TITLE PAGE

Information Type: ViiV Healthcare Non-Interventional Study Protocol

Title:	Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in People living with HIV (PLWH) initiating ARV regimen CAB+RPV LA in Collaboration with EuroSIDA

Compound Number:	GSK1265744, TMC278
Development Phase	IV
Effective Date:	01-Aug-2021
Subject:	Long acting ARV, Cabotegravir, Rilpivirine, Clinical Effectiveness, Adherence, Discontinuation, Resistance
Author(s):	PPD : ViiV Healthcare PPD : ViiV Healthcare PPD : GlaxoSmithKline PPD : University of Copenhagen PPD : University College London PPD University of Copenhagen PPD , University of Copenhagen

PASS information

Title	Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in People living with HIV (PLWH) initiating ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA
Protocol version identifier	v1.0
Date of last version of protocol	[Date DD Month YYYY]
EU PAS (ENCEPP) register number	Study not registered yet
Active substance	Cabotegravir Rilpivirine
Medicinal product	VOCABRIA® 30 mg film-coated tablets VOCABRIA® 400 mg prolonged release suspension for injection (2 mL) VOCABRIA® 600 mg prolonged release suspension for injection.(3 mL) Edurant® 25 mg film-coated tablets Rekambys® 600 mg prolonged release suspension for injection. (2 mL) Rekambys® 900 mg prolonged release suspension for injection. (3 mL)
Product reference	Cabotegravir - EU/1/20/1481/001-003 Rilpivirine - EU/1/20/1482/001-002
Procedure number	Cabotegravir - EMEA/H/4976 Rilpivirine - EMEA/H/5060
Marketing authorisation holder(s)	ViiV Healthcare B.V. Janssen-Cilag International NV
Joint PASS	Yes

Research question and objectives	Following the initiation of any ARV regimen containing CAB and/or RPV LA among people living with HIV, the study will aim to assess usage patterns, durability, discontinuation, and virologic outcomes. Objectives: 1. Describe CAB and/or RPV LA containing regimens usage patterns 2. Assess adherence, durability and discontinuation of CAB+RPV LA regimen 3. Assess the clinical effectiveness (i.e. proportion of individuals experiencing virologic failure) among PLWH who are on CAB+RPV LA regimen 4. Monitor for resistance and next treatment response among individuals who switched off CAB+RPV LA (where data is available)
Country(-ies) of study	Albania, Argentina, Austria, Belarus, Belgium, Bosnia & Herzegovina, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Lithuania, Luxembourg, Netherlands, North Macedonia, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovenia, Spain, Sweden, Switzerland, Ukraine, United Kingdom
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1. LIST OF ABBREVIATIONS

ADE	AIDS-defining Event
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
AST	Aspartate aminotransferase
ART	Antiretroviral Therapy
ARV	Antiretroviral
BCG	Bacillus Calmette–Guérin
BMI	Body Mass Index
CAB	Cabotegravir
CD4	Cluster of Differentiation 4
CD8	Cluster Differentiation 8
CKD	Chronic Kidney Disease
CRF	Case Review Form
CVD	Cardiovascular Disease
CVF	Confirmed Virologic Failure
DAA	Direct-acting Antiviral
DEXA	Dual-energy X-ray Absorptiometry
DNA	Deoxyribonucleic Acid
DUS	Drug Utilization Study
EC	Ethics Committee
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ESLD	End stage liver disease
EU	European Union
GI	Gastrointestinal
GCP	Good Clinical Practice
HbA1c	Haemoglobin A1c
HBsAG	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCP	Healthcare Provider
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HICDEP	HIV Collaboration Data Exchange Protocol
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
INR	International Normalized Ratio
INSTI	Integrase Strand Transfer Inhibitor
IQR	Interquartile Range
LA	Long Acting
LAI	Long Acting Injectable
LDL	Low Density Lipoprotein
LOD	Limit of Detection

MAH	Marketing Authorization Holder
MI	Myocardial Infarction
MTCT	Mother-to-Child Transmission
NADM	Non-AIDS Defining Malignancies
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
PASS	Post Authorization Safety Study
PCR	Polymerase Chain Reaction
PLWH	Person Living with HIV
PMTCT	Prevention of Mother-to-Child Transmission
REDCap	Research Electronic Data Capture
RNA	Ribonucleic Acid
RPV	Rilpivirine
QA	Quality Assurance
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SmPC	Summary of Product Characterization
SOP	Standard Operating Procedure
STI	Structured Treatment Interruption
TB	Tuberculosis
VL	Viral Load

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2. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

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

Investigator Name: PPD

PPD

Investigator Signature

PPD

Date PPD

3. ABSTRACT

(a) Title with subtitles including version and date of the protocol and name and affiliation of the main author:

Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in People living with HIV (PLWH) initiating ARV regimen CAB+RPV LA in Collaboration with EuroSIDA; v1.0; 26Jan2021; PPD , MBBS, MPH, PhD, PPD , Epidemiology & Real World Evidence, ViiV Healthcare

(b) Rationale and background:

Cabotegravir (CAB), a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI), in combination with Rilpivirine (RPV), an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies /mL) on a stable antiretroviral (ART) regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INSTI class. Prior to the initiation of CAB long acting (LA) injection, CAB tablets together with RPV tablets should be taken for approximately one month (at least 28 days) to assess tolerability to CAB and RPV.

The Marketing Authorization Holder (MAH) proposes a five-year Drug Utilization Study (DUS) to be conducted in a real-world clinical setting. This prospective observational cohort study will aim to better understand the individual population receiving CAB and/or RPV LA containing regimens in routine clinical practice, usage patterns, adherence, post marketing clinical effectiveness of these regimens and monitor for resistance among virologic failures for whom data on resistance testing are available.

(c) Research question and objectives:

Following the initiation of any ARV regimen containing CAB and/or RPV LA among people living with HIV (PLWH), the study will aim to assess usage patterns, durability, discontinuation, and virologic outcomes.

1. Describe CAB LA and/or RPV LA containing regimens usage patterns

2. Assess adherence, durability and discontinuation for persons starting CAB+RPV LA regimen

3. Assess the clinical effectiveness (i.e. proportion individuals experiencing virologic failure) among PLWH who initiate CAB+RPV LA regimen)

4. Monitor for resistance and next treatment response among individuals who switched off CAB+RPV LA regimen, where VL data are available and resistance testing has been done as part of routine clinical practice

5. Evaluate the effectiveness of routine risk minimisation measures for regimen adherence, discontinuation due to incorrect route of administration and off-label use of CAB+RPV LA regimen

(d) Study design:

This post authorization safety study (PASS), a non-interventional prospective observational cohort study will be nested within the EuroSIDA study, using data from individual medical records from participating clinical sites will be conducted over a period of five years to meet the study objectives.

(e) Population:

The study population will include PLWH over the age of 18 years, from EuroSIDA clinical sites who are new users of CAB and/or RPV LA containing regimens over a period of 5 years. Persons will be eligible for inclusion from the date of starting the treatment regimens after approval and commercial availability of the regimens.

(f) Variables:

The EuroSIDA study collects a comprehensive range of data including demographics, infection-related laboratory data, other laboratory data, antiretroviral start and stop dates and reasons for discontinuation, paraclinical and clinical events.

(g) Data sources:

EuroSIDA is a well-established, prospective observational cohort study of more than 13,000 individuals under active follow-up in over 100 hospitals in 34 European countries, and Israel and Argentina. Following the approval and commercial availability of CAB+RPV LA, the study will collect prospective data on individuals initiating CAB and/or RPV LA containing regimens, over the course of 5 years.

(h) Study size:

Sample size will depend on the market uptake of CAB and/or RPV LA following its commercial availability in European countries. Based on possible uptake of CAB+RPV LA and rates of discontinuation or virologic failure, the likely precision of the estimates can be determined using Exact Clopper Pearson confidence limits under different scenarios.

(i) Data analysis:

Descriptive analyses will summarize the study population exposed to CAB and/or RPV LA. Discontinuations of CAB+RPV LA will be summarized and logistic regression will be used to identify factors associated with missing 1 or more dose and receiving an injection 7 or more days late. Multivariable logistic regression models will investigate the factors associated with virologic failure at 6 months, 12 months and 24 months after CAB+RPV LA initiation and resistance patterns presented for those with resistance data available.

(j) Milestones:

The study will start after the protocol is approved by the EMA, and CAB+RPV LA is registered and commercially available in the relevant countries and is expected to continue through 2026 or later, for a total of five years of study period. Annual interim reports with cumulative data will be submitted and a final report is expected to be submitted in September 2026.

4. AMENDMENTS AND UPDATES

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

5. MILESTONES

Milestone	Planned date
Draft Protocol Submission	Dec 31, 2020
Study Start (Protocol Approval)	Estimated - June 2021
1st Interim Report	Draft -Dec, 2022 Final- Mar, 2023
2nd Interim Report	Draft -Dec, 2023 Final- Mar, 2024
3rd Interim Report	Draft -Dec, 2024 Final- Mar, 2025
4th Interim Report	Draft -Dec, 2025 Final- Mar, 2026
Data Collection Completion	June 2026 or 5 years following commercial availability of CAB
Final Report	Sep 2026
Supplemental Report	Depends on when the last individual discontinuing the CAB+RPV LA regimen completes 4-years of follow up

6. RATIONALE AND BACKGROUND

6.1. Background

Cabotegravir (CAB), a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI), in combination with Rilpivirine (RPV), an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated as a complete regimen for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral (ART) regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INSTI class. Prior to the initiation of CAB long acting (LA) injection, CAB tablets together with RPV tablets should be taken for approximately one month (at least 28 days) to assess tolerability to CAB and RPV.

Treatment with CAB+RPV LA should be prescribed by a physician experienced in the management of HIV infection. Each injection should be administered by a healthcare provider (HCP). Prior to starting the regimen, the HCP should carefully select individuals who agree to the required injection schedule and counsel individuals about the importance of adherence to scheduled dosing visits to help maintain virologic suppression and reduce the risk of viral rebound and potential development of resistance associated with missed doses. Following discontinuation of CAB+RPV LA injection, it is essential to adopt an alternative, fully suppressive ARV regimen per the summary of product characterization (SmPC).

The Marketing Authorization Holders (MAH) propose a five-year Drug Utilization Study (DUS) to be conducted in a real-world clinical setting. This prospective observational cohort study will aim to better understand the individual population receiving CAB and/or RPV LA containing regimens in routine clinical practice, usage patterns, adherence, post marketing clinical effectiveness of these regimens and monitor for resistance among virologic failures for whom data on resistance testing are available.

6.2. Rationale

There is a need to understand the CAB and/or RPV LA containing regimens utilization in a real-world clinical setting. Adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance with missed doses is critical for long term maintenance of viral suppression. Impact of non-adherence on virologic failure and emergence of resistance need to be assessed in a real world clinical setting among a more heterogeneous population than often represented in clinical trials.

7. RESEARCH QUESTIONS AND OBJECTIVE(S)

Following the initiation of any ARV regimen containing CAB and/or RPV LA among PLWH, the study will aim to assess usage patterns, durability, discontinuation, and virologic outcomes.

The specific objectives are to:

1. Describe CAB and/or RPV LA containing regimens usage patterns
    - Descriptive analysis of study population by baseline demographic and clinical characteristics
    - Monitor for use of oral lead-in
    - The potential regimen combinations are listed below (Note that CAB+RPV LA is the only approved regimen)
        a. CAB+RPV LA regimen only
        b. CAB LA monotherapy
        c. CAB LA use in combination with ARVs other than RPV LA
        d. RPV LA monotherapy
        e. RPV LA use in combination with ARVs other than CAB LA
        f. CAB LA+RPV LA+other ARVs
        g. Combined group b-f

2. Assess adherence, durability and discontinuation for persons starting CAB+RPV LA regimen ;
    - Proportion of individuals discontinuing the regimens of interest will be assessed.
        - Reasons for discontinuation will be assessed.
    - Non-adherence to the dosing schedule will be assessed by:
        a. Estimating the number of individuals that missed one or more consecutive injections without taking daily oral bridging therapy or any other oral ARV regimen while not on CAB+RPV LA containing regimens and mean and median number of injections missed during a 12-month period
        b. 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
        c. Estimating the number of individuals who missed one or more consecutive injections without taking daily oral bridging therapy or those who received the injections seven or more days later than their scheduled injection visit (Combined group a OR b) and describe patient characteristics for the individuals that are non-adherent.
    - Number of individuals with incorrect route of administration will be described.

3. Assess the clinical effectiveness (i.e. proportion of individuals experiencing virologic failure) among PLWH who initiate CAB+RPV LA regimen
    a. Estimate the proportion of individuals with virologic failure, during the first 6 months after initiation of CAB+RPV LA
    b. Estimate the proportion of individuals with virologic failure, at 6, 12 and 24 months after initiation of CAB+RPV LA
    c. Stratified analyses for 3a and 3b will be conducted for VL at regimen initiation (<50 copies/mL and ≥50 copies/mL).
    d. Assessment of VL for PLWH on other regimen combinations (b-f in objective 1) at 6, 12 and 24 months after initiation of the regimen

4. Monitor for resistance and next treatment response among individuals who discontinued CAB+RPV LA, where VL data are available and resistance testing has been done as part of routine clinical practise
    - Describe the ARV regimen individuals are switched to after discontinuation of CAB+RPV LA containing regimens
    - Monitor for resistance (where this has been done as part of routine clinical practise) during the 48 months following the switch
    - Describe virologic outcomes at 12, 24, 36 and 48 months after discontinuation of CAB+RPV LA containing regimens

5. Evaluate the effectiveness of routine risk minimisation measures for regimen adherence, discontinuation due to incorrect route of administration and off-label use of CAB+RPV LA regimen
    - Assess off-label use as described in objective 1
    - Estimate proportion of treatment naive or individuals not suppressed initiating regimen
    - Assess non-adherence to the dosing schedule as described in objective 2
    - Assess the frequency of discontinuation due to incorrect route of administration

8. RESEARCH METHODS

8.1. Study Design

A prospective observational cohort study nested within the EuroSIDA study, using data from individual medical records from participating clinical sites will be conducted over a period of five years to meet the study objectives.

This study will be conducted through collaboration with EuroSIDA, a well-established, prospective observational cohort study of more than 13,000 individuals under active follow up in over 100 hospitals in 34 European countries, and Israel and Argentina [1].

For this non-interventional study, treatment and laboratory testing decisions will be made by the treating physician according to standard practice, taking into account the treatment history, individual characteristics, the approved SmPc for CAB+RPV oral and LA

formulations, contemporary regimen and local guideline or recommendations. All individuals who discontinue the regimen for any reason, will be followed for up to 48 months after discontinuation. The study protocol will be implemented by the EuroSIDA coordinating center.

8.2. Study Population and Setting

Study Population:
The study population will include PLWH over the age of 18 years, from EuroSIDA clinical sites who are new users of CAB and/or RPV LA containing regimens over a period of 5 years. Persons will be eligible for inclusion from the date of starting the treatment regimens after approval and commercial availability of the regimens. Only the first exposure to CAB and/or RPV LA containing regimens will be included in the primary analyses.

The potential regimen combinations are listed below (Note that CAB+RPV LA is the only approved regimen):

a. CAB+RPV LA regimen only
b. CAB LA monotherapy
c. CAB LA use in combination with ARVs other than RPV LA
d. RPV LA monotherapy
e. RPV LA use in combination with ARVs other than CAB LA
f. CAB LA+RPV LA+other ARVs
g. Combined group b-f

EuroSIDA Cohort description:
The EuroSIDA study was initiated in 1994 and is a prospective observational cohort study of more than 22,000 individuals followed in over 100 hospitals in 34 European countries, and Israel and Argentina. The main objective of the study is to assess the impact of ARV drugs on the outcome of the general population of PLWH living in Europe.

In EuroSIDA, annual data collection is performed directly from clinics on individuals using comprehensive standardized clinical record forms via REDCap or electronic data transfer using the HICDEP format that includes information on outcomes and covariates [2]; further information is available at https://www.hicdep.org/. For each person, the date of starting and stopping each ARV drug is recorded. ATC codes for all ARVs and most non ARVs are collected. Dates of diagnosis of all AIDS defining diseases are recorded, using the 1993 clinical definition of AIDS from the Centers for Disease Control and Prevention. All EuroSIDA data undergo extensive data checks, queries and central clinical event validation to ensure a high quality and completeness of data.

Table 1. EuroSIDA currently contributing countries and geographical regions

Southern Europe	Central Western Europe	Northern Europe	Central Eastern Europe	Eastern Europe
Spain	France	United Kingdom	Poland	Estonia
Portugal	Belgium	Ireland	Czech Republic	Lithuania
Italy	Luxembourg	Netherlands	Bosnia-Herzegovina	Belarus
Greece	Switzerland	Denmark	Hungary	Ukraine
	Austria	Sweden	Romania	Russia
	Germany	Norway	Serbia	Georgia
		Finland	Slovenia	
		Iceland	Croatia	
*Israel			Albania	
*Argentina			North Macedonia	

*non-European countries

Data Collection:

Following the approval and commercial availability of CAB+RPV LA, the study will collect prospective data on individuals initiating CAB and/or RPV LA containing regimens, over the course of 5 years. The EuroSIDA coordinating center will receive data from the clinical sites per the protocols established for data collection.

An additional data collection form will be used to enhance the routinely collected data from clinical sites. Dates of treatment, documented history of resistance at regimen initiation, resistance and HIV subtype data at virologic failure and after discontinuation and switching to another ARV regimen will be collected via the enhanced data collection using study specific additional CRFs. The additional CRF will collect baseline data at regimen initiation, 6 months, 12 months & 24 months for all individuals on the CAB and/or RPV LA containing regimen of interest and at 12 months, 24 months, 36 months & 48 months for those who discontinue the regimen and switch to other ARV regimens.

8.3. Clinical Variables

The EuroSIDA study collects a comprehensive range of variables, as summarised in Table 2 below.

Table 2. Variables routinely collected in the EuroSIDA Study

Demographics and basic information	Date of birth, date first seen at department, sex, country of origin, ethnicity, height, weight, date of first HIV-1-antibody positive test, mode of HIV-1 transmission, smoking status, alcohol abuse, drug user information, predisposition to MI or stroke among relatives
Infection-related Laboratory data	HIV-ribonucleic acid (“RNA”), HCV antibody test, HCV-RNA, HBsAg result, HBV-DNA, CD4 count, CD8 count, SARS-CoV-2 PCR and antibody

Other Laboratory data	total cholesterol, HDL, LDL, haemoglobin A1c (HbA1c) and/or glucose, triglycerides, serum creatinine, ALT, AST, bilirubin, albumin, INR, platelets, haemoglobin, proteinuria
Medical treatment	All ARV start and stop dates and reasons for discontinuation (including injection site reaction and injection fatigue) and treatment for HCV, hypertension, treatment for CVD and/or diabetes, Tuberculosis treatment, opioid maintenance therapy, dyslipidaemia incl. start and stop dates
Paraclinical data	Systolic and diastolic blood pressure, liver biopsy, fibroscan, DEXA scan, plasma samples
Clinical events	Syphilis, AIDS defining events (OIs including tuberculosis), myocardial infarction, stroke, diabetes, invasive cardiovascular procedures, end-stage liver disease, end-stage renal disease, AIDS and NADMs, liver and kidney transplantation, fractures

8.3.1. Exposure definitions

The study period for data collection will start at the date of initiation of oral lead-in with CAB and/or RPV. The follow-up period for data analyses will start with first injection of CAB and/or RPV LA containing regimens and end at up to 48 months after discontinuation of the last injection.

Details about use of CAB and/or RPV LA containing regimens will be collected on a separate CRF. The data collected include dates of all planned and actual injections, use of oral bridging therapy for CAB+RPV LA, HIV subtype and resistance testing prior to initiation or at time of discontinuation of LA.

8.3.2. Outcome definitions

1.Regimen discontinuations: Discontinuation of CAB+RPV LA regimen for any reason during the study period will be captured, tabulated and reported.

Individuals who receive the oral lead-in but never initiate the CAB+RPV LA regimen will be tabulated separately but not included in the primary analysis.

Discontinuation of CAB +RPV LA will be defined as the latest date of the next scheduled injection which is missed and where bridging therapy has not been started. For example, for monthly dosing, if the first injection of CAB+RPV LA was received on June 1st, the second injection should be received on July 1st (allowed time window for second injection is June 24th to July 8th). The third injection should follow the timing of the first injection and should be received on August 1st (allowed time window for third injection is July 25th to August 8th). If not, date of discontinuation will be defined as August 8th (Monthly dosing).

For every 2 month dosing, if the first injection of CAB+RPV LA was received on June 1st, the second injection should be received on July 1st (allowed time window for second injection is June 24th to July 8th). The third injection should follow the timing of the first injection and should be received on September 1st (allowed time window for third injection is August 25th to September 8th). If not, date of discontinuation will be defined as September 8th (Every 2 month dosing).

Discontinuation will also be captured, tabulated and reported for any other CAB and/or RPV containing regimen.

Durability will be measured as proportion of individuals continuing on the regimen at the end of 6, 12 and 24 months.

Adherence will be assessed by estimating the number of individuals that missed one or more consecutive injections without taking daily oral bridging therapy or any other oral ARV regimen while not on CAB+RPV LA regimen and mean and median number of injections missed during a 12-month period. We will also estimate the number who received the injections seven or more days later than their scheduled injection visit and median duration of delayed injections in persons using bridging therapy.

In the standard follow-up data collection in EuroSIDA reasons for discontinuation are recorded as below.

Table 3. EuroSIDA – Reasons for Treatment Discontinuation

Code	Reason for Stopping Treatment
1	Treatment failure (i.e. virological, immunological, and/or clinical failure
1.1	Virological failure
1.2	Partial virological failure
1.3	Immunological failure - CD4 drop
1.4	Clinical progression
1.5	Resistance (based on test result)
2	Abnormal fat redistribution
3	Concern of cardiovascular disease
3.1	Dyslipidaemia
3.2	Cardiovascular disease
4	Hypersensitivity reaction (skin eruption etc.)
5	Toxicity, predominantly from abdomen/G-I tract
5.1	Toxicity - GI tract
5.2	Toxicity - Liver
5.3	Toxicity - Pancreas
6	Toxicity, predominantly from nervous system
6.1	Toxicity - peripheral neuropathy
6.2	Toxicity - neuropsychiatric
6.3	Toxicity - headache
7	Toxicity, predominantly from kidneys

8	Toxicity, predominantly from endocrine system
8.1	Diabetes
9	Haematological toxicity (anemia etc.)
10	Hyperlactataemia/lactic acidosis
11	Bone toxicity
15	Social contra-indication
16	Contra-indication unspecified
16.8	Contra-indication expired
16.9	Contra-indication – other
17	MTCT regimen completed
70	Pregnancy - toxicity concerns (during pregnancy)
75	Pregnancy - switch to a more appropriate regimen for PMTCT
88	Death
90	Side effects - any of the above but unspecified
90.1	Comorbidity
91	Toxicity, not mentioned above
91.1	Toxicity, unspecified
92	Availability of more effective treatment (not specifically failure or side effect related)
92.1	Simplified treatment available
92.2	Treatment too complex
92.3	Drug interaction
92.31	Drug interaction - commencing TB/BCG treatment
92.32	Drug interaction - ended TB/BCG treatment
92.33	Change in eligibility criteria (e.g. child old enough for tablets; refrigerator no longer available)
92.4	Protocol change
92.5	Regular treatment termination (used in tblMED e.g. for DAA's against HCV, antibiotics)
92.6	End of empiric treatment
92.9	Change in treatment not due to side-effects, failure, poor adherence or contra-indication
92.91	Change to generic drug
92.92	Change to branded drug
93	Structured Treatment Interruption (STI)
93.1	Structured Treatment Interruption (STI) - at high CD4
94	Individual's wish/decision, not specified above
94.1	Non-compliance
94.2	Defaulter
95	Physician's decision, not specified above
96	Pregnancy (see also more specific codes 70 and 75
96.1	Pregnancy intended
96.2	Pregnancy ended
97	Study treatment
97.1	Study treatment commenced
97.2	Study treatment completed

97.6	Drug not available
98	Other causes, not specified above
	Incorrect route of administration
	Injection fatigue (not related to safety)
	Injection Site Reaction
	Lost to follow-up
99	Unknown

2. Clinical effectiveness: Primary analysis for clinical effectiveness will include only those initiating the regimen per label i.e. initiating CAB+RPV LA with VL<50 copies/mL at regimen initiation. The following VL measures will be used for effectiveness assessment:

1. Proportion of individuals, virologically suppressed/undetectable (<50 copies/mL) at 6, 12 and 24 months following initiation of CAB+RPV LA regimen

2. Proportion of individuals with VL <200 copies/mL at 6, 12 and 24 months following initiation of CAB+RPV LA regimen

3. Proportion of individuals with confirmed virologic failure (CVF) during the first 6 months, and at 6, 12 and 24 months following initiation of CAB+RPV LA regimen defined as:
    - Two consecutive HIV RNA VL levels ≥200 copies/mL **or**
    - One HIV RNA VL level ≥200 copies/mL and regimen discontinuation within 4 months of VL ≥200 copies/mL

3. Resistance Testing:

Since this is a non-interventional study aiming to capture individual care in real world setting, the study will not mandate resistance testing following discontinuation of CAB+RPV LA regimen. Health care providers following the local treatment guidelines decide what laboratory and resistance tests are to be conducted. Data thus generated, including available HIV-1 subtypes, will be captured and analyzed by the study team.

8.3.3. Confounders and effect modifiers

The study will examine the effect of potential confounders and effect modifiers as shown in Table 2 above on the risk for outcomes of interest.

Demographic variables

- Age
- Sex
- Route of HIV Infection
- Number of years since HIV diagnosis
- Ethnic origin
- Geographic region
- Date of ART initiation

- Date CAB and/or RPV LA started

Virologic variables at regimen initiation

- HIV VL at initiation of CAB LA and/or RPV LA containing regimens (and in the 12 months prior to regimen start)
  - Continuous (copies/mL)
  - Categorical:
    - <50 copies/mL (or < LOD in clinics where LOD > 50 copies/mL)
    - ≥50 to <200 copies/mL
    - ≥200 to <10,000 copies/mL
    - ≥10,000 to <100,000 copies/mL
    - ≥100,000 copies/mL

Immunologic variables at regimen initiation

- CD4 cell count at initiation of CAB LA and/or RPV LA containing regimens (and in the 12 months prior to regimen start)
  - Continuous (cells/µL)
  - Categorical:
    - CD4 ≥ 500 cells/µL
    - CD4 count ≥350 to <500 cells/µL
    - CD4 count <350 cells/µL
- CD4 nadir prior to initiation of CAB LA and/or RPV LA based ARV regimens

Clinical variables at regimen initiation

- HIV Subtype where available
- History of previous use of integrase inhibitor-based or NNRTI-based regimen
- History of previous antiretroviral exposure
- History of previous virologic failure
- History of previous HIV drug resistance and any historical HIV-1 subtype information, where available
- Body Mass Index (BMI), height, weight
- History of AIDS-defining Events (ADE)
- Concurrent medications (Etravirine, Rifampicin, Rifapentine, Rifabutin, Ribavirin, Ketoconazole, Fluconazole, Itraconazole, Clarithromycin, Erythromycin and other medications where data are available)
- Comorbidities (all defined to be consistent with published EuroSIDA analyses)
  - HCV co-infection [3]
  - HBV co-infection [4]
  - End Stage Liver Disease (ESLD) (hepatocellular carcinoma, ascites, hepatorenal syndrome, grade III/IV hepatic

encephalopathy, unspecified liver decompensation, oesophageal variceal bleeding, liver transplantation) [3]
- Cardiovascular Disease (CVD) (myocardial infarction, stroke, invasive coronary procedure) [3]
- Chronic Kidney Disease (CKD) (confirmed [>3 months apart] eGFR <60/ml/min/1.73m^2 in persons with eGFR at regimen initiation $\geq$60/ml/min/1.73m^2 and confirmed 25% decline in eGFR in persons with eGFR at regimen initiation < 60/ml/min/1.73m^2) [5]
- Non-AIDS defining malignancies (NADM) (excluding hepatocellular carcinoma) [3]

8.4. Study size

Sample size will depend on the market uptake of CAB and/or RPV LA following its commercial availability in European countries. Table 4 below gives an indication of the likely precision of the estimates of the proportion who discontinue or experience virologic failure using Exact Clopper Pearson confidence limits under different scenarios.

Table 4. Possible uptake of CAB+RPV LA and rates of discontinuation and virological failure

Confidence Level	Sample Size (N)	CI Width	Virologic failure or discontinuation (P)	Lower Limit	Upper Limit
0.95	100	0.0054	0.01	0	0.0054
0.95	100	0.05	0.02	0.02	0.07
0.95	100	0.079	0.03	0.006	0.085
0.95	100	0.097	0.05	0.016	0.113
0.95	100	0.127	0.1	0.049	0.176
0.95	100	0.165	0.2	0.127	0.292
0.95	200	0.035	0.01	0.001	0.036
0.95	200	0.045	0.02	0.005	0.05
0.95	200	0.053	0.03	0.011	0.064
0.95	200	0.066	0.05	0.024	0.09
0.95	200	0.088	0.1	0.062	0.15
0.95	200	0.115	0.2	0.147	0.262
0.95	500	0.227	0.01	0.003	0.23
0.95	500	0.026	0.02	0.01	0.036
0.95	500	0.032	0.03	0.017	0.049
0.95	500	0.04	0.05	0.033	0.073
0.95	500	0.055	0.1	0.075	0.13
0.95	500	0.072	0.2	0.166	0.238
0.95	1000	0.013	0.01	0.005	0.018

0.95	1000	0.019	0.02	0.012	0.031
0.95	1000	0.023	0.03	0.02	0.043
0.95	1000	0.028	0.05	0.037	0.065
0.95	1000	0.038	0.1	0.082	0.12
0.95	1000	0.05	0.2	0.176	0.226

8.5. Data management

Data collection, submission, clarification, keying and quality assurance follows the Standard Operating Procedures for EuroSIDA (Instructions for follow-up, Information on plasma collection, Sample list, List of diagnoses used in study , List of clinical definitions used in study, EuroSIDA SOP for data transfer, HICDEP - HIV Collaboration Data Exchange Protocol) (see https://chip.dk/Studies/EuroSIDA/Study-documents) as well as the EuroSIDA Data Handling and Quality Control Plan.

The EuroSIDA coordination office is also responsible for querying sites and collecting adequate source data.

8.5.1. Data handling conventions

EuroSIDA data are submitted either through the electronic case report system Research Electronic Data Capture (REDCap) or electronically using the HICDEP format. Data are handled according to above mentioned standard operating procedures (SOPs) (https://chip.dk/Studies/EuroSIDA/Study-documents). In addition, all data is pseudonymized before transfer to CHIP and is held securely. The data is held on password secured computers in London. EuroSIDA have the relevant data protection clearance, Data Protection Agency No: RH-2018-15

8.5.2. Timings of Assessment during follow-up

All sites in EuroSIDA provide follow-up information to the coordinating centre in October-December each calendar year. All relevant information for each individual occurring since last data capture is provided to the coordinating centre. For example, if a person has 3 CD4 counts measured since last data download, and started and stopped 3 ARVs for different reasons, all this information is provided rather than just the information at most recent visit. An updated version of the database is usually available for statistical analysis 6 months later, allowing the study to provide data on the individuals followed up to approximately 6-12 months prior to the close of the database.

8.6. Data analysis

Between 5-10 EuroSIDA participating clinics (of 100 clinics) have a viral load measured with a limit of detection of >50 copies/ml. Individuals starting CAB+RPV LA regimen with a viral load limit of detection >50 copies/ml will be excluded from primary analyses for clinical effectiveness. We will summarise data for all other users and compare them to those included for generalisability and to help interpret the data.

AIM 1. Describe CAB and/or RPV LA containing regimens usage patterns

New users of CAB and/or RPV LA containing regimens aged >18 years will be characterized using demographics, clinical, immunologic and virologic characteristics at baseline (i.e. at initiation of regimen) stratified by different regimens noted in groups a-g above.

Individual characteristics and baseline covariates will be described using median (interquartile range [IQR]) values for continuous data and relative frequencies for categorical data. Characteristics of those starting different CAB and/or RPV LA containing regimens will be compared using chi-squared tests for categorical variables and non-parametric tests for continuous variables.

Those who start oral lead in but do not start LA regimen will be tabulated separately and demographics will be described.

AIM 2. Assess adherence, durability and discontinuation for persons starting CAB+ RPV LA regimen

Individuals who receive the oral lead-in but never initiate the CAB+RPV LA regimen will be tabulated separately but not included in the primary analysis. Reasons for discontinuation will be assessed using the reasons for discontinuation as reported to EuroSIDA.

Treatment and regimen usage patterns of CAB+RPV LA regimen will be described using frequency distributions while duration of continuous treatment will be described using the mean, median, range, and standard deviation. Number of individuals with incorrect route of administration will be described.

Non-adherence to dosing schedule will be assessed by estimating the number of individuals that missed one or more consecutive injections without taking daily oral bridging therapy or any other oral ARV regimen while not on CAB+RPV LA regimen and median number of injections missed during a 12-month period. We will also estimate the number who received the injections seven or more days later than their scheduled injection visit and median duration of delayed injections in persons using bridging therapy. In addition, the number of individuals who missed one or more consecutive injections without taking daily oral bridging therapy or those who received the injections seven or more days later than their scheduled injection visit will be assessed and patient characteristics for those individuals that are non-adherent will be described.

Logistic regression will be used to identify factors associated with not starting CAB+RPV LA in those that start lead in, to compare those missing injections where bridging treatment is used, non-adherence and to identify factors associated with discontinuation of CAB+RPV LA (when there are more than 30 endpoints). Potential explanatory variables are listed above. The model building strategy will follow EuroSIDA protocol and include variables significant in univariate analyses as well as *a priori* pre-specified variables of interest.

AIM 3. Assess the clinical effectiveness (i.e. proportion individuals experiencing virologic failure and proportion with undetectable VL) among PLWH who initiate CAB+RPV LA regimen

The study will estimate the proportion with virologic failure during the first six months and at six, twelve and twenty four months after the start of the treatment with injectable regimen. Given that this study involves persons in routine clinical care, and who may not attend clinic appointments at 6, 12 or 24 months, a window of 12 weeks around the date in question will be used for virologic failure. Thus, the proportion with virologic failure during first six months, at 6, 12 or 24 months $\pm$ 6 weeks will be used; and if none is available, the first measurement during first six months, after 6, 12 or 24 months (and at most 6 weeks after the measurement).

Descriptive analyses will compare those with and without virologic failure to assess any differences in baseline characteristics of the two groups. Detailed analysis of additional risk factors will be limited to persons with 6, 12 or 24 months of follow-up. Multivariable logistic regression models will investigate the factors associated with virologic failure at 6 months, 12 months and 24 months after CAB+RPV LA initiation. Potential explanatory variables are listed above. We will also investigate the impact of missed doses and use of oral bridging therapy by using the data collected via the CRF. Multivariate analyses will be performed when > 30 persons on CAB+RPV LA have virologic failure and analyses will be limited to persons with > 6-, 12- or 24-months follow-up. The model building strategy will follow EuroSIDA protocol and include variables significant in univariate analyses as well as *a priori* pre-specified variables of interest. Primary analysis for clinical effectiveness will include individuals on CAB+RPV LA, with VL of <50/copies/mL at regimen initiation. In addition, all the analyses will be conducted separately for individuals on CAB+RPV LA with VL of ≥50 copies/mL at regimen initiation.

Our primary analyses of virologic outcomes will censor follow-up at discontinuation of CAB+RPV LA, last visit or death, whichever occurs first, an on-treatment approach to analysis. Sensitivity analyses will use an intent to treat approach and virologic outcomes will be assessed regardless of regimen discontinuation.

We will perform additional sensitivity analysis limited to those who start CAB+RPV LA with resistance data available, to confirm no present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INSTI class.

AIM 4. Monitor for resistance and next treatment response among individuals who switched off CAB+RPV LA regimen

Monitoring for resistance

Since this is a non-interventional study aiming to capture individual care in real world setting, the study will not mandate resistance testing following discontinuation of the regimen of interest. Health care providers following the local treatment guidelines decide

what laboratory and resistance tests are to be conducted. Data thus generated will be captured and analyzed by the study team.

Descriptive statistics will describe and compare the ARV regimen individuals are switched to after discontinuation of CAB+RPV LA regimen. As resistance testing will not be common, we will describe the characteristics of those with and without resistance testing at virologic failure and again at virologic failure during the 12, 24, 36 and 48 months after switching regimens and use logistic regression to identify factors associated with resistance testing. Where more than 1 resistance test is available during the 12, 24, 36 and 48 months after stopping CAB+RPV LA regimen, cumulative resistance data will be collected and reported.

Study will monitor for resistance at virologic failure and again at virologic failure during the 12, 24, 36 and 48 months following the switch, where resistance data are available. Resistance patterns in those with resistance testing will be summarized. Depending on the number of resistance tests performed and amount of resistance detected, logistic regression will be used to identify factors associated with resistance to CAB+RPV LA. Potential explanatory variables are listed above including missed and delayed doses and use of bridging therapy.

Next treatment response

The study will describe virologic success at 12, 24, 36 and 48 months after discontinuation of CAB+RPV LA regimen, using virologic failure definition as described above. Given that this study involves persons in routine clinical care, and who may not attend clinic appointments every 12 months, a window of 12 weeks around the date in question will be used for virologic testing data. Thus, the proportion with virologic success at 12, 24, 36 and 48 months $\pm$ 6 weeks will be used; and if none is available, the first measurement after 6 or 12 months will be used.

Descriptive analyses will compare those with and without virologic success at 12, 24, 36 and 48 months after stopping the CAB+RPV LA regimen, as well as the next regimen started and time to start the next regimen following discontinuation of the regimen. If numbers allow for further analyses, multivariable logistic regression models will investigate the factors associated with virologic success at 12, 24, 36 and 48 months after switching off CAB+RPV LA regimen. Potential explanatory variables are listed above. Multivariate analyses will be performed when > 30 persons in the relevant treatment group have virologic success and analyses will be limited to persons with > 12 months follow-up. The model building strategy will follow EuroSIDA protocol and include variables significant in univariate analyses as well as *a priori* pre-specified variables of interest.

AIM 5. Evaluate the effectiveness of routine risk minimisation measures for regimen adherence, discontinuation due to incorrect route of administration and off-label use of CAB+RPV LA regimen

The purpose of this aim is to monitor to see if label guidance is adhered to, off label usage, adherence and discontinuation due to incorrect route of administration. This analysis on effectiveness of routine risk minimisation measures will be stratified for each region in the Eurosida cohort.

Analysis of off-label users – regimen combinations other than CAB+RPV LA (b -g in objective 1)

Descriptive Analysis:

As noted in Aim 1 above, analysis will be performed on the off-label users of CAB and/or RPV LA containing regimens. They will be characterized using demographics, clinical, immunologic and virologic characteristics at baseline (i.e. at initiation of regimen) stratified by different regimens noted in groups b-g above.

Adherence and Discontinuation:

Non-adherence to the dosing schedule and discontinuation due to incorrect route of administration will be assessed as described under Aim 2.

Clinical Outcomes:

Analysis will be conducted for the off-label users of CAB and/or RPV LA containing regimens separately to assess clinical outcome similar to description under Aim 3 above.

Descriptive analyses will compare those with and without virologic failure to assess any differences in baseline characteristics of the two groups. Multivariable logistic regression models will investigate the factors associated with virologic failure at 6 months, 12 months and 24 months after regimen initiation. We will also investigate the impact of missed doses and use of oral bridging therapy by using the data collected via the CRF Multivariate analyses will be performed when > 30 persons on the regimen of interest have virologic failure and analyses will be limited to persons with > 6-, 12- or 24-months follow-up.

Depending on the numbers, additional analysis stratifying by VL at regimen initiation (<50 copies/mL and ≥50 copies/mL) will be conducted. We will perform additional sensitivity analysis limited to those who start one of the other regimens with resistance data available, to confirm no present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INSTI class.

Completeness of data

Not all variables within EuroSIDA are complete for all persons; missing data is rarely missing at random from observational cohort studies. Data may be categorized, including a category for missing, persons may be completely excluded with missing data, or imputation can be used. None of these approaches is likely to be unbiased, but with a small number of primary endpoints anticipated, excluding those with missing data would not be a reasonable approach to analysis.

8.7. Quality control and Quality Assurance

Quality procedures are described in the "SOP for electronic data collection v4.1 (Autumn 2020)" (link) which includes the Quality Assurance measures for the data entry, as well as the Quality Control measures for the data entered. The results will be checked and quality assured by the statistics team responsible for the analysis in the first instance. The study results are then checked by a statistician from CHIP familiar with EuroSIDA and cohort studies but not directly involved in the CAB studies. The report will also be checked by the senior statistician and by the administrative team at CHIP for internal consistency and for continuity between successive years reports.

8.8. Limitations of the research methods

This is a study of routine clinical care and reflects treatment practice across the EuroSIDA consortium. Following up of study participants for 4 years after discontinuation of the CAB + RPV LA regimen will increase the potential for loss to follow up as would be expected, in a real world setting.

Not all clinical centres in EuroSIDA use a limit of detection for viremia of 50 copies/ml; 5-10 clinics continue to use an assay with a higher limit of detection. These centres are Eastern European countries where the uptake of CAB and/or RPV LA containing regimens are anticipated to be low. Individuals starting one of the regimens where the viral load as a limit of detection > 50 copies/ml will be excluded from analyses. We will compare those excluded by using a limit of detection for viremia of 50 copies/ml to those included.

Confounding by indication, whereby persons are selected for specific regimens, cannot be ruled out. Resistance testing is not routinely performed in many EuroSIDA clinics and the proportion of persons with resistance results may be low. Resistance testing may be targeted at specific groups of individuals and the results may not be applicable to the whole study population. While EuroSIDA has extensive experience at capturing data via REDCAP and CRFs, collecting this data retrospectively through additional CRFs might reduce data quality. Not all clinics will provide information, despite reminders, and the quality of the data might be lower or missing. Persons with or without data might be different, for example, persons who have died or lost to follow-up might not have data available. The results from this study should be interpreted cautiously, with careful consideration given to the limitations of the observational study design.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

The EuroSIDA cohort study is conducted according to the Declaration of Helsinki in its current version, the requirements of Good Clinical Practice (GCP) as defined in current EU GCP Directive, Human Subject Protection and Data Protection Acts or with the local law and regulation, whichever affords greater protection of human subjects.

Participating clinical sites will adhere to their appropriate local ethics approval procedures as requirement to be involved in the well-established and long-running EuroSIDA observational cohort. If required by the national or local ethical committee the persons enrolled in the study will sign the Individual Informed Consent form before any study related activities begin.

Individuals are informed that data and plasma samples collected will be pseudonymized, stored safely and analysed in accordance with the scientific programme in EuroSIDA to study their HIV infection and associated diseases.

9.2. Subject confidentiality

Principles of medical confidentiality in relation to Study Subjects are maintained in accordance with GCP Guidelines and national regulations.

Individuals in the EuroSIDA study are de-identified and assigned a unique 7-digit PID number at the sites where they are enrolled. The de-coding list is held by the individual site in a safe location.

All study data is marked with this 7-digit PID number. Date of birth is collected as date, month and year of birth, and no unique person identifiers are present on data submitted to the coordinating centre. All data (hardcopies, computerised and samples) at the coordinating centre are stored and protected in accordance with current regulatory laws and approved by The Danish Data Protection Agency (DK: Datatilsynet, approval no. 2012-58-0004, RH-2018-15, I-Suite nr.: 6140)

The Principal Investigators and staff at the EuroSIDA centres will keep any information and data related to the EuroSIDA study provided by the coordinating centre, and all data and records generated in the course of conducting the study, confidential and will not use the information, data, or records for any purpose other than conducting the study.

Every reasonable step will be taken to protect the privacy of individual health information and to prevent misuse of this information. The individual records (paper/digital) may be seen by institutional Review Boards (IRBs) or Ethic Committees (ECs) who review the study to make sure it is ethically acceptable and by research staff and study monitors, and their designees.

Personal data shall not be disclosed to third parties save where this is required directly or indirectly to satisfy the requirements of the Protocol or for the purpose of monitoring or Safety Reporting. The identity of Study Subjects shall not be disclosed to third parties without prior written consent of the Study Subject and then only in accordance with the requirements of the applicable data protection act. Investigators and the EuroSIDA coordinating office shall ensure that only those of their officers and employees directly concerned with carrying out Study related activities are granted access to Confidential Information. All parties undertake not to disclose to any third party Confidential Information save where disclosure is required by a Regulatory Authority or by law, and not to make use of Confidential Information other than in accordance with this Protocol, unless the prior written consent been obtained.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

There is no potential to collect individual level data on serious and non-serious adverse events (AEs), pregnancy exposures, device deficiencies and device related events or incidents related to any ViiV Healthcare product during the conduct of this research, as the minimum criteria needed to report AEs, pregnancy exposures, and incidents are not collected. Specifically, the data are insufficient to establish attribution between a potential safety event and an individual using a ViiV Healthcare product as the study design is to analyse deidentified, secondary data collected from individual medical records. Therefore, a study specific pharmacovigilance plan will not be developed.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Milestones

This study-specific protocol will be submitted by 31 December 2020 for the EMA's review and endorsement. The study will start only after the protocol is approved by the EMA, and CAB+RPV LA is registered and commercially available in the relevant countries and is expected to continue through 2026 or later, for a total of five years of study period. Annual interim reports with cumulative data will be submitted and a final report is expected to be submitted in March 2027.

11.2. Target Audience

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

11.3. Study reporting and publications

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

1. Laut K, Kirk O, Rockstroh J, et al. The EuroSIDA study: 25 years of scientific achievements. HIV Med 2020;21(2):71-83. doi: 10.1111/hiv.12810 [published Online First: 2019/10/28]
2. Kjaer J, Ledergerber B. HIV cohort collaborations: proposal for harmonization of data exchange. Antivir Ther 2004;9(4):631-33.

3. Mocroft A, Lundgren J, Gerstoft J, et al. Clinical Outcomes in Persons Coinfected With Human Immunodeficiency Virus and Hepatitis C Virus: Impact of Hepatitis C Virus Treatment. Clin Infect Dis 2019 doi: 10.1093/cid/ciz601 [published Online First: 2019/09/11]
4. Peters L, Mocroft A, Grint D, et al. Uptake of tenofovir-based antiretroviral therapy among HIV-HBV-coinfected patients in the EuroSIDA study. Antivir Ther 2018;23(5):405-13. doi: 10.3851/IMP3218 [doi]
5. Mocroft A, Kirk O, Reiss P, et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. AIDS 2010;24(11):1667-78.

ANNEX 1. CASE REPORT FORM

CRF completed by: text field

CRF completed date: Year/month/day

(These two items should be included for each follow up injection and hepatotoxicity form)

Data entry instructions

Standard text reg. comma vs. full stop, test not performed, unknown dates

Link to document about data entry, contact for questions etc.

Patient ID: xxx-xxxx

Date of birth: Year/month/day

HIV subtype

Has an HIV subtype test been performed prior to initiation of long-acting antiretroviral therapy yes/no

(If yes)

Date of latest HIV subtype test prior to initiation of long-acting antiretroviral therapy Year/month/day

Subtype drop down menu with subtypes

Oral lead-in antiretroviral therapy

Drug 1 (drop down menu)

1) Cabotegravir
2) Rilpivirine

Start date Year/month/day

Stop date Year/month/day

Was oral lead-in antiretroviral therapy stopped because the patient has initiated long-acting antiretroviral therapy Yes/no

If yes, Treatment section below will open

If no, following will open

Reason for discontinuation Drop down menu with all reasons listed in table 2 in the protocol

Drug 2 etc

(This section of the form refers to the first LAI)

After the first injection with long-acting antiretroviral therapy (LAI), the CRF will capture information about the following scenario's as set out below;

1) The patient receives LAI as planned

2) The planned LAI is not given, and the patient **starts bridging therapy**. After end of bridging therapy there are three possibilities:
    a. LAI is resumed in which case we want to know date of injection, dosage etc
    b. A decision to stop LAI has been made in which case we want to know why LAI was stopped
    c. Switched to a different ART regimen

3) The planned LAI is not given, and the patient **does not start bridging therapy**. We want to know if the patient later restarts LAI.
    a. LAI is resumed in which case we want to know date of injection, dosage etc
    b. A decision to stop LAI has been made in which case we want to know why LAI was stopped
    c. Switched to a different ART regimen

The CRF will only capture the first exposure to LAI. The second injection for the two-month schedule is given one month after the first injection and hence we will allow three months after the first injection to see if the regimen was resumed (≤2 months) or re-initiated (>2 months). In

case of resumption of LAI after missed second injection in two months or less, we will still consider it first exposure.

Similarly, the third injection (and injections thereafter) for the two-month schedule is given two months after the second injection and hence we will allow four months after the second injection to see if the regimen was resumed (≤3 months) or re-initiated (>3 months). In case of resumption of LAI after missed third injection in three months or less, we still consider it first exposure.

Treatment with long-acting antiretroviral therapy

Which long-acting antiretroviral drugs have been initiated? (drop down menu)

1) long acting cabotegravir + long acting rilpivirine

2) long acting cabotegravir without rilpivirine

3) long acting rilpivirine without cabotegravir

Dosage: 400/600 mg (CAB) / 600/900 mg (RPV) (drop down menu)

Date of first injection: Year/month/day

Intended dosing schedule of long-acting antiretroviral therapy Monthly/Every 2 Month

HIV resistance testing (only pops up for the first injection and if CAB + RPV has been selected)

Has a HIV resistance test been performed prior to initiation of long-acting cabotegravir + rilpivirine yes/no

If yes

Date of latest most recent resistance test prior to initiation of long-acting antiretroviral therapy Year/month/day

Method used drop down menu

Please upload a copy of the resistance test report (result will be based on central review)

(After completion of date of first injection, a new section will open for second injection with target date one month after the first injection. All the questions below refer to subsequent injections after the first)

Has the patient received the next planned injection with long-acting antiretroviral drugs
yes/no

If yes, **Which long-acting antiretroviral drugs were given?** (drop down menu)

1) long acting cabotegravir + long acting rilpivirine

2) long acting cabotegravir without rilpivirine

3) long acting rilpivirine without cabotegravir

Dosage: 400/600 mg (CAB) / 600/900 mg (RPV) (drop down menu)

Date of injection: Year/month/day

Intended dosing schedule of long-acting antiretroviral therapy Monthly/Every 2 Month

(if the patient switches from monthly to two-monthly injections or vice versa, a new question pops up)

Reason for switching to monthly (or 2 monthly) injection schedule (drop down menu)

1. Convenience
2. To reduce cost
3. To reduce side effects
4. Personal reasons
5. Other (+ text field)

(After completion of date of second injection, a new section will open for third injection with target date two month/3 months [for monthly and 2 monthly schedules, respectively] after the first injection. As long as the patient receives injections as scheduled, the target date for the next injection is determined by the start date + 1 month/2 months ± 7 days for each injection depending on schedule)

(All injections until 24 months+ six weeks after initiation of LAI will be collected)

If no to question whether planned injection has been given, following question will appear:

<table>
<tr><td colspan="6">Has the patient started bridging therapy?</td></tr>
<tr><td colspan="4">YES</td><td colspan="2">NO</td></tr>
<tr><td colspan="4">If yes, new question will show:
Reason for starting bridging therapy (LAI drugs out of stock, personal decision, inability to come for the injection, injection site adverse effect, other + text field)</td><td colspan="2"></td></tr>
<tr><td colspan="4">Start date:
Stop date:</td><td colspan="2">Has the patient later restarted long-acting antiretroviral therapy?</td></tr>
<tr><td colspan="4">After a stop date has been entered, new question will show:</td><td colspan="2"></td></tr>
<tr><td colspan="4">Has the patient restarted long-acting antiretroviral therapy?</td><td rowspan="2">YES</td><td rowspan="2">NO</td></tr>
<tr><td colspan="3">YES</td><td>NO</td></tr>
<tr><td colspan="3">Which long-acting drugs have been given?</td><td rowspan="8">Reasons for discontinuation (drop down menu with all reasons in table 3 in the protocol)

*If death – please complete CoDe form
*If liver, other or unknown causes – please complete hepatotoxicity form</td><td colspan="2">Which long-acting drugs have been given?</td><td rowspan="8">Reasons for discontinuation

*If death – please complete CoDe form
*If liver, other or unknown causes – please complete hepatotoxicity form</td></tr>
<tr><td>long acting cabotegravir + long acting rilpivirine</td><td>2) long acting cabotegravir without rilpivirine</td><td>3) long acting rilpivirine without cabotegravir</td><td>long acting cabotegravir + long acting rilpivirine</td><td>2) long acting cabotegravir without rilpivirine</td><td>3) long acting rilpivirine without cabotegravir</td></tr>
<tr><td colspan="3">Dosage: 400/600 mg (CAB) / 600/900 mg (RPV) (drop down menu)</td><td colspan="3">Dosage: 400/600 mg (CAB) / 600/900 mg (RPV) (drop down menu)</td></tr>
<tr><td colspan="3">Date of injection:</td><td colspan="3">Date of injection:</td></tr>
<tr><td colspan="3">Intended schedule:</td><td colspan="3">Intended schedule:</td></tr>
<tr><td colspan="2">Monthly</td><td>Every 2 Month</td><td colspan="2">Monthly</td><td>Every 2 Month</td></tr>
</table>

(All those reported CAB + RPV discontinuations due to virological failure (reason 1, 1.1, 1.2) will prompt collection of resistance test results. A reminder will be sent after 1 and 2 years of follow up after failure. In addition to these specific reasons prompting collection of HIV resistance testing data, we will also perform checks for viral load>limit of detection to identify people with viral failure)

HIV resistance testing after virological failure of long-acting cabotegravir + rilpivirine

CRF completed by: text field

CRF completed date: Year/month/day

Resistance testing:

Has an HIV resistance test been performed after long-acting cabotegravir + rilpivirine have been discontinued? Yes/no

If yes, **Please enter all resistance tests performed after discontinuation of cabotegravir + rilpivirine**

Test 1 Year/month/day

Method used drop down menu

Please upload a copy of the resistance test report (result will be based on central review)

Test 2 Year/month/day

Method used drop down menu

Please upload a copy of the resistance test report (result will be based on central review)

Etc.

EuroSIDA hepatotoxicity event form

(The form is to be completed for all who stop LAI CAB or DTG/LAM or DTG/RPV due to liver related events (reason 5.2), any possible liver toxicity (reason 5 and 5.1), other causes (reason 98 above) or unknown (reason 99). Start and stop dates for DTG/LAM and DTG/RPV and reason for discontinuation will only be collected on the general follow up form.)

CRF completed by: text field

CRF completed date: Year/month/day

Data entry instructions

Standard text reg. comma vs. full stop, test not performed, unknown dates

Link to document about data entry, contact for questions etc.

Patient ID: xxx-xxxx

Date of birth: Year/month/day

Antiretroviral treatment

Which drug was discontinued?

1) long acting cabotegravir + long acting rilpivirine
2) long acting cabotegravir + any other antiretroviral regimen
3) long acting cabotegravir
4) Dolutegravir/lamivudine (two-drug regimen)

5) Dolutegravir/rilpivirine (two-drug regimen)

Date of first injection/tablet: Year/month/day

Date of last injection/tablet: Year/month/day

Hepatic laboratory values

For all laboratory values, please enter all results within three months prior to and one month after latest date of cabotegravir injection (with or without rilpivirine) or date of stopping DTG/LAM and DTG/RPV

ALT (alanine aminotransferase)

ALT measured? Yes/no

Date of measurement: Year/month/day

Unit: 1) U/L (IU/L)

2) Other (if Other is selected there will be prompt to write unit)

Value:

Upper limit of normal:

AST (aspartate aminotransferase)

AST measured? Yes/no

Date of measurement: Year/month/day

Unit: 1) U/L (IU/L)

2) other

Value:

Upper limit of normal:

ALP (alkaline phosphatase)

ALP measured?	Yes/no
Date of measurement:	Year/month/day
Unit:	1) g/dL
	2) U/L (IU/L)
	2) other
Value:	
Upper limit of normal:	

Total bilirubin

Total bilirubin measured?	Yes/no
Date of measurement:	Year/month/day
Unit:	1) µmol/L
	2) mmol/L
	3) other
Value:	
Upper limit of normal:	

Albumin

Albumin measured?	Yes/no
Date of measurement:	Year/month/day
Unit:	1) g/dL
	2) g/L
	3) other

Value:

Upper limit of normal:

INR (International Normalized Ratio)

INR measured?	Yes/no
Date of measurement:	Year/month/day
Value:	

Prothrombin time (PT)

PT measured?	Yes/no
Date of measurement	Year/month/day
Value:	Seconds

Lipase

Was lipase measured?	Yes/no
Date of measurement	Year/month/day
Value:	U/L

Clinical symptoms and findings in relation to treatment with long-acting cabotegravir (with or without rilpivirine) or oral dolutegravir/lamivudine or dolutegravir/rilpivirine

Has pancreatitis been diagnosed?	Yes/no
Has ascites been diagnosed?	Yes/no
Date of first diagnosis:	Year/month/day

(If yes, a reminder to "Please remember to complete a RESPOND event form" pops up)

Has hepatic encephalopathy been diagnosed? Yes/no

Date of first diagnosis: Year/month/day

(If yes, a reminder to "Please remember to complete a RESPOND event form" pops up)

Did the patient undergo liver transplantation due to hepatoxicity? Yes/no

Date of liver transplantation: Year/month/day

(If yes, a reminder to "Please remember to complete a RESPOND event form" pops up)

Did the patient die due to hepatoxicity? Yes/no

Date of death: Year/month/day

(If yes, a reminder to "Please remember to complete a CoDe event form" pops up)

Causal relationship

Please evaluate the causal relationship of the laboratory results and symptoms recorded in this form with long acting cabotegravir treatment:

1) Not related
2) Reasonable possibility of relationship
3) Unknown

If the laboratory results and symptoms are not believed to be causally related to long acting cabotegravir treatment, please provide alternative explanation: (text field)

Source documentation

Source documentation might in some cases be relevant. You can either fax or upload the documents.

Fax number: +PPD

Upload files:

NOTE: Please ensure that any identifying information is unreadable. We will delete any uploaded documents that have readable identifying information.

ANNEX 2. ENCePP CHECKLIST FOR STUDY PROTOCOLS

Study title: Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in People living with HIV (PLWH) initiating ARV regimen CAB+RPV LA in Collaboration with EuroSIDA

EU PAS Register® number: Study not registered yet
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	5
1.1.3 Progress report(s)	☒	☐	☐	5
1.1.4 Interim report(s)	☒	☐	☐	5
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Study will be registered with EU PAS Register after protocol is approved

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	6
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.2
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Comments:

The purpose of this prospective observational cohort study is to better understand the individual population receiving CAB and/or RPV LA containing regimens in routine clinical practice, usage patterns, adherence, post marketing clinical effectiveness and monitor for resistance among virologic failures for whom data on resistance testing are available. Hence there are no specific hypotheses to be tested.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.6
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	8.6
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	8.2
	4.2.2 Age and sex	☒	☐	☐	8.2
	4.2.3 Country of origin	☒	☐	☐	8.2
	4.2.4 Disease/indication	☒	☐	☐	8.2
	4.2.5 Duration of follow-up	☒	☐	☐	8.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☒	☐	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	

Comments:

The purpose of this study is to better understand the CAB and/or RPV LA containing regimens utilisation in real-world clinical setting, specifically usage patterns, adherence, post marketing clinical effectiveness and monitor for resistance among virologic failures for whom data on resistance testing are available. Hence exposure is not categorised or comparators are not utilized.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

The purpose of this study is to better understand the CAB and/or RPV LA containing regimens utilisation in real-world clinical setting, specifically treatment

discontinuation, post marketing clinical effectiveness and resistance testing among virologic failures for whom data on resistance testing are available and we anticipate small number of primary endpoints. Hence validity of outcome is not measured or specific outcomes relevant for HTA are not utilized.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	8.3.3
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	8.3.3
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.3.3

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.3.3

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.2 & 8.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.2 & 8.3.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.2 & 8.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.2 & 8.3.1

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.2 & 8.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.2 & 8.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.2
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.6
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	8.4
10.3 Are descriptive analyses included?	☒	☐	☐	8.6
10.4 Are stratified analyses included?	☒	☐	☐	8.6
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	8.6
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.6
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.6

Comments:

Sensitivity analyses will be conducted as appropriate

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.5 & 9.2
11.2 Are methods of quality assurance described?	☒	☐	☐	8.7
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	8.7

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.8
12.1.2 Information bias?	☒	☐	☐	8.8
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	8.8
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.4

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.1
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	9.1
13.3 Have data protection requirements been described?	☒	☐	☐	9.2

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11.3

Comments:

Name of the main author of the protocol: PPD.

Date: 01/August/2021

Signature: _____ PPD _____