

Protocol

Study ID: 217671

Official Title of Study: CAB LA PrEP Cohort: Prospective Cohort Study to Assess Effectiveness and Safety of, and Adherence and Resistance to Cabotegravir for Pre-Exposure Prophylaxis in the United States

Date of Document: 08-Apr-2024

TITLE PAGE

Information Type: ViiV Healthcare Non-Interventional Study Protocol

Title:	CAB LA PrEP Cohort: Prospective Cohort Study to Assess Effectiveness and Safety of, and Adherence and Resistance to Cabotegravir for Pre-Exposure Prophylaxis in the United States
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Compound Number: GSK1265744

Development Phase IV

Effective Date: 25-Mar-2022

Subject: Cabotegravir, CAB LA, PrEP Cohort

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TABLE OF CONTENTS

	PAGE
1. LIST OF ABBREVIATIONS	3
2. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE.....	6
3. ABSTRACT	9
4. AMENDMENTS AND UPDATES.....	11
5. MILESTONES	11
6. BACKGROUND AND RATIONALE	12
6.1 Background.....	12
6.2 Rationale.....	14
7. RESEARCH QUESTION AND OBJECTIVES.....	14
8. RESEARCH METHODS	17
8.1 Study Design	17
8.2 Study Population and Setting.....	17
8.3 Variables.....	18
8.3.1 Exposure Definitions	18
8.3.2 Demographic and Clinical Characteristics	18
8.3.3 Outcome Definitions.....	19
8.4 Data Source	23
8.5 Study Size.....	23
8.6 Data Management.....	24
8.6.1. Data handling conventions.....	24
8.7 Data Analysis.....	25
8.7.1. Essential analysis	25
8.8 Quality Control and Quality Assurance	28
8.9 Limitations of the Research Methods	28
9. PROTECTION OF HUMAN SUBJECTS.....	29
9.1. Ethical approval and subject consent.....	29
10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS.....	31
11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS	31
11.1. Milestones.....	31
11.2. Target Audience	31
11.3. Study Reporting and Publications.....	31
12. REFERENCES	32
13. ANNEX 1.....	33
13.1. ICD-9/ICD-10 codes.....	33

1. LIST OF ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ASCVD	Atherosclerotic Cardiovascular Disease
AST	Aspartate Aminotransferase
ART	Antiretroviral Therapy
ARV	Antiretroviral
BAA	Business Associate Agreement
BILI	Total Bilirubin Elevation
BMI	Body Mass Index
CAB	Cabotegravir
CVD	Cardiovascular Disease
DAIDS	Division of AIDS
DILI	Drug Induced Liver Injury
DTG	Dolutegravir
eGFR	Estimated Glomerular Filtration Rate
EU	European Union
EMR	Electronic Medical Record
ePHI	Electronic Protected Health Information
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
FTC	Emtricitabine
HDL	High Density Lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HSR	Hypersensitivity Reaction
ICD	International Classification of Disease
IRB	Institutional Review Board
INSTI	Integrase Strand Transfer Inhibitor
ISR	Injection Site Reaction
LA	Long Acting
LCT	Liver Chemistry Test
LDL	Low Density Lipoprotein
MAH	Marketing Authorization Holder
MSM	Men Who Have Sex with Men
OLI	Oral Lead In
PK	Pharmacokinetic
PLWH	People Living with HIV
PrEP	Pre-Exposure Prophylaxis
PT	Prothrombin Time
RAL	Raltegravir

RNA	Ribonucleic Acid
RPV	Rilpivirine
QA	Quality Assurance
sFTP	Secure File Transfer Protocol
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SPP	Specialty Pharmacy
STI	Sexually Transmitted Infection
TAF	Tenofovir Alafenamide
TDF	Tenofovir Disoproxil Fumarate
TGW	Transgender Women
ULN	Upper Limit of Normal
US	United States
USPI	US Prescribing Information

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2. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE

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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: Richard Elion

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Investigator Signature

25-Mar-2022

Date

Investigator Name: Janna Radtchenko

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Investigator Signature

25-Mar-2022

Date

3. ABSTRACT

Rationale/Background:

Cabotegravir (CAB, GSK1265744) is a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI), with attributes favourable for both HIV treatment and prevention indications. CAB, as a component of a dual antiretroviral maintenance therapy regimen in combination with the long acting (LA) formulation of Rilpivirine (RPV) LA, has been approved in several countries/regions (including the US, EU, Canada, and Australia) for the treatment of HIV-1 infection in adults.

ViiV Healthcare is developing oral CAB tablets and CAB LA extended-release suspension for injection for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in individuals weighing at least 35 kg. In the pivotal Phase IIb/III studies HPTN 083 and HPTN 084, the PrEP regimen containing CAB LA dosed every 2 months was demonstrated to be superior to daily oral TDF/FTC for the prevention of HIV infection in men who have sex with men (MSM), transgender women (TGW) and cisgender women.

The totality of data from the CAB PrEP pivotal and supportive clinical studies, PK modelling/simulation and the overall data from the CAB Treatment program supports the use of CAB PrEP as a novel, well-tolerated, effective, LA PrEP agent. CAB LA for PrEP approved in the United States by the FDA on December 20, 2021 for use in at-risk adults and adolescents weighing at least 35 kilograms (77 pounds) for PrEP to reduce the risk of sexually acquired HIV. 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 (Vocabria) for four weeks to assess how well they tolerate the drug (FDA, 2021).

The Marketing Authorization Holder (MAH) proposes a five-year post authorization study to be conducted in a real-world clinical setting in the US. This prospective observational cohort study will aim to better understand the population receiving CAB LA for PrEP in routine clinical practice, usage patterns, adherence, post marketing clinical effectiveness, discontinuations, and monitor for resistance among individuals diagnosed with HIV infection while on CAB PrEP.

Objectives:

Following the initiation of CAB LA for PrEP, the study will aim to assess usage patterns, adherence, effectiveness, safety, and resistance among individuals diagnosed with HIV infection.

The specific objectives are to:

- 1) Describe the population initiating CAB LA for PrEP, including proportion of individuals who use oral lead in (OLI) and proportion of those with direct to injection (DTI)
- 2) Monitor for adherence by assessing the frequency of delayed and missed injections without oral PrEP

- 3) Monitor for incidence of HIV infection while on CAB for PrEP and describe the timing of diagnosis of incident HIV infections relative to timing of CAB PrEP usage
- 4) Monitor for occurrence of drug induced liver injury (DILI) and hypersensitivity reaction (HSR) following CAB LA injections
- 5) Evaluate incidence of and risk for developing resistance among individuals with diagnosis of HIV infection while on CAB LA for PrEP

Study Design:

This will be a 5-year long prospective cohort study of adults and adolescents ≥ 35 kgs initiating CAB LA for PrEP in real-world clinical setting in the US.

Analysis Methods:

Descriptive analyses will summarize baseline characteristics of study participants and covariables will be reported as frequencies/median (IQR) at baseline and at follow-up. Time to HIV diagnosis will be assessed using Kaplan-Meier curve. Cox proportional hazards models will be constructed to compare time to HIV diagnosis adjusting for participant characteristics. Adherence will be estimated using the date of injections over 6 and 12-month periods. Frequency of resistance will be described among individuals who acquire HIV infection while on CAB LA for PrEP.

Limitations:

This real-world study will use data from electronic medical records (EMRs), so some limitations, such as potential incompleteness of some variables and lost to follow-up, are possible.

Milestones:

The study will start once CAB LA PrEP is commercially available in the US and is expected to continue through 2026, for a total of five years of study period. Annual interim reports with cumulative data will be submitted and the study final report is expected to be completed in September 2027.

4. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	15 March 2022	Section 3, 7 & section 8	Abstract, Study objectives, outcome definitions, sample size and analyses	To address FDA's comments

5. MILESTONES

Milestone	Planned date
Draft Protocol Submission to the FDA	January 2022
Final Protocol Submission to the FDA	March 2022
Study Start (after Protocol Approval)	April 2022
1 st Interim Report	June 2023
2 nd Interim Report	June 2024
3 rd Interim Report	June 2025
4 th Interim Report	June 2026
Data Collection Completion	April 2027
Final Report	September 2027

6. BACKGROUND AND RATIONALE

6.1 Background

Across populations and PrEP regimens, oral PrEP significantly reduced the risk of HIV acquisition compared with placebo. Trials in MSM with oral PrEP use of more than 70% adherence demonstrated the highest PrEP effectiveness (risk ratio = 0.30, 95% confidence interval: 0.21-0.45, $P < 0.001$) compared with placebo. Trials with low PrEP use did not show a significantly protective effect (Fonner et al., 2016). An effective, well-tolerated, long acting (LA) PrEP agent could potentially offer substantial advantages over currently available PrEP regimens, including daily oral tenofovir-based fixed drug combinations (FDC) that require long-term adherence for corresponding efficacy for PrEP. CAB LA PrEP regimen may ensure better adherence and efficacy among PrEP users.

Cabotegravir (CAB, GSK1265744) is a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI), with attributes favourable for both HIV treatment and prevention indications. CAB, as a component of a dual antiretroviral maintenance therapy regimen in combination with the LA formulation of Rilpivirine (RPV) LA, has been approved in several countries/regions (including the US, EU, Canada, and Australia) for the treatment of HIV-1 infection in adults.

ViiV Healthcare is developing oral CAB tablets and CAB LA extended-release suspension for injection for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in individuals weighing at least 35 kg. The totality of data from the CAB PrEP pivotal and supportive clinical studies, PK modelling/simulation and the overall data from the CAB Treatment program supports the use of CAB PrEP as a novel, well-tolerated, effective, LA PrEP agent. CAB LA for PrEP (Apretude) was approved in the United States by the FDA on December 20, 2021, for use in at-risk adults and adolescents weighing at least 35 kilograms (77 pounds) for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV. 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 (Vocabria) for four weeks to assess how well they tolerate the drug (FDA, 2021).

As a component of the CAB PrEP regimen, CAB tablets may be used as optional oral lead in (OLI) to assess tolerability of CAB prior to administration of CAB LA injections and as oral PrEP in individuals who miss planned dosing with CAB LA injection.

Efficacy assessment from pivotal studies (HPTN 083 and HPTN 084), designed to assess the safety and efficacy of CAB PrEP when compared to the active comparator daily oral TDF/FTC for HIV PrEP in the most key affected populations globally (i.e., MSM and TGW [enrolled in HPTN 083] and cisgender women [enrolled in HPTN 084]) demonstrated superiority.

In 083, CAB PrEP demonstrated superior efficacy among MSM and TGW when compared to daily oral TDF/FTC (HR 0.34; 95% CI 0.18 to 0.62, two-sided $p=0.0005$), with an approximate 66% reduction in the rate of incident infections. There were 39 HIV

incident infections in the TDF/FTC group (incidence rate 1.22/100 PY) and 13 incident infections occurred in the CAB group (incidence rate 0.40/100 PY).

In 084, CAB PrEP demonstrated superior efficacy among cisgender women when compared to daily oral TDF/FTC (HR of 0.11 (95% CI 0.04 to 0.31), $p < 0.0001$) demonstrating an 89% reduction in the rate of incident infections for CAB. There were 36 HIV incident infections in the TDF/FTC group (incidence rate 1.85/100 PY) and 4 HIV incident infections occurred in the CAB group (incidence rate 0.20/100 PY).

CAB tablets are indicated for short term PrEP to reduce the risk of sexually acquired HIV-1 infection in at-risk individuals weighing at least 35 kg. The tablets may be used as:

- Oral lead in for one month to assess tolerability of CAB prior to administration of the injection.
- Oral PrEP in individuals who miss planned dosing with CAB LA injection.

CAB LA injections are indicated for PrEP to reduce the risk of sexually acquired HIV-1 infection in at-risk individuals weighing at least 35 kg.

Detailed dosing information on initiation and maintenance doses or optional oral lead in and injectable CAB, handling delayed or missed injection can be found in the US Prescribing Information (USPI). CAB PrEP was well-tolerated with a safety profile comparable to the active comparator daily oral TDF/FTC in the pivotal studies, excluding the incidence of injection site reactions (ISR), which occurred more frequently in CAB participants.

Elevated aminotransferases have been observed with CAB during the CAB Treatment program in HIV-infected individuals, and hepatotoxicity is a known adverse drug reaction (ADR) for CAB. Possible or probable cases of DILI have been observed on the CAB PrEP program and DILI has been observed in participants on CAB therapy for HIV treatment. DILI reported with PrEP demonstrates similar characteristics including being mild to moderate in severity and reversible upon discontinuation of CAB. Clinical and laboratory monitoring should be considered, and CAB should be discontinued if hepatotoxicity is confirmed, and individuals managed as clinically indicated.

HSRs have been reported with INSTIs other than CAB (including RAL and DTG) and are characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. It is not clear if HSRs can occur with INSTIs in the HIV-uninfected population or whether the underlying HIV infection affects the incidence of HSRs. No cases of confirmed HSR have been reported with use of either oral or LA CAB for treatment or prevention. Therefore, labelling will warn prescribers about this possibility. Prescribing physicians should remain vigilant and should discontinue CAB and other suspected agents immediately, should signs or symptoms of HSR develop. The individual's clinical status, including liver aminotransferases should be monitored and appropriate therapy initiated.

This 5-year prospective, non-interventional study in the US will aim to understand the population receiving CAB LA for PrEP in real world clinical practice, usage patterns,

adherence, post marketing clinical effectiveness, discontinuations, and monitor for hepatotoxicity related to administration of CAB for PrEP and HSR, and resistance among individuals who acquire HIV infection while on CAB PrEP. The data generated from this study will enhance our understanding of CAB LA for PrEP.

6.2 Rationale

The potential benefits of CAB as a new, LA PrEP regimen with superior efficacy as compared to an active comparator taken daily outweigh the risks of acquiring HIV infection and subsequent resistance development.

There is a risk for HIV infection if the individual vulnerable to HIV acquisition does not adhere to the CAB PrEP dosing schedule, and protective levels of CAB may decrease to a level where HIV infection can occur. There may also be risk for HIV infection if the individual does not use other HIV-1 prevention strategies, including knowledge of HIV-1 status, regular testing for other sexually transmitted infections, condom use, etc. A warning and precaution are included in product labelling with recommendation that individuals should be counselled periodically to strictly adhere to the recommended CAB dosing schedule and the use of other prevention strategies.

There is also a risk for the development of resistance in individuals with unrecognized or acute HIV-1 infection at the time of starting CAB PrEP. In addition, there is risk of HIV-1 infection during or following CAB PrEP discontinuation, i.e., during the CAB exposure that is detectable >52 weeks post injection (PK tail), and subsequent emergence of CAB resistant HIV-1 strains. A warning and precaution are included in product labelling with recommendation for monitoring to clinically reassess individuals for risk of HIV acquisition and to test to confirm HIV negative status. Although not treatment limiting, CAB LA usage has the risk of hepatotoxicity and potential for HSRs.

This 5-year long prospective, non-interventional study will aim to further understand and quantify the risks in real world clinical setting. The additional data generated will continue to inform clinical practice of CAB LA for PrEP usage.

7. RESEARCH QUESTION AND OBJECTIVES

The study will aim to assess usage patterns, adherence, effectiveness, safety, and resistance among individuals initiating CAB LA for PrEP.

The specific objectives are to assess:

- 1) CAB LA for PrEP Usage pattern:
 - a) Describe the population initiating CAB LA PrEP by:
 - i. Baseline demographics (age, sex, gender, race/ethnicity, geographic region, BMI)

- ii. Risk factors for HIV acquisition: STI diagnoses, substance use including injection drug use
 - iii. PrEP: History of previous PrEP use
 - iv. OLI or DTI: proportion of individuals who use OLI prior to initiating injections and proportion of individuals who go direct to injection (DTI)
- b) Describe the individuals initiating CAB OLI or CAB LA PrEP with undiagnosed HIV infections by baseline demographics and PrEP history.
 - c) Describe oral PrEP used to cover planned, delayed or missed CAB LA injections
 - d) Frequency of testing for HIV infection and methods used for HIV-1 diagnosis

Undiagnosed (prevalent) HIV infections will be defined as positive laboratory HIV antigen/antibody test or positive viral load (RNA assay) following first prescription of CAB OLI and separately, following first CAB LA for PrEP injection. The date of the assay should be at the time of the first prescription or injection while the result may be reported within 4-6 weeks after first prescription or injection. Prevalent HIV infections will be shown for those who received CAB OLI and those who used DTI strategy.

- 2) Adherence: Monitor for adherence by assessing the frequency of delayed and missed injections without oral PrEP
 - a) Delayed and missed injections (non-adherence to the scheduled dosing)
 - i. Determine the number of individuals that miss one or more consecutive injections without taking daily oral PrEP
 - ii. Assess the mean and median number of injections missed during the 6-month and 12-month period
 - iii. Determine the number of individuals who receive the injections seven or more days later than their scheduled injection visit and median duration of delay
 - iv. Describe characteristics of the individuals that are non-adherent
 - b) Discontinuation of CAB LA PrEP
 - i. Determine the proportion of individuals who discontinue CAB LA PrEP after 6, 12, 24 and 36 months
 - ii. Describe reasons for discontinuation of CAB LA PrEP
 - iii. Describe characteristics of the individuals who discontinue CAB LA PrEP
- 3) Effectiveness: Monitor for incidence of HIV infections while on CAB for PrEP and describe the timing of diagnosis of incident HIV infections with respect to timing of CAB for PrEP usage

- a) Describe the proportion and number of incident HIV-1 infections while on CAB for PrEP among individuals in the following groups:
 - i. Infected during OLI
 - ii. Infected while on CAB LA: Incident HIV infections, defined as HIV infection diagnosed after start of CAB injections while adhering to CAB LA PrEP regimen
- b) Describe the timing of diagnosis of HIV infection with respect to timing of CAB for PrEP usage among individuals in the following groups:
 - i. Infected during OLI
 - ii. Infected while on CAB LA: Incident HIV infections while adhering to CAB LA PrEP regimen
- c) Describe the proportion of incident infections among those who start with OLI and those who go to DTI separately and the timing of diagnosis of incident HIV infection for the overall group, and separately for the OLI and DTI groups.

The proposed study is a non-interventional study and will collect data from routine clinical practice and plans to capture all prevalent HIV-1 infections, including those captured during screening. However, there are no plans to collect and store serum samples for subsequent testing as this is not part of standard of care.

- 4) Safety: Monitor for occurrence of hepatotoxicity DILI and hypersensitivity reaction (HSR) following CAB LA injections
 - a) Describe the frequency of DILI (hepatotoxicity related to the administration of CAB for PrEP) after starting CAB LA at 6, 12, 24 and 36 months after initiation
 - i. Incidence proportion and rate of DILI following administration of CAB LA PrEP
 - ii. Incidence proportion and rate of CAB LA discontinuation due to DILI
 - b) Describe the frequency of HSR after starting CAB LA at 6, 12, 24 and 36 months after initiation
 - i. Incidence proportion and rate of HSR following administration of CAB LA PrEP
 - ii. Incidence proportion and rate of CAB LA discontinuation due to HSR

5) Resistance: Evaluate incidence of and risk for developing resistance to integrase inhibitors (INSTI) among individuals in the following groups:

- a) Incident HIV infections while adhering to CAB LA for PrEP and development of resistance during treatment for HIV infection
- b) CAB LA PrEP discontinued
 - i. without subsequent oral PrEP & potential risk for HIV infection and viral resistance during CAB LA PK tail
 - ii. switched to oral PrEP and acquire HIV infection during the 12-month follow up period and develop resistance during subsequent treatment with ARVs
- c) Individuals with undiagnosed HIV infections and subsequent emergence of resistance while on CAB monotherapy

Resistance testing: Since this is a non-interventional study aiming to capture standard of care in real world setting, the study will not mandate resistance testing following discontinuation of CAB LA for PrEP. Health care providers following CDC guidelines for LA PrEP, USPI and applicable local guidelines will decide what laboratory and resistance tests are to be conducted while an individual is on CAB LA for PrEP. Data thus generated, including available HIV-1 subtypes, will be captured and analysed by the study team.

8. RESEARCH METHODS

8.1 Study Design

This will be a 5-year long prospective cohort study of adult and adolescents ≥ 35 Kgs, initiating CAB LA for PrEP, in real world clinical setting, in the United States. All treatment decisions will be made by the healthcare provider per guidelines for LA PrEP and USPI. This study will use electronic medical records (EMR), claims and dispensing data for analysis.

8.2 Study Population and Setting

HIV negative adults and adolescents ≥ 35 kgs initiating CAB PrEP will be eligible for inclusion from the date of starting OLI or CAB LA injections, once CAB LA for PrEP is commercially available in the US.

- All CAB LA for PrEP users will be followed for at least 3 years from the time of initiation while on CAB LA PrEP and/ 12 months after last injection if they discontinue CAB LA PrEP.
- Individuals with incident HIV infection will be followed for 12 months from the start of ART and their virologic suppression and emergence of resistance to ARVs & cross resistance to other integrase inhibitors will be monitored.
- Individuals initiating CAB PrEP with undiagnosed prevalent HIV-1 infection will be followed for 12 months from the start of ART and their virologic suppression and emergence of resistance to ARVs & cross resistance to other integrase inhibitors will be monitored.

- Participants discontinuing CAB LA PrEP will be monitored for 12 months for diagnosis of HIV infection and additional 12 months if infected to monitor for ARV effectiveness & potential emergence of resistance.
- Testing for incident HIV infection & resistance: Testing frequency for HIV infection and resistance if needed, is expected to be per guidelines for LA PrEP and USPI.

The participating clinical sites and health care providers will be strongly encouraged to report all pregnancies occurring while using CAB for PrEP, prospectively (i.e., reported prior to the outcome of pregnancy is known) to the Antiretroviral Pregnancy Registry (+1-800-258-4263 or www.APRegistry.com).

8.3 Variables

8.3.1 Exposure Definitions

Exposure will be defined as first prescription of CAB OLI or LA injections for PrEP.

8.3.2 Demographic and clinical characteristics

Clinical characteristics will be measured at baseline and at 12, 24, 36 months as available

- Age at index date
- Sex and Gender
- Race/ethnicity (Black, White, Hispanic/Latino, other)
- Region (Midwest, Northeast, South, West) based on the individual's 3-digit zip code
- Urbanicity (urban, suburban, small/medium metro, rural), defined by practice/clinic ZIP code
- Insurance status (none, public, private, other)
- Substance abuse status (based on IC9/10 codes)
- Alcohol abuse (based on IC9/10 codes)
- Charlson Comorbidity Index (CCI)
- Comorbidities
- Body Mass Index (BMI), weight, height
- PrEP prescriber/provider specialty
- High risk sexual behavior (ICD 10 Z72.5, Z72.51, Z72.53, Z11.3, Z11.4, Z11.59)
- STIs (chlamydia, syphilis, gonorrhoea, syphilis, and other venereal diseases combined)
- Use of recreational drugs (cocaine, narcotics, psychodysleptics [hallucinogens], psychoactive substance, antiepileptic, sedative-hypnotic and anti-parkinsonism drugs)
- Cardiovascular
 - Hypertension as ≥ 130 mmHg systolic, ≥ 90 mmHg diastolic
 - Triglycerides ≥ 1.5 g/l
 - LDL > 100 mg/dL, Index of Total Cholesterol / HDL Cholesterol

- ASCVD risk >7.5%
 - CVD incidence based on ICD codes (see annex)
- Hepatic: the following liver chemistry tests (LCT) data will be collected when tested for:
 - 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) where available
 - Lipase levels where available
 - Fib-4
 - Hepatitis C and hepatitis B incidence and chronic infection
- **Risk factors for HIV acquisition**
 - STI diagnoses in the past 12 months (yes, no; see ICD9/10 codes in the Annex)
 - Substance use in the past 12 months (yes, no; see ICD9/10 codes in the Annex)
- **History of PrEP use**
 - Current or any prior daily PrEP use (yes, no)
 - Time and duration on prior daily PrEP use
 - <2 months, 2-6 months, 7-12 months, 12+ months
 - Number of months on PrEP in the last 12 months (mean and median)
 - Type of daily PrEP used (TDF, TAF)
 - Use of CAB oral lead in prior to initiating injections

8.3.3 Outcome Definitions

a) Incident HIV diagnoses – confirmation of HIV positive status:

- Frequency (number and proportion) of incident infections during CAB OLI and while adhering to CAB LA PrEP regimen will be assessed. Additionally, frequency of incident infections will be assessed among those initiating CAB OLI and those initiating DTI.
- HIV diagnosis (International Classification of Diseases, 9th revision [ICD-9] codes: 042.x-044.x and ICD 10th revision [ICD-10] codes: B20.x-B22.x, B24.x) and
 - At least one of the following:
 - Positive HIV-1 antigen/ antibody lab results followed by confirmatory viral RNA test
 - One detectable viral load

Incident HIV infections are new infections diagnosed after initiation of CAB PrEP, having confirmed HIV negative status using HIV RNA test, at the time of PrEP initiation.

Prevalent HIV infections are defined as undiagnosed HIV infections at the time of PrEP initiation and will be defined as positive HIV antigen/antibody test and/or positive viral load from sample collected at the time of initiation, following first prescription of CAB OLI and separately, following first CAB LA PrEP injection. Note the test result may be reported within 4-6 weeks after the sample was collected. Proportion and number of persons with prevalent and incident HIV infections will be reported for CAB OLI and CAB LA PrEP separately.

This study is designed to capture data documented in electronic medical records in real world clinical setting, provision of '4-6 weeks after starting PrEP for diagnosis included above accounts for time needed to obtain the diagnostic testing results, confirmation and uploading it to the EMR. So, the 4-6 week period included above indicates the timing of reporting and documenting the result in the real-world clinical setting. Assessment of 'prevalent infection' vs. 'incident infection' will take into consideration the date the diagnostic test sample was collected and sent to the lab for testing.

b) Proportion of individuals receiving CAB LA PrEP with diagnosis of HIV infection after 6, 12, 24, 36 months of follow-up time

c) Time to diagnosis of incident HIV infections

- Time to diagnosis will be defined as months from first CAB LA injection or OLI till the first confirmed positive HIV-1 antigen/antibody result, detectable viral load and HIV diagnosis.
- Time to diagnosis of HIV infection will be shown separately for individuals infected during OLI and while adhering to CAB LA injection schedule.

d) ART regimen and VL testing among CAB PrEP users with prevalent and incident infections:

ART regimen and VL testing data during 12 months of the follow up period for the following groups will be described:

- i. Individuals with incident infections
- ii. Individuals with undiagnosed prevalent infections at the time of CAB PrEP initiation
- iii. Durability of INSTI-based vs. non-INSTI based regimens (e.g., the numbers and proportions of those who achieve and maintain virologic suppression, the time to virologic suppression, the time to virologic breakthrough), as well as any INSTI resistance-associated substitutions that are detected upon ART failure

e) Adherence and Durability

- i. Adherence to CAB LA PrEP including OLI will be estimated from data collected via EMR and pharmacy dispensing data.

- ii. Non-adherence to the dosing schedule will be assessed at 6, 12, 24 and 36 months by:
 - Estimating the number of individuals that missed one or more consecutive injections without taking daily oral bridging PrEP while not on CAB LA injections and mean and median number of injections missed during a 6 and a 12-month period
 - Estimating the number of individuals who received the injections seven or more days later than their scheduled injection visit and median duration of delayed injections
 - Estimating the number of individuals who missed one or more consecutive injections without taking daily oral bridging PrEP or those who received the injections seven or more days later than their scheduled injection visit (Combined group a OR b) and describe patient characteristics for the individuals that are non-adherent
- iii. Discontinuation will be defined as 2 injection cycles (~127 consecutive days) in which no injections were administered without oral PrEP
- iv. Describe the frequency and the regimen used for oral PrEP to cover planned delayed or missed injections

f) Frequency of resistance to INSTIs and specific mutations among the following groups:

- i. CAB LA PrEP started when the individual had undiagnosed HIV infection & subsequent emergence of resistance while on CAB monotherapy
- ii. CAB LA PrEP discontinued
 - without subsequent oral PrEP & potential risk of HIV infection and viral resistance during CAB LA PK tail (12 months)
 - switched to oral PrEP and acquire HIV infection during the 12-month follow up period and develop resistance during subsequent follow up for 12 months of treatment with ARVs
- iii. Incident HIV infections while adhering to CAB LA for PrEP and development of resistance during treatment for HIV infection

g) Frequency of DILI and hypersensitivity reactions following CAB OLI and CAB LA injections assessed at 6, 12, 24 and 36 months.

Hepatotoxicity related to administration of CAB for PrEP (drug-induced liver injury, DILI) as described below will be tabulated:

DILI case definition: Determination of suspected or potential DILI will be based on liver chemistry criteria (ALT, BILI and ALP) in addition to all relevant clinical information based on Aithal et al, 2011. An independent adjudication committee will review all potential and suspected cases of DILI that meet the liver chemistry criteria for DILI for drug attribution to CAB for PrEP. The adjudication committee will be provided with all relevant clinical

information collected from data in the EMR, to enable a comprehensive review and assessment potential DILI caused by CAB PrEP.

Liver chemistry criteria for DILI including any one of the following:

- i. More than or equal to fivefold elevation above the (ULN) for ALT
- ii. More than or equal to twofold elevation above the ULN for ALP (particularly with accompanying elevations in concentrations of 5'-nucleotidase or γ -glutamyl transpeptidase in the absence of known bone pathology driving the rise in ALP level)
- iii. More than or equal to threefold elevation in ALT concentration and simultaneous (within +/- 2 weeks) elevation of BILI concentration exceeding 2 $\times$ ULN after starting CAB LA PrEP at 6, 12, 24, 36 months after initiation

If the person has had previous liver injury and hence abnormal LCT prior to starting CAB for PrEP, ULN is replaced by the mean baseline values obtained at baseline, (i.e., 5 $\times$ baseline for ALT, 2 $\times$ baseline for ALP and 2 $\times$ baseline for BILI with associated 3 $\times$ baseline elevation in ALT). Classification of the clinical severity of DILI involves use of the peak measured values for each of the biochemical parameters during the course of DILI.

Cases of suspected or potential DILI with attribution to CAB for PrEP will be tabulated according to the DILI severity grade as below:

DILI severity index is based on DILI biochemical criteria: Category (1-4)

Severity (CCI) and Description are as follows:

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

- Description of HSR: Signs and symptoms of HSR reported with INSTI include, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, mucosal involvement [oral blisters or lesions], conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing or a diagnosis of HSR as documented in the EMR. Clinical status, including liver transaminases, will be considered and frequency of HSRs will be assessed at 6, 12, 24, 36 months after study start.

All potential cases of HSR will be reviewed and confirmed by the

independent adjudication committee. The committee will carefully assess all the signs and symptoms, and all relevant clinical information available in the EMR, where considering the combination of events, time to onset of occurrence, organ systems involvement, evolution of outcome as well as patient characteristics and medical history may suggest an immediate or delayed type HSR to make the determination.

- Regimen discontinuation following DILI or HSR will be reviewed and confirmed by the adjudication committee.

8.4 Data Source

Prospective longitudinal data collection using EMR and dispensing data from proprietary Trio Health HIV clinic database will be used for this study. As of June 2021, the database contains records of over 60,000 PLWH with ARV prescriptions, over 12,000 individuals with oral PrEP prescriptions, and over 500,000 individuals without HIV diagnosis or PrEP use. The data are collected at 11 large geographically distributed HIV-treating US clinics. The TRIO dispensing database is approximately 50% of the EMR cohort and is distributed similarly to the EMR database by geography, gender, race, and ethnicity.

8.5 Study Size

The study is not a hypothesis testing study but is designed to assess usage of CAB LA for PrEP in real world clinical setting. The overall number of participants in the cohort study will depend on the uptake of the CAB LA for PrEP and how widely it will be used in the US. The study aims to include at least 1000 participants initiating CAB LA for PrEP. There is no formal statistical hypothesis to be tested in these analyses.

Table 1 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.

Table 1: 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

Confidence Level	Sample Size (N)	CI Width	Incident HIV infection rate (%)	Lower Limit	Upper Limit
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	4000	0.3394	0.25	0.1199	0.4593
0.95	4000	0.4655	0.5	0.3057	0.7712
0.95	4000	0.644	1	0.7153	1.3593
0.95	4000	0.78	1.5	1.1466	1.9266
0.95	4000	0.8941	2	1.589	2.4831
0.95	4000	0.9938	2.5	2.0386	3.0324
0.95	5000	0.3003	0.25	0.1313	0.4316
0.95	5000	0.4134	0.5	0.3238	0.7372
0.95	5000	0.5732	1	0.7431	1.3163
0.95	5000	0.6951	1.5	1.1816	1.8767
0.95	5000	0.7971	2	1.6302	2.4273
0.95	5000	0.8863	2.5	2.0852	2.9715

8.6 Data Management

8.6.1. Data handling conventions

Trio Health Advisory Group, Inc. has developed and built a proprietary technology platform (“Trio platform”) for specialty pharmacies (SPPs) and physicians to collaborate, communicate and manage patient information for the purpose of improving patient care. This is not a research platform, but a platform incorporated into clinical patient care. In States where the State Law mandates a patient consent for the collection of HIPAA compliant data, the SPP obtained patient consents.

Data security and protection of privacy are of utmost importance in every aspect of this work and central to Service Provider’s IT mission. Service Provider’s Information Security Risk Management Policy defines the process of selecting and implementing security measures which are sufficient to reduce the risks to electronic Protected Health Information (“ePHI”), including “Personal Information” and “Private Information”. “Personal Information” means any information concerning a natural person which, because of name, number, personal mark, or other identifier, can be used to identify such natural person. “Private Information” means Personal Information in combination with (1) social security number; (2) driver’s license number or non-driver identification card number; or (3) account number, credit, or debit card number, in combination with any required security code, access code, or password that would permit access to an individual’s financial account. For this study, only de-identified data will be used by

TRIO Health's study analytic team and no personally identifiable information is made available to ViiV Healthcare, the study sponsor.

Service Provider Patient De-Identification accounts for data "at rest" and data "in transit". For data at rest, identifying entries in a patient record are encrypted using Microsoft SQL Server native cryptographic functions using symmetric key, which can be viewed by only by those users who have permission to view their own domain of individuals' PHI data. The users who do not have appropriate permission to see ePHI information on any individuals, will instead see a patient ID, which is a random, system generated, non-repeating number, having no correlation to any information about the patient. This is accomplished using symmetric key encryption.

To protect "Data In-Transit" which is data that traverses over the public Internet, Service Provider utilizes the Secure File Transfer Protocol (SFTP) and secure browser and secure, encrypted email platform.

8.7 Data Analysis

8.7.1. Essential analysis

Specific analytic methods are shown for each study objective. All CAB LA PrEP users will be followed for 3 years. All individuals with incident HIV infection will be followed for 12 months. Participants discontinuing CAB LA PrEP will be monitored for 12 months for HIV infection and additional 12 months if diagnosed with HIV infection, to monitor for ART effectiveness & potential emergence of resistance. In the event of a delay of ART initiation post HIV diagnosis, the study team will strive to follow the individual for 12 months since ART initiation. Interim results will be generated at 12, 24, 36, 48 months since study initiation and final results will be generated at 60 months since study initiation.

Analysis for Objective 1 (Description of CAB for PrEP Usage pattern)

For individuals initiating CAB for PrEP, baseline demographics (age, sex, gender, race/ethnicity, BMI, geographic region), history of previous PrEP use and use of CAB oral lead in prior to initiating injections will be described. Comorbidities, STIs, risk factors for HIV acquisition, will be reported as frequencies at baseline and at 6, 12, 24, 36 months of follow-up. Proportion of individuals using oral PrEP to cover planned, delayed or missed CAB LA injections will also be provided. Frequency of testing for HIV once initiated CAB for PrEP will be evaluated.

Prevalent HIV infections are defined as undiagnosed HIV infections at the time of PrEP initiation and will be defined as positive HIV antigen/antibody test and/or positive viral load from sample collected at the time of initiation (first prescription of CAB oral lead and, separately, first CAB LA PrEP injection). Note the test result may be reported within 4-6 weeks after the sample was collected. Prevalent HIV infections will be reported at baseline while on CAB OLI and while on CAB LA. Also, prevalent HIV infections will be reported for those who received CAB OLI and separately for those with direct to injection (DTI) strategy.

Incident HIV infections are new infections diagnosed after initiation of CAB PrEP, having confirmed HIV negative status using HIV RNA test, at the time of PrEP initiation. Incident HIV infection reporting is described in objective 3.

Analysis for Objective 2 (Monitor for adherence by assessing the frequency of delayed and missed injections without oral PrEP)

Adherence will be estimated using the dates of injections. Proportion and number of individuals with ≥ 1 delayed and ≥ 1 missed injection over 6, 12, 24, 36-month periods will be provided. Additionally, mean (median) number of delayed and missed injections will be provided for each period. Proportion and number of individuals with ≥ 7 days delay of CAB LA PrEP injection over 6, 12, 24, 36-month periods will be provided. Additionally, mean (median) number of days delayed will be provided for each period.

Characteristics of persons with delayed or missed injections will be compared with those that are on time with the injections for 6, 12, 24, 36-month periods using t-test for continuous variables (Wilcoxon rank sum test for not normally distributed variables) or chi-square test for categorical variables.

Proportion and number of individuals who discontinue CAB LA PrEP over 6, 12, 24, 36 month-periods and overall will be provided. Additionally, distribution of individuals who discontinued by most common discontinuation reasons will be provided. Characteristics of persons who discontinue vs persons who stay on therapy will be compared for 6, 12, 24, 36-month periods using t-test for continuous variables (Wilcoxon rank sum test for not normally distributed variables) or chi-square test for categorical variables.

If feasible, risk of delayed or missed injections and separately risk of discontinuation will be assessed using negative binomial model with log-link function accounting for sex, age group, race/ethnicity, and other characteristics found significant in univariate analysis.

Analysis for Objective 3 (Effectiveness: Monitor for incidence of HIV infection while on CAB for PrEP)

Frequency of undiagnosed prevalent HIV infection at CAB PrEP initiation will be assessed as described for objective 1. The primary effectiveness measure for objective 3 is proportion of individuals with incident HIV infection during OLI and separately during CAB LA PrEP and will be calculated at 6, 12, 24, 36 months and over the entire length of follow-up. The proportion of incident infections among those who start with OLI and those who go to DTI will also be reported separately along with the timing of diagnosis of incident HIV infection for the overall group, and separately for the OLI and DTI groups.

Adherence patterns and characteristics of individuals with incident HIV infection will be compared with those without incident HIV diagnosis, using t-test for continuous variables (Wilcoxon rank sum test for not normally distributed variables) or chi-square test for categorical variables. Participant characteristics significantly impacting acquisition of

HIV infection based on univariate analysis will be selected for multivariable analysis. Risk for HIV infection and characteristics affecting risk for HIV infection will be assessed using negative binomial model with log-link function with binary outcome (diagnosed with HIV infection vs not) if feasible.

Time to diagnosis of HIV infection will be defined as time from first CAB LA PrEP injection to the first diagnosis of HIV infection using laboratory antigen/antibody test, confirmed by viral RNA test. Time to diagnosis of HIV infection will be assessed using Kaplan-Meier curve. Differences in time to diagnosis will be assessed by sex, gender, race/ethnicity, geographic region, payer status, and risk factors (e.g. STI, previous PrEP usage) to HIV acquisition. Additionally, time to diagnosis will be shown for people who acquired the infection while prescribed oral CAB lead in (if applicable). Time to diagnosis in this group will be defined as time from first CAB oral prescription to the first positive HIV-1 antigen/antibody lab result, confirmed by viral RNA test.

If feasible, Cox proportional hazards models will be constructed to compare time to diagnosis of HIV infection by subgroup (e.g., payer) adjusting for additional variables (e.g., sex, race/ethnicity, geographic region).

ART regimen and VL testing among CAB PrEP users with undiagnosed prevalent infections and incident infections will be described separately, during the 12 months of follow up period. In the event of a delay of ART initiation post HIV diagnosis, the study will strive to follow the individual for 12 months after ART initiation. Durability of INSTI-based vs. non-INSTI based regimens (e.g., the numbers and proportions of those who achieve and maintain virologic suppression, the time to virologic suppression, the time to virologic breakthrough), as well as any INSTI resistance-associated substitutions that are detected upon ART failure will also be assessed and reported.

Analysis for Objective 4 (Safety: Monitor for occurrence of DILI and HSR)

Proportion and number of individuals with DILI and hypersensitivity reaction following CAB OLI and CAB LA injections will be shown separately at 6, 12, 24, 36 months after initiation and over the entire length of follow-up. Proportion and number of individuals discontinuing CAB OLI and CAB LA PrEP due to DILI or HSR will be shown at 6, 12, 24, 36 months and over the entire length of follow-up. Discontinuation of CAB LA PrEP or CAB OLI will be based on medical records indicating date when discontinuation decision was made by a physician and will be reviewed and confirmed by independent adjudication committee. Frequency of hepatotoxicity and HSR events will be reported separately for OLI period and during injections.

Analysis for Objective 5 (Resistance monitoring)

Proportion and number of individuals developing drug resistance to INSTIs based on genotypic data will be assessed among the 4 different groups as follows:

- a) Individuals with undiagnosed prevalent HIV infection, initiating CAB OLI or CAB LA PrEP will be followed for 12 months after ART initiation and monitored for resistance

- b) Individuals with incident HIV while on CAB LA PrEP will be followed for 12 months following ART initiation and monitored for resistance
- c) Individuals who discontinue CAB LA PrEP will be followed for 12 months and if they acquire HIV will be followed for another 12 months after ART initiation to monitor for resistance
- d) Individuals who switch to oral PrEP and acquire HIV infection during the 12-month follow up period while on oral PrEP will be followed for another 12 months after ART initiation and monitored for resistance

Proportion and number of patients developing specific mutations in each group will be provided along with HIV subtype. Description of the methodologies used to evaluate resistance will be described.

8.8 Quality Control and Quality Assurance

The database is already in existence due to the processes in place with Trio Health's participating practices and Specialty Pharmacy partners. Trio Health will evaluate and adjudicate the data with the practices and Specialty Pharmacy partners. The collected data may not reflect the universe of care in the US. For data gaps or inconsistencies, preference will be given to listwise deletion where data are incomplete (Li et al., 2012).

For all analyses, sample sizes less than the starting group size will be provided.

8.9 Limitations of the Research Methods

1. Selection Bias: Study subjects will be taken from Trio Health's larger database that collects data on all individuals in care of HIV treatment centers regardless of patient demographics and treatment regimen. The study will not be influencing who will be starting PrEP or subsequent treatment regimen that individuals receive in this heterogeneous, random population. This method of collecting all-comers minimizes selection bias.
2. Recall Bias: The data is reflective of information recorded by the physician and would only be flawed if recorded improperly at the practice. Recall bias is not applicable to the script or dispensing data, as it reflects actual transactions that occur at the pharmacy.
3. Dispensing Data: This data is collected from sites that predominantly have 340 B programs. This may place some limitations on information related to patient assistance program participation, rate of data refresh, (range in sites from daily to monthly), denial of claims.

In addition to acknowledged bias, the dataset limitations are below:

- Trio Health's database may not reflect the universe of care in the US.
- Data ultimately stems from the provider, aside from dispensing information, in which the provider acts as a data conduit. Errors in input at the provider site will

not be identified unless subsequently fixed by the provider and communicated to Trio Health.

- Treatment for other conditions handled by specialists is not accounted for so comorbidities may be underestimated.
- Individuals who move for treatment at a facility not captured by Trio database or those lost to follow-up cannot be distinguished. Overall, some lost to follow-up is expected but this study will make every effort to minimize that.
- Other confounders such as income level, education, condom use, PrEP use by sexual partners are not available in the EMRs that form the main source of data.
- Due to using EMR, some variables, like reasons for discontinuation, may not be complete for every individual.

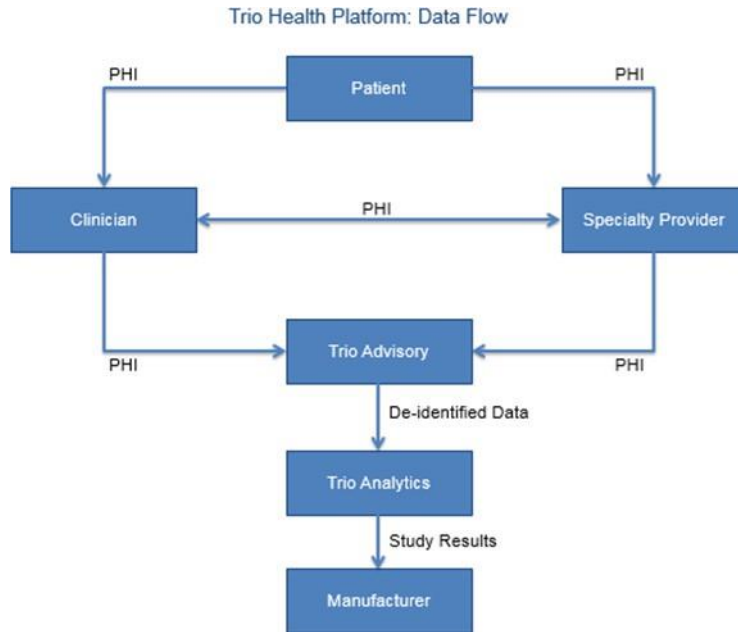
Despite the above limitations, the study possesses the following strengths. The study will collect real-world usage and care patterns from geographically diverse, established cohort using robust proven data collection methodology and patient deidentification. The study will be guided by input from Trio Health Scientific Steering Committee consisting of leading academic and community physicians specializing in treatment of HIV as well as leading physicians from participating clinics.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

Trio Health data collection and process was approved by Western IRB as an institutional review board exemption under 45 CFR 46.101(b)(4) and therefore does not require full IRB review. Trio Health will submit finalized protocol to a central IRB (Advarra) with the request to grant exemption for full review and share the protocol with participating sites. If sites require local (internal) IRB review, they will handle the submission to their local IRBs.

Trio Health Platform Data Flow



Trio Advisory

Each SPP and Physician signs a Participation Agreement and a Business Associate Agreement (BAA) between itself and Trio Advisory, which covers sharing of PHI. Patient Consent is obtained through the process. Given that Physician and SPP are both Covered Entities, no agreement is required to share PHI between these parties.

Trio Analytics

Trio Advisory provides Trio Analytics with De-Identified Data. The De-Identified Data is further abstracted by removing the physician and the practice name associated with each patient. Therefore, the data Trio Analytics receives is identified as Patient PPD, Physician PPD and Practice PPD. Physicians are classified solely by practice types (e.g., Academic or Community) along with location by State and Region.

An intercompany agreement exists between Trio Analytics and Trio Advisory under which Trio Advisory, for a fee, will provide Trio Analytics with an unlimited license to use the De-Identified Data. The De-Identified Data may be used by Trio Analytics in the following ways:

- i. Creation of SPP or Physician customized analytics
- ii. General analytics
- iii. Studies for Manufacturers, Payors, other third parties
- iv. General studies
- v. Licensing or raw data (excluding identification information for SP's) to third parties (government agencies, financial institutions, etc.)
- vi. Patient awareness and education

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a non-interventional study based on secondary use of data collected to support clinical care. The study uses de-identified data and there is no potential to collect individual level data on serious and non-serious adverse events (AEs), 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, 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.

The participating clinical sites and health care providers will be strongly encouraged to report all pregnancies occurring while using CAB for PrEP, prospectively (i.e., reported prior to the outcome of pregnancy is known) to the Antiretroviral Pregnancy Registry (+1-800-258-4263 or www.APRegistry.com).

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Milestones

This study-specific protocol will be submitted for FDA's review and endorsement. The study will start once CAB LA for PrEP is approved and commercially available in the US and is expected to continue through 2026 or later. Annual interim reports with cumulative data will be submitted and a final report is expected to be submitted in September 2027.

11.2. Target Audience

The target audience for these data includes healthcare providers, regulatory and health authorities.

11.3. Study Reporting and Publications

Annual interim reports with cumulative data will be submitted and a final report is expected to be submitted to the agency in September 2027. Interim and final study results will be included in safety and regulatory reports as appropriate. Study results will be made available externally through peer reviewed manuscript and conference presentation. Describe plans and schedule for internal and external dissemination and communication of progress reports, study results, and publications.

12. REFERENCES

- FDA News Release. FDA Approves First Injectable Treatment for HIV Pre-Exposure Prevention. <https://www.fda.gov/news-events/press-announcements/fda-approves-first-injectable-treatment-hiv-pre-exposure-prevention>. Accessed 3/3/2022.
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13. ANNEX 1.

13.1. ICD-9/ICD-10 codes

<u>Comorbidity</u>	<u>ICD-9</u>	<u>ICD-10</u>
Alcohol use	291, 305.0X, 303.0, 303.9, 357.5, 425.5, 535.3, 571.0-571.3, 655.4, 760.71, 980.0, 980.1, E86.0, E860.1, E860.2, E860.9, 790.3	F10.3-F10.9, F10.0, F10.1, F10.2, G62.1, G31.2, G72.1, I42.6, K29.2, K70-K70.4, K70.0, Q86.0, P04.3, O35.4, K86.0, X45, Y15, T51.0, T51.1, T51.9, X65, R78.0, 099.31X, Z71.41
Cardiovascular diseases	391.X, 393.X-398.X, 401.X-405.X, 410.X-414.X, 415.X-417.X, 420.X-429.X, 430.X-438.X, 440.X-449.X, 451.X-459.X	I01.X, I05.X-I09.X, I10.X-I16.X, I20.X-I25.X, I26.X-I28.X, I30.X-I52.X, I60.X-I69.X, I70.X-I79.X, I80.X-I89.X, I95.X-I99.X
Cirrhosis	571.2, 571.5, 571.6	K74.4, K74.5, K74.6X
Depression	296.2X, 296.3X, 296.9X, 300.0X, 300.2X, 300.4, 300.5, 300.7, 308.X, 309.X, 311.X	F32.X-F33.X, F34.X, F38.X, F40.X-F41.X, F43.X
Diabetes	249.X, 250.X	E08.X-E.11.X, E13.X
Hepatitis B	0.70.2X, 070.3X	B16.X, B18.00, B18.1
Hyperlipidemia	272.4, 272.2	E78.5, E78.2
Hypertension	401.X-405.X	I10.X-I16.X
Hypogonadism	257.2	E29.1
Neuropsychiatric disorders	290.X-294.X, 295.X-299.X, 300.X, 303.X-316.X	F01.X-F09.X, F10.X-F19.X, F20.X-F29.X, F30.X-F39.X, F40.X-F48.X, F50.X-F51.X, F53.X-F55.X, F59.X
Osteoporosis	733.X	M80.X-M81.X, M85.X
Osteoporosis/Osteoarthritis	733.X, 715.X	M80.X-M81.X, M85.X, M86.X-M90.X, M15.X-M19.X
Smoking	305.1X, 649.0, 649.01, 649.02, 649.03, 989.84, V15.82, V69.8, 492.X, 491.X	F17.X, T65.2X, Z87.891, Z72.0, 099.33X, J43.X, J44.X
Substance abuse	304.X, 305.X, 968.5, 969.6, E938.5, E854.1, E939.6, 965.X, E850.0, E935.0, 292.X, V654.2	Z71.51, F11-16, F18-19, T40.X

<u>Comorbidity</u>	<u>ICD-9</u>	<u>ICD-10</u>
Charlson Comorbidities		
Cancer (any)	140.x-172.x, 174.x-195.8, 200.x-208.x, 238.6	C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.x
Cerebrovascular disease	362.34, 430.x-438.x	G45.x, G46.x, H34.0, I60.x-I69.x
Chronic pulmonary disease	416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0
Dementia	290.x, 294.1, 331.2	F00.x-F03.x, F05.1, G30.x, G31.1
Diabetes with complication	250.4-250.7	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7
Diabetes without complication	250.0-250.3, 250.8, 250.9	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Hemiplegia	334.1, 342.x, 343.x, 344.0-344.6, 344.9	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9
HIV	042.x-044.x	B20.x-B22.x, B24.x
Liver disease (mild)	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7	B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4
Liver disease (moderate/ severe)	456.0-456.21, 572.2-572.8	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Metastatic cancer	196.x-199.1	C77.x-C80.x

<u>Comorbidity</u>	<u>ICD-9</u>	<u>ICD-10</u>
Myocardial infarction	410.x, 412.x	I21.x, I22.x, I25.2
Peptic ulcer disease	531.x-534.x	K25.x-K28.x
Peripheral vascular disease	093.0, 437.3, 440.x, 441.x, 443.1-443.9, 447.1, 557.1, 557.9, V43.4	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0-583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2
Rheumatic disease	446.5, 710.0-710.4, 714.0-714.2, 714.8, 725.x	M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0
Gonorrhea	098.0, 098.1, 098.2, 098.3, 098.6, 098.7, 098.89, V02.7, 647.1	A54.00, A54.1, A54.2, A54.5, A54.6, A54.8, A54.9, 098.2
Syphilis	091.X, 092.X, 093.X, 094.X, 095.X, 096.X, 097.X, 647.0	A51.X, A52.X, A53.X, 098.1
Chlamydia	078.8, 078.88, 079.8, 079.88, 079.9, 079.98, 099.41, 099.5, 099.5, 099.51, 099.52, 099.53, 099.54, 099.55, 099.56, 099.59	A55, A56, A74.8, A74.9
SYPHILIS AND OTHER VENEREAL DISEASES	090-099	A50-A64
High-risk behavior	V01.79, V01.6, V01.89, V01.9, V69.2, V69.8, V15.89, E920.5	Z20.6, Z20.2, Z20.828, Z20.89, Z20.9, Z72.51, Z72.52, Z72.89, Z72.53, Z77.21, W46.X
Use or adverse effect of narcotics, psychodysleptics [hallucinogens], psychoactive substance	304.4, 304.5, 305.3, 305.5, 305.7	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6, T40.8, T40.9, F16, F19, F11
Use of or adverse effects of cocaine	304.2, 305.6	T40.5, F14
Use or adverse effect of antiepileptic, sedative-hypnotic and anti-parkinsonism drugs	304.0, 304.1, 304.7, 305.4	T42, F13