NON-INTERVENTIONAL STUDY PROTOCOL

STUDY DETAILS

UNIQUE IDENTIFIER (CTMS)	306339
TITLE	Oral and Long-Acting Injectable Cabotegravir Preexposure Prophylaxis Use Among U.S. Veterans Using Veterans Health Administration Services, 2021-2025
STUDY ACCOUNTABLE PERSON	PPD, ViiV Healthcare
SCIENTIFIC LEAD	PPD, ViiV Healthcare
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ASSET ID	GSK1265744
GSK or ViiV ASSET	Cabotegravir (Apretude)
EFFECTIVE DATE	19 December 2025
INDICATION	HIV pre-exposure prophylaxis

DATA COLLECTION TYPE	SECONDARY
SAFETY OBJECTIVE	NO
ASSET INVOLVEMENT	YES
TSS/PASS ASSESSMENT PERFORMED	YES
STUDY CLASSIFICATION	Voluntary PASS/TSS
EVALUATING A PRODUCT (TIER TYPE)	Tier 1
REGULATORY COMMITMENT	No

TITLE PAGE

Study ID: 306339

Division: Global Medical

Information Type: Non-Interventional Study Protocol

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Author(s):

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STUDY INFORMATION

Title	Oral and Long-Acting Injectable Cabotegravir Preexposure Prophylaxis Use Among U.S. Veterans Using Veterans Health Administration Services, 2021-2025
Protocol version identifier	1.0
Date of last version of protocol	NA
EU PAS (ENCEPP) register number	TBD
Active substance	Cabotegravir
Medicinal product	Apretude
Product reference	N/A
Procedure number	N/A

Marketing authorisation holder(s)	ViiV Healthcare
Research question and objectives	• **Objective Set 1**: Estimate annual HIV diagnosis rates among Veterans in care and describe the history of PrEP use among newly diagnosed HIV patients • **Objective Set 2**: Characterize Veterans not on PrEP but who could benefit from it and evaluate rates of HIV/STI testing and diagnoses over 12 months. • **Objective Set 3**: - Describe demographic, clinical and sexual behavioral characteristics of Veterans initiating oral or cabotegravir long-acting (CAB LA) PrEP - Estimate the proportion of CAB LA PrEP users initiating PrEP with oral lead-in (OLI) versus direct-to-injection (DTI). - Describe adherence to oral PrEP and CAB LA injectable PrEP - Describe patterns of PrEP use, including discontinuation, resumption, and duration of use for both oral and CAB LA PrEP. - Describe HIV and STI testing, diagnoses, and antimicrobial treatment prescription for STI by PrEP modality - For CAB LA PrEP users diagnosed with HIV, analyze the timing of HIV diagnoses relative to PrEP usage, injection schedules, HIV treatment, virologic suppression, STI diagnoses, and HIV drug resistance.
Country(-ies) of study	United States
Lead Author	PPD

MARKETING AUTHORISATION HOLDER(S

Marketing authorisation holder(s)	ViiV Healthcare Company 410 Blackwell St. Durham, NC 27701
MAH contact person	N/A

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LIST OF ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
BMI	Body Mass Index
CAB	Cabotegravir
CDC	Centers for Disease Control
CDW	Corporate Data Warehouse
CI	Confidence intervals
DTI	Direct to injection
EHR	Electronic health record
FDA	Food and Drug Administration
FTC	Emtricitabine
FU	Follow-up
GSK	GlaxoSmithKline
HBV	Hepatitis B virus
HCP	Healthcare provider
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HSV	Herpes Simplex Virus
IHD	Individual Human Data
IRB	Investigational Review Board
LA	Long acting
LEN	Lenacapavir
MSM	Men having Sex with Men
NA	Not applicable
OLI	Oral lead-in
PEP	Post-exposure prophylaxis
PHI	Protected health information
PrEP	Pre-exposure prophylaxis
PTSD	Post-traumatic stress disorder

QPPV	Qualified Person Responsible for Pharmacovigilance
STI	Sexually transmitted infection
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
US	United States
VA	Veterans Affairs
VACS Index	Veterans Aging Cohort Study Index
VHA	Veterans Health Administration
ZIP	Zone Improvement Plan

TRADEMARK INFORMATION

Trademarks of the <<GSK\ViiV>> group of companies	Trademarks not owned by the <<GSK\ViiV>> group of companies
APRETUDE	Not applicable

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: Oral and Long-Acting Injectable Cabotegravir Preexposure Prophylaxis Use Among U.S. Veterans Using Veterans Health Administration Services, 2021-2025

Compound Number: GSK1265744

PPD

15 December 2025

Adrienne Guignard
Primary Author/NI Scientific Lead

Date (DD Month YYYY)

PPD

19 December 2025

Vani Vannappagari
VP and Global Head, Epidemiology and Real World Evidence

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Date (DD Month YYYY)

PPD

18-Dec-2025

Jens Ulrich Stegmann
ViiV QPPV

Date (DD Month YYYY)

1.2. Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described 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 receive the appropriate information throughout the study.

Investigator Name: Mihaela Aslan, PhD

PPD

Investigator Signature

Date (DD Month YYYY)

2. SYNOPSIS

Title: Oral and Long-Acting Injectable Cabotegravir Preexposure Prophylaxis Use Among U.S. Veterans Using Veterans Health Administration Services, 2021-2025

Rationale and Background

HIV remains a significant public health challenge in the US, with over 39,000 new diagnoses in 2023, predominantly among men, racial and ethnic minorities, and individuals aged 20–44. Pre-exposure prophylaxis (PrEP), including daily oral and long-acting injectable options, is highly effective in preventing HIV when used as recommended. However, uptake remains low, with only 36% of eligible individuals receiving PrEP in 2022. This study among individuals receiving Veterans Health Administration care seeks to generate real-world evidence on PrEP use patterns, adherence, HIV testing, STI screening, and incident HIV diagnoses among individuals using oral or injectable PrEP. The findings aim to inform strategies that optimize its effectiveness and maximize its public health impact.

Research Question and Objective(s)

Objective set 1 -Veterans in care with no evidence of HIV infection at the beginning of the calendar years under analysis

1.1- Estimate the annual incidence proportion of HIV diagnoses among Veterans in care without evidence of HIV infection at the beginning of each calendar year under analysis

1.2- Among Veterans with an incident HIV diagnosis, characterize history of PrEP use.

Objective set 2- Veterans in care with no evidence of HIV infection who are not on PrEP but could benefit from PrEP *(refer to protocol section 7.2.1 for inclusion criteria)*

2.1- Describe the characteristics of Veterans in care who are not on PrEP but could benefit from PrEP

2.2- Estimate HIV testing and diagnoses rates, as well as rates of STI screening/testing rates, STI diagnoses among Veterans in care who are not on PrEP but could benefit from PrEP, over a 12-month period of follow-up

Objective set 3- Veterans in care with no evidence of HIV infection who initiate PrEP (oral or CAB LA injectable) during the study eligibility period for PrEP initiation

3.1- Describe the population of Veterans in care who initiated oral PrEP or CAB LA injectable PrEP, including their demographic and clinical characteristics, the year of PrEP initiation and the duration of follow-up

3.2- Describe the proportions of Veterans in care initiating CAB LA PrEP who used oral lead in (OLI) and proportion of those with direct to injection (DTI).

3.3- Describe adherence to oral and CAB LA injectable PrEP

a) Oral PrEP use only: number days oral PrEP supplied divided by number of days in the observation period

b) CAB LA injectable PrEP

- Number of days covered by CAB LA PrEP divided by the number of days in the observation period
- Timing and completion of initiation injections

- Among complete initiators with at least one maintenance injection, timing of maintenance injections: all on time, any late injection (short delay not requiring reinitiation, long delay requiring reinitiation)

- Baseline characteristics of users with all injections on time versus users with any late maintenance injection

3.4- Describe patterns of PrEP use

a) Oral PrEP:

- Discontinuation: any discontinuation, resumption of oral PrEP

- Duration of oral PrEP use for the first period of use

b) CAB LA injectable PrEP

- Discontinuation: any discontinuation, resumption of long-acting injections (with CAB LA injectable or LEN LA injectable) or oral PrEP after discontinuation

- Oral bridging between discontinuation of CAB LA injections and resumption of CAB LA injections

- Duration of CAB LA PrEP use in months

  - first period of use

  - cumulative use throughout the study period in case of discontinuation followed by resumption of CAB LA PrEP injection(s)

-Baseline characteristics of users discontinuing CAB LA PrEP versus users who did not discontinue

- Proportion of CAB LA PrEP users with at least one maintenance injection who are on CAB LA PrEP at 12 months and 24 months after initiation and at the end of the study period

3.5- Described patterns of HIV and other STI testing/screening, diagnosis and STI treatment

a) Assess the incidence of HIV testing and HIV diagnosis during the first period of PrEP use by PrEP modality

b) Estimate the incidence of testing for STI diagnosis and STI diagnosis by PrEP modality

- in the 6 months preceding PrEP initiation

- during the first period of PrEP use

c) Describe the proportion of diagnosed STI with a relevant antimicrobial prescription

3.6- Among CAB LA PrEP users diagnosed with HIV (during CAB LA PrEP use or after CAB LA PrEP discontinuation)

a) Describe the timing of incident HIV diagnoses relative to timing of CAB LA PrEP usage and testing for HIV

b) Describe adherence to PrEP injection schedule, HIV treatment, virologic suppression, concomitant STI diagnosis, and HIV drug resistance

Study Design

This is a cohort study using data from the Veterans Affairs National Sample, which is composed of Veterans who receive healthcare services through the Veterans Health Administration (VHA). This national sample is representative of the Veteran population, capturing a wide range of demographic, clinical, and social characteristics.

Population
The study will include different cohorts:
- Veterans in care with no evidence of HIV infection at the beginning of the calendar years under analysis
- Veterans in care with no evidence of HIV infection who could benefit from PrEP but are not on PrEP (identified based on risk factors for HIV acquisition or factors linked to behaviors increasing the risk of HIV acquisition which are generally documented in Veterans health records)
- Veterans in care with no evidence of HIV infection who initiate PrEP (oral or CAB LA injectable) during the study eligibility period

Main variables
Exposures:
- History of PrEP use (for Veterans with a new HIV diagnosis)
- Oral PrEP and CAB LA PrEP (for Veterans initiating a PrEP regimen during the study period)

Outcomes:
- PrEP adherence and continuation patterns
- HIV testing
- Incident HIV diagnosis
- STI testing, diagnosis and treatment prescription

Data Sources
In this study, we used data extracted from VHA's Corporate Data Warehouse (CDW), a comprehensive, continually updated repository of information from VHA's electronic health records (EHR) and administrative files. The CDW dataset includes health care encounters, laboratory tests and results, medications, diagnoses, patient demographics, and residential ZIP codes.

Study Size
For the objective related to HIV incidence among Veterans, the study will leverage data from the entire eligible population of Veterans in care.
Regarding PrEP usage patterns, a feasibility assessment identified 15,477 oral PrEP users and 748 CAB LA PrEP users between January 1, 2021 and June 30, 2025.

Data Analysis
All analyses in this study will be descriptive, focusing on estimating frequencies of outcomes across various objectives:

Veterans in care without HIV (Objective 1.1)
For each calendar year, the number and percentage of new HIV diagnoses among Veterans in care will be reported.

Veterans in care with a new HIV diagnosis (Objective 1.2)
Among newly diagnosed individuals, PrEP usage and characteristics of PrEP users will be described using counts, proportions, medians, and interquartile ranges.

Veterans who are not on PrEP and who could benefit from PrEP (Objective set 2)
For Veterans not on PrEP but who could benefit from it, baseline characteristics will be summarized at their first qualifying visit, while rates of HIV and STI testing/diagnoses within 12 months will be calculated using Poisson regression.

Veterans using PrEP (Objective set 3)
Objective 3.1- Baseline demographic and clinical characteristics will be described at the start of PrEP use during the study period, by regimen type (oral or CAB LA), using median and interquartile ranges or counts and proportions.
Objective 3.2- Proportions of CAB LA PrEP users initiating via oral lead-in or direct-to-injection will be reported.
Objective 3.3 and 3.4- PrEP adherence and usage patterns will be described using median and interquartile range for continuous data as well as absolute and relative frequencies for categorical data. Characteristics of individuals with and without delayed CAB LA injections as well as individuals with and without discontinuation will be compared using Pearson's chi-square tests for categorical variables and Mann-Whitney tests for continuous variables.
Objective 3.5- Incidence rates and confidence intervals for HIV testing, HIV diagnosis, STI testing/screening and STI diagnosis will be calculated using univariate Poisson regression. STI treatment prescription will be described using absolute and relative frequencies for categorical data.
Objective 3.6- For CAB LA PrEP users diagnosed with HIV, a timeline including details of oral PrEP prescriptions prior to CAB LA PrEP start, injections received, HIV tests performed, HIV treatment, viral load measurements, HIV drug resistance will be provided for each individual.

3. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
-	-	-	-	-

4. MILESTONES

Table 1: Study milestones

Milestone	Planned date
Final Protocol	19 December 2025
Tables Results	Q2 2027
Final Study Report	Q3 2027

5. RATIONALE AND BACKGROUND

HIV remains a persistent problem in the United States (US). In 2023, over 39,000 people were diagnosed with HIV in the US and 6 territories and freely associated states (US CDC, 2025). Over 80% were men, with 66% attributed to male-to-male sexual contact. Hispanic and Black individuals each accounted for more than a third. Ages 15-24 and 25–44 accounted for 18% and 60% of diagnoses, respectively. The South region represented 51% of new cases. The 2021 HIV/AIDS Strategy identified five priority populations disproportionately impacted by HIV: gay, bisexual, and other men who have sex with men (MSM), black women, transgender women, youth aged 13–24 years, people who inject drugs (White House, 2021).

Pre-exposure prophylaxis (PrEP), which consists in the use of antiretroviral medications by HIV-negative individuals with a substantial risk of contracting an HIV infection, is highly effective at preventing HIV when taken as indicated (Cancio-Suárez, 2023). As of August 2025, there are two daily oral medications for PrEP approved by the U.S. Food and Drug Administration (FDA). There are also two FDA-approved long-acting injectable forms of PrEP, one that is administered every other month and the other is administered twice yearly. Oral PrEP was introduced as a form of HIV prevention when the single tablet combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) was approved by the FDA on July 16, 2012 (Roehr, BMJ 2012). The second oral PrEP option, a single tablet combination of tenofovir alafenamide (TAF) and FTC was approved on October 3, 2019 (The Lancet HIV, 2019).
Cabotegravir long-acting (CAB LA) is an injectable PrEP administered every two months for use in at-risk adults and adolescents and received FDA approval in December 2021 (US FDA, 2021). CAB LA may be initiated with optional short-term oral lead-in (OLI). Clinical trials have demonstrated the superior efficacy of CAB LA PrEP over daily oral TDF/FTC for HIV prevention (Durham, 2023). A second long-acting option for HIV prevention (Lenacapavir - LEN) was approved by the US FDA in June 2025 (Mullard, 2025). It is delivered in subcutaneous injections given every 6 months.

The US Centers for Disease Control and Prevention (CDC) recommend that people consider PrEP if they are HIV negative, have had anal or vaginal sex in the past six months, and have a sexual partner with HIV (especially if the partner has an unknown or detectable viral load), or

have not consistently used a condom, or have been diagnosed with a sexually transmitted infection (STI) in the past six months (US CDC, 2024). PrEP is also recommended to people who inject drugs and have an injection partner with HIV, or share needles, syringes, or other equipment to inject drugs. People who have been prescribed PEP (post-exposure prophylaxis) and report continued risk behavior or have used multiple courses of PEP may as well consider taking PrEP. People may also choose to take PrEP, even if these behaviors do not apply to them.

In 2022, of approximately 1.2 million people in the US who could benefit from PrEP, it was estimated that only around 36% had received a PrEP prescription (Fanfair, 2023). The Department of Veterans Affairs (VA) is the largest HIV care provider in the US; PrEP is a covered benefit for all enrolled Veterans (Huang, 2018). An analysis of 2014-2022 data of the Veterans Health Administration (VHA) showed an increase in the number of Veterans prescribed PrEP annually, from 361 in 2014 (5.6 per 100,000 Veterans in VHA care) to 6050 in 2022 (89.4 per 100,000) (Huang, 2025). While adherence to oral PrEP was high among Veterans in the period 2012-2016 (Huang, 2018), recent adherence data, including for long-acting injectable PrEP, are lacking. To be eligible for CAB-LA PrEP in the Veterans Health Administration, individuals must be at substantial risk of HIV acquisition (sex without condoms, recent or frequent sexually transmitted infections, sexual relationship with HIV infected partner, injection drug abuse with equipment sharing), prescribed cabotegravir by a provider experienced in PrEP, and meet at least one of the following additional criteria: intolerance to TDF/FTC or TAF/FTC, renal dysfunction, challenges with adherence to daily oral PrEP, or very high risk of HIV acquisition. Patients are excluded if they have significant noncompliance with follow-up or drug interactions with CAB (VA, 2022).

HIV testing is required to confirm that patients do not have HIV before starting PrEP (US CDC, 2025). People on daily oral PrEP need to see a health care provider every 3 months for repeat HIV tests, prescription refills, and follow-up. People using injectable PrEP need to see a healthcare provider every two or six months for an HIV test and the injections, depending on which option they chose (HIV.gov, 2025 a). Screening for other sexually transmissible infections (STIs) is an important part of PrEP clinical follow-up and monitoring (Jenness, 2017). It allows for early detection and treatment of STIs that would otherwise go undetected.

Understanding patterns of PrEP use is key to optimizing its effectiveness in HIV prevention and improve clinical practice and public health benefits. Analyzing how people use PrEP can help design effective strategies for uptake, adherence and continuation leading to better public health outcomes. This study will provide real-world evidence on PrEP use patterns, HIV testing and STI screening in individuals on either oral or LA PrEP, as well as potential incident HIV diagnoses on PrEP.

6. RESEARCH QUESTION AND OBJECTIVE(S)

Objective set 1 -Veterans in care with no evidence of HIV infection at the beginning the calendar years under analysis

1.1- Estimate the annual incidence proportion of HIV diagnoses among Veterans in care (actively enrolled in VHA care) without evidence of HIV infection at the beginning of

each calendar year under analysis

1.2- Among Veterans with an incident HIV diagnosis, characterize history of PrEP use.

Objective set 2- Veterans in care with no evidence of HIV infection who are not on PrEP but could benefit from PrEP

2.1- Describe the characteristics of Veterans in care who are not on PrEP but could benefit from PrEP

2.2- Estimate HIV testing and diagnoses rates, as well as rates of STI screening/testing rates, STI diagnoses among Veterans in care who are not on PrEP but could benefit from PrEP, over a 12-month period of follow-up

Objective set 3- Veterans on care with no evidence of HIV infection who initiate PrEP (oral or CAB LA injectable) during the study period

3.1- Describe the population of Veterans in care who initiated oral PrEP or CAB LA injectable PrEP, including their demographic, clinical and sexual behavioral characteristics, the year of PrEP initiation and the duration of follow-up

3.2- Describe the proportions of Veterans on care initiating CAB LA PrEP who used oral lead in (OLI) and proportion of those with direct to injection (DTI).

3.3- Describe adherence to oral and CAB LA injectable PrEP

a) Oral PrEP use only: number days oral PrEP supplied divided by number of days in observational period

b) CAB LA injectable PrEP
- Number of days covered by CAB LA PrEP divided by the number of days in the observation period
- Timing and completion of initiation injections
- Among complete initiators with at least one maintenance injection, timing of maintenance injections: all on time, any late injection (short delay not requiring reinitiation, long delay requiring reinitiation)
- Baseline characteristics of users with all injections on time versus users with any late maintenance injection

3.4- Describe patterns of PrEP use

a) Oral PrEP:
- Discontinuation: any discontinuation, resumption of oral PrEP
- Duration of oral PrEP use for the first period of use

b) CAB LA injectable PrEP
- Discontinuation: any discontinuation, resumption of long-acting injections (with CAB LA injectable or LEN LA injectable) or oral PrEP after discontinuation
- Oral bridging between discontinuation of CAB LA injections and resumption of CAB LA injections
- Duration of CAB LA PrEP use in months

  - first period of use
  - cumulative use throughout the study period in case of discontinuation followed by resumption of CAB LA PrEP injection(s)
- Baseline characteristics of users discontinuing CAB LA PrEP versus users who did not discontinue
- Proportion of CAB LA PrEP users with at least one maintenance injection who are on CAB LA PrEP at 12 months and 24 months after initiation and at the end of the study period

3.5- Described patterns of HIV and other STI testing/screening, diagnosis and STI treatment

a) Assess the incidence of HIV testing and HIV diagnosis during the first period of PrEP use by PrEP modality

b) Estimate the frequency of testing for STI diagnosis and STI diagnosis by PrEP modality
   - in the 6 months preceding PrEP initiation
   - during the first period of PrEP use

c) Describe the proportion of diagnosed STI with a relevant antimicrobial prescription

3.6- Among CAB LA PrEP users diagnosed with HIV (during CAB LA PrEP use or after CAB LA PrEP discontinuation)

a) Describe the timing of incident HIV diagnoses relative to timing of CAB LA PrEP usage and testing for HIV
b) Describe adherence to PrEP injection schedule, HIV treatment, virologic suppression, concomitant STI diagnosis, and HIV drug resistance

7. RESEARCH METHODS

7.1. Study Design

This is a cohort study using data from the Veterans Affairs National Sample, which is composed of Veterans who receive healthcare services through the Veterans Health Administration (VHA). This national sample is representative of the Veteran population, capturing a wide range of demographic, clinical, and social characteristics.
Data will be extracted from VHA's Corporate Data Warehouse (CDW), a comprehensive, regularly updated repository of information from VHA's electronic health records and administrative files. It includes patient-level data such as demographics, clinical encounters (diagnoses, interventions), laboratory and imaging results, medication details, health services utilization, and long-term health outcomes.

The study period will range from January 1, 2021, to December 31, 2025. Initiation of PrEP regimen will be assessed during the period January 1, 2021 to June 30, 2025, to allow for at least 6 months of observation following PrEP initiation.

The study will include different cohorts, as described in Table 2.
Veterans who are not on PrEP but could benefit from PrEP will be identified based on risk factors for HIV acquisition or factors linked to behaviors increasing the risk of HIV acquisition which are generally documented in Veterans health records. These risk factors include: tested for or diagnosed with a bacterial STI in the past 12 months (gonorrhea, syphilis, chlamydia) (US CDC, 2024)[1], tested for HIV in the past 12 months, ever had alcohol use disorder (Williams, 2016), ever used illicit non-injection drugs (HIV.gov, 2024), ever used injectable drugs (CDC, 2024), Black women (CDC, 2024; Reaves, 2025), men who have sex with men (CDC, 2022; Mayer, 2021), individuals aged 18-24 years (HIV.gov, 2025 b), any history of PrEP use (Hojilla, 2021; Krakower, 2019).

[1] The US CDC recommends PrEP for people with a bacterial STI diagnosis in the past 6 months. This has been extended to testing for a bacterial STI in the past 12 months for this protocol.

Table 2: Description of study cohorts

Objectives	Criteria	
Objective 1a - Among all Veterans without evidence of HIV infection	**Population/exposure**	No evidence of HIV diagnosis at beginning of each calendar year of the study period under analysis
	Index date	N/A
	Censoring criteria	N/A
	Endpoint	HIV diagnosis
Objective 1b - Among Veterans with a new HIV diagnosis during the study period	**Index date**	Date of HIV diagnosis
	Censoring criteria	NA
	Endpoint	PrEP use (never, use within 12 months before diagnosis, use >12 months before diagnosis)
Objective set 2 – among Veterans without evidence of HIV infection who are not on PrEP but could benefits from PrEP	**Population/exposure**	At least one of the following criteria: tested for or diagnosed with a bacterial STI in the past 12 months (gonorrhea, syphilis, chlamydia), tested for HIV in the past 12 months, ever had alcohol use disorder, ever used illicit non-injection drugs, ever used injectable drugs, Black women, men who have sex with men, individuals aged 18-24 years, any history of PrEP use
	Index date	First visit during the study period with criteria indicating the individual could benefit from PrEP
	Censoring criteria	Death, loss to follow-up, end of the study period, 12 months after index date, PrEP initiation, whatever comes first
	Endpoints	HIV testing, HIV diagnosis, Screening/testing for other STIs, STI diagnoses
Objective set 3 – among Veterans with a PrEP prescription	**Exposure groups**	Oral PrEP, CAB LA PrEP
	Index date	Start of first PrEP regimen during the study period (dispensing date for oral PrEP, injection date for CAB LA)
	Censoring criteria for calculation of proportion of days covered	Death, loss to follow-up (12 months after last clinical contact), study end, 12 months after index date whatever comes first
	Endpoints	Adherence to PrEP schedule, discontinuation and resumption of PrEP, STI screening/testing, STI diagnosis, STI treatment prescription, HIV testing and diagnosis

7.2. Study Population and Setting

7.2.1. Inclusion criteria

• Veterans in care without evidence of HIV infection (Obj. 1.1)- individuals will be included if they meet all of the following criteria:

- At least one VHA health encounter in the calendar year
- ≥18 years of age
- No evidence of HIV infection at the beginning of the calendar year under analysis

• Veterans in care with a new HIV diagnosis (Obj. 1.2):

- Incident HIV diagnosis (refer to definition in section 7.3.3)

• Veterans in care without evidence of HIV infection who are not on PrEP but who could benefit from PrEP (Objective set 2)- individuals meeting all of the following criteria:

- At least one VHA health encounter during the study period
- ≥18 years of age
- Any of the following criteria indicating that the individual has a risk factor for HIV acquisition or a factor linked to behaviors increasing the risk of HIV acquisition and may benefit from PrEP:
    - tested for or diagnosed with a bacterial STI in the past 12 months (gonorrhea, syphilis, chlamydia),
    - tested for HIV in the past 12 months,
    - ever had alcohol use disorder,
    - ever used illicit non-injection drugs,
    - ever used injectable drugs,
    - Black women,
    - men who have sex with men,
    - individuals aged 18-24 years,
    - any history of PrEP use
- No evidence of HIV infection at the first health encounter with a criteria for PrEP

• Veterans in care using oral PrEP only (objective set 3)

- At least one VHA health encounter during the study period
- ≥18 years of age
- Received at least one oral PrEP prescription (TDF/FTC, TAF/FTC) between January 1 2021 and 31 December 2024
- No evidence of HIV infection at the time of the first oral PrEP prescription in the study period
- Have not received a CAB LA PrEP injection between January 1, 2021, and June 30, 2025

• Veterans in care using CAB LA for PrEP (objective set 3)

- At least one VHA health encounter during the study period
- ≥18 years of age
- Received at least one CAB LA PrEP injection between January 1, 2021 and June 30, 2025

- No evidence of HIV infection at the time of the first CAB LA PrEP injection in the study period

7.3. Variables

7.3.1. Exposure definitions

Veterans without HIV (Objective 1a)
Not applicable

Veterans with a new HIV diagnosis (Objective 1a)
PrEP use (never, ever: use within ≤12 months before diagnosis, use >12 months before diagnosis)

Veterans who could benefit from PrEP (Objective set 2)
Not applicable

Veterans initiating a PrEP regimen during the study period (Objective set 3)
PrEP type (oral TDF/FTC, oral TAF/FTC or CAB LA).

7.3.2. Baseline characteristics

The following variables will be assessed for objectives 2.1 and 3.1 at index date:

- **Demographic characteristics**
  - Age (years)
  - Birth sex
  - Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Pacific Islander, White, Not reported)
  - Ethnicity (Hispanic, not Hispanic)
  - Geographic Region (Northeast, Midwest, South, West, US Territories)
  - Rurality (Highly rural, Rural, Urban)
  - Marital/Relationship status
  - Homelessness in the past 12 months

- **Clinical characteristics**
  - Number of outpatient visits in the 12 months prior to index date
  - Number of primary care outpatient visits in the 12 months prior to index date
  - Comorbidity burden using the Charlson Comorbidity Index
  - PrEP prescriber specialty
  - Psychiatric diagnoses (major depression, bipolar disorder, post-traumatic stress disorder - PTSD, schizophrenia)
  - Substance use (smoking, alcohol use disorder, injection and non-injection illicit drug use disorder)
  - BMI

- VACS Index 2.0

- **Sexual Behavior and Health**

- History of STI (ever)
  - Syphilis
  - Gonorrhea
  - Chlamydia
  - Chancroid
  - Lymphogranuloma venereum
  - *Mycoplasma genitalium*
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Genital herpes – Herpes Simplex Virus (HSV) 1 or 2
  - Trichomoniasis infection
  - Genital Human papilloma virus (HPV) including warts
- History of STI (past 3 months)
  - Syphilis
  - Gonorrhea
  - Chlamydia
  - Chancroid
  - Lymphogranuloma venereum
  - *Mycoplasma genitalium*
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Genital herpes
  - Trichomoniasis infection
  - Genital Human papilloma virus (HPV) including warts
- History of PrEP use

7.3.3. Outcome definitions

♦**Veterans without HIV (Objective 1)**
Incident HIV diagnosis: a new HIV diagnosis is defined as either having a (1) positive screening antibody test with positive confirmatory antibody testing, (2) positive HIV viral load, or (3) documentation of HIV on the EHR problem list.
All potential HIV incident diagnosis will be subject to a detailed review for confirmation.

♦ **People with a new HIV diagnosis (Objective 1.a)**
Not applicable

♦ **People without HIV who are not on PrEP and could benefit from PrEP (Objective set 2)**
♦ **HIV testing & STI screening (Objective 2.2)**

- HIV testing
  - Frequency and rate of HIV tests over 12-month period following the index date

- Type of HIV tests

- HIV diagnoses
  - Frequency and rate of new HIV diagnosis within 12 months of index date (first visit with at least one criteria for PrEP)
    Follow-up (FU) will be censored at first of:
    - HIV diagnosis
    - 12 months after index date
    - End of the study period
    - Loss to follow-up
    - Death

- STI testing/screening
  - Frequency and rate of STI testing events, overall (testing for multiple STIs on the same day will count as 1 testing event) and by type of STI tested
    Type of STI:
    - Syphilis
    - Gonorrhea
    - Chlamydia
    - Chancroid
    - Lymphogranuloma venereum
    - *Mycoplasma genitalium*
    - Hepatitis B virus (HBV)
    - Hepatitis C virus (HCV)
    - Genital Herpes (HSV-1, HSV-2)
    - Trichomoniasis
    - Genital Human papilloma virus (HPV) including warts

    Follow-up (FU) will be censored at first of:
    - HIV diagnosis
    - 12 months after index date
    - End of the study period
    - Loss to follow-up
    - Death

- STI diagnoses
  - Frequency and rate of new diagnosis of STI as noted in medical record or positive test result
  - STI diagnoses for
    - Syphilis
    - Gonorrhea
    - Chlamydia
    - Chancroid
    - Lymphogranuloma venereum
    - *Mycoplasma genitalium*
    - Hepatitis B virus (HBV)
    - Hepatitis C virus (HCV)
    - Genital Herpes (HSV-1, HSV-2)
    - Trichomoniasis

- Genital Human papilloma virus (HPV) including warts

♦ **<u>PrEP users</u> (Objective set 3)**

♦ **Use of oral lead-in (Objective 3.2)**

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

♦ **Adherence (Objective 3.3)**

a) Oral PrEP coverage in the 12 months following initiation

PrEP dispensing is considered as a proxy for PrEP use. The number of dispensing events will be described.

The number of pills dispensed/days covered per dispensing event will be calculated.

Proportion of days of access to oral PrEP in the 12 months following index PrEP initiation

Follow-up (FU) will be censored at first of:

- 12 months after index date
- Loss to follow-up
- Death
- Study end

b) Adherence to CAB LA PrEP schedule

- Proportion of days covered by CAB LA PrEP in the 12 months following initiation: number of days covered by CAB LA PrEP divided by the number of days in the observation period

Follow-up will be censored at first of:

a) 12 months after index date
b) Loss to follow-up
c) Death
d) Study end

Coverage by LA PrEP will be determined based on the duration of days covered by the medication, according to the label.

- 1st injection: coverage = 37 days (30 days of coverage + 7-day injection window)
- Subsequent injections: coverage = 67 days (60 days of coverage + 7-day injection window)

Each calendar day will only be counted once, even if there is an overlap between coverage from the prior injection and date of the next injection.

- **Complete versus incomplete initiation**:

- Among all Veterans with ≥ 1 CAB LA injection:

→ Complete initiation (2nd injection received within 67 days following the 1st injection)

- 2nd initiation injection on time: 2nd injection between 23 and 37 days following the first injection
- 2nd initiation injection late: 2nd injection between 38 and 67 days following the first injection

→ Incomplete initiation: >67 days without injection following the first injection

- Among incomplete initiators

Any additional injection(s) >67 days after the 1st injection (Yes/no)
If yes:

- Timing of the 1st additional injection after the last injection of the "incomplete initiation" (interval in days, number with interval of 68-97 days and interval >97 days)
- Complete versus incomplete reinitiation
- Interval between the first two reinitiation injections (≤37; 38-67, 68-97, 98-127; ≥128 days apart)

• **Timing of CAB LA PrEP maintenance injections**: among complete initiators with at least one maintenance injection
Determined based on the time between initiation injections (Table 3)

- Total number of maintenance injections per individual
- All on time
- Any late maintenance injection (short delays not requiring reinitiation, long delays requiring reinitiation): number of short and long delays, number of individuals with 1, 2, 3 or more short delays, number of individuals with 1, 2, 3 or more long delays, median duration of short and of long delays

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

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

♦ **Patterns of PrEP use (Objective 3.4)**

a) Oral PrEP

• Discontinuation: any discontinuation, resumption of oral PrEP after discontinuation
Two durations will be used to identify discontinuation of oral PrEP:

- Oral PrEP prescription not refilled within 30 days of the previous dispensing
- Oral PrEP prescription not refilled within 90 days of the previous dispensing

• Duration of oral PrEP use for the first period of use

b) CAB LA PrEP: among complete initiators with at least one maintenance injection

• Total number maintenance injections administered during first period of CAB LA PrEP use (overall and by person)

• Total follow-up time for complete CAB LA initiators with at least one maintenance injection (from first CAB LA PrEP injection to study end, loss to follow-up, death or HIV acquisition, whatever comes first)

• Discontinuation: number of individuals discontinuing CAB LA PrEP and number of individuals resuming LA PrEP injections (additional CAB LA or LEN LA injections after discontinuation and time between the last injection prior discontinuation and the first injection post-discontinuation) or oral PrEP

• Oral bridging between discontinuation of CAB LA injections and resumption of CAB LA injections

• Months on regimen until first censoring (first period of CAB LA PrEP use)
Calculated as: days from first initiation injection to censoring (study end, loss to follow-up, death, HIV acquisition, discontinuation)

• Cumulative months on regimen across all CAB LA PrEP use (including additional injections after discontinuation)
  - Continuous time on CAB LA PrEP will be calculated as:
    - If no discontinuation: days from first initiation injection to censoring (study end, loss to follow-up, death, HIV acquisition)
    - If discontinuation: days from first initiation injection to discontinuation date (i.e., 127 days after last injection)
  - Among individuals with additional injections after discontinuation, the cumulative months on CAB LA regimen will be calculated across all episodes of continuous CAB LA PrEP use
  - Individuals with incomplete initiation of their first period of CAB LA PrEP use will be excluded from this analysis even if they have additional injections after incomplete initiation

• On CAB LA PrEP at timepoints of interest – among CAB LA users with no discontinuation and among CAB LA users with discontinuation
  - 12 months: injection received between ≥238 to ≤365 days after index (up to 127 days before the 12-month mark)
  - 24 months: injection received between ≥603 to ≤730 days after index (up to 127 days before the 24-month mark)
  - Study end: injection received up to 127 days before or on study end date

♦ **HIV testing & STI testing/screening during first period of PrEP use (Objectives 3.5)**

- <u>HIV testing</u>
  - Incidence proportion and incidence rate of HIV testing between the start of PrEP and the first discontinuation
  - Timing of HIV tests:
    - Oral PrEP: on-schedule testing defined as receiving an HIV test ≤7 days before/at start, and 3 months (76-104 days) after each test
    - CAB LA PrEP: on-schedule testing defined as receiving an HIV test

≤7 days before/at first injection, and 14 days prior each subsequent injection

- HIV diagnosis: incidence proportion and incidence rates between index date and the 1st discontinuation

- STI testing/screening
  - Assessed during the first period of PrEP use (oral or injectable)
    - Incidence proportion and incidence rate for STI testing/screening for
      - Gonorrhea
      - Chlamydia
      - Syphilis
      - Chancroid
      - Lymphogranuloma venereum
      - *Mycoplasma genitalium*
      - Hepatitis B virus (HBV)
      - Hepatitis C virus (HCV)
      - Genital Herpes (HSV-1, HSV-2)
      - Trichomoniasis
      - Genital Human papilloma virus (HPV) including warts
    - Interval between the first 2 tests for gonorrhea, chlamydia, syphilis done during the first period of PrEP use
      - Testing 3 months (76-104 days) after last test
      - Testing 6 months (168-196 days) after last test
      - Testing 12 months (351-379 days) after last test

- STI diagnoses
  - New diagnosis of STI as noted in medical record or positive test result
  - STI diagnoses for
    - Syphilis
    - Gonorrhea
    - Chlamydia
    - Chancroid
    - Lymphogranuloma venereum
    - *Mycoplasma genitalium*
    - Hepatitis B virus (HBV)
    - Hepatitis C virus (HCV)
    - Genital Herpes (HSV-1, HSV-2)
    - Trichomoniasis
    - Genital Human papilloma virus (HPV) including warts

- Relevant prescription for a selected list of STIs
  Proportion of STI diagnosis with a prescription within 14 days following diagnosis as follows:
  - Syphilis: benzathine penicillin G, aqueous crystalline penicillin G, procaine penicillin G + probenecid, doxycycline
  - Gonorrhea: ceftriaxone, ceftriaxone + doxycycline, gentamicin + azithromycin,

cefixime, cefotaxime
- Chlamydia: doxycycline, azithromycin, levofloxacin, amoxicillin
- Chancroid: azithromycin, ceftriaxone, ciprofloxacin, erythromycin base
- Lymphogranuloma venereum: doxycycline, azithromycin, erythromycin base
- *Mycoplasma genitalium*: doxycycline + azithromycin, doxycycline + moxifloxacin
- Trichomoniasis: metronidazole, tinidazole
- Genital herpes: acyclovir, famciclovir, valacyclovir

♦ **Incident HIV diagnosis among CAB LA PrEP users (Objective 3.6)**

- HIV diagnosis during periods of CAB LA PrEP use

  Describe:
  - HIV testing (timing and detailed assay results)
  - Adherence to injection schedule
  - HIV treatment
  - Viral load measurements timing and results and if viral suppression was obtained
  - Concomitant STI diagnosis
  - HIV drug resistance

- HIV diagnosis after CAB LA PrEP discontinuation

  Describe:
  - HIV testing (timing and detailed assay results)
  - Days between the last CAB LA injection and HIV diagnosis

7.3.4. Confounders and effect modifiers

Not applicable; this study is descriptive in nature.

7.4. Data sources

The Veterans Health Administration (VHA) is the largest integrated health care system in the United States, providing care at 1,380 health care facilities, including 170 VA Medical Centers and 1,193 outpatient sites of care of varying complexity (VHA outpatient clinics) to over 9.1 million Veterans enrolled in the VA health care program (US Department of Veterans Affairs, 2025).

In this study, we used data extracted from VHA's Corporate Data Warehouse (CDW), a comprehensive, continually updated repository of information from VHA's electronic health records (EHR) and administrative files. The CDW dataset includes health care encounters, laboratory tests and results, medications, diagnoses, patient demographics, and residential ZIP codes. The VACS-National Sample represents all ~13.5 million patients who have accessed VA care since 2000, with ~6 million patients accessing care annually (Yale School of Medicine, 2024).

7.5. Study size

This study is not designed for hypothesis testing but aims to evaluate usage patterns of oral PrEP and CAB LA PrEP in clinical practice. Additionally, it seeks to describe the incidence of HIV diagnoses among Veterans in care, including their PrEP history, as well as the incidence of HIV and other STI diagnoses among Veterans not on PrEP but potentially eligible for it. The study focuses on multiple outcomes of interest, with several parameters to be estimated.

For the objective related to HIV incidence among Veterans, the study will leverage data from the entire eligible population of Veterans in care.

Regarding PrEP usage patterns, a feasibility assessment identified 15,477 oral PrEP users and 748 CAB LA PrEP users between January 1, 2021 and June 30, 2025.
Table 4 provides precision estimates for proportions using a 95% confidence level, calculated using the standard confidence intervals equation [$p \pm 1.96\sqrt{((p*(1-p)/N)}$]. In the oral PrEP group, confidence interval widths for evaluated proportions range from 0.01 to 0.02. For the CAB LA PrEP group, the confidence interval width ranges from 0.04 to 0.07.
For instance, if the proportion of individuals having a complete CAB LA PrEP initiation is 80%, the 95% confidence interval around this estimate will be 77-83%.

Table 4: Precision estimates based on sample size and event proportions, using a 95% confidence level

PrEP formulation	Sample Size	Event Proportion	Lower Limit	Upper Limit	CI Width
CAB LA	748	0.1	0.08	0.12	0.04
	748	0.2	0.17	0.23	0.06
	748	0.3	0.27	0.33	0.07
	748	0.4	0.36	0.43	0.07
	748	0.5	0.46	0.54	0.07
	748	0.6	0.57	0.64	0.07
	748	0.7	0.67	0.73	0.07
	748	0.8	0.77	0.83	0.06
	748	0.9	0.88	0.92	0.04
Oral PrEP	15477	0.1	0.10	0.10	0.01
	15477	0.2	0.19	0.21	0.01
	15477	0.3	0.29	0.31	0.01
	15477	0.4	0.39	0.41	0.02
	15477	0.5	0.49	0.51	0.02
	15477	0.6	0.59	0.61	0.02
	15477	0.7	0.69	0.71	0.01
	15477	0.8	0.79	0.81	0.01
	15477	0.9	0.90	0.90	0.01

7.6. Data management

Study related data will be requested, accessed, maintained, cleaned and analyzed from the central data repository in a study specific DataMart on the VA Informatics and Computing Infrastructure (VINCI) and a local VA server (vhaconapp17.v01.med.va.gov). Data will be accessible only to a limited number of trained and certified VA employees. All researchers approved to utilize the resource will be required to maintain all relevant VA trainings and credentialing for research and agree to sign the rules of behavior for use of the data and computing environment.

7.7. Data analysis

All analyses conducted for this study will be descriptive and will aim at estimating frequencies of outcomes.

7.7.1. Primary analysis

7.7.1.1. Main Analytical approach

Veterans in care without HIV (Objective 1.1)
For each calendar year during the study period, the number and percentage of new HIV diagnoses will be reported out of all individuals receiving care in the VHA healthcare system.

Veterans in care with a new HIV diagnosis (Objective 1.2)
Among newly diagnosed people with HIV, PrEP use (never, use within ≤12 months before diagnosis, use >12 months before diagnosis) and PrEP users' characteristics will be described using counts and proportions for categorical variables and median and interquartile ranges for continuous variables.

Veterans who are not on PrEP and who could benefit from PrEP (Objective set 2)
Baseline demographic and clinical characteristics will be described at the first visit during the study period meeting one of the criteria (index date), using median and interquartile ranges for continuous variables and counts and proportions for categorical variables. The frequency and rate (per 100 person-years) of HIV testing, HIV diagnoses, STI testing/screening, and STI diagnoses will be described within 12-months of the index date.
Rates of HIV tests and diagnoses as well as STI tests and diagnoses over this 12-month period will be estimated using univariate Poisson regression

Veterans using PrEP (Objective set 3)
Objective 3.1- Baseline demographic and clinical characteristics will be described at the start of PrEP use during the study period, by regimen type (oral or CAB LA), using median and interquartile ranges for continuous variables and counts and proportions for categorical variables.

Objective 3.2- The proportions of Veterans on care initiating CAB LA PrEP who used oral lead in (OLI) and proportion of those with direct to injection (DTI) will be calculated.

Objective 3.3 and 3.4- PrEP adherence and usage patterns will be described using median and interquartile range for continuous data as well as absolute and relative frequencies for categorical data. The percentage of days with access to oral PrEP and CAB LA PrEP will be described over the first 12 months after index PrEP initiation. Characteristics of individuals with and without delayed CAB LA injections as well as individuals with and without discontinuation will be compared using Pearson's chi-square tests for categorical variables and Mann-Whitney tests for continuous variables.

Objective 3.5- Incidence rates and confidence intervals for HIV testing, HIV diagnosis, STI testing/screening and STI diagnosis will be calculated using univariate Poisson regression. STI treatment prescription will be described using absolute and relative frequencies for categorical data.

Objective 3.6- For CAB LA PrEP users diagnosed with HIV, a timeline including details of oral PrEP prescriptions prior to CAB LA PrEP start, injections received, HIV tests performed, HIV treatment, viral load measurements, HIV drug resistance will be provided for each individual.

7.7.1.2. Data handling conventions

Study related data will be requested, accessed, maintained, cleaned and analyzed from the central data repository in a study specific DataMart on the VA Informatics and Computing Infrastructure (VINCI) and a local VA server (vhaconapp17.v01.med.va.gov). Data will be accessible only to a limited number of trained and certified VA employees. All researchers approved to utilize the resource will be required to maintain all relevant VA trainings and credentialing for research and agree to sign the rules of behaviour for use of the data and computing environment.

7.8. Quality control and Quality Assurance

The West Haven VA Healthcare System serves as the overall study Coordinating and Data Management Center (CC) for the VACS. The CC supervises, coordinates, implements, and evaluates a number of study activities related to study conduct, quality control, data management and analysis, and site activities, monitoring enrollment and flow of study data elements, and overseeing quality assurance procedurest Data double entry, range and logic checks, and interim data analysis is conducted for quality control purposes. The CERC will institute quality assurance measures for all analysis conducted per study protocols. Quality assurance measures will consist of the following:

- The CERC data analysist/statistician/epidemiologist will determine an appropriate approach for data analysis using one of the methodologies outlined in the CERC Quality Management/Data Management catalogue.

- The analysis will follow the procedures as defined by the written work instruction and accompanying code for the corresponding methodology, thereby ensuring that the methodology is being applied in a manner consistent with CERC practices.
- Once the analysis is complete, a member of the VACS and/or CERC team will conduct independent analysis on the same data set using the CERC work instructions and code for the corresponding methodology.
- Any discrepancies identified through the independent analysis will be addressed by the study team and brought to resolution. Such resolution may include, but is not limited to, adjustment to the analysis approach or code.

Significant discrepancies will be brought to the Executive Committee for disposition.

7.9. Limitations of the research methods

CAB LA PrEP injections are directly observed in clinical settings; thus, injection records in the EHR provide certainty that PrEP was received and the exact timing of injections. In contrast, oral PrEP use and timing cannot be ascertained with the same level of precision. Oral PrEP dispensing is a proxy for PrEP use. The date of oral PrEP initiation is defined as the first PrEP dispensing date; subsequent PrEP dispensing events are considered renewals.

The identification of incident HIV diagnosis relies on HIV testing being conducted. Therefore, information on incident HIV diagnosis and exact timing may be subject to measurement error.

In addition, detailed behavioral and personal information indicating that an individual could benefit from PrEP is not systematically recorded in the EHR. Thus, Veterans who are not on PrEP but could benefit from PrEP will be identified based on risk factors for HIV acquisition or factors linked to behaviors increasing the risk of HIV acquisition which are generally documented in Veterans health records. This approach may result in identifying a broader group of individuals than if individual detailed behavioral information was available.

7.9.1. Study closure/uninterpretability of results

Not applicable: observational study.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Ethical approval and subject consent

This is a data analysis study only and it will be submitted for approval to the VA Connecticut Local Institutional Review Board (IRB). Our study is interested in identifying

and following participants within the VA who were enrolled in the Veterans Aging Cohort Study (VACS) National between January 1, 2021, and June 30, 2025, and meet other inclusion criteria.
The VACS study was approved by the institutional review boards of Yale University and VA Connecticut Healthcare System. It has been granted a waiver of informed consent and is compliant with the Health Insurance Portability and Accountability Act.

8.2. Subject confidentiality

This project will use data contained in the Veterans' electronic medical records; accordingly, no discomforts associated with the study are anticipated. Despite significant precautions, it is possible that data security could be breached and an unauthorized individual could gain access to participant data. However, the risk of a confidentiality breach is minimal because the study is "in silico". Access to VINCI is strictly controlled by the VA Office of Information Technology (OI&T). Monitoring and tracking within the computing environment will allow for ongoing auditing of activities.

9. LEGAL BASIS FOR PROCESSING INDIVIDUAL HUMAN DATA

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

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

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

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

Reporting of adverse events/reactions (Spontaneous Events)

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

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

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

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