Protocol

Cabotegravir and Rilpivirine Real World Experience

CORAL

A non-interventional, mixed-methods, prospective cohort study to characterise the real-world implementation, roll out, safety and patient experience of the long-acting injectable HIV treatment regimen of 2-monthly cabotegravir and rilpivirine

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2. Summary of changes

Protocol version	Protocol section	Change
2.0	17	End of study definition has been added: The 'end of study' is the point at which last participant final visit individual data has been entered into the electronic data capture system and all the qualitative work has been completed. Thereafter, the 'end of study' the close out visit will be performed. The study will only be considered 'closed' when all participants have completed their final study visit, all assessments completed, all the data have been entered into the database and all data queries resolved, close out visit conducted, the database locked and data analysis performed and reports written.
2.0	12.5.2	Information on notification of pregnancies added: Pregnancies arising on cabotegravir and rilpivirine should also be notified to ViiV within 7 days of awareness of pregnancy. The pregnancy notification form will be provided by the coordinating centre if required.
2.0	22.1	Updated Gantt chart inserted

3. Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the national guidelines for the conduct of clinical research.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies and serious breaches of GCP from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Date:
30/10/23

Signature: .....  .....

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Signature:  Date:

..... 30/10/2023

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4. Table of Contents

5. List of Abbreviations

Drug Class Name	
INSTI	integrase strand transfer inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NNRTI	nonnucleoside reverse transcriptase inhibitor
PI	protease inhibitor
General Terminology	
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
BHIVA	British HIV Association
BMI	Body Mass Index
CAB	Cabotegravir
CRF	Case Report Form
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HRA	Health Regulatory Authority
HIV	Human immunodeficiency virus
ISERP	Independent Safety Epidemiology Review Panel
IQR	Inter-Quartile Range
LA	Long-acting
µL	Microlitre
mL	Millilitre
NHS	National Health Service
PLWH	People living with HIV
PD	Protocol Deviation
PROM	Patient Reported Outcome Measures
PV	Protocol Violation
QA	Quality assurance
REDCap	Research Electronic Data Capture
REC	Research Ethics Committee
RPV	Rilpivirine
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SMG	Study Management Group
SUSAR	Suspected Unexpected Serious Adverse Reaction
VL	Viral load (HIV-1 RNA)

6. Protocol Summary

Short title	Cabotegravir and Rilpivirine Real World Experience (CORAL)
Long title	A non-interventional, mixed-methods, prospective cohort study to characterise the real world implementation, roll out, safety and patient experience of the long-acting injectable HIV treatment regimen of 2-monthly cabotegravir and rilpivirine
Funder	ViiV Healthcare
Rationale	The long-acting (LA) injectable antiretroviral therapy regimen of cabotegravir and rilpivirine (LA CAB+RPV) given 2-monthly is a remarkable, promising and widely welcomed paradigm shift in HIV treatment. However, there are currently no real-world data on the implementation strategies planned in different clinical settings, the feasibility and acceptability of LA CAB+RPV to patients and clinicians, nor clinical outcomes with the regimen outside of clinical trial settings. Based on British HIV Association guidelines on the use of the injectable regimen it is currently not known what proportion of people living with HIV (PLWH) in the UK would be eligible for LA CAB+RPV nor how many considered eligible will be offered the regimen, and how many of those offered will actually take it up. Characterising this adoption cascade, as well as the individual and system-related factors at play, is important as it will enable a better understanding of the ultimate uptake and impact of LA CAB+RPV
Primary objectives	1. ADOPTION: To quantify the LA CAB/RPV adoption cascade
Secondary objectives	2. ACCEPTIBILTY: a. To explore the acceptability of LA CAB+RPV amongst PLWH and health care workers delivering the regimen through a participant questionnaire, healthcare practitioner questionnaire and qualitative research. b. To compare patient-reported outcomes including quality of life, treatment satisfaction and treatment preference in those on LA CAB+RPV compared to those who remain on oral ART (demographically similar but not eligible for LA ART) 3. FEASIBILITY: a. To describe feasibility of the regimen through outcomes in the participant and healthcare practitioner questionnaires b. To explore barriers and facilitators to effective implementation of LA CAB+RPV

	4. FIDELITY: To describe the fidelity of regimen delivery and associated monitoring compared to intended use in BHIVA guidelines 5. EFFECTIVENESS: a. To characterise the UK-wide population who are switched to LA CAB+RPV and indications for switch b. To describe virological and clinical outcomes at one year of therapy in those on LA CAB+RPV and in those remaining on oral ART (demographically similar but not eligible for LA ART) c. To identify where actionable adjustments to implementation can be made to optimise overall adoption, sustainability and effectiveness of LA CAB+RPV
Primary outcome measures	1. ADOPTION: a. Proportion of clinical cohort eligible for LA CAB+RPV according to BHIVA guidance b. Proportion of eligible adults offered/discussed a switch to LA CAB+RPV c. Proportion who accept the switch to LA CAB+RPV d. Proportion who remain on LA CAB+RPV at one year and reasons for switching off the regimen
Design	This is a mixed methods, non-interventional, multi-centre, prospective observational study with a nested qualitative component at UK NHS HIV treatment centres.
Population	Approximately 10-20 adults receiving LA CAB+RPV and 5-10 matched controls on oral ART will be included from each participating centre
Duration	Each participant in the observational cohort study will contribute at least 1 year of longitudinal data to the study. The total duration of the study at each participating HIV centre will be 2 years to allow time for recruitment and follow-up. The total duration of the study at the Coordinating Centre will be 3.5 years to allow time for study set up followed by data collection, cleaning and analysis.
Statistical methods	This is primarily a descriptive study. Descriptive statistics will be used explain the demographics, clinical and treatment characteristics of all participants (age, BMI, race/ethnicity, co-morbidities, ART history). Data will be presented as summary statistics as appropriate (mean, median, standard deviation, IQR, maximum and minimum for continuous measurements, and numbers and proportions for categorical measurements).
Sample size	Across all study sites the aim is to recruit a minimum of 150 adults receiving LA CAB+RPV into the prospective cohort study and ~50 adults who remain on oral ART as the comparator population.

	Around 20-30 participants will participate in the nested qualitative study. Around 30 healthcare workers will contribute data through focus group discussions and questionnaires

7. Background and Rationale

The long-acting injectable antiretroviral therapy regimen of cabotegravir and rilpivirine (LA CAB+RPV) given 2-monthly is a remarkable, promising and widely welcomed paradigm shift in HIV treatment [1-4]. The regimen was recently approved by the National Institute for Clinical Excellence (NICE) and roll out is underway in the United Kingdom (UK) National Health Service (NHS) [5]. Current trial data suggest it is an efficacious regimen and is well-liked by the majority of trial participants [1-4][6]. There are multiple advantages over traditional oral antiretroviral therapy, such as it being less user-dependent, removing the burden of daily pill-taking, and being more easily concealed, reducing concerns around stigma [7].

Outside of trials, to date LA CAB+RPV has only been used in select circumstances on compassionate grounds in small numbers of individuals unable to take oral therapy. Therefore, there are currently no real-world data on the implementation strategies planned in different clinical settings, the feasibility and acceptability of LA CAB+RPV to patients and clinicians, nor clinical outcomes with the regimen outside of clinical trial settings [8, 9]. HIV services throughout the UK are currently planning and executing local roll out of LA ART but it is not yet known how this will be individualised based on patient needs and service capacity. Clinical trial data does not address the practical needs of the stakeholders responsible for introducing the intervention and more data are urgently needed in this area. This is especially pertinent to LA CAB+RPV considering it requires increased frequency of visits and HIV viral load (VL) monitoring, adequately trained clinical staff, robust injection appointment management systems, oral bridging in events of delayed injections and all this must be incorporated into existing clinic work streams and human resources [10].

The British HIV Association (BHIVA) have released guidance on eligibility for LA ART based on the following nine criteria [9]:

1. significant need for injectable antiretroviral therapy;
2. viral suppression for at least 6 months;
3. no known or suspected NNRTI or INSTI resistance;
4. no history of virological failure or unplanned treatment interruption on NNRTI or INSTI-containing ART regimens;
5. no prior history of INSTI monotherapy;
6. ability to tolerate and commit to a 2-monthly attendance schedule for injections;
7. accepting of small risk of virological failure despite complete adherence;
8. BMI <30 kg/m^2 AND non-A1/A6 subtype if baseline resistance unavailable;

9. not requiring a tenofovir-based regimen for treatment or prevention of hepatitis B virus

BHIVA also recommend that those who started on LA CAB+RPV in a clinical trial or as part of a compassionate access programme may continue it. Additionally, HIV VL monitoring is recommended at every visit, with prompt recall advised in cases of viral rebound due to concerns about rapid emergence of 2-class resistance [9].
Based on the above criteria, it is currently not known what proportion of PLWH in the UK today would be eligible for LA CAB+RPV and it is possible that the numbers will vary across different demographic groups and settings. It is also not clear how many PLWH considered eligible will be offered the LA CAB+RPV regimen, and how many of those offered LA ART will actually take it up. Characterising this adoption cascade, as well as the individual and system-related factors at play, is important as it will enable a better understanding of the ultimate uptake of LA CAB+RPV.

As current efficacy data are largely from clinical trials, adherence to injection schedules may have been greater than that which will be observed in real-world settings. It will be prudent to assess whether adherence to the treatment regimen is replicated in real world settings, or whether instances of PLWH requiring bridging oral therapy are more frequent, and how this would be operationalised. Local strategies used to support timely administration of injections can be described and may require scaling up alongside the regimen roll out e.g. text reminders, App-based mobile health technology, use of community support workers.

In summary, there are currently no real-world data available on implementation approaches being adopted in UK HIV services, barriers and facilitators to the widespread uptake of LA CAB+RPV, acceptability of the regimen amongst clinicians and PLWH, and virological outcomes. Information on adoption, acceptability, fidelity and effectiveness will be important to guide policymakers, commissioners, HIV services, other stakeholders and PLWH in the optimal roll-out of LA CAB+RPV in the UK.

8. Hypothesis

There are likely to be challenges in the implementation of LA CAB+RPV as part of routine clinical care in real-world settings; characterising these barriers will aid the development of strategies to overcome them. However, high levels of effectiveness and acceptability will be demonstrated in those who do switch to LA CAB+RPV in a real-world setting.

9. Objectives

9.1. Primary Objective

1. ADOPTION: To describe the strategies being deployed in different UK HIV services to deliver LA CAB+RPV and to quantify the adoption cascade in terms of what proportion of each clinic cohort are: a) eligible for LA CAB+RPV in accordance with BHIVA

guidelines; b) have a switch to LA CAB+RPV discussed; c) accept a switch to LA CAB+RPV; and to ascertain reasons for attrition at each step of the cascade (Fig. 1).

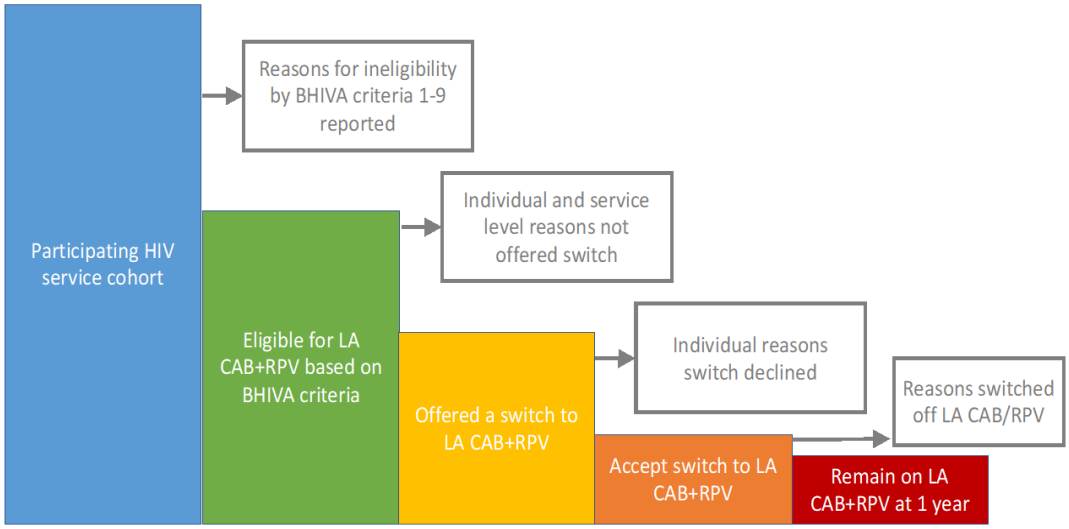

Figure 1. Adoption cascade

9.2. Secondary Objectives

2. ACCEPTABILITY:
    a. To explore the acceptability of LA CAB+RPV amongst PLWH and health care workers delivering the regimen through a participant questionnaire, healthcare practitioner questionnaire and qualitative research.
    b. To compare patient-reported outcomes including quality of life, treatment satisfaction and treatment preference in those on LA CAB+RPV compared to those who remain on oral ART (demographically similar but not eligible for LA ART)

3. FEASIBILITY:
    c. To describe the feasibility of using the regimen from a clinical and patient perspective through outcomes in the participant and healthcare practitioner questionnaires
    d. To explore barriers and facilitators to effective implementation of the LA CAB+RPV regimen

4. FIDELITY: To describe the fidelity of regimen delivery and associated monitoring compared to intended use in BHIVA guidelines

5. EFFECTIVENESS:
    e. To characterise the UK-wide population who are switched to LA CAB+RPV and indications for switch

f. To describe virological and clinical outcomes at one year of therapy in those on LA CAB+RPV and in those remaining on oral ART (demographically similar but not eligible for LA ART)
g. To identify where actionable adjustments to implementation can be made to optimise overall adoption, sustainability and effectiveness of LA CAB+RPV

10. Outcome Measures

There are no interventional components to the study. Service-specific approaches to implementation of LA CAB+RPV in use at the study sites at study outset will be described, contrasted and compared.

Objective	Outcome measures
Implementation outcomes	
ADOPTION 1. To quantify the adoption cascade	a. Proportion of clinical cohort eligible for LA CAB+RPV according to BHIVA guidance b. Proportion of eligible adults offered/discussed a switch to LA CAB+RPV c. Proportion who accept the switch to LA CAB+RPV d. Proportion who remain on LA CAB+RPV at one year and reasons for switching off the regimen
ACCEPTIBILITY 2a. To explore the acceptability of LA CAB+RPV amongst PLWH and health care workers delivering the regimen through a participant questionnaire, healthcare practitioner questionnaire and qualitative research. 2b. To compare patient-reported outcomes including quality of life, treatment satisfaction and treatment preference in those on LA CAB+RPV compared to those who remain on oral ART (demographically similar but not eligible for LA ART)	a. The acceptability and experiences of the regimen amongst participants (PLWH) and healthcare workers delivering LA CAB+RPV through outcomes in the participant and HCP questionnaires b. The patient reported outcomes will be described through: i. Outcomes in the participant questionnaire and treatment preference in those switched to LA CAB+RPV ii. HIV-related quality of life - HIVPROM (11)
FEASIBILITY	a. Outcomes in the healthcare worker and participant questionnaires

3a. To describe feasibility through outcomes in the participant and healthcare practitioner questionnaires 3b. To explore barriers and facilitators to effective implementation	b. Experiences, barriers and facilitators at both the individual and service level from qualitative work
FIDELITY	a. Proportion of injections delivered within the visit window b. Number of oral bridging courses per patient per year c. Fidelity to 2-monthly HIV viral load monitoring (+/- 2 weeks of target date)
Effectiveness outcomes	
EFFECTIVENESS 5a. To characterise the UK-wide population who are switched to LA CAB+RPV and indications for switch 5b. To describe virological and clinical outcomes at one year of therapy in those on LA CAB+RPV and in those remaining on oral ART (demographically similar but not eligible for LA ART) 5c. To identify where actionable adjustments to implementation can be made to optimise overall adoption, sustainability and effectiveness of LA CAB+RPV	a. Proportion of those who begin LA CAB+RPV who remain virologically suppressed at 12 months (by FDA snapshot algorithm and intention to treat approach), and the proportion of those on oral ART who remain virologically suppressed at 12 months after the baseline date b. Proportion of each group who have experienced virological failure at 12 months c. HIV-related medical events at 12 months d. Change in CD4 count from baseline to month 12 (where available) e. Change in renal function (estimated glomerular filtration rate, eGFR) from baseline to month 12 At the conclusion of the study, lessons learned about barriers and facilitators to effective implementation will be reported. Actionable interventions which services can use to optimise adoption and overall effectiveness of the regimen will also be proposed

11. Methodology

11.1. Study design

This is a non-interventional, multi-centre, prospective observational study with a nested qualitative component at UK NHS HIV treatment centres. The study is being coordinated by a research team at Brighton and Sussex Medical School which is part of the University of Sussex. The individual components of the study are described separately below:

11.1.1. Observational study using routinely collected clinic data

The study will capture data from HIV-1 positive adults receiving long-acting cabotegravir and rilpivirine as part of their treatment regimen. All HIV-1 positive adults (≥ 16 years) who initiated long-acting cabotegravir and rilpivirine-based ART any time from 6 months prior to study site initiation will be eligible to be included in this study. A demographically similar comparator group on oral ART will also be invited to join the study. Routinely collected medical data from eligible and consenting participants' medical records will be extracted at key intervals, as laid out in the Schedule of Activities (see section 12.3.4), and entered into an electronic data capture system (Research Electronic Data Capture, REDCap). Variables of interest include demographic data, HIV treatment history, laboratory findings, which are all collected routinely in line with the BHIVA monitoring guidelines.

The total duration of patient follow-up is at least 1 year from the time of enrolment. The final analysis will be conducted following database lock after the last study participant has reached the 12 months treatment milestone and all data queries have been resolved.

Patients who received LA ART outside of the BHIVA criteria e.g. on compassionate grounds are of interest and can be included in the prospective study; the reasons for BHIVA criteria ineligibility and outcomes (duration of therapy, virological and clinical) will be described.

11.1.2. Questionnaire with participants

All participants will also be invited to complete a participant questionnaire comprising two sections: 1) personal experiences with HIV treatment and LA CAB+RPV; 2) quality of life as determined through HIV Patient Reported Outcome Measures (HIV PROM) questions. The questionnaire will be administered at three time points as laid out in the Schedule of Activities (see section 12.3.4). The questionnaires will be administered on-line through REDCap unless a paper-based questionnaire is preferred by the participant.

The participants on oral ART will complete a shorter questionnaire on quality of life as determined through HIV Patient Reported Outcome Measures (HIV PROM) at three time points as laid out in the Schedule of Activities (see section 12.3.4)

11.1.3. In-depth interviews with subset of participants

A subset of participants (2-3 per site) will be invited to an in-depth interview where a topic guide of open-ended questions will facilitate a deeper understanding of the participant's experiences and perceptions. Qualitative data from in-depth interviews will be audio-recorded and transcribed for thematic analysis. Participants who are interviewed will be

reimbursed for their time with a £20 shopping voucher. This is in addition to the reimbursement given for completing questionnaires.

11.1.4. Interview and questionnaire with healthcare workers delivering CAB/RPV

A healthcare worker questionnaire will be administered with healthcare workers involved in delivering the long-acting regimen. A focus group discussion / interview will also be conducted with a representative sample of healthcare workers (e.g. Pharmacist, Nurse, Consultant) delivering the long-acting regimen at the participating clinics. This will collect information on implementation approach deployed, experiences and outcomes to date, perceived barriers and facilitators of regimen use on BHIVA-recommended clinical use and compassionate grounds.

11.1.5. Notes review to understand adoption cascade

A registry dataset of patients eligible for LA CAB/RPV will be generated from the main clinic database. Over the following 12 months, the clinic will then quantify the number of patients ever offered a switch to LA CAB+RPV, the number who accept the switch and the number who remain on the regimen for at least 1 year duration. Reasons for not being offered or declining a switch to LA CAB+RPV will be recorded.

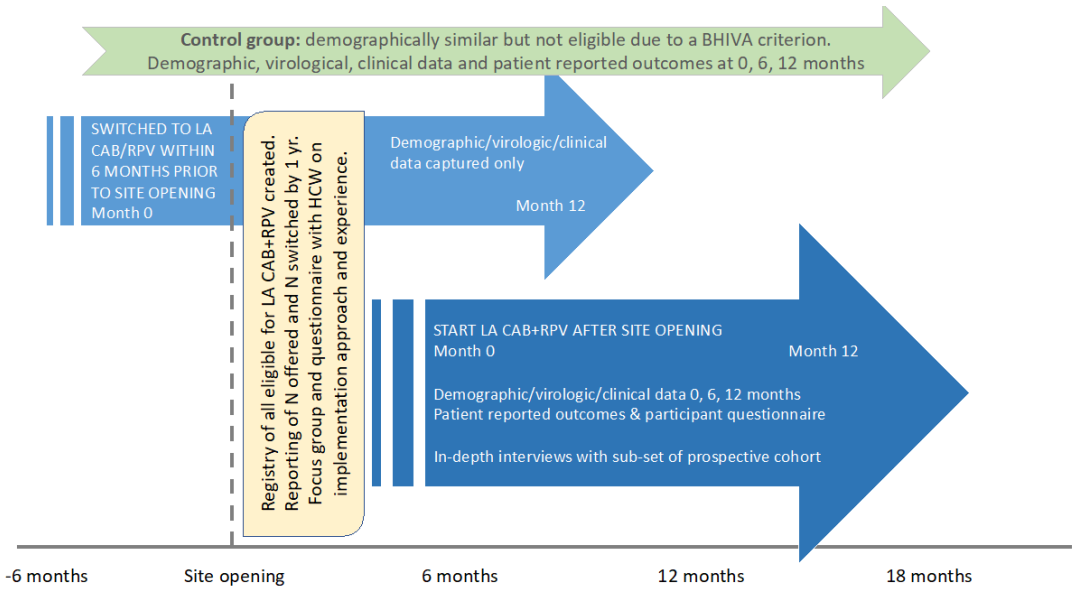

Figure 2. Schematic of study including qualitative and quantitative aspects

11.2. Study population

The study will be conducted in approximately 10-12 NHS HIV departments in the UK (4-5 in England, 1-2 in Wales, 1-2 in Scotland and 1 in Northern Ireland). To ensure the data are representative of the UK, participating clinics will be distributed across England, Wales, Scotland and Northern Ireland and of varying cohort size (small, medium and large), geographical area (urban; rural) with a diverse clinic population. It is anticipated that 5-20 patients in LA CAB+RPV and 3-6 patients on oral ART will be enrolled from each centre depending on cohort size. Patients who were initiated on LA CAB+RPV within the prior 6

months will be identified by a member of the clinical team or research team, from review of clinic records and databases as appropriate at each centre. Patients beginning LA CAB+RPV in the 6-12 months after site initiation will be eligible to join prospectively.

It is intended that approximately 10-20 patients on LA CAB+RPV and 5-10 controls will be included from each participating centre to represent a proportionate spread from the study sites, but this will be dependent on local LA CAB+RPV uptake. Oversampling may be performed in the larger centres in order to maintain an overall sample size of up to ~150 on LA ART.

In addition, approximately three healthcare workers in different roles at each participating clinic will be interviewed and asked to complete a questionnaire.

11.2.1. Inclusion criteria for observational study using routinely collected clinic data

1. Understands the participant information and study requirements and has capacity to consent.

2. Willing to comply with study procedures

3. Age 16 years or above

4. Is a member of one of the following groups:

    - LA group - PLWH who have been recently switched (within the prior 6 months) or are prospectively switched to LA CAB+RPV during the enrolment period. This includes those who have received LA CAB+RPV outside of BHIVA criteria or on compassionate grounds.

    - Oral ART group - PLWH who are demographically similar but not eligible for LA CAB+RPV according to BHIVA eligibility criteria and who continue oral ART within the study period (e.g. those who are HBVcoreAb+ or who have an underlying drug resistance mutation that precludes use of LA CAB+RPV). Intervention group to oral group will be matched 3:1 by calendar period and other key variables where possible.

11.2.2. Exclusion from observational study using routinely collected clinic data

1. In the opinion of the investigator is unable or unwilling to comply with the study requirements

2. Aged < 16 years of age

12. Study procedures

12.1. Identification of potential participants for observational study using routinely collected clinic data

Potential participants will be identified by a member of the site HIV clinical research team and invited to participate by their HIV doctor/nurse or a member of the research team, who will briefly explain the study outline either in-person, by telephone or email. If the potential participant expresses an interest in joining the study then they will be sent the electronic participant information sheet (PIS) and informed consent form (ICF), or the informed consent process can be completed in person by the research team if this better suits the potential participant's needs.

12.2. Informed consent

Individual-level consent to join the observational cohort will be sought from study participants (adults on LA CAB+RPV and comparator group on oral ART) prior to any study procedures. Potential observational cohort participants will be identified by the local research team. Potential participants will be briefly verbally introduced to the aims and requirements of the study by the local research team. Those who are deemed to have mental capacity to provide informed consent and are keen to proceed to receiving the full participant information (PIS) will then we provided with a link to the on-line participant information sheet (PIS) and informed consent form (ICF) via email or text message by the local research team. If the participant cannot complete on-line informed consent for any reason, written consent will be sought by the site research team using a paper-based PIS and ICF. Once a participant has provided informed consent and joined the study the ICF will be filed locally and the coordinating centre team will be notified.

The participant will be informed that participation is voluntary and that he/she can withdraw his/her consent at any time without any consequence for his/her treatment or future relationship to the clinic/hospital. The PIS must be read and the ICF signed before any study related activities can begin.

For the qualitative work (in-depth interviews with a sub-set of cohort participants and interviews/focus group discussions and questionnaire with healthcare workers) a separate informed consent process will be undertaken by a member of the research team at Brighton and Sussex Medical School. The qualitative participant information and informed consent process will be also be administered on-line where possible but paper-based PIS/ICFs will be available where necessary.

12.3. Prospective observational study

12.3.1. Collation of routinely collected clinic data

Routine blood testing is performed as part of routine clinical care per the BHIVA HIV Monitoring Guidelines [9]. No research blood testing is performed. Routinely collected clinic data from the participants in the LA CAB+RPV group and oral ART comparator group will be submitted by the participating clinic investigator (research nurse or research assistant) at

baseline, 6 and 12 months via a REDCap case report form. HIV viral load will be collected at every time point that it is measured from the time of participant enrolment.

It is possible to include data on consenting adults who started the injectable regimen up to 6 months prior to the clinic being activated as a study site. These individuals will not be asked to complete the participant questionnaires but their routinely collected clinic data is still valuable to the study objectives.

Continuation of the cohort study period for a longer duration may be possible if funding is made available for cohort and data management. Participants would be contacted to ask whether there are willing for their routinely collected clinic data to be shared beyond the initial 12-month data collection period. This would not involve any additional procedures for the participant.

12.3.2. Data items to be collected

The following items are collected:

- Demography and basic information: Date of birth, gender, country of origin, ethnicity, height, weight, date of first HIV-1 positive test and mode of HIV-1 transmission.

- Laboratory data: HIV VL at all points of testing, CD4 count where available, hepatitis C status, hepatitis B serology, as well as routine laboratory data that describe the function of the kidneys and liver. Biomarkers of metabolic disease will also be collected.

- Medical treatment: Current HIV treatment regimen, prior ART regimen, number of HIV drugs and drug classes used in the past, year of first treatment regimen. Medical treatment related to co-infections and co-morbidities.

- Clinical events: Medical history and any interim clinical events (including AIDS, myocardial infarction, stroke, kidney failure, liver failure, cancer, bone fractures etc). Interim medical events will be assessed for seriousness and relatedness (an adverse reaction that may be possibly, probably or definitely related to the injections).

12.3.3. Participant questionnaire

An on-line participant questionnaire will be administered at baseline, and again at months 6 and 12 with both individuals on the injectable regimen and oral comparator. The participants on LA CAB+RPV will complete both sections of the questionnaire (LA CAB+RPV experience and HIV Patient Reported Outcome Measures), whereas those on oral ART will only complete the HIV PROM section. Where individuals are unable to use the on-line questionnaire a paper-based self-administered or research staff-administered questionnaire will be used. The questionnaire will be piloted and refined through a public participant involvement process.

Participants who complete a questionnaire will be remunerated with a shopping voucher to compensate for their time and effort.

12.3.4. Schedule of Activities

The following activities will take place for PLWH enrolled in the prospective cohort study.

Table 1. Schedule of Activities for Participants

	individual baseline M0*	Individual month 6 (+/- 2 months)	Individual month 12 (+/- 2 months)
Informed consent process	X		
ROUTINELY COLLECTED CLINIC DATA			
Baseline characteristics, height	X		
Comorbidities	X	X	X
HIV / ART history	X		
HIV VL (all interim VLs collected)	X	X	X
CD4+ T cell count (if available)	X	X	X
Creatinine, eGFR, HbA1c, lipids, ALT, weight (if available)	X	X	X
Interim medical events requiring medical attention/treatment		X	X
QUESTIONNAIRES			
Participant questionnaire: • Section A: LA CAB+RPV treatment experience and preference • Section B: HIV PROM (oral comparator group only complete section B)	X	X	X
QUALITATIVE			
In-depth interviews (~n=3 at each site)		X	
*Individuals who have been switched to LA CAB+RPV during the 6 months prior to the clinic site being opened for enrolment are eligible to join the prospective cohort study for the collection of routine clinic data. Their individual baseline is the date that they were switched to LA CAB+RPV. eGFR = estimated glomerular filtration rate, ALT = alanine transaminase, HbA1c = haemoglobin A1c, HIV VL = HIV viral load, HIV PROM = HIV patient reported outcome measures			

Approximately three healthcare workers from each participating clinic will be asked to complete a single questionnaire and engage with an interview / focus group discussion.

12.4. Nested qualitative study

12.4.1. Participant in-depth interview

A subset of PLWH in the prospective cohort study at each site will be approached to consent for an in-depth interview about their experiences with the injectable regimen after receiving approximately 6 months of injectable treatment. The in-depth interviews will be conducted by a research assistant from Brighton and Sussex Medical School at the University of Sussex. An additional consent process will be undertaken (see section 21.3) and consenting individuals will be interviewed on-line where possible. Interviews will take a maximum of 1 hour and will be audio-recorded then transcribed and anonymised for analysis. It is anticipated that interviewing approximately 3 individuals at each site will reach thematic saturation. Where interviews cannot be conducted on-line then a member of the research team can support an in-person interview. A study participant will only be interviewed once during their follow-up period. Anyone interviewed will be remunerated with a £20 shopping voucher to compensate for their time and effort.

12.4.2. Healthcare worker questionnaire and focus group discussion

Approximately three key healthcare workers from each participating clinic will be asked to complete a short on-line questionnaire about their experience with LA CAB+RPV.

We will interview the key healthcare workers responsible for delivering the service at each clinic including the **lead HIV/ID Consultant, the Clinical Nurse Specialist and Pharmacist or any other member of staff involved with the delivery of** LA CAB+RPV. The interview / focus group can take place at any time point during the study site participation in the study. An on-line consent process will be completed prior to any focus group taking place. Personal data will be anonymised.

12.5. Safety reporting

If a serious adverse event (SAE) has occurred during the participant follow up period and the SAE is **possibly, probably or definitely related to LA CAB+RPV (i.e. a suspected serious adverse reaction)** it should be reported to the ViiV safety team as soon as possible in the interest of pharmacovigilance. The definition of possible, probable or definitely related events is shown below.

12.5.1. Assessing adverse events for seriousness, causality and expectedness of adverse events

A serious adverse event is any untoward medical occurrence that meets one of the following criteria:

1. fatal
2. immediately life-threatening
3. results in hospitalisation or a prolongation of an existing hospitalisation (does not include visits to A+E without admission, admissions for social reasons or elective procedures for cosmetic surgery).
4. abnormal pregnancy outcome
5. causes severe disability/incapacity

The causality of the SAE should be assessed when deciding whether to report the SAE to ViiV. If any doubt exists please discuss with the site Principal Investigator.

Causality of adverse events	
Unrelated	No evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after a study procedure). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after a study procedure). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship with study procedures and the influence of other factors is unlikely.

Definite	There is clear evidence to suggest a causal relationship with study procedures and other possible contributing factors can be ruled out.

Expectedness of the event in relation to LA CAB/RPV or underlying disease (HIV or associated comorbidities) must then be determined. Expected side effects from the product are listed in the summary of medical product characteristics (SmPC) (https://viivhealthcare.com/content/dam/cf-viiv/viiv-healthcare/en_GB/medicines/CABENUVA-VOCABRIA-PM-26-Mar-2021.pdf).

If an SAE is deemed to be related to LA CAB/RPV and unexpected according to the SmPC then is a suspected unexpected serious adverse reaction (SUSAR), which requires expedited reporting and a high level of scrutiny.

12.5.2. Reporting of SAEs and SUSARs

With the support of the local research team, the SAE reporting process should be performed by the **participant's responsible clinician** who is likely to have the best understanding of the participant's medical history, the event and its clinical course. The safety reporting form is in Appendix 21.5. It should be reported to ViiV and the Sponsor within 24 hours of the site research team becoming aware of the event. Pregnancies arising on cabotegravir and rilpivirine should also be notified to ViiV within 7 days of awareness of pregnancy. The pregnancy notification form will be provided by the coordinating centre if required. The email address for notifications are:

Sponsor: researchgovernance@sussex.ac.uk, f.cresswell@bsms.ac.uk
ViiV: OAX37649@GSK.com

SUSARs should be reported as above but also require reporting to the research ethics committee (REC) within 15 days. This would be handled by the Sponsor.

12.6. Registry dataset to quantify the adoption cascade

Participating clinics will be asked to perform a local database search and create a registry dataset of all participants eligible for the LA CAB+RPV regimen according to the BHIVA guidance, or who have already commenced the LA regimen. From this registry dataset, over the following 12 months, the clinic will then quantify the number ever offered a switch to LA CAB+RPV, the number who accept the switch and the number who remain on the regimen for at least 1 year duration. Reasons for not being offered or declining a switch to LA CAB+RPV will be recorded.

13. Risks and benefits for participants

13.1. Risks

Participation in this study does not include any risk for the participants as the study does not test any drugs and participation in this study does not interfere with the treatment/care participants may receive at their regular HIV clinic. Pregnant women may participate in the study, as no interference with their treatment or pregnancy in any way will take place. Within the HIV service clear pathways for the management of medical complications exist and all issues will follow these pre-defined pathways.

13.2. Benefits

There are no direct benefits to the participants. However, the benefit of conducting observational research includes advancing scientific understanding of how LA ART is being implemented in the UK; this knowledge may guide treatment recommendations to the benefit of people living with HIV.

14. Withdrawal from study

Withdrawal from the study may be required if the participant withdraws consent as they no longer wish to participate. The decision to withdraw and the reason will be documented in the eCRF. The participant will be informed that data and samples collected up to that point will be retained for the purposes of the study, with their permission.

If a participant is lost to follow-up they can remain in the cohort and their missed visits will be documented in the eCRF. It is important to allow data collection on these individuals in case they return at a later date as describing their outcomes is of interest.

If an individual transfers out to another clinic it may not be possible to collect their routine clinic data (e.g. viral load data) however they can still complete questionnaires and therefore can remain in the cohort. The reason the laboratory data is missing will be recorded in the eCRF.

15. Ethical Considerations

The investigator(s) will ensure that this study is conducted in full conformity with the *7th* revision of the 1964 Declaration of Helsinki. The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines and Addendum ICH GCP E6 (R2)).

15.1. Ethics committee approval

Prior to the enrolment of participants, the Sponsor's research ethics committee (REC) and the Health Regulatory Authority (HRA) must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Participant Information Sheets and Informed Consent Forms, any other written information that will be provided to the participants, any advertisements that will be used and details of any subject compensation.

Any proposed amendments to the protocol or informed consent forms must be submitted to the REC for approval and may be implemented only after REC approval has been obtained. The amended protocol will be sent to participating sites for local approval to be granted and the approved version will be shared with all staff involved in the study.

15.1.1. Annual progress reports

The REC will be sent annual safety reports on the anniversary of each REC approval until the end of study, in order to facilitate their continuing review of the study (reference. ICH GCP E6 Section 3.1.4). The REC will be informed of the End of Study, as defined in this protocol, within the required timelines.

15.1.2. Health Research Authority approval

HRA approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing. The HRA and all participating sites also need to be notified of all protocol amendments to categorise the amendment and assess whether the amendment affects the institutional approval for each site.

15.1.3. Non-compliance with the Protocol

Deviations from research protocols and GCP occur commonly, the majority of these instances are technical deviations that do not result in harm to the participants or significantly affect the scientific value of the reported results of the trial. Protocol deviations (PD) or violations (PV) should be documented in the deviation case report form in REDCap in order for corrective and preventative actions to be taken.

The Investigators will review all PDs and PVs. PVs will also be reported to the Sponsor. It is the responsibility of the Sponsor to assess the impact of the breach on the scientific value of the and an assessment of whether the PV constitutes a serious breach will be made.

15.1.4. Serious Breach

A serious breach is defined as a breach of the principles/conditions of GCP, or of the trial protocol, that affect to a significant degree the safety of trial participants or the scientific value of the trial. The Sponsor should be notified within 24 hours of identification of a serious breach. The judgement on whether a breach is likely to have a significant impact on the scientific value of the trial depends on a variety of factors e.g. the type and extent of the data affected by the breach, the overall contribution of the data to key analysis parameters, the impact of excluding the data from the analysis etc. Examples of serious breach:

- Breach of GCP or protocol leading to the death, hospitalisation or permanent disability of a participant
- Proof of fraud relating to clinical trial records or data
- Persistent or systematic non-compliance with GCP or protocol that has a significant impact on the integrity of trial participants in the UK
- Failure to comply with safety reporting requirements.

The Sponsor will notify REC within 7 days of becoming aware of a serious breach.

15.1.5. Insurance and Indemnity

The Sponsor has civil liability insurance, as well as negligent harm and non-negligent harm insurance policies which apply to this study.

15.1.6. Informed consent process

Informed consent will be obtained from all participants using REC approved Participant Information Sheet(s) (PIS) and Informed Consent Form(s) (ICF).

The participant will be informed about the rationale and requirements of the study via the electronic PIS. Or where there are any reading difficulties, or if the potential participant has questions, the PIS can be downloaded and printed and an in-person consent process with the research team can be completed. Potential participants will be given an adequate amount of time to consider their participation in the study. If they decide to participate in the study they will be asked to sign the ICF on-line, which will then be countersigned by site Investigator on-line. The participant will be emailed a copy of the signed ICF, another copy will be downloaded and filed in the participant's research records at the site.

The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time from the study without giving reasons and without prejudicing further treatment.

15.1.7. Confidentiality

The Investigators must ensure that the participant's confidentiality is maintained in accordance with Good Clinical Practice (GCP) Guidelines. Study participants are de-identified and anonymised with a Unique Patient Identifier (PID). A de-coding list is held in a safe location by the individual site and it is the responsibility of cohort PI/local study staff to secure this. All data shared will contain the PID number and no unique person identifiers. On the eCRF or other documents submitted to the Sponsor, the participant will be identified by a participant ID number only. Only the Central Data Manager will have access to the participant ICF where the name is evident.

The Investigator shall permit direct access to participants' records and source documents for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor and REC.

15.1.8. Data Protection

The investigator will preserve the confidentiality of all participants taking part in the study, which will be conducted in accordance with the General Data Protection Regulation (GDPR). The investigators and study site staff will comply with the requirements of the Data Protection Act 2018 concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

15.1.9. Remuneration

Participants are not remunerated for joining the cohort study. However, the time participants spend on a questionnaire, or for those who undergo an in-depth interview, will be remunerated with a £20 shopping voucher.

The participating research site is reimbursed for completed deliverables e.g. enrolment, eCRFs submitted in REDCap, completion of clinic registry for the adoption cascade.

16. Data Management

The research tools and eCRFs are in English. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by subjects must use vocabulary that is clearly understood, and be in the language appropriate for the study site.

16.1. Source data

Source documents include original documents related to the study data (e.g. patient medical records which can be paper-based or electronic). Adequate source documentation must be maintained at participating sites to allow reliable verification and validation of the study data.

For questionnaires that are administered directly on-line the eCRF is the source document.

16.2. Data collection and Database

Study data will be collected on an electronic case report forms (eCRFs). The principal means of data collection from participant visits will be Electronic Data Capture (EDC) using the REDCap database. Data are entered into REDCap system by trained site personnel. Data entered by the site team will include demographics, medical history, HIV treatment history, blood test results, protocol deviations etc.

The participants will be sent on-line REDCap questionnaires at month 0, 6 and 12 and by answering the questions will be directly entering data. If the participant is unable to directly enter data on the REDCap questionnaires the data from a paper-based questionnaire can be entered into REDCap on behalf of the participant by a member of the study team.

All changes made following initial submission of data will have an electronic audit trail with a date. Specific instructions and further details will be outlined in the study specific eCRF completion manual.

16.3. Data storage and archiving

The investigator must retain essential documents until notified by the Sponsor, and for at least ten (10) years after study completion. Participant files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor. All data collected during the study will be stored in the UK.

Data is held securely by the Sponsor for at least 10 years on a password-protected electronic folder in the University of Sussex hosting service (One Drive).

16.4. Data sharing

We will be proactive in ensuring that this valuable data is used to its full potential. The Study Management Group (SMG) will welcome proposals for collaborations from other academic groups as well as the study funders. Those potentially interested should submit a proposal to the SMG containing information about the project, analysis plan and data requirements. Proposals will then be discussed by the SMG and will be approved if it is felt to be scientifically valid with appropriate methodology. Any request for sharing the study dataset must be approved by the SMG.

17. Statistical Considerations

As this is primarily a descriptive study no formal power calculation is required. The inclusion of a group of people receiving oral ART is to give an indication of the outcomes that would be seen had the participant not switched to LA CAB+RPV, but it is not our intention at this stage to formally compare groups due to the expected differences in characteristics of the two groups. Across all study sites the aim is to recruit a minimum of 150 adults receiving LA CAB+RPV into the prospective cohort study and ~50 adults who remain on oral ART as the comparator population. Around 20-30 participants will participate in the qualitative study.

Detailed description of the statistical analyses, any deviation from the protocol, and assumptions employed will be presented in a detailed Statistical Analysis Plan (SAP) that will be prepared prior to database closure and initiation of any statistical analyses below.

The demographic, clinical and treatment characteristics of all participants (age, BMI, race/ethnicity, co-morbidities, ART history) will be presented as summary statistics (mean,

median, standard deviation, IQR, maximum and minimum for continuous measurements, and numbers and proportions for categorical measurements), stratified by group (LA CAB+RPV, oral ART).

We anticipate most participants will have virological suppression at baseline; in such participants the proportion of participants with sustained virologic suppression at 6 and 12 months will be described. For those who are not virologically suppressed at enrolment, changes in viral load will be described.

Amongst those with available longitudinal CD4 count data, renal data (creatinine / eGFR) and lipid data (total cholesterol, total:HDL cholesterol ratio and triglycerides) the mean change from baseline in the LA CAB+RPV group and the oral group will be described.

The number and proportion of participants who discontinue LA CAB+RPV and the reason for discontinuation will be described.

The 'end of study' is the point at which last participant final visit individual data has been entered into the electronic data capture system and all the qualitative work has been completed. Thereafter, the 'end of study' the close out visit will be performed. The study will only be considered 'closed' when all participants have completed their final study visit, all assessments completed, all the data have been entered into the database and all data queries resolved, close out visit conducted, the database locked and data analysis performed and reports written.

18. Study Management and Oversight

The study has undergone independent peer review at the Protocol Review Panel at University of Sussex.

The study will be managed via the Brighton and Sussex Medical School Department of Global Health and Infection at the University of Sussex. The study management group (SMG) consisting of the Chief Investigators, Co-Investigators, Study Manager, Data Manager will be responsible for the day-to-day conduct of the study and will troubleshoot any operational issues.

As this is a low-risk non-interventional protocol, there is no requirement for a data safety monitoring committee for this study. University of Sussex safeguarding policies will be followed https://www.sussex.ac.uk/safeguarding/.

18.1. Monitoring

The study will be monitored periodically by study monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

18.2. Audit

The study may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection. The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the The UK policy framework for health and social care research (2017).

18.3. Public Involvement

Members of the public are actively involved in the creation of the protocol, participant information sheets and informed consent forms. Community events will be organised over the course of the study to ensure that findings are shared in an appropriate format and that public advice on suitable dissemination strategies is sought.

19. Publication Policy

Information concerning the study, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The Investigator may use this information for the purposes of the study only. All information obtained as a result of the study will be regarded as confidential, at least until appropriate analysis and review by the investigator(s) are completed.

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A full publication policy, including timelines for receipt of feedback and guidelines for authorship will be drafted.

20. Conflicts of Interest

The study is funded by ViiV healthcare who manufacture cabotegravir.

21. References

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3. Orkin C, Arasteh K, Gorgolas Hernandez-Mora M, et al. Long-Acting Cabotegravir and Rilpivirine after Oral Induction for HIV-1 Infection. The New England journal of medicine **2020**; 382(12): 1124-35.
4. Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-Acting Cabotegravir and Rilpivirine for Maintenance of HIV-1 Suppression. The New England journal of medicine **2020**; 382(12): 1112-23.
5. National Institute of Clinical Excellence. Cabotegravir with rilpivirine for treating HIV-1. Technology appraisal guidance, **2022** 05/01/2022.
6. Chounta V, Snedecor SJ, Wu S, Van de Velde N. Indirect comparison of 48-week efficacy and safety of long-acting cabotegravir and rilpivirine maintenance every 8 weeks with daily oral standard of care antiretroviral therapy in participants with virologically suppressed HIV-1-infection. BMC Infectious Diseases **2022**; 22(1): 428.
7. Cresswell FV, Lamorde M. Implementation of long-acting antiretroviral therapy in low-income and middle-income countries. Current opinion in HIV and AIDS **2022**; 17(3): 127-34.
8. Waters L, Sparrowhawk A. Clinical implementation of long-acting antiretroviral treatment in high-income countries: challenges and advantages. Current opinion in HIV and AIDS **2022**; 17(3): 121-6.
9. Association BH. Interim BHIVA guidance on long-acting cabotegravir/rilpivirine (LA-CAB/RPV) for antiretroviral therapy. Available at: https://www.bhiva.org/file/62012a06e2920/interim-BHIVA-guidance-on-LA-CAB-RPV-for-antiretroviral-therapy.pdf.
10. Venkatesan P. Long-acting injectable ART for HIV: a (cautious) step forward. Lancet Microbe **2022**; 3(2): e94.

22. Appendices

22.1. GANTT chart

	2023				2024				2025				2026				2027			
Activity /Month	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
STUDY SET UP AND MANAGEMENT																				
Contract execution																				
Protocol development																				
Questionnaire development																				
Topic guide development																				
Pre-sponsorship meeting submission																				
Respond to comments from pre-sponsorship meeting																				
IRIS submission																				
HRA / REC approvals																				
Local approval and adoptions																				
Set up collaborations with ~10 participating NHS trusts / HIV clinics																				
Engagement with stakeholders																				
RESEARCH ACTIVITIES																				
Completion of registry dataset to outline adoption cascade																				
Participant enrolment into obervational cohort																				
Entry of routenly collected clinic data																				
Questionnaires with participants																				
Interviews with PLHIV																				
Questionnaires and focus groups with clinician																				
Transcription of interviews and focus groups																				
Analysis of interviews and focus groups																				
Data cleaning																				
Data analysis																				
WRITE UP & DISSEMINATION																				
Qualitative manuscript, participant experiences																				
Qualitative manuscript, clinician experiences																				
Adoption cascade manuscript																				
Observational cohort manuscript																				
Presentation at conferences (IAS 2026, EACs 2026, CROI 2027)																				
Community dissemination																				

22.2. Safety Reporting Form

N1	
at is the adverse event term?	Record one SAE diagnosis per line, or a sign/symptom if the diagnosis is not available. If a diagnosis subsequently becomes available, this then should be entered and the sign/symptom crossed out, initialled and dated by the investigator. A separate form should be used for each SAE. However, if multiple SAEs which are temporally or clinically related are apparent at the time of initial reporting then these may be reported on the same page. If this was recorded previously as a non-serious event but has progressed to serious, put a line through the Non-Serious AE record and transcribe the details onto the SAE form.
is the date and time the adverse event started?	Record the start date and time of the first occurrence of the event or signs/symptoms of the serious event, not the date and time the event became serious.
was the outcome of this adverse event?	All SAEs must be followed until the events are resolved, the condition stabilises, the events are otherwise explained, or the subject is lost to follow-up. Indicate if the event was 'Recovered/Resolved' or 'Recovered/Resolved with sequelae'. If the SAE is ongoing at the time the subject completes the study or becomes lost to follow-up, the outcome must be recorded as 'Not recovered/Not resolved' or 'Recovering/Resolving'. Also enter 'Not recovered/Not resolved' if the SAE was ongoing at the time of death, but was not the cause of death, enter fatal for the SAE which was the direct cause of death.
t date and time did the adverse event end?	Record the end date. This is the date the SAE Recovered/Resolved, or if the outcome was fatal, record the date the subject died. If the event Recovered/Resolved with sequelae, enter the date the subject's medical condition resolved or stabilised. Leave blank if the SAE is 'Not recovered/Not resolved' or 'Recovering/Resolving'. Record the end time of the SAE.
as the maximum severity/grade of the adverse event?	Record the maximum severity/grade that occurred over the duration of the event. Amend the severity/grade if it increases. Refer to the protocol for the Severity/Grade definition for the study.
linically Significant Action Taken dy Treatment(s) as a Result of the SAE	Indicate the response to the adverse event, whether it be from the investigator, local physician not in the study, or the subject. Drug withdrawn = Administration of study treatment(s) was permanently discontinued. Dosereduced = Dose is reduced for one or more study treatment(s). Doseincreased = Dose increased for one or more study treatment(s). Dosenotchanged = Study treatment(s) continues even though an adverse event has occurred. Drug interrupted = Administration of one or more study treatment(s) was stopped/interrupted temporarily but then restarted. Not applicable = Subject was not receiving study treatment(s) when the event occurred (e.g., pre-or post-dosing) or the subject died and there was no prior decision to discontinue Study Treatment(s).
) adverse event cause the subject e discontinued from the study?	Indicate 'Yes' if the event(s) were directly responsible for the subject's withdrawal from the study, otherwise indicate 'No'.
ne site was made aware of the SAE	Record Date/Time site was made aware of the SAE.
event related to study treatment?	It is a regulatory requirement for investigators to assess relationship to study treatment(s) based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. 'A reasonable possibility' is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support 'a reasonable possibility' include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.
ship to Specific Study Treatment(s)	If relationship to study treatment is Yes, specify which Study Treatment(s) caused the event.

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SERIOUS ADVERSE EVENTS (SAE) (Page 2 of 4)

DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

SECTION 2

A serious adverse event is any untoward medical occurrence that, at any dose:

a) results in death.

b) is life-threatening.

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) requires hospitalisation or prolongation of existing hospitalisation.

Note: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is 'serious'.

When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered 'serious'. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) results in disability/incapacity, or

Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e) is a congenital anomaly/birth defect.

f) other.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

g) possible drug-induced liver injury

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SERIOUS ADVERSE EVENTS (SAE) (Page 3 of 4)
INVESTIGATOR INSTRUCTIONS

SECTION 4 **If Study Treatment was Stopped, Did the Reported Event(s) Recur After Further Study Treatment(s) Were Administered?**	If deliberate or inadvertent administration of further dose(s) of study treatment(s) to the subject occurred, did the reported adverse event recur?
SECTION 9 **Details of Study Treatment(s)**	Complete this section using the information in the Study Treatment page. Details of all study treatment(s) taken until the time of the SAE should be included. Provide specific details in Section 11 Narrative Remarks if the subject has taken an overdose of study treatment(s), including whether it was accidental or intentional.

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THE INVESTIGATOR MUST INFORM GSK OF SERIOUS ADVERSE EVENTS BY E-MAIL OR TELEPHONE (E-MAIL PREFERRED) WITHIN 24 HOURS OF BECOMING AWARE OF THE EVENT. ALL OF THE HEADER INFORMATION MUST BE COMPLETED BEFORE SENDING BACK TO GSK.
(The original pages must remain in the Case Report Form/Study File).

Once form has been completed please email to mailbox:
OAX37649@GSK.com (or fax +44(0)20 8754 7822)

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SERIOUS ADVERSE EVENTS (SAE) (Page 4 of 4)
MONITOR DATA VALIDATION CHECKS

- Check that either 'Yes' or 'no' box at the top of the page has been completed.
- Start dates must be provided for the reporting of serious adverse event data. If the exact date is not known, liaise with the investigator to ensure that a best estimate is provided.
- Ensure that **no** medical or investigational procedures are captured on Serious Adverse Events pages.
- **Death** should not be recorded as an SAE but should be recorded as the outcome of an SAE. The condition that resulted in the death should be recorded as the SAE.
- Confirm that any SAEs marked as **Recovering/Resolving** or **Not recovered/Not resolved** have been followed up for details of resolution.
- If the subject permanently discontinued study treatment due to an SAE; and will continue with early study treatment discontinuation study participation, confirm the following variables are consistent for the SAE which resulted in permanent discontinuation of study treatment:
  - Most Clinically significant Action Taken with Study Treatment(s) as a Result of the SAE on the SAE form is recorded as 'Drug Withdrawn'
  - Primary reason for study treatment discontinuation on the Study Treatment Discontinuation page is 'Adverse event.'
  - Study Conclusion page will remain blank until subject completes post early study treatment discontinuation visit(s).
- If the subject was withdrawn from the study due to an SAE, confirm the following variables are consistent for the SAE which resulted in Study Withdrawal
  - Did the adverse event cause the subject to be discontinued from the study? Should be recorded as 'Yes.'
  - Primary reason with Withdrawal on the Study Conclusion page is recorded as 'Adverse Event.'
  - Study Treatment Discontinuation form is completed with appropriate reason for study treatment discontinuation.

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Protocol Identifier	Subject Identifier	Centre Number	Randomisation Number	

SERIOUS ADVERSE EVENT (SAE)

Did the subject experience a serious adverse event during the study? [Y] ☐ Yes [N] ☐ No *If Yes, record details below.*

SECTION 1

What is the adverse event term?	What is the date of the adverse event started?	What is the time of the adverse event started?	What was the outcome of this adverse event?	What date did the adverse event end?	What time did the adverse event end?	What was the maximum severity/ grade of the adverse event?	Most Clinically Significant Action Taken with Study Treatment(s) as a Result of the SAE	Did the adverse event cause the subject to be discontinued from the study?	Date site was made aware of the SAE	Time site was made aware of the SAE	Is this event related to study treatment?	Relationship to Specific Study Treatment(s)
Diagnosis Only (*if known*) Otherwise Sign/Symptom	Day Month Year	Hr : Min 00:00-23:59	1=Recovered/ Resolved 2=Recovering/ Resolving 3=Not recovered/ Not resolved 4=Recovered/ Resolved with sequelae 5=Fatal	*If fatal, record date of death.* Day Month Year	Hr : Min 00:00-23:59	1=Mild/ Grade 1 2=Moderate/ Grade 2 3=Severe/ Grade 3 4=Grade 4 5=Grade 5	1=Drug withdrawn 2=Dose reduced 3=Dose increased 4=Dose not changed 5=Drug interrupted X=Not applicable	Did the subject withdraw from study as a result of this SAE? Y=Yes[1] N=No	Day Month Year	Hr : Min 00:00-23:59	Is there a reasonable possibility the SAE may have been caused by the study treatment? Y=Yes N=No	If Yes, specify the study treatment(s) caused the event
e.g., Anaphylaxis	***25 JAN 18***	***13:25***	***1***	***27 JAN 18***	***10:20***	***1***	***4***	***Y***	***30 JAN 18***	***13:25***	***Y***	***GSK123456***
		:			:					:		
		:			:					:		

[1] *Complete Study Conclusion page and ✓Adverse event as reason for withdrawal.*

SECTION 2 Seriousness *(specify reason(s) for considering this a SAE, ✓all that apply:*

[A] ☐ Results in death
[B] ☐ Is life-threatening
[C] ☐ Requires hospitalisation or prolongation of existing hospitalisation
[D] ☐ Results in disability/incapacity
[E] ☐ Congenital anomaly/birth defect
[F] ☐ Other, *specify* _____ (*see definition of SAE*)
[G] ☐ Possible drug-induced liver injury (see definition in SAE section of the protocol)

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SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 3
Demography Data

Year of birth ☐☐☐☐ (Year) Sex ☐ Male ☐ Female Weight ☐☐☐.☐ kg Height ☐☐☐ cm

SECTION 4 If Study Treatment(s) was Stopped, Did the Reported Event(s) Recur After Further Study Treatment(s) were Administered?

☐ Yes ☐ No ☐ Unknown at this time ☐ Not applicable

SECTION 5 Possible Causes of SAE Other Than Study Treatment(s), ✓*all that apply:*

☐ Disease under study
☐ Medical condition(s) *specify* _____
☐ Lack of efficacy
☐ Withdrawal of study treatment(s)
☐ Concomitant medication(s) *specify* _____
☐ Activity related to study participation *(e.g., procedures)*
☐ Other, *specify* _____

SECTION 6 RELEVANT Medical Conditions

Specify any RELEVANT past or current medical disorders, allergies, surgeries that can help explain the SAE. Ensure each medical condition recorded in this section is also recorded in the appropriate Medical Conditions form.	**Date of Onset** Day Month Year	**Condition Present at Time of the SAE?** Y= Yes N=No	***If No, Date of Last Occurrence*** Day Month Year

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SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 7 Other RELEVANT Risk Factors *Provide any family history or social history (e.g., smoking, alcohol, diet, drug abuse, occupational hazard) relevant to the SAE). Ensure each risk factor recorded in this section is also recorded in the appropriate Medical Conditions form.*

SECTION 8 RELEVANT Concomitant Medications *Include details of any concomitant medication(s) that may help explain the SAE, may have caused the SAE or was used to treat the SAE. Ensure each concomitant medication recorded in this section is also recorded in the Concomitant Medication form.*

Drug Name *(Trade Name preferred)*	Dose	Unit	Frequency	Route	Taken Prior to Study? Y=Yes N=No	Start Date Day Month Year	Stop Date Day Month Year	Ongoing Medication? Y=Yes N=No	Reason for Medication
e.g., Zantac	***150***	***mg***	***BID***	***PO***	***N***	***25 JAN 18***	***27 JAN 18***	***N***	***Gastric ulcer***

SECTION 9 Details of Study Treatment(s)

Was treatment blind broken at investigational site? ☐ Yes ☐ No ☐ Not applicable

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Protocol Identifier	Subject Identifier	

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 10 Details of RELEVANT Assessments *Provide details of any tests or procedures carried out to diagnose or confirm the SAE (e.g., laboratory data with units and normal range) if data for this SAE have not been previously entered, and the CRF includes a page for the test, ensure the data is also entered on the page.*

SECTION 11 Narrative Remarks *(provide a brief narrative description of the SAE and details of treatment given)*

Investigator's signature _____
(confirming that the data on the SAE pages are accurate and complete)

Date ☐☐ ☐☐☐ ☐☐ Day Month Year

Investigator's name (print) _____

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