirine LA regimen in the OPERA Cohort – Protocol Amendment

Compound Number: GSK1265744, TMC278

Effective Date:

17 May 2024

Subject: Long-acting ARV, Cabotegravir, Rilpivirine, Utilization, Adherence, Discontinuation, Clinical outcomes

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STUDY INFORMATION

Title	Patient Characteristics, Adherence and Clinical Outcomes among People Living with HIV (PLWH) Initiating Cabotegravir + Rilpivirine LA regimen in the OPERA Cohort – Protocol Amendment
Protocol version identifier	Amendment V1
Date of last version of protocol	16 August 2021
Active substance	Cabotegravir Rilpivirine
Medicinal product	VOCABRIA® 30 mg film-coated tablets Edurant® 25 mg film-coated tablets Cabenuva
Product reference	NDA 212887 VOCABRIA (cabotegravir) tablets NDA 202022 EDURANT (rilpivirine) tablets NDA 212888 CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), co-packaged, for intramuscular use
Marketing authorisation holder(s)	ViiV Healthcare
Research question and objectives	Using real-world clinical data from a large US cohort, this study will describe utilization, adherence and clinical outcomes among people with HIV initiating CAB+RPV LA regimen.
Country(-ies) of study	United States
Author	PPD ViiV Healthcare PPD

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	ViiV Healthcare
MAH contact person	PPD

UNIQUE IDENTIFIER	216990
TITLE	Patient Characteristics, Adherence and Clinical Outcomes among People Living with HIV (PLWH) Initiating Cabotegravir + Rilpivirine LA regimen in the OPERA Cohort – Protocol Amendment
STUDY ACCOUNTABLE PERSON	PPD Epidemiology and RWE
CONTRIBUTING AUTHORS	PPD PPD, Epividian PPD, Epividian PPD PPD Epividian
ASSET ID	GSK1265744, TMC278
GSK ASSET	Cabotegravir + Rilpivirine LA (CABENUVA)
EFFECTIVE DATE	17 May 2024
INDICATION	HIV-1
SAFETY OBJECTIVE	YES

DATA COLLECTION TYPE	SECONDARY
TSS/PASS ASSESSMENT PERFORMED	Yes

REVISION CHRONOLOGY

Date	Version	Change(s) since last version
16 August 2021	Original	N/A
17 May 2024	Amendment	• Extending the study for additional 3 years and updating the milestones table • Study population: o Including PWH 13 years and older o Excluding treatment naïve individuals • Primary objective: o Factors associated with confirmed virologic failure is listed as a separate primary objective • Secondary objective: o Sub-group analyses are listed as a secondary objective • Oral lead-in and oral bridging will not be assessed

SUMMARY OF CHANGES

"Patient characteristics, Adherence, and Clinical Outcomes among People Living with HIV (PLWH), Initiating Cabotegravir + Rilpivirine LA Regimen in OPERA cohort" (Study #216990) is a ViiV-sponsored two-year observational cohort study utilizing prospectively collected electronic health record (EHR) data obtained from the OPERA cohort that commenced in December 2020 (effective date: 16 August 2021).

The proposed plan is to extend the study for three years, from two years to five years, to assess the demographics, utilization patterns, persistence, adherence, and effectiveness of Cabotegravir (CAB) + Rilpivirine (RPV) LA in OPERA cohort over the first five years of availability of the regimen.

Proposed changes to study population:

The proposed changes to the study population are listed below:

1. The initial study included people with HIV (PWH) 18 years and older and this study will include PWH who are 13 years of age or older so that we can describe the adolescent population.
2. The initial study included all individuals initiating CAB+RPV LA regimen and this study will only include the treatment experienced individuals as we did not observe any treatment naïve individuals initiating CAB+RPV LA in the initial study.

Proposed changes in study objectives:

The proposed changes to the study objectives are:

1. Primary objective:
    a. Factors associated with confirmed virologic failure was not listed as a separate primary objective in the initial study but was assessed as part of virologic effectiveness analysis. It is called out as a separate primary objective in this study as we will enough numbers to conduct this analysis.
2. Secondary objective:
    a. Sub-group analyses by viral load (<50 copies/mL, 50 - <200 copies/mL, and ≥200 copies/mL), BMI (<30 and ≥30 kg/m^2) and age (<18, 18-50, 50-64, ≥65 years) at initiation to assess characteristics, adherence, persistence, discontinuation and virologic effectiveness are explicitly called out as a secondary objective in this study. Some of the sub-groups listed were evaluated in the initial study but was not listed as a study objective.
3. Oral lead-in and oral bridging explored in the initial study will not be assessed in this study as these events cannot be reliably observed in the OPERA data.

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LIST OF ABBREVIATIONS

ADAP	AIDS Drug Assistance Program
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
BAA	Business Associate Agreements
BIC	Bictegravir
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
ECAB	Epidemiology & Clinical Advisory Board
EHR	Electronic Health Record
FDA	Food and Drug Administration
FTC	Emtricitabine
HIPAA	Health Insurance Portability and Accountability Act
HITECH	Health Information Technology for Economic and Clinical Health
HIV	Human Immunodeficiency Virus
INSTI	Integrase Strand Transfer Inhibitor
IQR	Interquartile Range
IRB	Institutional Review Board
LA	Long Acting
mL	Milliliter
MIPS	Merit-based Incentive Payment System
MSM	Men who have Sex with Men
OPERA®	Observational Pharmaco-Epidemiology Research and Analysis
PHI	Protected Health Information
PWH	People with HIV
PWID	People Who Inject Drugs
RPV	Rilpivirine
QA	Quality Assurance
RNA	Ribonucleic Acid
TAF	Tenofovir
µL	Microliter
US	United States
VACS	Veterans Aging Cohort Study
VL	Viral load

TRADEMARK INFORMATION

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VOCABRIA™

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OPERA®

1. *RESPONSIBLE PARTIES

MARKETING AUTHORISATION HOLDER
ViiV Healthcare Company

Sponsor Legal Registered Address:
ViiV Healthcare Company
410 Blackwell St.
Durham, NC 27701

1.1. SPONSOR SIGNATORY

Title: Patient Characteristics, Adherence and Clinical Outcomes among People Living with HIV (PLWH) Initiating Cabotegravir + Rilpivirine LA regimen in the OPERA Cohort – Protocol Amendment

Compound Number: GSK1265744, TMC278

PPD

10 May 2024

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Date (DD Month YYYY)

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10 May 2024

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17-May-2024

Jens Ulrich Stegmann
ViiV QPPV

Date (DD Month YYYY)

*SYNOPSIS

***Title** Patient Characteristics, Adherence and Clinical Outcomes among People Living with HIV (PLWH) Initiating Cabotegravir + Rilpivirine LA regimen in the OPERA Cohort – Protocol Amendment

***Rationale and background**

The advancements in antiretroviral therapy (ART) over the past three decades have produced a marked reduction in both morbidity and mortality associated with HIV infection. To further improve HIV treatment options, recent clinical development has been focused on long-acting formulations. Cabotegravir + rilpivirine long-acting (CAB+RPV LA) injectable is the first complete long-acting antiretroviral regimen approved for treatment of HIV-1 in the US. It is indicated for people with HIV (PWH) who are virologically suppressed (HIV-1 RNA viral load [VL] <50 copies per mL) on a stable antiretroviral regimen, with no history of treatment failure and no known or suspected resistance to CAB or RPV. While clinical studies have established the efficacy, safety, and tolerability of CAB+RPV LA, this study will assess the utilization patterns, adherence, and effectiveness of this regimen in real-world clinical setting over the first five years of availability.

***Research question and Objective(s)**

The overall objective of this study is to describe characteristics and assess clinical outcomes among people with HIV in the Observational Pharmaco-Epidemiology Research and Analysis (OPERA®) cohort who receive CAB+RPV LA regimen.

Primary Objectives:

1. To describe baseline demographics, clinical characteristics and patterns of use among PWH receiving CAB+RPV LA at Year 3, Year 4, and Year 5 of availability

2. To assess the persistence, adherence and discontinuation among PWH receiving CAB+RPV LA at Year 3, Year 4, and Year 5 of availability

3. To assess virologic effectiveness among PWH receiving CAB+RPV LA at Year 3, Year 4, and Year 5 of availability

4. To assess factors associated with confirmed virologic failure among PWH receiving CAB+RPV LA regimen at Year 3, Year 4, and Year 5 of availability

Secondary Objectives:

1. Sub-group analyses by viral load (VL <50, 50-<200 and ≥ 200 copies/mL) at initiation, BMI (<30 and ≥30 kg/m2) at initiation and age (<18, 18-50, 50-64, ≥65 years) at initiation to assess characteristics, adherence, persistence, discontinuation and virologic effectiveness

2. To estimate the frequency of documented injection site reactions and hypersensitivity reactions among PWH receiving CAB+RPV LA injections at Year 3, Year 4, and Year 5 of availability

***Study Design**

This is an observational study utilizing prospectively collected electronic health record (EHR) data obtained from the OPERA® cohort. The study population will include treatment experienced PWH who are 13 years or older, are active in care in OPERA, and received at least one CAB+RPV LA injection between 21JAN2021 and 31DEC2023, 21JAN2021 and 31DEC2024, and 21JAN2021 and 31DEC2025. PWH will be followed from the date of their first CAB+RPV injection until discontinuation of CAB+RPV regimen, death, loss to follow-up (12 months after last clinical contact), or study end (29FEB2024, 28FEB2025, and 28FEB2026).

***Population**

Inclusion criteria:

- People with HIV
- ≥13 years old
- Treatment experienced
- Active in care in OPERA defined as having a clinical encounter in the 24 months prior to 31DEC2023, 31DEC2024, 31DEC2025
- Received at least one CAB+RPV LA injection between 21JAN2021 and 31DEC2023, 31DEC2024, 31DEC2025

Exclusion criteria:

- Received CAB+RPV LA regimen as part of a clinical trial
- Treatment naïve

***Variables**

Outcomes:

- Persistence/Durability
- Discontinuation
- Adherence
- Virologic effectiveness

Potential confounders to be evaluated:

- Baseline: age, gender, race, ethnicity, region, marital status, risk of HIV transmission, payer type, CD4 cell count, viral load, prior regimen, years since HIV diagnosis and ART initiation, weight, BMI, co-infections, comorbidities, concomitant medications

***Data sources**

The OPERA cohort is a multi-site observational database built from the complete patient health records managed in EHR systems from more than 400 participating healthcare providers at 142 separate locations throughout the US. 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 PWLH linked to care in the U.S.

***Study size**

Over two years (21JAN2021 and 28FEB2023), there were 1,843 individuals who were 18 years of age or older with HIV-1 in OPERA who were active in care and had received their first CAB+RPV injection. Of these, 1,578 had viral loads <50 copies/mL at first injection, 136 had viral loads 50 to < 200 copies/mL, and 93 had viral loads ≥200 copies/mL (36 had no viral load data available at first injection). Study size is expected to increase over the course of this study.

***Data analysis**

Baseline characteristics and outcomes will be described using counts and relative frequencies for categorical variables and medians with interquartile ranges (IQR) for continuous variables. For outcomes assessed at any point during follow-up, incidence rates will be estimated using unadjusted Poisson regression, accounting for person-time since index (i.e., first CAB+RPV LA injection). Analyses will be stratified by viral load (<50 copies/mL vs. 50 - <200 copies/mL vs. ≥200 copies/mL), BMI (<30 kg/m2 vs. ≥30 kg/m2) and age (<18, 18-50, 50-64, ≥65 years) at initiation of CAB+RPV regimen. Factors associated with confirmed virologic failure will be assessed using multiple logistic regression.

2. *AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	17 May 2024	Study objectives and study population	Amendment	Extending the study for additional 3 years Study population: • Including PWH 13 years and older • Excluding treatment naïve individuals Primary objective: • Factors associated with confirmed virologic failure is listed as a separate primary objective Secondary objective: • Sub-group analyses are listed as a secondary objective Oral lead-in and oral bridging will not be assessed
<<n>>	<<Date>>	<<Text>>	<<Text>>	<<Text>>
<<n>>	<<Date>>	<<Text >>	<<Text>>	<<Text>>

3. *MILESTONES

Milestone	Planned date
Draft protocol	December 2023
Final protocol	February 2024
Analysis Start Date	April 2024
Yr 3 Preliminary Tables	May 2024
Yr 3 Final Tables	August 2024
Yr 4 Preliminary Tables	May 2025

Yr 4 Final Tables	August 2025
Yr 5 Preliminary Tables	July 2026
Yr 5 Final report of study results	October 2026

4. *RATIONALE AND BACKGROUND

Antiretroviral therapy (ART) has transformed human immunodeficiency virus (HIV) infection from a fatal illness to a chronic disease.[1] The advancements in antiretroviral therapy (ART) over the past three decades have produced a marked reduction in both morbidity and mortality associated with HIV infection. Since then, the introduction of single-tablet regimens (STR) and once-daily dosing has been associated with increased adherence and improved clinical outcomes in HIV and other illnesses. To further improve HIV treatment options, recent clinical development has been focused on long-acting formulations; formulations that may be dosed once-weekly, once-monthly, and once-bi-monthly. Various routes of delivery for these long-acting formulations are currently being explored, including oral delivery, intravenous infusion, intra-muscular injection, subcutaneous injection, and implantable/removable device delivery.[2-6]

Cabenuva®, a 2-drug co-packaged product of Cabotegravir, a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI), and Rilpivirine, an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either Cabotegravir or Rilpivirine.

The novel long-acting ART therapy delivered through intramuscular injection – CAB+RPV LA – has been shown to be non-inferior to daily oral therapy. Prior to starting the regimen, the healthcare provider (HCP) should carefully select people with HIV (PWH) who agree to the required injection schedule and counsel individuals about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance associated with missed doses.

CAB, in combination with RPV, has a prolonged PK which presents patients with the opportunity to take their HIV treatment once monthly or once every two months instead of daily; potentially allowing for much improved adherence. While clinical studies have established the efficacy, safety and tolerability of Cabenuva®, this study will assess the utilization patterns, adherence and effectiveness of the regimen in the real-world clinical setting. Understanding patient characteristics and clinical outcomes of this regimen in a heterogeneous population is of great importance to providing optimal care for PWH.

Rationale

CAB+RPV LA is the first long acting intramuscular injection with an oral lead in, and differing doses for initiation and maintenance. While clinical studies have established the efficacy, safety and tolerability of Cabenuva®, this study will assess the utilization patterns, adherence and effectiveness of the regimen in real world clinical setting. Understanding patient characteristics and clinical outcomes of this regimen in heterogeneous population is of great importance to provide optimal care of PWH.

5. *RESEARCH QUESTION AND OBJECTIVE(S)

The overall objective of this study is to describe characteristics and assess clinical outcomes among people with HIV in the Observational Pharmaco-Epidemiology Research and Analysis (OPERA®) cohort who receive CAB+RPV LA regimen.

Primary Objectives:

1. To describe baseline demographics, clinical characteristics and patterns of use among PWH receiving CAB+RPV LA at Year 3, Year 4, and Year 5 of availability

2. To assess the persistence, adherence and discontinuation among PWH receiving CAB+RPV LA at Year 3, Year 4, and Year 5 of availability

3. To assess virologic effectiveness among PWH receiving CAB+RPV LA at Year 3, Year 4, and Year 5 of availability

4. To assess factors associated with confirmed virologic failure among PWH receiving CAB+RPV LA regimen at Year 3, Year 4, and Year 5 of availability

Secondary Objectives:

1. Sub-group analyses by viral load (VL <50, 50-<200 and ≥ 200 copies/mL) at initiation, BMI (<30 and ≥30 kg/m2) at initiation and age (<18, 18-50, 50-64, ≥65 years) at initiation to assess characteristics, adherence, persistence, discontinuation and virologic effectiveness

2. To estimate the frequency of documented injection site reactions and hypersensitivity reactions among PWH receiving CAB+RPV LA injections at Year 3, Year 4, and Year 5 of availability

6. *RESEARCH METHODS

6.1. Study Design

This is an observational study utilizing prospectively collected electronic health record (EHR) data obtained from the OPERA® cohort.

6.2. *Study Population and Setting

All women with HIV, 13 years or older, treatment experienced and receiving CAB+RPV LA regimen will be included.

Study Period:

- **Year 3:**
  - Period of eligibility: 21JAN2021-31DEC2023
  - Period of observation: 21JAN2021-29FEB2024
- **Year 4:**
  - Period of eligibility: 21JAN2021-31DEC2024
  - Period of observation: 21JAN2021-28FEB2025
- **Year 5:**
  - Period of eligibility: 21JAN2021-31DEC2025
  - Period of observation: 21JAN2021-28FEB2026

Inclusion criteria:

- People with HIV
- ≥13 years old
- Treatment experienced
- Active in care in OPERA defined as having a clinical encounter in the 24 months prior to 31DEC2023, 31DEC2024, 31DEC2025
- Received at least one CAB+RPV LA injection between 21JAN2021 and 31DEC2023, 31DEC2024, 31DEC2025

Exclusion criteria:

- Received CAB+RPV LA regimen as part of a clinical trial
- Treatment naïve

Index date

- Date of first CAB+RPV LA injection

Censoring criteria:

- Discontinuation of CAB+RPV LA regimen
- Death
- Loss to follow-up (12 months after last clinical contact)
- Study end (end of observation period: 29FEB2024, 28FEB2025, 28FEB2026)

6.3. *Variables

6.3.1. Exposure definitions

Exposure is defined as receiving CAB+RPV LA injectable regimen.

6.3.2. Outcome definitions

6.3.2.1. Baseline characteristics

- Demographic characteristics at index
  - Age (years, as well as categorized as 13-17, 18-44, 45-55, 56+)
  - Sex (male, female)
  - Race (African American/Black, Asian, White, other race, unknown)
  - Ethnicity (Hispanic, non-Hispanic)
  - Marital status (Single, married/domestic partner, widowed, separated/divorced, unknown)
  - Geographic region (Northeast, Midwest, South, West, US Territories)
  - Risk of HIV transmission (MSM, PWID, Heterosexual, Vertical, Other)
  - Payer type (Medicaid, Medicare, Commercial insurance, AIDS Drug Assistance Programs (ADAP)/Ryan White, Cash)
- Clinical characteristics at index
  - Years since HIV diagnosis
  - Years since ART initiation
  - AIDS diagnosis at baseline
  - Years since first OPERA visit
  - Veterans Aging Cohort Study (VACS) Mortality Index score
  - Pregnancy (ever Y/N, and currently Y/N)
  - Weight (kg)
  - BMI (kg/m^2)
  - Co-infections
    - Hepatitis B co-infection
    - Hepatitis C co-infection
    - Syphilis infection (ever)
  - Comorbidities
    - Autoimmune disease
    - Cardiovascular disease
    - Invasive cancer
    - Endocrine disorder
    - Mental health disorder
    - Liver disease
    - Bone disorder
    - Peripheral neuropathy
    - Renal disease
    - Hypertension
    - Substance abuse
    - Any of the above
  - Concomitant Medications
    - Anticonvulsants
      - Carbamazepine
      - Oxcarbazepine

        - Phenobarbital
        - Phenytoin
    - Antimycobacterials
        - Rifampin
        - Rifapentine
        - Rifabutin
    - Glucocorticoids
        - Dexamethasone
    - Macrolide or ketolide antibiotics
        - Azithromycin
        - Clarithromycin
        - Erythromycin
    - Narcotic analgesic
        - Methadone
- ART regimens prior to CAB+RPV LA
    - Number of core agents experienced
    - Number of ARV classes experienced
    - Duration of last ARV regimen
    - Prior core agent class
- Baseline virologic characteristics
    - HIV viral load
        - Test result available (yes/no)
        - Continuous (copies/mL and $\log_{10}$ copies/mL)
        - Categorical
            - <50 copies/mL
            - ≥50 to <200 copies/mL
            - ≥200 to <1,000 copies/mL
            - ≥1,000 to <10,000 copies/mL
            - ≥10,000 to <100,000 copies/mL
            - ≥100,000 copies/mL
            - Missing
- Baseline immunologic characteristics
    - CD4 cell count
        - Test result available (yes/no)
        - Continuous (cells/µL)
        - Categorical
            - >500 cells/µL
            - >350 to ≤500 cells/µL
            - >200 to ≤350 cells/µL
            - >50 to ≤200 cells/µL)
            - ≤50 cells/µL
            - Missing

6.3.2.2. Patterns of use

Patterns of use will be described in terms of the CAB+RPV LA dosing schedule at initiation

and last follow-up. Initiation doses (first 2 doses) will be categorized as monthly (600/900 mg at 1st injection followed by 400/600 mg as of the 2nd injection) or every other month (600/900 mg at all injections). Dosing at last follow-up will be categorized as monthly (400/600 mg) or every other month (600/900 mg).

6.3.2.3. Persistence/Durability

Persistence/Durability will be measured as time on CAB+RPV LA regimen (months, continuous) as well as the number and proportion of PWH receiving CAB+RPV LA regimen at study end.

Among PWH still receiving CAB+RPV LA regimen at study end, time on CAB+RPV LA will be reported (months, continuous).

Among PWH who discontinued CAB+RPV LA regimen at any point during follow-up, time receiving CAB+RPV regimen prior to discontinuation (months, continuous) will be reported. Among discontinuers with ≥1 VL available during follow-up, viral load at discontinuation will be assessed (VL <200 copies/mL vs. ≥200 copies/mL).

6.3.2.4. Discontinuation

Discontinuation will be defined as ≥68 days after last injection (monthly dosing) or ≥128 days after last injection (every other month dosing).

6.3.2.5. Adherence

Adherence will be assessed by estimating the number of individuals that missed one or more consecutive injections without taking daily oral bridging therapy or any other oral ARV regimen while not on CAB+RPV LA regimen and mean and median number of injections missed. The number of individuals who received the injections seven or more days later than their scheduled injection visit and median duration of delayed injections in persons using bridging therapy will be evaluated.

6.3.2.6. Virologic effectiveness

Maintaining virologic suppression: Among PWH who were suppressed (VL <50 copies/mL) at baseline, the number and proportion who remain suppressed (VL <50 copies/mL) throughout all of follow-up will be reported, as well as the number and proportion who are suppressed (VL <50 copies/mL) at last follow-up. Proportion of individuals with VL <50 copies/mL during the first 6months, and at 6, 12 and 24 months following initiation of CAB+RPV LA regimen will be described.

Achieving virologic suppression: Among PWH who were viremic (VL ≥50 copies/mL) at baseline, the number and proportion who achieve a VL <200 or VL <50 copies/mL at any point during follow-up will be reported, as well as the number and proportion who achieve a VL <200 or VL <50 copies/mL at last follow-up. Proportion of individuals with VL <200 and VL <50 copies/mL during the first 6months, and at 6, 12 and 24 months following initiation of CAB+RPV LA regimen will be described.

Confirmed virologic failure: Confirmed virologic failure will be defined as 2 consecutive follow-up VLs ≥200 copies/mL OR 1 follow-up VL ≥200 copies/mL + discontinuation within 4 months of VL ≥200 copies/mL. The number and proportion of PWH with confirmed virologic failure will be reported as well as the time to virologic failure (months). Proportion of individuals with confirmed virologic failure (CVF) during the first 6months, and at 6, 12 and 24 months following initiation of CAB+RPV LA regimen will be described.

6.3.3. Confounders and effect modifiers

6.3.3.1. Confounders

The following baseline characteristics will be evaluated as potential confounders:

- Demographic characteristics at index
  - Age (years, as well as categorized as 13-17, 18-44, 45-55, 56+)
  - Sex (male, female)
  - Race (African American/Black, Asian, White, other race, unknown)
  - Ethnicity (Hispanic, non-Hispanic)
  - Marital status (Single, married/domestic partner, widowed, separated/divorced, unknown)
  - Geographic region (Northeast, Midwest, South, West, US Territories)
  - Risk of HIV transmission (MSM, PWID, Heterosexual, Vertical, Other)
  - Payer type (Medicaid, Medicare, Commercial insurance, AIDS Drug Assistance Programs (ADAP)/Ryan White, Cash)
- Clinical characteristics at index
  - Years since HIV diagnosis
  - Years since ART initiation
  - AIDS diagnosis at baseline
  - Years since first OPERA visit
  - Veterans Aging Cohort Study (VACS) Mortality Index score
  - Weight (kg)
  - BMI (kg/m^2)
  - Co-infections
    - Hepatitis B co-infection
    - Hepatitis C co-infection
    - Syphilis infection (ever)
  - Comorbidities
    - Autoimmune disease
    - Cardiovascular disease
    - Invasive cancer
    - Endocrine disorder
    - Mental health disorder
    - Liver disease

        - Bone disorder
        - Peripheral neuropathy
        - Renal disease
        - Hypertension
        - Substance abuse
        - Any of the above
    - Concomitant Medications
        - Anticonvulsants
            - Carbamazepine
            - Oxcarbazepine
            - Phenobarbital
            - Phenytoin
        - Antimycobacterials
            - Rifampin
            - Rifapentine
            - Rifabutin
        - Glucocorticoids
            - Dexamethasone
        - Macrolide or ketolide antibiotics
            - Azithromycin
            - Clarithromycin
            - Erythromycin
        - Narcotic analgesic
            - Methadone
- ART regimens prior to CAB+RPV LA
    - Number of core agents experienced
    - Number of ARV classes experienced
    - Duration of last ARV regimen
    - Prior core agent class
- Baseline virologic characteristics
    - HIV viral load
        - Test result available (yes/no)
        - Continuous (copies/mL and $\log_{10}$ copies/mL)
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            - <50 copies/mL
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            - ≥1,000 to <10,000 copies/mL
            - ≥10,000 to <100,000 copies/mL
            - ≥100,000 copies/mL
            - Missing
- Baseline immunologic characteristics
    - CD4 cell count
        - Test result available (yes/no)
        - Continuous (cells/µL)
        - Categorical
            - >500 cells/µL
            - >350 to ≤500 cells/µL

- >200 to ≤350 cells/μL
- >50 to ≤200 cells/μL)
- ≤50 cells/μL
- Missing

6.3.3.2. Effect modifiers

Participant characteristics, adherence, persistence, discontinuation and virologic effectiveness will be compared in subgroups stratified by viral load at initiation (<50 copies/mL vs. 50 - <200 copies/mL vs. ≥200 copies/mL), BMI (≥30 kg/m2 vs. <30 kg/m2) and age (<18, 18-50, 50-64, ≥65 years) at initiation.

6.4. *Data source

The OPERA® clinical cohort is a multi-site observational database built from the complete patient health records managed in EHR systems from more than 400 participating caregivers at 142 separate locations throughout the US (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 US. 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 1. United States Map of OPERA® HIV+ Population and Centers for

Disease Control (CDC) State-by-State Estimates (2017)

6.5. *Study size

Over two years (21JAN2021 and 28FEB2023), there were 1,843 individuals who were 18 years of age or older with HIV-1 in OPERA who were active in care and had received their first CAB+RPV injection. Of these, 1,578 had viral loads <50 copies/mL at first injection, 136 had viral loads 50 to <200 copies/mL, and 93 had viral loads ≥200 copies/mL (36 had no viral load data available at first injection). Study size is expected to grow for Year 3, Year 4, and Year 5 making these calculations underestimates.

Confidence intervals, constructed using the asymptotic (Wald) method based on a normal approximation, are presented in Table 1, and are designed to give estimates of precision for a variety of sample sizes and event probabilities.

The example sample sizes in Table 1 reflect the overall sample size as well as the strata based on viral load at first CAB+RPV LA injection.

Table 1. Confidence Intervals for Proportions

Confidence Level	Sample Size	CI Width	Event Proportion	Lower Limit	Upper Limit
0.95	1843	0.01	0.01	0.01	0.01
0.95	1843	0.02	0.05	0.04	0.06
0.95	1843	0.03	0.1	0.09	0.11
0.95	1843	0.04	0.2	0.18	0.22

Confidence Level	Sample Size	CI Width	Event Proportion	Lower Limit	Upper Limit
0.95	1843	0.04	0.3	0.28	0.32
0.95	1843	0.04	0.4	0.38	0.42
0.95	1843	0.05	0.5	0.48	0.52
0.95	1843	0.04	0.6	0.58	0.62
0.95	1843	0.04	0.7	0.68	0.72
0.95	1843	0.04	0.8	0.78	0.82
0.95	1843	0.03	0.9	0.89	0.91
0.95	1578	0.01	0.01	0.01	0.01
0.95	1578	0.02	0.05	0.04	0.06
0.95	1578	0.03	0.1	0.09	0.11
0.95	1578	0.04	0.2	0.18	0.22
0.95	1578	0.05	0.3	0.28	0.32
0.95	1578	0.05	0.4	0.38	0.42
0.95	1578	0.05	0.5	0.48	0.52
0.95	1578	0.05	0.6	0.58	0.62
0.95	1578	0.05	0.7	0.68	0.72
0.95	1578	0.04	0.8	0.78	0.82
0.95	1578	0.03	0.9	0.89	0.91
0.95	136	0.03	0.01	-0.01	0.03
0.95	136	0.07	0.05	0.01	0.09
0.95	136	0.10	0.1	0.05	0.15
0.95	136	0.13	0.2	0.13	0.27
0.95	136	0.15	0.3	0.22	0.38
0.95	136	0.16	0.4	0.32	0.48
0.95	136	0.17	0.5	0.42	0.58
0.95	136	0.16	0.6	0.52	0.68
0.95	136	0.15	0.7	0.62	0.78
0.95	136	0.13	0.8	0.73	0.87
0.95	136	0.10	0.9	0.85	0.95
0.95	93	0.04	0.01	-0.01	0.03
0.95	93	0.09	0.05	0.01	0.09
0.95	93	0.12	0.1	0.04	0.16
0.95	93	0.16	0.2	0.12	0.28
0.95	93	0.19	0.3	0.21	0.39
0.95	93	0.20	0.4	0.30	0.50
0.95	93	0.20	0.5	0.40	0.60
0.95	93	0.20	0.6	0.50	0.70
0.95	93	0.19	0.7	0.61	0.79
0.95	93	0.16	0.8	0.72	0.88
0.95	93	0.12	0.9	0.84	0.96

CI, confidence interval

This study will measure numerous health outcomes. CI widths are widest for proportions of 50%. Based on an overall sample size of 1843, the study will allow for estimation of parameters with a maximum CI width of 0.05. Based on strata sizes of 1578, 136, and 93, the study will allow for estimation of parameters with maximum CI widths of 0.05, 0.17 and 0.20, respectively.

6.6. *Data management

6.6.1. Data handling conventions

The data used in this research study will be deidentified data and research staff will not have access to personally identifiable information. All data are managed according to regulations such as the Health Insurance Portability and Accountability Act (HIPAA) and the Health Information Technology for Economic and Clinical Health (HITECH) Act. These regulations and guidelines expand upon the ethical principles detailed in the 1964 Declaration of Helsinki. Epividian will own the data and be responsible for data integrity and privacy. ViiV Healthcare will not have access to individual patient-level data (including personally identifiable information).

6.6.2. Resourcing needs

Not applicable.

6.6.3. Timings of Assessment during follow-up

Year 3	
Observation	21JAN2021 through 29FEB2024
Analysis	2Q2024
Year 4	
Observation	21JAN2021 through 28FEB2025
Analysis	2Q2025
Year 5	
Observation	21JAN2021 through 28FEB2026
Analysis	3Q2026

6.7. *Data analysis

6.7.1. Primary Analysis

6.7.1.1. Main Analytical approach

Baseline characteristics and outcomes will be described using counts and relative frequencies for categorical variables and medians with interquartile ranges (IQR) for continuous variables. For outcomes assessed at any point during follow-up, incidence rates will be estimated using unadjusted Poisson regression, accounting for person-time since index (i.e., first CAB+RPV LA injection).

Analyses will be stratified by viral load (<50 copies/mL vs. 50 to <200 copies/mL vs. ≥200 copies/mL), BMI (<30 kg/m2 vs. ≥30 kg/m2) and age (<18, 18-50, 50-64, ≥65 years) at first CAB+RPV LA injections as sample size allows to assess characteristics, adherence, persistence, discontinuation and virologic effectiveness. Other demographic and clinical variables may also be considered for stratification, if relevant.

Factors including age, sex, race, geographic region, BMI, IDU, CD4 count, any comorbidities associated with confirmed virologic failure will be assessed using multiple logistic regression.

6.7.1.2. Sensitivity analyses

No sensitivity analyses are planned

6.7.2. Secondary analysis/Exploratory analysis

Not applicable

6.8. *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.

6.9. *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 US. 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 are collected at point-of-care and are 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 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.

6.9.1. Study closure/uninterpretability of results

Not applicable; these are descriptive analyses of observational, real-world data.

6.10. *Other aspects

7. *PROTECTION OF HUMAN SUBJECTS

7.1. Ethical approval and subject consent

Clinical information is originally compiled into separate Clinical Health Outcomes Reporting and Utilization Service (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 (HITECH) Act.

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.

7.2. 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.

8. *LEGAL BASIS FOR PROCESSING INDIVIDUAL HUMAN DATA

- The authors confirm that study data is Individual Human Data (IHD) not owned by 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.

9. *MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study has safety objectives.

Collection of adverse events/reactions (Solicited Events)

The purpose of the study is to monitor exposure to CABENUVA and to evaluate persistence, adherence, discontinuation and virologic effectiveness among PWH receiving CABENUVA regimen. For CABENUVA regimen, pre-defined safety events of interest persistence, adherence, discontinuation and virologic effectiveness, will be systematically recorded in aggregate. These will be summarised in final study reports. This study is based on secondary use of existing health data and as such Individual Case Safety Reporting (ICSRs) to regulatory agencies is not required.

Reporting of adverse events/reactions (Spontaneous Events)

The purpose of the study is to monitor patients exposed to CABENUVA and to evaluate pre-defined safety events in aggregate. There is no potential to collect serious and non-serious spontaneous AEs, pregnancy exposures, or incidents related to any 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. Therefore, a study-specific safety-management plan will not be developed.

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 ViiV product. This study is based on data previously collected for other purposes e.g., routine healthcare encounters. As such, there is no requirement for the collection and reporting of Individual Case Safety Reports (ICSRs).

10. *PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

The final study report to be submitted to sponsor. Study results will be submitted to scientific conferences and for peer reviewed journal publication.

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