

**Protocol title**

Drug Utilization, Adherence, Effectiveness and Resistance: A Retrospective/Prospective Observational Cohort Study in People Living with HIV (PLWH) Initiating ARV Regimen CAB+RPV LA in Collaboration with EuroSIDA (EuroSIDA Cabotegravir+Rilpivirine Utilization Study)

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# \*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  |
| BMI | Body Mass Index |
| CAB | Cabotegravir |
| CD4 | Cluster of Differentiation 4 |
| CD8 | Cluster Differentiation 8 |
| CRF | Case Review Form |
| CVD | Cardiovascular Disease |
| DEXA | Dual-energy X-ray Absorptiometry  |
| DNA | Deoxyribonucleic Acid |
| DUS | Drug Utilization Study |
| EC | Ethics Committee |
| EMA | European Medicines Agency |
| ESLD  | End stage liver disease |
| EU  | European Union  |
| GCP | Good Clinical Practice |
| GDPR | General Data Protection Regulation |
| 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 |
| LA | Long-Acting |
| LAI | Long-Acting Injectable  |
| LDL | Low Density Lipoprotein  |
| LOD | Limit of Detection |
| MI | Myocardial Infarction |
| NADM | Non-AIDS Defining Malignancies |
| NNRTI | Non-Nucleoside Reverse Transcriptase Inhibitor |
| PASS | Post Authorization Safety Study  |
| PLWH | Person Living with HIV |
| REDCap | Research Electronic Data Capture |
| RNA | Ribonucleic Acid |
| RPV  | Rilpivirine |
| QA | Quality Assurance |
| SAE | Serious Adverse Event |
| SmPC | Summary of Product Characterization |
| SOP | Standard Operating Procedure |
| TB | Tuberculosis |
| VL | Viral Load |

This section is consistent with the requirements of the Food and Drug Administration (FDA) form 1572, if this form is used for the site.

This signature page is for the primary investigator. If other investigators are involved, please include a list of all investigators and their contact information in an appendix

If appropriate, include a statement describing composition and duties of any Study Advisory Committee along with dates or milestones for Committee meetings. This section can be deleted if there is no advisory committee.

# \*Study Rationale and Background

**Title**

Drug Utilization, Adherence, Effectiveness and Resistance: A Retrospective/Prospective Observational Cohort Study in People Living with HIV (PLWH) Initiating ARV Regimen CAB+RPV LA in Collaboration with EuroSIDA (EuroSIDA Cabotegravir+Rilpivirine Utilization Study)

**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 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+RPV long-acting injection (LAI), the patient, in consultation with a healthcare provider, may decide to take CAB tablets together with RPV tablets for approximately one month (at least 28 days) to assess tolerability to CAB+RPV LAI.

This observational cohort study, including patients from a real-world clinical setting, will aim to understand better the individual population receiving CAB+RPV long-acting (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.

# research questionS and OBJECTIVE(S)

Following the initiation of an ARV regimen containing CAB+RPV LA among people living with HIV (PLWH), this study will aim to assess usage patterns, durability, discontinuation, and virologic outcomes. The objectives are as follows:

1. Describe CAB LA and RPV LA containing regimens usage patterns
2. Assess adherence, durability, and discontinuation among individuals initiating CAB+RPV LA regimen
3. Assess the clinical effectiveness (i.e. proportion of individuals experiencing virologic failure) among PLWH after initiating CAB+RPV LA regimen
4. Monitor for resistance and next treatment response among individuals who discontinue CAB+RPV LA regimen, where viral load (VL) data are available and resistance testing has been conducted 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

## Study population and setting

**Study population**

The study will retrospectively and prospectively include PLWH over the age of 18 years, from EuroSIDA clinical sites who have initiated CAB+RPV LA after December 17, 2020, including participants who have discontinued CAB+RPV LA for any reason.

If not all CAB+RPV LA users are included from a given clinical site, participants should be randomly selected among all patients who have initiated CAB+RPV LA after December 17, 2020. The primary analyses will include only the first exposure to CAB+RPV LA containing regimens.

**Inclusion criteria**

* HIV-1 positive persons followed at a EuroSIDA clinical site
* Age > 18 years old
* Initiated CAB+RPV LA containing regimens after December 17, 2020, including participants who have since discontinued the treatment for any reason.
* Has signed EuroSIDA CAB+RPV and RESPOND data repository consent form

**Exclusion criteria**

* Participants are already enrolled in EuroSIDA

**EuroSIDA Cohort description**

The EuroSIDA study was initiated in 1994 and is a prospective observational cohort study of more than 24,000 individuals followed at over 100 hospitals across 35 European countries, as well as Israel and Argentina [1]. The main objective of the study is to assess the impact of ARV drugs on the outcomes 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 Research Electronic Data Capture (REDCap) or electronic data transfer using the HIV Collaboration Data Exchange Protocol (HICDEP) format which includes information on outcomes and covariates [2]; further information is available at https://www.hicdep.org/. For each participant, the start and stop dates for each ARV drug are recorded. ATC codes for all ARVs and most non-ARVs are collected. Dates of diagnosis of all AIDS defining diseases are recorded, according to the 1993 clinical definition of AIDS from the Centers for Disease Control and Prevention. All EuroSIDA data undergo extensive checks, queries and central clinical event validation to ensure high quality and completeness.

# research methods

## \*Study design

 A retrospective and prospective observational cohort study, nested within the EuroSIDA study, will be conducted using data from individual medical records at participating EuroSIDA clinical sites. This study will span a period of five years to meet its objectives, wih potential additional safety follow-up time allowing for review of virological outcomes up to 48 months after discontinuation.

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 Summary of Product Characterization (SmPc) for CAB+RPV oral and LA formulations, contemporary regimen and local guidelines 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 centre.

## Clinical variables

The variables listed in Table 2 will be collected in REDCap at the time of enrolment and once annually during prospective follow up on EuroSIDA clinical follow-up form.

**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, pregnancy |
| **Infection-related Laboratory data** | HIV-ribonucleic acid (“RNA”), HCV antibody test, HCV-RNA, HBsAg result, HBV-DNA, CD4 count, CD8 count |
| **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, CVD and/or diabetes treatment, tuberculosis (TB) 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 (including TB), myocardial infarction, stroke, diabetes, invasive cardiovascular procedures, end-stage liver disease, end-stage renal disease, AIDS and NADMs, liver and kidney transplantation, fractures |

* Data regarding CAB+RPV LA usage will be collected in a separate REDCap form and will include detailed information on trial history, HIV subtype, HIV resistance, CAB+RPV lead-in therapy, dosage, dates of injection, reasons for delayed injections, bridging therapy and adverse reactions of CAB+RPV LAI and reasons for discontinuation. Data on possible hepatotoxicity due to CAB+RPV LAI is collected on a separate REDCap form. All data since the initiation of CAB+RPV will be collected retrospectively at the time of enrolment and once annually for participants under prospective follow up.
* Clinical events: AIDS, myocardial infarction, stroke, invasive cardiovascular procedures, kidney failure, liver failure, cancer, bone fractures, cause of death.

**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 the discontinuation of a CAB+RPV LA regimen. Healthcare 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.

**Data sources**

Data will be collected from patient medical charts and files from participating EuroSIDA sites and entered in REDCap.

## Study size

Approximately 500-750 participants will be included. In statistical analyses, new participants will be merged with existing EuroSIDA participants using CAB+RPV LA for an estimated total sample size of 1000.

## Data analysis

Descriptive analyses will summarize the study population exposed to CAB+RPV LA. Adherence, durability and discontinuations of CAB+RPV LA will be summarized and logistic regression will be used to identify factors associated with missing 1 or more doses 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. For PASS studies, please ensure that all future amendments and deviations are documented

These analyses will be performed by statisticians based at CHIP. Due to the expertise required, certain analyses will require collaborations or certain aspects of the analyses services to be performed outside European Union (EU), statisticians based in Sydney Australia at the Kirby Institute, University of New South Wales. All collaborators and service providers outside the EU are to abide by GDPR and EU requirements, and samples will not be sent outside the EU without data transfer agreements.
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## Data management

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

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

### Data handling conventions

EuroSIDA data are submitted either through the secure electronic case report system 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 has the relevant data protection clearance, Data Protection Agency No: RH-2018-15.

The Capital Region of Denmark, Denmark (RegionH), is the data controller for the EuroSIDA and the EuroSIDA Cabotegravir+Rilpivirine Utilization Study. The Data Protection Officer (DPO) for the Cabotegravir+Rilpivirine Utilization Study is also RegionH. The contact details of the DPO in Denmark will be provided to study participants.

### Timings of assessment during follow up

All sites in EuroSIDA provide follow-up information to the coordinating centre from October to December of each calendar year. Each site submits all relevant information for each individual that has occurred since the last data capture. For example, if a person has 3 CD4 counts measured and has started and discontinued 3 ARVs for different reasons since the last data download, all of this information is provided rather than just the information from the 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 database closure.\*

## \*Quality control and quality assurance

The EuroSIDA Cabotegravir+Rilpivirine Utilization Study study will undergo extensive quality assurance (QA) procedures and has the following QA processes in place:

* + - * Data quality checks/rules in REDCap that automatically detect and notify users when erroneous data is entered, i.e. units measured beyond set limitations, etc.
			* Lists identifying missing data or data requiring further clarification or correction are generated and sent to sites for review and resolution
			* 100% QA review and validation of Cause of Death and Event forms by Medical Personal
			* Extensive data cleaning procedures once data has been downloaded to the database. 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 further be reviewed by the senior statistician and the administrative team at CHIP for internal consistency and continuity between successive years' reports.

## \*Limitations of the research methods

This is a study of routine clinical care and reflects treatment practice across the EuroSIDA study. Following up of study participants for 48 months 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 detection limit. These centres are Eastern European countries where the uptake of CAB+RPV LA containing regimens is anticipated to be low. Individuals starting one of the regimens where the VL has 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 individuals are selected for specific regimens, cannot be ruled out. Resistance testing is not routinely performed in many EuroSIDA clinics and the proportion of individuals with resistance results may be low. Resistance testing may target specific groups of individuals and the results may not apply to the whole study population. While EuroSIDA has extensive experience in capturing data via REDCap and Case Review Form (CRF), collecting this data retrospectively through additional CRFs might reduce data quality. Not all clinics will provide information, despite reminders, and the data quality might suffer due to incomplete or missing information. Differences might exist between individuals with and without data, for example, those who have died or been lost to follow-up might not have data available. Therefore, the results from this study should be interpreted with caution and with careful consideration given to the limitations of the observational study design.

# \*protection of human subjects

## 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 the current EU GCP Directive, Human Subject Protection and Data Protection Acts or with the local law and regulation, whichever offers greater protection of human subjects.

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

Participants are informed that their data will be pseudonymized, stored safely and analysed following the scientific programme in EuroSIDA to study their HIV infection and associated diseases.

As data controller, the Capital Region of Denmark, supported by the Coordinating Centre, stores, shares and protects data in compliance with current legislation. The study is registered according to the EU’s GDPR 2016/679vi.

EuroSIDA is registered at ClinicalTrials.gov (Identifier: NCT02699736).

## Subject confidentiality

Principles of medical confidentiality concerning study subjects are maintained under 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 secure location.

All study data is marked with this 7-digit PID number. Date of birth is collected as the day, 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 under 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 all information and data related to the EuroSIDA study provided by the coordinating centre, as well as any data and records generated during the course of conducting the study, confidential and will not use the information, data, or these 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 or digital) may be reviewed by Institutional Review Boards (IRBs) or Ethics Committees (ECs) to ensure the study is ethically acceptable, as well as by research staff, study monitors, and their designees.

Personal data shall not be disclosed to third parties, save where this is required directly or indirectly to meet the requirements of the Protocol or for purposes related to monitoring or safety reporting. The identity of Study Subjects shall not be disclosed to third parties. Investigators and the EuroSIDA coordinating office shall ensure that only staff and employees directly involved 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 as outlined in this Protocol unless prior written consent has been obtained.

# \*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 or device related events, or incidents related to CAB, RPV or any other medical treatments during the conduct of this study, 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 CAB, RPV or any other medical treatment as the study design involves analysing de-identified, secondary data collected from individual medical records. Therefore, a study specific pharmacovigilance plan will not be developed.

# plans for disseminating and communicating study results

## Target audience

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

# milestones

The study will enrol an expected 500-750 participants until a total of 1000 participants who have initiated CAB+RPV LAI (including those already in EuroSIDA). Follow up will continue until at least end of 2025 and possibly until end of 2030 depending on available funding.

The data will be included in an ongoing post-authorisation safety study as aggregated de-identifiable data only. Annual interim reports with cumulative data will be submitted and a final report is expected to be submitted in March 2027.

# references

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