TITLE PAGE

Division: Epidemiology

Information Type: ViiV Healthcare Non-Interventional Study Protocol

Title:	CAB LA PrEP Cohort: Prospective Cohort Study to Assess Adherence and Effectiveness of, and Monitor for Hepatotoxicity and Resistance to, Cabotegravir for Pre-Exposure Prophylaxis in Europe
Compound Number:	GSK1265744
Effective Date:	26-Jul-2024
Subject:	HIV Pre-exposure prophylaxis, PrEP Adherence, Resistance
Author(s):	PPD, ViiV Healthcare PPD, NEAT-ID PPD, NEAT-ID PPD, NEAT-ID PPD, ViiV Healthcare PPD ViiV Healthcare PPD, ViiV Healthcare
Indication Studied:	HIV Pre-exposure Prophylaxis

*STUDY INFORMATION

Title	CAB LA PrEP Cohort: Prospective Cohort Study to Assess Adherence and Effectiveness of, and Monitor for Hepatotoxicity and Resistance to, Cabotegravir for Pre-Exposure Prophylaxis in Europe
Protocol version identifier	v1.2
Date of last version of protocol	26-Jul-2024
EU PAS (ENCEPP) register number	Study not yet registered
Active substance	J05AJ04, cabotegravir
Medicinal product	cabotegravir
Product reference	Apretude
Procedure number	EMEA/H/C/005756
Marketing authorisation holder(s)	ViiV Healthcare B.V.
Research question and objectives	Following the initiation of CAB LA for PrEP, the study will aim to assess usage patterns, adherence, effectiveness, safety of CAB LA for PrEP, and resistance among individuals who acquire HIV while on CAB LA for PrEP.
Countries of study	Potential countries for inclusion: Belgium, France, Ireland, Italy, Spain, United Kingdom
Author	PPD

MARKETING AUTHORISATION HOLDER(S) *

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

UNIQUE IDENTIFIER	221935
TITLE	CAB LA PrEP Cohort: Prospective Cohort Study to Assess Adherence and Effectiveness of, and Monitor for Hepatotoxicity and Resistance to, Cabotegravir for Pre-Exposure Prophylaxis in Europe
STUDY ACCOUNTABLE PERSON	PPD - Epidemiology
CONTRIBUTING AUTHORS	PPD, NEAT-ID PPD, NEAT-ID PPD, NEAT-ID PPD, ViiV Healthcare PPD, ViiV Healthcare PPD, ViiV Healthcare
ASSET ID	GSK1265744
GSK ASSET	Cabotegravir (PrEP)
EFFECTIVE DATE	26-Jul-2024
INDICATION	HIV Pre-exposure Prophylaxis (PrEP)
SAFETY OBJECTIVE	YES
DATA COLLECTION TYPE	SECONDARY
TSS/PASS ASSESSMENT PERFORMED	Yes

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ART	Antiretroviral therapy
ARV	Antiretroviral
ASCVD	Atherosclerotic Cardiovascular Disease
AST	Aspartate Aminotransferase
BILI	Total Bilirubin Elevation
BMI	Body mass index
CAB	Cabotegravir
CI	Confidence interval
CVD	Cardiovascular Disease
DILI	Drug-induced liver injury
DTI	Direct to injection
EDC	Electronic data capture
EMA	European Medicines Agency
EC	Ethics Committee
EU	European Union
FDC	Fixed drug combinations
FTC	Emtricitabine
GSK	GlaxoSmithKline
HDL	High Density Lipoprotein
HIV	Human immunodeficiency virus
HR	Hazard Ratio
HSR	Hypersensitivity reaction
INSTI	Integrase strand transfer inhibitor
IQR	Interquartile range
ISR	Injection site reaction
LA	Long-acting
LCT	Liver chemistry tests
LDL	Low Density Lipoprotein
MAH	Marketing Authorization Holder
MSM	Men who have sex with men
OLI	Oral Lead-in
PK	Pharmacokinetic
PrEP	Pre-exposure prophylaxis
QPPV	Qualified Person Responsible For Pharmacovigilance
RPV	Rilpivirine
RNA	Ribonucleic Acid
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SmPC	Summary of Product Characteristic
STI	Sexually Transmitted Infection
TAF	Tenofovir Alafenamide
TDF	Tenofovir disoproxil fumarate

TGW	Transgender women
ULN	Upper limit of normal
US	United States
VL	Viral load

Trademark Information

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SPSS

1. RESPONSIBLE PARTIES

MARKETING AUTHORISATION HOLDER

ViiV Healthcare B.V.

Sponsor Legal Registered Address:

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1.1. SPONSOR SIGNATORY:

Title:	CAB LA PrEP Cohort: Prospective Cohort Study to Assess Adherence and Effectiveness of, and Monitor for Hepatotoxicity and Resistance to, Cabotegravir for Pre-Exposure Prophylaxis in Europe
Compound Number:	GSK1265744

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25-Jul-2024

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26-Jul-2024

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ViiV QPPV

Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

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

Investigator Name:

PPD

Investigator Signature	17-Jul-2024 Date

2. SYNOPSIS

Title: CAB LA PrEP Cohort: Prospective Cohort Study to Assess Adherence and Effectiveness of, and Monitor for Hepatotoxicity and Resistance to, Cabotegravir for Pre-Exposure Prophylaxis in Europe

Rationale and 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 and regions (including the US, EU, Canada, and Australia) for the treatment of HIV-1 infection in adults.

ViiV Healthcare has developed 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 tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for HIV prevention 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, pharmacokinetic (PK) modelling/simulation and the overall data from the CAB Treatment program has supported the use of CAB PrEP as a novel, well-tolerated, effective, LA PrEP agent. CAB LA for PrEP has been approved in several countries and regions (including the US, Australia, Zimbabwe, South Africa, Brazil, Botswana, and Malawi), and received market authorisation in the European Union by the EMA on 15 September 2023 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.

CAB LA for PrEP (Apretude) is given first as two initiation injections administered one month apart, and then every two months thereafter. Individuals can either start their treatment with Apretude, known as direct to injection (DTI), or take oral cabotegravir (Vocabria) for four weeks to assess how well they tolerate the drug, otherwise known as optional oral lead-in (OLI).

The Marketing Authorization Holder (MAH) proposes a five-year post authorization study to be conducted in collaboration with NEAT-ID Network, a well-established network of clinical sites across Europe. 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 who receive an HIV diagnosis while on CAB LA for PrEP.

Research question and Objectives:

Following the initiation of CAB LA for PrEP, the study will aim to assess usage patterns, adherence, effectiveness, safety of CAB LA for PrEP, and resistance among individuals who receive an HIV diagnosis while on CAB LA for PrEP.

The specific objectives are to:

1) Describe the population initiating CAB LA for PrEP, including proportion of individuals who use OLI and proportion of those with DTI

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

3) Monitor for incidence of HIV diagnosis while on CAB for PrEP and describe the timing of incident HIV diagnoses 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 an HIV diagnosis while on CAB LA for PrEP

Study Design:

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

Population

HIV-negative adults and adolescents (at least 12 years of age) ≥35 kgs initiating CAB LA for PrEP initiating OLI or CAB LA injections.

Variables

The exposure of interest in this study is use of CAB for PrEP per the approved SmPC for CAB oral and LA formulations.

Primary outcomes of interest include:

- Incident HIV diagnoses
- Proportion of individuals receiving CAB LA PrEP who receive an HIV diagnosis after 6, 12, 24, 36, and >36 months of follow-up time
- Time to incident HIV diagnoses
- ART regimen and VL testing among CAB PrEP users with prevalent and incident infections
- Adherence and Durability
- Frequency of resistance to INSTIs and specific mutations

- Frequency of DILI and HSRs following CAB OLI and CAB LA injections assessed at 6, 12, 24, 36, and >36 months

Data sources

Data will be collected from participating European clinical sites within the NEAT ID Network. Data will be collected by electronic transfer of deidentified electronic medical data from each site.

Study size

The study aims to include a target of at least 500 participants initiating CAB LA for PrEP across Europe.

Data analysis:

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 while on CAB LA for PrEP.

Milestones:

CCI [redacted]

3. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1.1	19-Apr-2024	Sections 6-7, 10	Update	Incorporating comments raised by EMA in their assessment report of the initially submitted protocol.
1.2	25-Jul-2024	Sections 2, 4	Update	Updating milestone estimated dates, aligning study title throughout protocol, and minor formatting.

4. MILESTONES

Milestone	Estimated date
Draft Protocol Submission to EMA	December 2023
Final Protocol Submission to EMA	April 2024
Registration in the EU PAS register	August 2024
Study Start (after Protocol Approval)	August 2024
CCI [redacted]	

5. RATIONALE AND BACKGROUND

5.1. Background

Across populations and pre-exposure prophylaxis (PrEP) regimens, oral PrEP significantly reduced the risk of human immunodeficiency virus (HIV) acquisition compared with placebo. Trials in men who have sex with men (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 adherence did not show a significantly protective effect.[1] An effective, well-tolerated, long-acting (LA) PrEP agent could 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. Long-acting PrEP regimens 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 has developed 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) received market authorisation in the European Union by the EMA on 15 September 2023 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.[2]

Apretude is given first as two initiation injections administered one month apart, and then every two months thereafter. Individuals can either start their treatment with Apretude, known as direct to injection (DTI), or take oral cabotegravir (Vocabria) for four weeks as an optional oral lead-in (OLI) to assess how well they tolerate the drug. Oral cabotegravir may also be used as oral PrEP in individuals who miss planned dosing with CAB LA injection.[2]

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.[3,4]

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).[3]

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).[4]

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:

- OLI 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 OLI and injectable CAB, handling delayed or missed injection can be found in the Summary of Product Characteristic (SmPC).[2] 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 people with HIV, and hepatotoxicity is a known adverse drug reaction (ADR) for CAB. Possible or probable cases of drug-induced liver injury (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.

Hypersensitivity reactions (HSRs) have been reported in association with integrase inhibitors including cabotegravir. These reactions were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Apretude and other suspected medicinal products should be discontinued immediately, should signs or symptoms of hypersensitivity develop (including, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema). Clinical status, including liver aminotransferases should be monitored and appropriate therapy initiated.[2]

This 5-year prospective, non-interventional study across Europe 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 while on CAB PrEP. The data generated from this study will enhance our understanding of CAB LA for PrEP.

5.2. 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 potentially low risks of acquiring HIV and subsequent resistance development. There is a risk for HIV acquisition if the individual does not adhere to the CAB PrEP dosing schedule, and protective levels of CAB decrease to a level where HIV acquisition can occur. There may also be risk for HIV acquisition 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 settings. The additional data generated will continue to inform clinical practice of CAB LA for PrEP usage.

6. RESEARCH QUESTION AND OBJECTIVE(S)

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 for PrEP by:
        i. Baseline demographics (age, sex, gender, ethnic origin, 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 DTI

b. Describe the individuals initiating CAB OLI or CAB LA PrEP with undiagnosed HIV acquisitions by baseline demographics and PrEP history

c. Describe oral PrEP used to cover planned, delayed or missed CAB LA injections

d. Assessing the frequency of testing for HIV and methods used for HIV-1 diagnosis, as well as assessing the timing of HIV testing relative to CAB LA for PrEP initiation injections and maintenance injections

Undiagnosed (prevalent) HIV acquisitions 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 will be shown for those who received CAB OLI and those who used DTI strategy.

2) Treatment adherence (Medication errors): Monitor for adherence by assessing the frequency of delayed and missed injections without oral PrEP bridging
    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 daily oral PrEP bridging
        ii. Assess the mean and median number of injections missed during the 6-month and 12-month period without oral PrEP bridging
        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, 36, 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 diagnoses while on CAB for PrEP and describe the timing of incident HIV diagnoses 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 diagnoses, defined as HIV diagnosed after start of CAB injections while adhering to CAB LA PrEP regimen

    b. Describe the timing of diagnosis of HIV 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 diagnoses 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 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 baseline. 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 DILI and HSRs following CAB LA injections
   a. Describe the frequency of DILI after starting CAB LA at 6, 12, 24, 36, and >36 months after initiation as defined in Section 7.3.2.
      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, 36, 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 diagnoses while adhering to CAB LA for PrEP and development of resistance during treatment for HIV
   b. CAB LA PrEP discontinued:
      i. without subsequent oral PrEP & potential risk for HIV acquisition and viral resistance during CAB LA PK tail
      ii. switched to oral PrEP and acquire HIV during the remainder of the follow-up period and develop resistance during subsequent treatment with ARVs
   c. Individuals with undiagnosed prevalent HIV at initiation of CAB PrEP and subsequent emergence of resistance while on CAB monotherapy

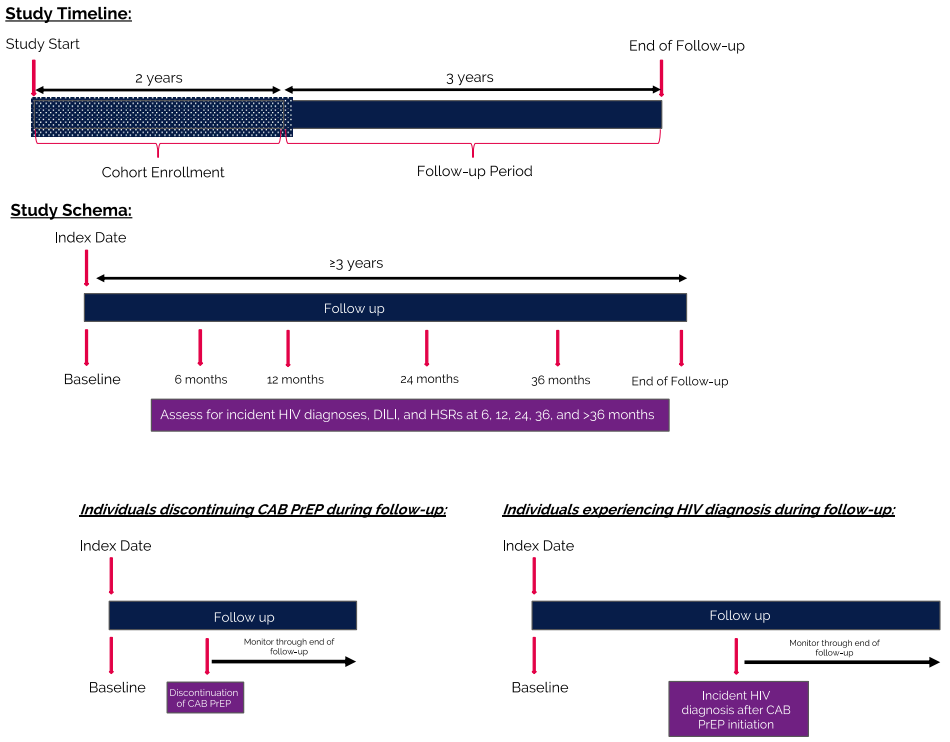
Resistance testing: Since this is a non-interventional study aiming to capture standard of care (SoC) in real world settings, the study will not mandate resistance testing following discontinuation of CAB LA for PrEP. Health care providers following the SmPC and applicable local guidelines will decide 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. Resistance will also be assessed among the individuals who are non-adherent to the injection regimen and acquire HIV.

7. RESEARCH METHODS

7.1. 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 settings across Europe. All treatment decisions will be made by the healthcare provider per guidelines for CAB LA for PrEP and SmPC. This study will use deidentified data from individual electronic medical records from participating clinical sites.



- All CAB LA for PrEP users will be followed for at least 3 years from the time of initiation while on CAB LA PrEP
- Individuals with an incident HIV diagnosis will be followed from the start of ART and their virologic suppression and emergence of resistance to ARVs through the end of the study follow-up period, and cross resistance to other integrase inhibitors will be monitored
- Individuals initiating CAB PrEP with undiagnosed prevalent HIV-1 infection will be followed from the start of ART and their virologic suppression and emergence of resistance to ARVs through the end of the study follow-up period, and cross resistance to other integrase inhibitors will be monitored
- Participants discontinuing CAB LA PrEP will be monitored for HIV acquisition and,if diagnosed, will be monitored for ARV effectiveness & potential emergence

of resistance as per SoC/local guidelines through the end of the study follow-up period

- Testing for incident HIV & resistance: Testing frequency for HIV and resistance if needed, is expected to be per guidelines for LA PrEP and SmPC

7.2. Study Population andSetting

7.2.1. Study Setting

Potential investigational sites within the NEAT-ID Network across Europe will be contacted for feasibility and resistance testing practices as part of their SoC. A formal feasibility assessment questionnaire will be conducted after the protocol is finalized and approved and will be used to determine sites' eligibility to participate in the study. This formal feasibility assessment will include assessing site's infrastructure to participate in research studies, number of any PrEP prescriptions in the previous year, availability of resistance testing, and HIV testing practices per local standard of care practices. Follow-up period will start from the date of the first participant enrolled in the study and will end five years after the date of first enrolment.

Participant data will be collected via extraction from electronic medical records (i.e., source data) by appropriately trained and authorized member(s) of the study team who must be identified and authorized in writing by the Principal Investigator (PI). A delegation of responsibility log will be maintained accordingly. In order to maintain confidentiality, the participants will be identified only by study number.

All data will be entered directly into the electronic data capture (EDC) by the sites and will be checked for completeness every 6 months by the data coordinating center. NEAT-ID's management team will store the data on a secure network drive with access to authorized personnel of the data management team only, maintained on a log of authorized personnel by the data coordinating center.

NEAT-ID team will perform site management activities to assess protocol issues, consent, data quality and study management quality performance.

7.2.2. Eligibility Criteria

HIV-negative adults and adolescents (at least 12 years of age) ≥35kg initiating CAB LA for PrEP will be eligible for inclusion from the date of starting OLI or CAB LA injections.

7.3. Variables

7.3.1. Exposure definitions

All new users of CAB LA for PrEP per the approved SmPC for CAB oral and LA formulations will be included in the study. The study period will include OLI, followed by injectable long acting regimen use.

7.3.2. Outcome definitions

1) **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 through at least one of the following:
    - Positive HIV-1 antigen/antibody lab results as well as an HIV-RNA-based test; if a combined testing strategy including both tests is not available, testing should follow local guidelines while taking Apretude.
    - One detectable viral load

Incident HIV is any new HIV diagnosis that occurs after the initiation of CAB PrEP, having confirmed HIV negative status using HIV RNA test, at the time of PrEP initiation.

Prevalent HIV is defined as any undiagnosed HIV 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 will be reported for CAB OLI and CAB LA PrEP separately.

This study is designed to capture data documented in health records in real world clinical settings, 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 health record. 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.

2) **Proportion of individuals receiving CAB LA PrEP with HIV diagnosis**

3) **Time to incident HIV diagnosis**
    a) 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.
    b) Time to HIV diagnosis will be shown separately for individuals infected during OLI and while adhering to CAB LA injection schedule.

4) **ART regimen and VL testing among CAB PrEP users with prevalent and incident infections:**
ART regimen and VL testing during the follow-up period for the following groups will be described:

a) Individuals with incident infections
b) Individuals with undiagnosed prevalent infections at the time of CAB PrEP initiation
c) 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

5) Adherence and Durability

a) Adherence to CAB LA PrEP including OLI will be estimated from data collected via health record data
b) Non-adherence to the dosing schedule will be assessed by:
   - Estimating the number of individuals that missed one or more consecutive injections without taking daily oral PrEP bridging 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 PrEP bridging or those who received the injections seven or more days later than their scheduled injection visit (Combined group a OR b) and describe characteristics for the individuals that are nonadherent
c) Discontinuation will be defined as 2 injection cycles (~127 consecutive days) in which no injections were administered without oral PrEP bridging
d) Describe the frequency and the regimen used for oral PrEP bridging to cover planned delayed or missed injections

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

a) CAB LA PrEP started when the individual had undiagnosed HIV and subsequent emergence of resistance while on CAB monotherapy
b) CAB LA PrEP discontinued
   - without subsequent oral PrEP & potential risk of HIV acquistion and viral resistance during CAB LA PK tail
   - switched to oral PrEP and acquire HIV during the follow-up period and develop resistance during subsequent follow-up period while on treatment with ARVs
c) Incident HIV diagnosis while adhering to CAB LA for PrEP and development of resistance during treatment for HIV

7) **Frequency of DILI and HSRs following CAB OLI and CAB LA injections assessed at 6, 12, 24, 36, and >36 months**.
Hepatotoxicity related to administration of CAB for PrEP (i.e., DILI) as described below will be tabulated:

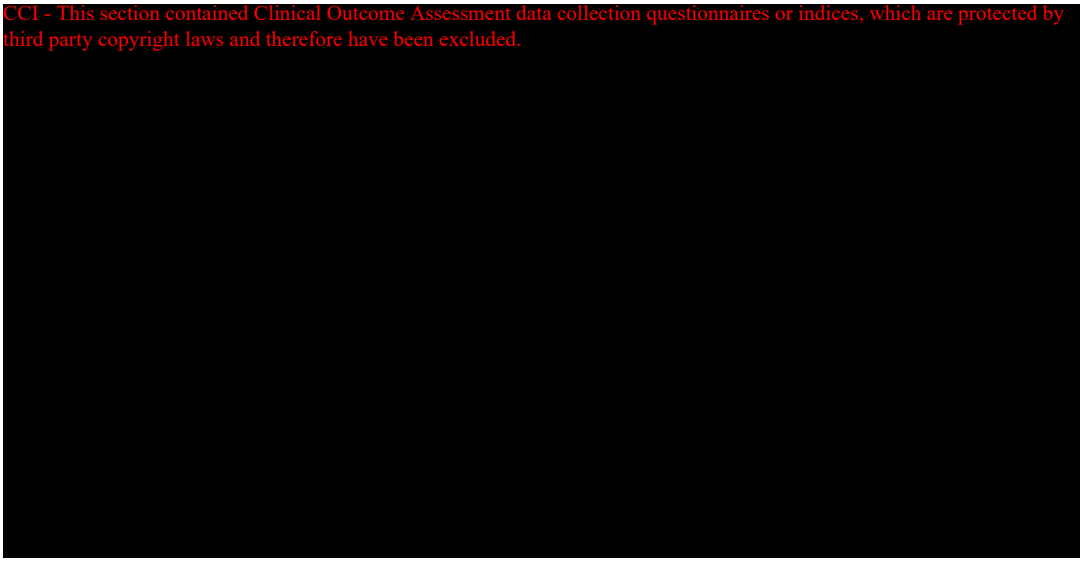
DILI case definition: Determination of suspected or potential DILI will be based on liver chemistry criteria (ALT, BILI and ALP) in addition to all relevant clinical information based on Aithal et al, 2011.[5] An independent adjudication committee will review all potential and suspected cases of DILI 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 health records, to enable a comprehensive review and assessment of potential DILI attributed to CAB PrEP.

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

a) More than or equal to fivefold elevation above the upper limit of normal (ULN) for ALT
b) 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)
c) More than or equal to threefold elevation in ALT concentration and simultaneous (within +/- 2 weeks) elevation of BILI concentration exceeding 2× ULN after starting CAB LA PrEP at 6, 12, 24, 36, and >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× baseline for ALT, 2x baseline for ALP and 2× baseline for BILI with associated 3× 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:



Description of HSR: Signs and symptoms of HSR reported with INSTIs include, but are not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema. Clinical status, including liver transaminases, will be considered and frequency of HSRs will be assessed at 6, 12, 24, 36, and >36 months after study start.

HSRs have been reported in association with integrase inhibitors including cabotegravir. These reactions were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Apretude and other suspected medicinal products should be discontinued immediately, should signs or symptoms of hypersensitivity develop (including, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema). Clinical status, including liver transaminases, will be considered, and frequency of HSRs will be assessed at 6, 12, 24, 36, and >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 health record, where considering the combination of events, time to onset of occurrence, organ systems involvement, evolution of outcome as well as characteristics and medical history may suggest an immediate or delayed type HSR to make the determination. The adjudication committee will be provided with all relevant clinical information collected from data in the health records, to enable a comprehensive review and assessment of potential HSRs attributed to CAB PrEP.

Regimen discontinuation will be reviewed, and cases of DILI or HSR will be confirmed by the adjudication committee. Discontinuation will be defined as 2 injection cycles (~127 consecutive days) in which no injections were administered without oral PrEP bridging.

7.3.3. Confounders and effect modifiers

The study will examine the effect of the following potential confounders and effect modifiers on the risk for outcomes of interest. These variables will be measured at baseline and at 6, 12, 24, 36, and >36 months as available.

Demographic Variables

- Age at index date
- Sex and Gender
- Ethnic Origin
- Geographic region (where provided)

Clinical Characteristics

- Substance use
- Alcohol use
- Charlson Comorbidity Index (CCI)
- Body Mass Index (BMI), weight, height
- High risk sexual behaviour
- STI testing in the past 12 months
- STI diagnoses in the past 12 months (chlamydia, syphilis, gonorrhoea, and other STIs combined)
- 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
- 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
- Use of recreational drugs (cocaine, narcotics, psychodysleptics [hallucinogens], psychoactive substance, antiepileptic, sedativehypnotic and anti-parkinsonism drugs)

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
    - 6-12 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

7.4. Data sources

Data will be collected from participating European clinical sites within the NEAT-ID Network. Selected sites will be contacted and asked to identify individuals initiating CAB LA for PrEP. The NEAT-ID Network coordinating center will receive data from the clinical sites for the study; data will be extracted from medical records to capture the study variables relevant to the study objectives, as listed in Section 7.3 Variables. Data will be entered into the EDC system from each site. All data will be deidentified and electronically transferred to the coordinating center. Sites will be regularly monitored for data quality and accuracy.

7.4.1. Study size

The study is not a hypothesis testing study, but it is designed to assess usage of CAB LA for PrEP in real world clinical settings. The overall number of participants in this cohort study will depend on the uptake of the CAB LA for PrEP and how widely it will be used across the NEAT-ID clinical sites.

The study aims to include a target of at least 500 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, using Exact Clopper Pearson confidence limits under different scenarios.

Table 1: Precision estimates

Confidence Level	Sample Size (N)	CI Width	Incident HIV rate (%)	Lower Limit	Upper Limit
0.95	500	1.1824	0.25	0.0118	1.1942
0.95	500	1.5093	0.50	0.0832	1.5925
0.95	500	1.9926	1.00	0.3255	2.3181
0.95	500	2.3679	1.50	0.6283	2.9962
0.95	500	2.6841	2.00	0.9631	3.6472
0.95	500	2.9617	2.50	1.3185	4.2802
0.95	1000	0.7568	0.25	0.0416	0.7984
0.95	1000	1.0004	0.50	0.1625	1.1629
0.95	1000	1.3507	1.00	0.4806	1.8313
0.95	1000	1.6201	1.50	0.8419	2.4620
0.95	1000	1.8462	2.00	1.2258	3.0720
0.95	1000	2.0442	2.50	1.6243	3.6685
0.95	2000	0.5012	0.25	0.0812	0.5824
0.95	2000	0.6776	0.50	0.2400	0.9176
0.95	2000	0.9283	1.00	0.6119	1.5402

0.95	2000	1.1202	1.50	1.0143	2.1345
0.95	2000	1.2810	2.00	1.4326	2.7136
0.95	2000	1.4217	2.50	1.8611	3.2828

Table 2 below shows the precision estimates for regimen discontinuation rates varying from 2.5% to 20% for a sample of 500 individuals.

Table 2. Precision estimates by discontinuation rate

Confidence Level	Sample Size (N)	CI Width	Discontinuation rate	Lower Limit	Upper Limit
0.95	500	0.0296	0.025	0.0132	0.0428
0.95	500	0.0403	0.050	0.0326	0.0729
0.95	500	0.0546	0.100	0.0751	0.1297
0.95	500	0.0646	0.150	0.1198	0.1844
0.95	500	0.0720	0.200	0.1658	0.2378

7.5. Data management

Following the availability of CAB LA for PrEP in Europe, the study will collect follow-up data prospectively on a target of at least 500 individuals initiating CAB LA for PrEP, for a follow-up period of at least 3 years. Participants who discontinue CAB LA for PrEP will be followed up through the end of the follow-up period after discontinuation.

The NEAT-ID Network coordinating centre will receive data from the clinical sites per the protocol for the study. A detailed data collection form will be used to collect comprehensive data needed for study analysis, including clinical sites including dates of injections, clinical and laboratory parameters (immunologic, biochemistry, haematology and pathology), resistance and HIV subtype data at HIV acquisition, and after discontinuation and switching to another PrEP regimen.

In order to maintain confidentiality, the subject will be identified only by subject number. Subject data will be collected via extraction from individual medical record as source data by appropriately trained and authorised member(s) of the study team who must be identified and authorised in writing by the Principal Investigator (PI). A delegation of responsibility log will be updated accordingly.

Sites will provide and upload data to the data management team who will store the data on a secure database with access to authorised personnel of the study management team only, maintained the log of authorised personnel by the sponsor representative.

7.5.1. Data handling conventions

Data will be handled in accordance with data handling guidelines provided to sites. The Study Monitor and Data Manager will review data on an on-going basis and raise any discrepancies with site staff as required. Identified only by subject number, the data are deidentified at all times.

7.5.2. Timings of Assessment during follow-up

Available data will be collected from enrolled participants every 6 months, and deidentified data will be reported to the data coordinating centre.

7.6. Data analysis

7.6.1. Essential analysis

Specific analytic methods are shown for each study objective. All CAB LA PrEP users will be followed for at least 3 years (36 months). All individuals with incident HIV acquisition will be followed through the end of the follow-up period. Participants discontinuing CAB LA PrEP will be monitored through the end of the follow-up period for HIV acquisition and, in the case of HIV acquisition, will be monitored for ART effectiveness and 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 through the end of the follow-up period. 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, ethnic origin (where available), BMI, geographic region), history of previous PrEP use and use of OLI prior to initiating injections will be described. Comorbidities, STIs, risk factors for HIV acquisition (e.g. HIV status of sexual partner, multiple sexual partners), will be reported as frequencies at baseline and at 6, 12, 24, 36, and >36 months of follow-up as available. 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, and timing of HIV testing relative to injection dates will be assessed.

Prevalent HIV is defined as any undiagnosed HIV 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 will be reported at baseline while on CAB OLI and while on CAB LA. Also, prevalent HIV will be reported for those who received CAB OLI and separately for those with direct to injection (DTI) strategy.

Incident HIV is any new HIV diagnosis that occurs after the initiation of CAB PrEP, having confirmed HIV negative status using HIV RNA test, at the time of PrEP initiation. Incident HIV 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 bridging)

Adherence will be estimated using the dates of injections. Proportion and number of individuals with ≥1 delayed (≥7 days)and/or ≥1 missed injection without oral PrEP bridging over 6, 12, 24, 36, >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, >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 without oral PrEP bridging will be compared with those that are on time with the injections for 6, 12, 24, 36, and >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, and >36-month-periods and overall will be provided. Additionally, distribution of individuals who discontinued by most common discontinuation reasons will be provided and will be used to understand whether individuals are missing injections or choosing to discontinue the regimen. Characteristics of persons who discontinue vs persons who stay on therapy will be compared for 6, 12, 24, 36, and >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 diagnoses while on CAB for PrEP)

Frequency of undiagnosed prevalent HIV 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 diagnosis 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 acquisition for the overall group, and separately for the OLI and DTI groups.

Adherence patterns and characteristics of individuals with incident HIV diagnosis 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 based on univariate analysis will be selected for multivariable analysis. Risk for HIV

acquisition and characteristics affecting risk for HIV acquisition will be assessed using negative binomial model with log-link function with binary outcome (HIV diagnosis vs not) if feasible.

Time to HIV diagnosis will be defined as time from first CAB LA PrEP injection to the first HIV diagnosis using laboratory antigen/antibody test, confirmed by viral RNA test. Time to HIV diagnosis will be assessed using Kaplan-Meier curve. Differences in time to diagnosis will be assessed by sex, gender, ethnicity (where available), geographic region, and risk factors (e.g. STI, previous PrEP usage) related, adherence to current PrEP 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 HIV diagnosis by subgroup adjusting for additional variables (e.g., sex, ethnicity, (where available) geographic region).

ART regimen and VL testing among CAB PrEP users with undiagnosed prevalent infections and incident infections will be described separately, during the follow-up period. In the event of a delay of ART initiation post HIV diagnosis, the study will strive to follow the individual after ART initiation and through the end of the follow-up period. 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 HSRs 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 the follow-up period. 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 the follow-up period. 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 an 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, initiating CAB OLI or CAB LA PrEP, will be followed through the end of the follow-up period after ART initiation and will be monitored for resistance

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

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

7.7. Quality Control and Quality Assurance

Data will be handled in accordance with data handling guidelines provided to sites. The Study Monitor and Data Manager will review data on an on-going basis and raise any discrepancies with site staff as required. Identified only by subject number, the data are deidentified at all times. All data transfers are fully documented.

Electronic data sets will provide an unmonitored subset of existing source data that will be subject to data validation. Site selection and training of site staff will ensure suitably qualified personnel are involved at every stage of the data gathering process.

The study coordinating center will be responsible for data handling and quality control. All data will be entered directly into the electronic data capture (EDC) system by appropriately trained and delegated site staff. Site selection and training of site staff will ensure suitably qualified personnel are involved at every stage of the data gathering process. The EDC will only collect data that is required as per the protocol and will be developed in line with the MACRO Utilisation SOP (DM-001). The data management team will review data on an on-going basis and raise any discrepancies with site staff as required, following the process set out in the Data Management Activities SOP (DM-002). Identified only by subject number, the data are processed in the pseudonymized format at all times. All data activities performed within the EDC will be captured by the system audit trail. Any transfers of data from the EDC will be documented following the processes as set out in the Data Management Activities SOP (DM-002).

The Neat ID Network team on behalf of the MAH will perform data review activities to assess protocol, consent and data quality issues. Any issues relating to study management quality performance will be reviewed and discussed during study team meetings. The Neat ID Network may decide to include this study in the annual audit schedule, as per Audit Activities SOP (QA-001). The audit conduct and reporting will be performed by the independent QA personnel and in accordance with the relevant regulations, the protocol and the applicable Standard Operating Procedures.

Site selection and training of site staff will ensure suitably qualified personnel are involved at every stage of the data gathering process.

7.8. Limitations of the research methods

Limitations of this study are common to non-randomized, non-interventional observational cohort studies. This is a study of routine clinical care and reflects treatment practice across NEAT-ID Network clinical sites. Confounding by indication, whereby persons are selected for specific regimens, cannot be ruled out. While the study aims to include a target of at least 500 individuals initiating CAB LA for PrEP, market uptake of the regimen and individuals' willingness to participate will dictate how quickly data will be collected.

Follow-up of study participants through the end of the follow-up period after discontinuation of CAB LA for PrEP or after HIV acquisition will increase the potential for loss to follow-up as would be expected, in a real-world setting. The results from this study should be interpreted cautiously, with careful consideration given to the limitations of the observational study design.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Ethical approval and subject consent

Before the start of data collection, this protocol and any accompanying material to be provided to the participants (subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted to an Ethics Committee (EC) in the relevant countries. The participating clinical sites will not begin any study activities until approval from the EC has been documented and the Sponsor (MAH) has provided as an activation letter to the clinical site investigator.

Any subsequent amendments that require review by the EC will not be implemented until the EC grants the amendments a favourable opinion which will be disseminated to the investigator and sites (NOTE: amendments may also need to be reviewed and accepted by the regulatory agencies and/or local EC departments before they can be implemented in practice at sites). In accordance with the requirements of the EC, an annual progress report will be submitted as needed to the EC. NEAT-ID team will notify the EC in each country with a participating site of the end of the study. If the study is ended prematurely, NEAT-ID will notify the EC, including the reasons for the premature termination.

8.2. Subject confidentiality

All investigators and study site staff will comply with the requirements of the current Data Protection Regulations with regards to the collection, storage, processing and disclosure of personal information and will uphold the Regulation's core principles.

- Only deidentified data is reported to the central study database. Identifiable individual information (held only by the site investigator in routine medical records) will be kept secure at all times and maintained in line with local applicable standard operating procedures. Access to this will be to the minimum number of individuals necessary for quality control, and audit reasons. There will be no entry of any directly identifiable data into the study database at any time.

9. *LEGAL BASIS FOR PROCESSING INDIVIDUAL HUMAN DATA

The authors confirm that study data is Individual Human Data (IHD) not owned by ViiV Healthcare, 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

Collection of adverse events/reactions (Solicited Events)

The purpose of the study is to monitor exposure to Apretude and to evaluate DILI and HSRs. For Apretude, pre-defined safety events of interest, DILI and HSRs, will be systematically recorded in aggregate. These will be summarised in interim, if applicable, and final study reports. This study is based on secondary use of existing health data and as such Individual Case Safety Reporting (ICSRs) to regulatory agencies is not required.

Reporting of adverse events/reactions (Spontaneous Events)

The purpose of the study is to monitor individuals exposed to Apretude and to evaluate pre-defined safety events in aggregate. There is no potential to collect serious and non-serious spontaneous AEs, pregnancy exposures, or incidents related to any GSK/ViiV product during the conduct of this research, as the minimum criteria of identifiable individuals, 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 individual and reporter and are insufficient to establish attribution between a potential safety event and an individual using a GSK/ViiV product. This study is based on data previously collected for other purposes e.g., routine healthcare encounters. As such, there is no requirement for the collection and reporting of Individual Case Safety Reports (ICSRs).

This is a non-interventional study based on secondary use of data collected to support clinical care. The study uses deidentified 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 safety management plan will not be developed.

Participating clinical sites and health care providers will be strongly encouraged to report all pregnancies occurring while using CAB LA 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. Target Audience

This study-specific protocol will be submitted for EMA's review and endorsement. The study will start once CAB LA for PrEP is commercially available in Europe and is expected to continue through 2029 or later. Annual interim reports with cumulative data will be submitted and a final report is expected to be submitted in July 2030.

11.2. Study reporting and publications

Annual interim reports with cumulative data will be submitted and a final report is expected to be submitted in July 2030. 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.

12. REFERENCES

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