TITLE PAGE

Information Type: ViiV Healthcare Non-Interventional Study Protocol

Title:	A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among People with HIV, Initiating Cabotegravir + Rilpivirine regimens

Compound Number:	GSK1265744
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Subject: Cabotegravir, long acting ARV, hepatotoxicity

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1. LIST OF ABBREVIATIONS

3TC	Lamivudine
AE	Adverse Event
ADE	AIDS-defining Event
AIDS	Acquired Immunodeficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ART	Antiretroviral Therapy
ARV	Anti-retroviral
AST	Aspartate Aminotransferase
BCG	Bacillus Calmette- Guérin
BILI	Bilirubin
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
DAA	Direct-acting Antiviral
DEXA	Dual-energy X-ray Absorptiometry
DILI	Drug Induced Liver Injury
DILIN	Drug-Induced Liver Injury Network
DNA	Deoxyribonucleic Acid
DR	Drug Regimens
DTG	Dolutegravir
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ERC	Endpoint Review Committee
ESLD	End Stage Liver Disease
EU	European Union
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA1c	Haemoglobin A1c
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HICDEP	HIV Collaboration Data Exchange Protocol
HIV-1	Human Immunodeficiency Virus type-1
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INR	International Normalized Ratio

INI	Integrase Inhibitor
INSTI	Integrase Strand Transfer Inhibitor
LA	Long Acting
LAI	Long Acting Injectable
LDL	Low Density Lipoprotein
LOD	Limit of Detection
LCT	Liver Chemistry Test
MAH	Market Authorization Holder
MI	Myocardial Infarction
MTCT	Mother to Child Transmission
NADM	Non-AIDS Defining Malignancies
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
OI	Opportunistic Infection
PASS	Post Authorization Safety Study
PCR	Polymerase Chain Reaction
PLWH	People Living With HIV
PMTCT	Prevention of Mother to Child Transmission
PT	Prothrombin Time
PYFU	Person-years of Follow-up
QA	Quality Assurance
REDCap	Research Electronic Data Capture
RNA	Ribonucleic Acid
RPV	Rilpivirine
RUCAM	Roussel Uclaf Causality Assessment Model
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SGOT	Serum Glutamic Oxaloacetic Transaminase (also called AST)
SGPT	Serum Glutamic Pyruvic Transaminase (also called ALT)
SmPC	Summary of Product characteristics
SOP	Standard Operating Procedure
STI	Structured Treatment Interruption
TB	Tuberculosis
ULN	Upper Limit of Normal
VL	Viral Load

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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2. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE

MARKETING AUTHORISATION HOLDER

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Vani Vannappagari Global Head, Epidemiology and Real World Evidence	**Date**
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Jens-Ulrich Stegmann 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: Dr PPD

Investigator Signature

Date

3. ABSTRACT

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 treatment (ART) regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INSTI class. Mild to moderate hepatoxicity, presenting as serum transaminase elevations, has been reported in a limited number of individuals receiving CAB during clinical development program, which resolved on cessation of drug treatment.

The market authorization holder (MAH) proposes a five-year long post authorization safety study (PASS) to monitor for hepatotoxicity and discontinuation of the regimen due to liver- related adverse events (AEs) following initiation of CAB+RPV regimen in comparison to two DTG based 2 drug regimens (2DR), DTG+RPV and DTG+3TC. Following the initiation of CAB+RPV, DTG+RPV or DTG+3TC among people living with HIV (PLWH), the study will aim to:

1. Characterize the rates and risks of hepatotoxicity by:
    - estimating the incidence of alanine aminotransferase (ALT) elevations and risk factors for elevations
    - estimating the incidence of cases of combined ALT and total bilirubin (BILI) elevations and risk factors for elevations

2. Estimate the number of individuals discontinuing CAB+RPV, DTG+RPV or DTG+3TC regimens due to any reason and specifically discontinuations due to liver-related adverse events

This will be a prospective observational cohort study conducted through collaboration with EuroSIDA, a well-established, prospective observational cohort study from 100 hospitals in 34 European countries, and Israel and Argentina. The EuroSIDA study collects a comprehensive range of data including demographics, infection related laboratory data, other laboratory data, antiretroviral (ARV) start and stop dates and reasons for discontinuation, paraclinical and clinical events.

Descriptive analyses will summarize the individuals exposed to each of the three proposed ART regimens. Incidence rates of discontinuation of the regimens and hepatotoxicity will be calculated and where sufficient events accrue multivariate regression will investigate factors associated with the endpoint of interest.

4. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
v1.0	June 2021	8.1, 8.2, 8.3 and 8.6	Study design, study population, variable definitions and data analysis	Address EMA comments
v2.0	October 2021	8.3 and 8.6	Variable definitions and data analysis	Address EMA comments

5. MILESTONES

Milestone	Planned date
Draft Protocol Submission	Dec 31, 2020
Register with EU PAS Register	Estimated – Nov, 2021
Study Start (Protocol Approval)	Estimated - Nov, 2021
1st Interim Report	Estimated - Draft - Dec, 2022 Estimated - Final - Mar, 2023
2nd Interim Report	Estimated - Draft - Dec, 2023 Estimated - Final - Mar, 2024
3rd Interim Report	Estimated - Draft - Dec, 2024 Estimated - Final - Mar, 2025
4th Interim Report	Estimated - Draft - Dec, 2025 Estimated - Final - Mar, 2026
Data Collection Completion	Estimated - Jun, 2026 or 5 years following commercial availability of CAB
Final Report	Estimated- Mar, 2027

6. BACKGROUND AND RATIONALE

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 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 number of cases of suspected drug induced liver injury (DILI) is very low in the context of overall product exposure and no severe cases have been identified. In Phase I, II, III and IIIb clinical studies, six participants exposed to oral CAB (60 mg n=2; 30 mg n=4) had suspected DILI, one of whom was a healthy volunteer. No participant receiving CAB LA has developed suspected DILI. Mild to moderate hepatoxicity, presenting as serum transaminase elevations, has been reported in a limited number of individuals receiving CAB during clinical development program, which resolved on cessation of drug treatment.

Since the risk for DILI and elevated transaminases is very low, it is considered manageable through routine monitoring of liver chemistry tests (LCT) and discontinuation of CAB treatment, where necessary. Healthcare providers should monitor liver chemistries and discontinue treatment with CAB if hepatotoxicity is suspected.

The market authorization holder (MAH) proposes a five-year long post authorization safety study (PASS) to be conducted in a real-world clinical setting. This prospective observational cohort study will monitor for hepatotoxicity and discontinuation of the regimen due to liver-related adverse events (AEs) following initiation of CAB+RPV including the month of oral lead in, followed by injectable long acting CAB. Findings will be compared to two other integrase based 2 drug regimen (DR) without LA injectable, DTG+RPV and DTG+3TC.

6.2. Rationale

Uncommon cases of DILI with oral CAB were observed during the clinical trials program for CAB and RPV. During Phase III studies although hepatotoxicity was observed at higher rates with CAB LA compared to the oral comparator ART, the difference was largely driven by acute viral hepatitis which occurred more frequently in subjects receiving CAB LA. Hepatotoxicity has been reported in a limited number of individuals receiving CAB with or without known pre-existing hepatic disease. A five-year long study, in a real-world clinical setting to monitor for hepatotoxicity and discontinuation of the regimen due to liver-related AEs will further quantify the risk of hepatotoxicity and to possibly determine associated risk factors.

7. RESEARCH QUESTION AND OBJECTIVE(S)

Study Objectives:

This study will focus on 3 separate treatment groups:

Group A. Treatment experienced individuals initiating CAB+RPV
Group B. Treatment experienced individuals initiating DTG+RPV
Group C. Treatment experienced individuals initiating DTG+3TC

Following the initiation of one of these regimens among treatment experienced PLWH, the study will aim to:

Primary objectives:

1. Characterize the rates and risks of hepatotoxicity by:
    - estimating the incidence of alanine aminotransferase (ALT) elevations and risk factors for elevations
    - estimating the incidence of cases of combined ALT and total bilirubin (BILI) elevations and risk factors for elevations

2. Estimate the number of individuals discontinuing the regimen due to any reason and specifically discontinuations due to liver-related adverse events

Secondary objective:

1. Stratified analysis for primary objectives 1 and 2 by HIV mono-infection and HIV and hepatitis B and/or hepatitis C co-infection

For primary objectives 1 and 2 and secondary objective 1, event rates and risk factors among individuals on CAB + RPV (Group A) will be compared with those from treatment experienced individuals initiating DTG based 2 DR (Group B & C) regimens.

8. RESEARCH METHODS

8.1. Study Design

A prospective 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. In addition to ALT and BILI, the study will also assess other LCTs including changes to aspartate aminotransferase (AST), Alkaline phosphatase (ALP), prothrombin time (PT), Albumin and lipase levels where available.

This safety study will be conducted through collaboration with EuroSIDA, a well-established, prospective observational cohort study of more than 13,000 PLWH under active follow up from 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 and RPV oral and LA formulations, contemporary regimen and local guideline or recommendations. The study protocol will be implemented by the EuroSIDA coordinating center.

8.2. Study Population and Setting

Study Population: The study population will include treatment experienced PLWH over the age of 18 years, who are new users of CAB+RPV, DTG+RPV or DTG+3TC regimens from EuroSIDA clinical sites after the date CAB+RPV is licensed for use across Europe.

EuroSIDA Cohort description: The EuroSIDA cohort was initiated in 1994 and is a prospective observational cohort study of more than 23,000 PLWH from 100 hospitals in 34 European countries, and Israel and Argentina. Currently, still over 13,000 individuals from 37 countries are under active follow-up. The main objective of the cohort is to assess the impact of ARV drugs on the long-term outcome of the PLWH in Europe[1].

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[2]; further information is available at https://www.hicdep.org/. For each person, the date of starting and stopping each ARV drug is recorded, as is the use of drugs for prophylaxis against opportunistic infections. 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
Israel	Austria	Sweden	Romania	Russia
Argentina	Germany	Norway	Serbia	Georgia
		Finland	Slovenia	
		Iceland	Croatia	
			Albania	
			North Macedonia	

Data Collection: Following the approval and commercial availability of CAB, the study will collect prospective data on PLWH initiating CAB+RPV, DTG+RPV or DTG+3TC regimen including the month of oral lead in for CAB+RPV, followed by injectable LA CAB+RPV, 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.

Monitoring for liver chemistry abnormalities will include the following, with a focus on alanine aminotransferase elevations and total bilirubin elevations, with a particular attention to the time of occurrence in relation to regimen initiation:

A. Alanine aminotransferase (ALT) elevations (ALT is also called serum glutamic pyruvic transaminase (SGPT))
B. Aspartate aminotransferase (AST) elevations (AST is also called serum glutamic oxaloacetic transaminase (SGOT))
C. Total bilirubin elevations (BILI)
D. Alkaline phosphatase (ALP) elevations where available
E. Albumin
F. Prothrombin time (PT) where available
G. Lipase levels where available

8.3. 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 scans, 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

The study will aim for enhanced data collection using an additional CRF to collect data on ALP and PT, where available.

8.3.1. Definitions of key variables

Virologic variables at regimen initiation

- HIV VL at initiation of CAB+RPV or DTG based 2 DR (DTG+RPV or DTG+3TC) (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 <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+RPV or DTG based 2 DR (DTG+RPV or DTG+3TC) (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+RPV or DTG based 2 DR (DTG+RPV or DTG+3TC)

Clinical variables at regimen initiation

- History of previous use of integrase inhibitor-based or NNRTI-based regimen
- History of previous antiretroviral exposure
- History of previous virologic failure and immune suppression
- Body Mass Index (BMI)
- 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 in previous EuroSIDA work, key references for definitions are included)
  - HCV co-infection[3]
  - HBV co-infection
  - End Stage Liver Disease (ESLD) including hepatocellular carcinoma, ascites, hepatorenal syndrome, grade III/IV hepatic encephalopathy, unspecified liver decompensation, oesophageal variceal bleeding, spontaneous bacterial peritonitis, liver transplantation[4]
  - Cardiovascular Disease (CVD) including myocardial infarction, stroke, invasive coronary procedure[5]
  - Chronic Kidney Disease (CKD) (confirmed [>3 months apart] eGFR <60/ml/min/1.73m^2 in persons with eGFR at regimen initiation ≥60/ml/min/1.73m^2 or confirmed 25% decline in eGFR in persons with eGFR at regimen initiation < 60/ml/min/1.73m^2)
  - Non-AIDS defining malignancies (NADM)[5]

8.3.2. Exposure definitions

All new users of CAB+RPV or DTG based 2 DR (DTG+RPV or DTG+3TC) will be included in this study based on their first exposure to one of the regimens of interest after the date when CAB+RPV becomes commercially available

The study period for CAB+RPV will include the month-long oral lead in, followed by injectable LA regimen use and for DTG+RPV and DTG+3TC will commence when the regimen is started. All individuals will be followed until the end of the study or discontinuation for those on DTG+RPV and DTG+3TC regimens; and an additional 6 months, for those who discontinue CAB+RPV LA regimen. This allows for capturing events comprehensively, during the time that the long acting ARVs could have potential effect. In addition, patients with a diagnosis of DILI, or ALT>5×ULN, or ALP>2×ULN, or ALT > 3×ULN and BILI>2×ULN will be followed for six months regardless of their discontinuation status.

8.3.3. Outcome definitions

1. **Hepatotoxicity:** elevations of ALT, BILI and/or ALP will be tabulated according to DILI severity grade as below.

2. **DILI case definition**:
   Determination of DILI will be based on ALT, BILI and ALP in in addition to all relevant clinical information based on Aithal et al 2011[6]. An independent adjudication committee, The Endpoint Review Committee (ERC), will review all potential and suspected cases of hepatotoxicity for drug attribution and determination of DILI (see section 4 Case Ascertainment below).

Clinical chemistry criteria for DILI: Any one of the following:

- More than or equal to fivefold elevation above the upper limit of normal (ULN) for ALT
- 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)
- More than or equal to threefold elevation in ALT concentration and simultaneous (within +/- 2 weeks) elevation of BILI concentration exceeding 2× ULN

If the person has had previous liver injury and hence abnormal LCT prior to starting treatment with CAB+RPV, DTG+RPV or DTG+3TC, 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 highest measured values for each of the biochemical parameters during the course of DILI.

DILI severity index[6] based on DILI biochemical criteria: Category (1-4) Severity (Mild –Fatal/transplant) and Description are as follows:

A. Mild: $^{ALT}/_{ALP}$ concentration reaching criteria for DILI but BILI concentration <2× upper limit of normal (ULN)
B. Moderate: Elevated $^{ALT}/_{ALP}$ concentration reaching criteria for DILI and BILI concentration ≥2× ULN, or symptomatic hepatitis
C. Severe: Elevated $^{ALT}/_{ALP}$ concentration reaching criteria for DILI, BILI concentration ≥2× ULN, and one of the following:
    a. International normalized ratio ≥1.5
    b. Ascites and/or encephalopathy, disease duration <26 weeks, and absence of underlying cirrhosis
    c. Other organ failure considered to be due to DILI
D. Fatal or transplantation: Death or transplantation due to DILI

3. Regimen discontinuations: Discontinuation of one of the regimens of interest (CAB+RPV, DTG+RPV or DTG+3TC) for any reason will be captured & summarized and discontinuations due to liver-related AEs will be tabulated separately and reported. Injection site reaction and injection fatigue will be added to the list of reasons for discontinuation included in the standard follow-up data collection form (Table 3).

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).

Table 3. Regimen Discontinuation Reasons in EuroSIDA

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

Code	Reason for Stopping Treatment
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
	Injection fatigue (not related to safety)
	Injection Site Reaction
99	Unknown

4. Case Ascertainment: All discontinuations will be reviewed for potential liver-related toxicity. All the reported discontinuations due to liver related events (reason 5.2 above), any possible liver toxicity (reason 5 and 5.1), other causes (reason 98 above) or unknown (reason 99) will prompt completion of a CRF requesting more detailed information. Information on LCTs will specifically be collected for these individuals. For all liver-related discontinuations and toxicity events, acute hepatitis due to infectious agents and other causes will be ruled out. An independent adjudication committee will be established at the start of the study to review and validate potential discontinuations due to liver-related AEs and to ensure minimization of misclassification. Potential DILI cases will

also be reviewed by the committee. History of previous liver injury and abnormal LCT at any time prior to starting CAB+RPV, DTG+RPV or DTG+3TC will be highlighted to the independent case review committee. Additionally, all ALT and BILI elevations reported will be assessed among those who discontinue for potential liver-related toxicity.

5. Endpoint Review Committee for DILI Assessment: The endpoint review committee (ERC) will be a scientific committee independent of the EuroSIDA Steering Committee and of study sponsors. The ERC will always have, as voting members, at least three experienced HIV clinicians with no potential conflict of interest of which at least one is a hepatologist.

The study will be using DILIN[6] for DILI assessment. DILIN's expert approach is more consistent in our experience with post marketing safety studies and thus our preference to not use RUCAM[9].

The independent review outcome is documented by each reviewer on a review form that is returned to the ERC coordinator. If needed the reviewers can request additional information for a conclusive review. However, each reviewer must provide an initial outcome based on the information available at the time of the initial review of the event. All reviewers must agree on the classification of an event. Disagreements among reviewers are adjudicated. The ERC coordinator sends to the reviewers the results of the initial review and all reviewers' comments, and the reviewers communicate by e-mail until consensus is reached. If the reviewers still disagree and consensus cannot be reached, classification of the event will be decided by majority vote.

The EuroSIDA Coordinating Office appoints an ERC Coordinator to manage the ERC process. An experienced physician from the coordination office will join the ERC group as non-voting member and together with the ERC coordinator will assist assessing the adequacy of the submitted event source documentation. The EuroSIDA Steering Committee approves the ERC members and appoints one of them the chair.

In addition, information on cases of elevated lipase levels, and diagnosis of pancreatitis will be provided to the independent adjudication of ERC for determination of clinical relevance of elevated lipase levels.

8.3.4. 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
- Race
- Geographic region
- Date of ART initiation

- Date CAB+RPV or DTG based 2 DR (DTG+RPV or DTG+3TC) started

Virologic variables at regimen initiation

- HIV VL at initiation of CAB+RPV or DTG based 2 DR (DTG+RPV or DTG+3TC) (and in the 12 months prior to regimen start)

Immunologic variables at regimen initiation

- CD4 cell count at initiation of CAB+RPV or DTG based 2 DR (DTG+RPV or DTG+3TC) (and in the 12 months prior to regimen start)
- CD4 nadir prior to initiation of CAB+RPV or DTG based 2 DR (DTG+RPV or DTG+3TC)

Clinical variables at regimen initiation

- History of previous use of integrase inhibitor-based or NNRTI-based regimen
- History of previous antiretroviral exposure
- History of previous virologic failure and immune suppression
- Body Mass Index (BMI)
- AIDS-defining Events (ADE)
- Concurrent medications
- Comorbidities (all defined as in previous EuroSIDA published analyses)

8.4. Study size

The uptake of CAB+RPV across Europe is unknown as is the likely rates of discontinuation and therefore Table 4 represents different possible scenarios under the conservative assumption that loss to follow-up is 10%[1]. The study is not designed to test hypothesis but rather monitor frequency of occurrence and discontinuation due to hepatotoxicity. In preliminary feasibility estimates of the size of the comparator groups, approximately 50 persons/year have started either DTG+RPV or DTG+3TC in each of 2018 and 2019.

Scenario A: 100 individuals start a CAB regimen per year, 10% discontinue per year for any reason and 1% discontinue per year due to hepatotoxicity.

Scenario B: 100 individuals start CAB regimen in year 1 of the project, increasing to 1000 by year 3 and then decreasing to 500 by year 5, 10% discontinue for any reason and 0.2% discontinue due to hepatotoxicity.

Scenario C: 100 individuals start CAB regimen in year 1 of the project, increasing to 1000 by year 5, 20% discontinue for any reason and 0.2% discontinue due to hepatotoxicity.

Table 4. Possible uptake of CAB and discontinuations

	Year of study				
	1	**2**	**3**	**4**	**5**
Scenario A					
N starting CAB	100	100	100	100	100
N under FU at end of year	80	144	196	237	270
Cumulative N discontinued	9	25	47	74	104
Cumulative N hepatotoxicity	1	3	5	7	10
Scenario B					
N starting CAB	100	500	1000	750	500
N under FU at end of year	81	469	1188	1566	1670
Cumulative N discontinued	9	61	194	368	554
Cumulative N hepatotoxicity	0	1	4	7	11
Scenario C					
N starting CAB	100	250	500	750	1000
N under FU at end of year	81	267	620	1107	1703
Cumulative N discontinued	9	39	108	231	421
Cumulative N hepatotoxicity	0	1	2	5	8

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 on all potential DILI events.

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. 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 and enrolment information to the coordinating centre in October-December each calendar year. All relevant information for each individual site 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

Descriptive: Baseline (i.e. at regimen initiation) characteristics of PLWH initiating CAB+RPV or DTG+RPV or DTG+3TC regimen will be described according to the variables listed above. Exposure to previous ARVs will be summarized. Characteristics will be stratified according to CAB+RPV or DTG+RPV or DTG+3TC regimen started and presented separately for those with and without pre-existing liver disease (defined as F4 liver fibrosis) as well by co-infection with hepatitis B (HBsAg positive) and/or C (HCV RNA positive).

Discontinuations: The number and percentage of individuals discontinuing CAB+RPV or DTG+RPV or DTG+3TC regimen for any reason will be summarized and discontinuations due to liver-related AEs will be tabulated separately. For LA, the date of discontinuation will be defined as the last date in the window for the next injection. The incidence of overall discontinuations will be summarized, with follow-up from date of regimen start to discontinuation, last visit or death, whichever occurs first. Only the first exposure to one of the regimens will be included in analyses. Incidence of discontinuation due to specific reasons will be presented when there are > 10 discontinuations for any reason. Multivariable Cox proportional hazards models or Poisson regression will consider the factors associated with discontinuation for any reason, and individually for any reason for discontinuation where there are more than 30 events. The model building strategy will follow EuroSIDA principles and adjust for factors which are significant in univariate analyses or *a priori* specified in the analysis plan.

Hepatotoxicity: The number and percentage of individuals with hepatotoxicity will be tabulated and reported, stratified by CAB+RPV or DTG+RPV or DTG+3TC regimen. The incidence of hepatotoxicity will be summarized, with follow-up from date of regimen start to discontinuation, last visit or death, whichever occurs first. Only the first exposure to one of the regimens will be included in analyses. The crude incidence of discontinuation overall and of hepatotoxicity will be described for each of the regimens and according to laboratory data, including LCT, where this has been reported. Multivariable Cox proportional hazards models or Poisson regression will consider the factors associated with hepatotoxicity where there are more than 30 events. The model building strategy will follow EuroSIDA principles and adjust for factors which are significant in univariate analyses or *a priori* specified in the analysis plan.

Hepatotoxicity or discontinuation due to liver-related adverse events may be a rare event and the study might not achieve sufficient events for constructing multivariate models. Where there are insufficient events for detailed analyses, we will provide a descriptive analysis of persons with or without hepatotoxicity or who discontinue due to a liver-related adverse event. We will describe the characteristics of those with an event, at the time of the event, compared to those without an event, at last follow-up. Time to occurrence of the event will be evaluated and time to event curves will be presented.

The results will also be presented stratified by pre-existing liver disease and by hepatitis B and/or chronic hepatitis C coinfection. As noted above, multivariable models will be constructed when there are more than 30 events in the strata of interest.

8.6.1. Sensitivity and stratified analyses

We will compare individual characteristics for those with and without baseline LCTs and perform a sensitivity analysis in the subset of individuals where baseline LCTs are available.

Among those with ALT greater than 3×ULN, the demographic and clinical characteristics will be compared between CAB+RPV and the comparator groups. The number and percentage of individuals with elevated ALT 3×ULN stratified by treatment regimen will be provided in the final report.

Stratified analysis for those continuing on the regimen and those switching to a different regimen among the patients with a diagnosis of DILI, or ALT>5×ULN, or ALP>2×ULN, or ALT > 3×ULN and BILI>2×ULN will be conducted.

Our primary analyses will censor follow-up at discontinuation of CAB+RPV or DTG+RPV or DTG+3TC, last visit or death. This assumes that any potential toxicity associated with CAB+RPV stops when the drug is discontinued, which may not be the case. We will conduct a sensitivity analysis of hepatotoxicity including an additional follow-up to six months after discontinuation of CAB+RPV.

8.6.2. 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.

8.8. Limitations of the research methods

This is a study of routine clinical care and reflects treatment practice across the EuroSIDA consortium. Confounding by indication, whereby persons are selected for specific regimens, cannot be ruled out. Not all clinics will routinely test ALT or BILI, and it is possible that those persons suspected of having liver-related toxicities may be more likely to have testing done, biasing the results. The ULN for ALT will vary between EuroSIDA laboratories but for all analyses an ULN of 40 will be used. Persons with or without data on laboratory markers might be different, for example, persons who have been lost to follow-up might not have data available. The results from this study should be interpreted cautiously, with careful consideration given the limitations of the observational study design.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and informed consent

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. EuroSIDA is conducted according to the Declaration of Helsinki and the requirements of Good Clinical Practice (GCP) as defined in the European Union's (EU) GCP Directive. As data controller, the EuroSIDA Coordinating Centre is located within the Capital Region of Copenhagen, Denmark, store, share and protects data in accordance with current legislation and under approval by The Danish Data Protection Agency (j.nr.: RH-2018-15), currently under the EU's General Data Protection Regulation (EU) 2016/679.

Where Informed Consent is required by the local and/or national Ethics Committees, this will be obtained from each individual before any study related procedure is performed. In accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) – Good Clinical Practice Guidelines the procedure for obtaining Informed Consent will be followed.

Principles of medical confidentiality in relation to Study Subjects are maintained. 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 present in the data source. 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 the individual level information accrued in the EuroSIDA database, from electronic health records in an aggregate manner. 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 after the protocol is approved by the EMA, and CAB 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 monitoring. 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 and according to the milestones as set out above (Section 5). Study results will be made available externally through peer reviewed manuscript and conference presentation.

12. REFERENCES

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13. APPENDIX 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 colspan="2" rowspan="2">YES

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" rowspan="2">Which long-acting drugs have been given?

long acting cabotegravir + long acting rilpivirine

2) long acting cabotegravir without rilpivirine

3) long acting rilpivirine without cabotegravir</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></tr>
<tr><td colspan="3">Dosage: 400/600 mg (CAB) / 600/900 mg (RPV) (drop down menu)</td><td colspan="2">Dosage: 400/600 mg (CAB) / 600/900 mg (RPV) (drop down menu)</td></tr>
<tr><td colspan="3">Date of injection:</td><td colspan="2">Date of injection:</td></tr>
<tr><td colspan="3">Intended schedule:</td><td colspan="2">Intended schedule:</td></tr>
<tr><td colspan="2">Monthly</td><td>Every 2 Month</td><td>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.