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Study protocol: the HOLA Study – Exploring the acceptability, appropriateness, feasibility and satisfaction of an implementation strategy for out-of-HOspital administration of the Long-Acting combination of cabotegravir and rilpivirine as an optional therapy in HIV-Infected patients from Spain – a hybrid implementation-effectiveness, phase IV, double arm, open label, multicentric study.

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Abstract

Introduction: The HOLA Study is a 12-month randomized, hybrid implementation-effectiveness, phase IV, double arm, open label, multicentric study including virologically suppressed people living with HIV (PWH). HOLA, which started in September 2023, evaluates acceptability, appropriateness, feasibility and satisfaction of out-of-hospital administration of cabotegravir and Rilpivirine (CAB+RPV LA).

Methods: A total of 110 PWH who are already under treatment with CAB+RPV LA or switch their antiretroviral therapy to CAB+RPV LA will be recruited from two main hospitals in Barcelona (Germans Trias I Pujol and Vall d'Hebrón) and Costa del Sol Hospital, in Marbella. The patients will be randomized 1:1 into a Hospital Group (administration of CAB+RPV LA in the hospital) and the Outpatient Group (Out-of-hospital administration) including community or primary care centers. The main

objectives of the study are to compare the acceptability at month 12 of the administration of CAB+RPV LA in and out-of-hospital centers from the perspective of patients, and to assess and compare the safety and tolerability of CAB+RPV LA. The study takes place at 9 clinical units in Catalonia, and Andalusia, [3 tertiary hospitals (recruiting centers), 1 community center, 1 STI clinic, and 4 primary care centers].

Ethics and dissemination: The current publication refers to version 3.0. of the protocol, with issue date on the 14th April 2024. The clinical trial will be conducted according to the principles of the Declaration of Helsinki, Fortaleza, Brazil, October 2013. This study will be conducted according to Spanish regulations regarding clinical trials (Royal Decree 1090/2015) and biomedical investigations (Organic Law 14/2007 of biomedical investigation and the Royal Decree 1716/2011), and the Clinical Trial Regulation (Regulation EU No 536/2014). Confidentiality requirements will follow the required Data Protection legislation. Enrolment completion in the study is expected by the end of May 2024, with an end of study expected in May 2025.

Trial registration number: NCT06185452 / 2023-503963-41-00

Keywords: implementation science, cabotegravir and rilpivirine long acting, CAB+RPV LA, HIV, patient-centered care

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Strengths and limitations

Strengths:

- The HOLA study through its implementation research in HIV healthcare will generate the knowledge required for policymakers, healthcare mediators and the community to modify the current models of care in PWH in order to improve their quality of life, shifting towards a patient-centered approach.
- The study includes participation of community centers and STI clinics due to their proximity with PWH and their implication in the PrEP implementation and rapid HIV diagnosis.
- The study addresses not only urban tertiary centers but also rural centers.

Limitations:

- There may be patients that do not wish to participate in the study due to concerns regarding the confidentiality of their HIV status at their primary care center, specifically in the case of rural areas; or due to preference for in-hospital treatment exclusively due to distance to the clinic and time availabilities.
- It is also important to note that the intervention is not exempt from certain risks, such as staff changes or logistic inconveniences, so it is important to plan for these in advance.
- Per protocol, a medical visit at the hospital at months 6 and 12 had to be included for routine medical care. For those participants who have been randomized to receive treatment at the out-of-hospital center, this is a limitation since it implies duplicating the visit in two centers. Further implementation efforts should take this into consideration.

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Introduction

UNAIDS is a strategic program aimed at guiding and coordinating governments and structures that are responsible for providing HIV services in order to save lives (unaids.org). Until 2020, the objectives were to ensure that 90% of people with HIV (PWH) were diagnosed, 90% of them on antiretroviral treatment (ART), and 90% of them virally suppressed, and these have been updated to 95-95-95 for 2025. Additionally, a new objective to improve the quality of life has been included (Coll, P et al. 2023). In fact, ART for the treatment of HIV infection has changed from a uniformly fatal into a potentially chronic disease and, currently, there are many potent, convenient, and well tolerated antiretroviral combinations available. However, ART should be prescribed as early as possible and, for the moment, in a life-lasting manner. For these reasons, there is a need for more convenient, less frequent treatment, to help address challenges associated with posology, psychosocial issues and adherence in PWH.

Long-acting (LA) injectable regimens are emerging as a treatment option that may simplify therapy for PWH and anticipate a shift in the treatment paradigm for these people (Moreno S, Rivero A, Ventayol P, et al. 2023). There are data confirming the non-inferiority of the LA intramuscular (IM) cabotegravir (CAB) and rilpivirine (RPV) compared with continuing a standard of care regimen in antiretroviral-naive adults with HIV-1 suppressed after 20 weeks in oral ARV with DTG/ABC/3TC (FLAIR study) (Orkin C, et al. 2021) and for the maintenance of viral suppression (ATLAS, ATLAS-2M and LATTE-2 studies) (Overton ET, et al. 2023; Swindells S, et al. 2020). Nonetheless, in Spain, this LA regimen must be administered in the hospital by a trained health team every 2 months, supposing a change in the dynamics of HIV units, which were previously reserved for a medical visit every 6 months. For these reasons, this option could be less convenient than conventional daily oral therapy for some people, since it implies visits to the hospital every 2 months for the administration of the injections.

A shared approach for the treatment administration with primary care or community centers may be appropriate to improve the patient's satisfaction while maintaining high-quality care for PWH. However, there is still insufficient evidence regarding the feasibility of decentralizing treatment for PWH, in particular in the context of Spain.

Given these considerations, the proposed study seeks to address these issues by implementing the out-of-hospital CAB + RPV LA administration. Alternative settings to receive CAB + RPV LA will offer new options to PWH that may increase their quality of life and improve psychosocial challenges. In additional to primary care centers, we are also interested in including community centers and STI clinics due to their proximity with PWH and their implication in the PrEP implementation and rapid HIV diagnosis. In addition, centers belong to two different regions from Spain, including not only urban tertiary centers but also rural centers.

Research questions

To assess the implementability of this approach in Spain, first, we propose a comparison of the acceptability, appropriateness, and feasibility of the administration of CAB + RPV LA between out-of-hospital settings and the local standard of care (hospital administration), as well as the patient's satisfaction. The study is also focused on the identification of the PWH profile who are the best candidates to this strategy and whose satisfaction is higher. Finally, we will distinguish patients who are naïve to CAB+RPV LA from those who are not to evaluate potential intra-group differences.

Aims and objectives

The primary objective of this post-approval study is to assess and compare the acceptability by the patient of the implementation of CAB+RPV LA from the perspective of participants receiving outside-hospital injections versus the participants receiving hospital injections by month 12, in order to support future scale up efforts. A co-primary objective of the study will be to assess and compare the safety and tolerability of CAB+RPV LA between the out-of-hospital administration and the in-hospital administration groups.

Secondary objectives are to assess and compare acceptability, appropriateness, and feasibility of the administration of CAB+RPV LA as perceived by patients and HCP/non-clinical staff, as well as patient's satisfaction, and expectations throughout all timepoints of the study; retention, engagement, and compliance; and to identify those patients in which the out-of-hospital administration is more suitable. Tertiary objectives are to assess and compare between groups the virological effectiveness; the change at month 12 vs baseline in patient's acceptability, satisfaction, and expectations among the subgroup of participants with previous experience with CAB+RPV LA; and to compare these to those patients who have never received CAB+RPV LA.

Methods and analysis

Study design

This is a 12-month, randomized, hybrid implementation-effectiveness, phase IV, double arm, open label, multicentric study including virologically suppressed PWH who start or are currently under treatment with CAB+RPV LA, to evaluate the out-of-hospital versus in-hospital administration of this combination in terms of acceptability, appropriateness, feasibility and satisfaction.

The study began in the **preparation stage**, where healthcare staff were engaged, informed, and trained about CAB+RPV LA and the delivery strategies. All processes and protocols were ensured to be in place before the first patient was enrolled, and adequate material and human resources were provided. Community and primary care healthcare workers were trained to help deliver the injections to patients.

The study then transitioned into the **initial implementation stage** when the first patients were recruited and enrolled. Patients were randomized 1:1 into a in-hospital group or out-of-hospital group and stratified according to age (<50 years old or ≥50), gender (male or female), as well as according to whether participants are already receiving CAB + RPV LA. As of October 2023, the first patient was enrolled. PWH naïve to CAB + RPV LA, during the oral treatment lead-in phase are attended at the reference hospital, to discard adverse events, and the first injection is administered in the hospital. They start receiving CAB + RPV LA injection doses at their in-hospital or out-of-hospital assigned center from the next CAB + RPV LA administration (month 2). For patients previously receiving CAB + RPV LA, the first study injection is given in the randomized center, at month 2.

No changes in treatment regimens are foreseen during the study period. In case of failure of one of the regimens, a new regimen will be decided using a resistance test as clinical routine.

In case adverse events to the medication occur, the investigator will decide if it is necessary to replace it.

Investigators may provide oral CAB and/or RPV as a short-term "bridging" strategy for participants who have begun LA CAB + RPV in case a patient cannot attend an appointment. Should a participant need "oral bridging", sites must contact the coordinating investigators for guidance on treatment strategies prior to a missed LA CAB+ PV dose and the missed dose should be accurately noted in the registry. Bridge to oral therapy with CAB+RPV is permitted in the event that a patient missed an injection. However, no more than two missing injections will be allowed as part of the study.

At the end of the study, the change of treatment will be done at the discretion of the physician.

Study setting

The study takes place at 9 clinical units in two regions of Spain, Catalonia, and Andalusia, [3 tertiary hospitals (recruiting centers), 1 community center, 1 STI clinic, and 4 primary care centers] (**Table 1**); and spans two implementation stages: preparation and initial implementation.

Outcome measures

The study includes both participant outcomes and staff outcomes, divided between primary, secondary and exploratory outcome measures:

Primary outcomes measures:

1. To assess and compare between groups the number of participants that show an average composite score ≥ 4 across the Acceptability of Intervention Measure (AIM) questionnaire at month 12.
2. To assess and compare between groups the differences among the proportion of participants with an average composite score ≥ 4 across the AIM questionnaires at month 12.
3. To assess and compare between groups the average composite score across the AIM questionnaires at 12. To assess and compare between groups the incidence and severity of CAB + RPV LA-related adverse events (AEs), all Serious Adverse Events (SAEs), injection site reactions (ISRs) or post-injection reactions through study completion, and proportion of patients who presented grade 3 or 4 CAB + RPV LA-related adverse events.
4. To assess and compare between groups the proportion of participants who discontinue CAB + RPV LA due to AEs/SAEs and due to CAB+RPV LA-related adverse events.

Secondary outcomes measures:

1. To assess and compare between groups the proportion of participants with an average composite score ≥ 4 across the AIM questionnaires at months 1 and 6.
2. To assess and compare between groups the proportion of participants with an average composite score ≥ 4 across the Intervention Appropriateness Measure (IAM) and Feasibility of Intervention Measure (FIM) questionnaires, at months 1, 6 and 12.

3. To assess and compare between groups the proportion of healthcare professionals and/or non- clinical staff that show an average composite score ≥ 4 across the AIM, IAM and FIM questionnaires at months 1, 6 and 12.
4. To assess and compare between groups the proportion of patients who report high satisfaction at each study time-points using the HIV Treatment Satisfaction Questionnaire "status" (HIVTSQs12).
5. To assess and compare between groups changes in satisfaction derived from HIVTSQs12, in the overall sample from baseline to months 1, 6 and 12.
6. To assess and compare between groups changes in satisfaction derived from the HIV Treatment Satisfaction Questionnaire "change" (HIVTSQc12) in the overall sample from baseline to month 12.
7. To assess and compare between groups the expectations of the CAB + RPV LA regarding the following areas: adherence to treatment, follow-up of medical visits, illness perception, physical and emotional quality of life, family and social relationships and work at baseline and month 6 and 12. Expectations will be assessed through 5-likert scales developed ad hoc for the study.
8. To assess and compare between groups the Patient Reported Outcome Measures (PROMs) at each study time-points using the Patient Reported Outcome Measures HIV Clinic Screening Tool (PROMS-CST- HIV) questionnaire, at baseline and months 1, 6 and 12. This questionnaire assesses PRO regarding anticipated stigma, emotional distress, sexuality, social support, material deprivation, sleep and fatigue, cognitive problems, physical symptoms.
9. To assess and compare between groups changes in PROMs throughout the time points in each group in the overall sample using the PROMS-CST- HIV questionnaire.
10. To assess and compare between groups changes in the health professionals' expectations using a Health Professional Expectations Questionnaire through study completion.
11. To assess and compare between groups the perception of injection, using the perception of injection (PIN) questionnaire at months 1, 2, 4, 6, 8, 10 and 12.
12. To assess and compare between groups the proportion and number of patients who miss their appointment for the CAB + RPV LA administration (out of the window period ±7 days) from baseline to month 6 and 12.
13. To assess and compare between groups the number and proportion of patients who early interrupt CAB + RPV LA every 2 months at month 6 and 12.
14. To compare among groups the proportion of patients who adopt oral bridging therapy.
15. To identify those patients in which the out-of-hospital administration is more suitable by comparing the previous endpoints, stratifying according to: age (<50 vs ≥50 years old), gender (male vs female), as well as according to if the participant is already receiving or not CAB + RPV LA.

Exploratory outcomes measures:

1. To assess and compare between groups the virological effectiveness of CAB + RPV LA at month 6 and 12:
    - Proportion of subjects who are virologically suppressed (plasma HIV-1 RNA ≤50 copies/mL).
    - Proportion of participants with confirmed virologic failure/rebound (2 consecutive HIV-1 RNA greater than or equal to 200 copies/mL).
    - Proportion of participants with blips.

2. To assess the average change at month 12 vs baseline in patient's acceptability, satisfaction, and expectations among the subgroup of participants with previous experience with CAB + RPV LA.
    - To compare the average change from baseline to month 12 in proportion of participants that show an average composite score ≥ 4 across the AIM questionnaire.
    - To compare the average change at month 12 vs baseline in patient's acceptability, satisfaction, and expectations among the subgroup of participants with previous experience with CAB + RPV LA in the context of a clinical trial at month 12
    - Average composite score across the AIM questionnaires.
    - To compare between both groups the percentage of patients who report high satisfaction at each study time-points using the HIVTSQs12 from baseline and month 1, 6 and 12.
    - To assess and compare changes in satisfaction derived from HIVTSQs12 from baseline to month 1, 6 and 12.
    - To assess and compare changes in satisfaction derived from HIVTSQc12 from baseline to month 12.
    - To assess and compare among groups the expectations of the CAB+RPV LA regarding the following areas: adherence to treatment, follow- up of medical visits, illness perception, physical and emotional quality of life, family and social relationships and work at baseline and months 6 and 12.
    - To compare among groups the Patient Reported Outcome Measures (PROMs) at each study time-points using the PROMS-CST-HIV questionnaire at baseline and months 6 and 12.
    - To assess and compare changes in the PROMs from baseline to months 1, 6 and 12 in each group.
3. To compare patient's acceptability, satisfaction, and expectations between patients under prior treatment with CAB + RPV LA and those patients who have never received CAB + RPV LA.
    - Difference in number and proportion of participants that show an average composite score ≥ 4 across the AIM questionnaires at month 12.
    - Difference in the average composite score across the AIM at month 12.
    - To compare between groups the percentage of patients who report high satisfaction at each study time-points using the HIVTSQs12 at baseline and month 1, 6 and 12.
    - To assess changes in satisfaction derived from HIVTSQs12 from baseline to month 1, 6 and 12.
    - To assess changes in satisfaction derived from HIVTSQc12 from baseline to month 12.
    - To assess and compare among groups the expectations of the CAB + RPV LA regarding the following areas: adherence to treatment, follow-up of medical visits, illness perception, physical and emotional quality of life, family and social relationships and work at baseline and months 6 and 12.
    - To compare among groups the PROMs at each study time-points using the PROMS-CST-HIV questionnaire at baseline and months 1, 6 and 12.
    - To assess changes in the PROMs throughout the time points in each group from baseline to months 1, 6 and 12.

Sample size

A total of 110 virologically suppressed PWH will be included in this study and will receive CAB + RPV LA in the hospital and/or out-of-hospital alternative facilities. A period of enrolment of 8 months will be considered.

Participant identification

Potential participants who will be receiving or are receiving CAB + RPV LA within their routine clinical care are referred to the study team by their physicians within the HIV clinics of the three main hospitals. The local HIV teams then inform participants of the trial and provide patient information leaflets with contact details of the study team.

Inclusion and exclusion criteria

Adult PWH (age ≥18 years) will be invited to participate if they have capacity to consent with the following criteria:

- Chronic HIV-1 infection
- Will receive CAB+RPV LA as part of their routine clinical care.
- Recommended triple or dual therapy for at least 12 months, including CAB+RPV LA.
- Virologically suppression for at least 6 months (2 consecutive determinations of undetectable viral load).
- Post-menopausal or fertile females that agree to avoid pregnancy during the study. If sexually active female; using an effective method of contraception (hormonal contraception, intra-uterine device (IUD), or anatomical sterility in self or partner from 14 days prior to the first IMP administration until at least 13 months after the last IMP administration; all female participants must be willing to undergo urine pregnancy tests at time points specified in the protocol.
- Patients which have access to an out-of-hospital center in which can be treated without inconvenience.
- Patient who agrees to participate in the study and signs the informed consent.

Exclusion criteria include:

- Active Hepatitis B infection
- History of virological failure or mutations to INSTI or NNRTI.
- Previous antiretroviral treatment interruption during the last 6 months or treatment interruptions for more than a month.
- Contraindication for intramuscular injections
- Pregnant or breastfeeding women or desiring to become pregnant in the near future.
- Current use of the following concomitant treatment: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampicin / rifampin, rifapentine, St. John's wort

Data collection

All participating sites will be assessed using a mixed-methods approach including questionnaires, templated data collection instruments and primary data sources (clinic records).

Treatment compliance and concomitant treatment

LA CAB + RPV compliance is guaranteed because study medication is to be administered by a designated study nurse at the clinical site. If the participant does not attend any visit, this information will be documented in the CRF.

All other treatments taken, apart from the study medication administered during the study period, will be considered concomitant treatments and should be documented in the CRF. Patients who participate in the study will be remembered that they should not start any new or continue any concomitant treatment without the knowledge and permission of the investigator. In the event that discomfort following injection occurs, dosing with paracetamol 1g every 8 hours for a total of 24 hours will be allowed, but never as a prophylaxis treatment. If discomfort persists, the patient must seek medical attention.

The following medications must not be administered concurrently: Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin, Rifabutin, Rifampicin / Rifampin, Rifapentine, St. John's wort, Dexamethasone. In addition, the following treatments must be discontinued: proton pump inhibitors and systemic dexamethasone (more than a single dose). Use of anticoagulation agents greater than 14 days are prohibited and systemic anticoagulation on the day of an IM injection should be avoided where possible.

Questionnaires

Participant questionnaires

Questionnaires will be provided to participants by nursing staff involved in the study during their scheduled clinic visit, at baseline, months 1, 6 and 12, except for the perception of injection (PIN) questionnaire which is to be filled in by the patient 2 days after injection, electronically.

Healthcare staff questionnaires

Staff will complete at baseline and at the end of the study (final test) a Health Professional Expectations Questionnaire. At months 1, 6 and 12, healthcare professionals and non-clinical staff will fill in the AIM / IAM / FIM health professional/ non-clinical staff questionnaires.

Data analysis

Study data will be collected through a study-specific /electronic Case Report Form (eCRF). All questionnaire data will be collected directly on the eCRF by patients using an electronic device (tablets). All participants who passed screening and entered the study (ie, completed baseline electronic case report form - eCRF) will be included in the analysis population. The staff who completes the study questionnaires will also be considered part of the study and they will have an identification number and their role in the study (investigator, nurse, pharmacist, administrative staff).

The primary complete analyses will be conducted when the last study participant has completed their CAB + RPV LA study treatment up to month 12. All study staff participant (site-level) questionnaire, survey data, and all study participant (subject-level) data will be included in the analysis. For the primary analysis on the primary endpoint at month 12, we will use the ITT-E population. The ITT-E and Per-Protocol populations will be used for the secondary analyses and those on secondary aims. All the analyses on the primary and secondary objectives will be performed on the overall (total sample) population and by study arm. Formal comparisons of the two study arms will not be tested

and the evaluations of the two study arms and their differences will be assessed in essentially descriptive terms.

Ethics and dissemination

The clinical trial will be conducted according to the principles of the Declaration of Helsinki, Fortaleza, Brazil, October 2013. This study will be conducted according to Spanish regulations regarding clinical trials (Royal Decree 1090/2015) and biomedical investigations (Organic Law 14/2007 of biomedical investigation and the Royal Decree 1716/2011), which develop the Clinical Trial Regulation (Regulation EU No 536/2014). Confidentiality requirements will follow the required Data Protection legislation.

After the study, the Coordinating Teams of the study will discuss results and strategies for future, as well as the data dissemination plan, in order to maximize the impact of this work on clinical care and policy. The publication of the trial results shall meet the requirements set out in Article 42 of Royal Decree 1090/2015. Results emerged from this study will be reported in the HIV national and international meetings as well as published in international journals with high impact factor.

Discussion

"Treat All" policies in Spain and other regions worldwide have favored access to ART, consequently reducing HIV-related morbidity and mortality, and increasing life expectancy in PWH. Thus, HIV treatment has shifted to a chronic care model of disease management (Antinori, A. et al. 2023). Despite these improvements in life expectancy, stigma is still present, and recent goals by the UNAIDS include a novel target of quality-of-life improvement (Antinori, A. et al. 2023; unaids.org). In line with this, inclusion of PROs is becoming a preference in the development of the latest clinical trials, as these may shed light into which factors related to ART and patient care are of utmost importance in improving health-related quality of life, patient satisfaction, and in reducing stigma. In particular, a recent study carried out in Germany found out that the frequency of dosing and the risk of long-term side effects have a major influence on the acceptance of novel therapy regimens and should be considered to increase patient adherence and satisfaction (Emmert M, et al. 2023).

Long-acting regimen with CAB + RPV provide non-inferiority in terms of safety and efficacy, while reducing the frequency of dosing. As such, the combination of CAB + RPV LA received the European Medicine Agency's positive opinion in October 2020 guided by positive outcomes of pivotal phase III/IIIb ATLAS, FLAIR and ATLAS-2M studies (Overton ET, et al. 2023; Orkin C, et al. 2021; Swindells S, et al. 2020). Additionally, the use of CAB + RPV LA reduces the frequency of dosing from daily to every two months, and may aid in addressing fear of disclosure, anxiety around medication adherence, and daily reminders of the HIV status and the chronicity of disease (De Los Rios P, et al. 2019).

In the current clinical programs in Spain, this LA formulation has to be administered by a trained health team every 2 months in the hospital. Bringing treatment closer to patients may bring benefits to them in terms of satisfaction and reduction of stigma. However, evidence in the feasibility of the out-of-hospital delivery of CAB + RPV LA in Spain in non-existent. Implementation outcome measures are essential for monitoring and evaluating the feasibility of a change in procedures, such as the one described (Weiner

BJ, et al. 2017). Prior evidence in implementation science for this treatment comes mainly from the CARISEL (Cabotegravir and Rilpivirine Implementation Study in European Locations) study, a hybrid Phase III implementation-effectiveness trial implementing CAB + RPV LA for PWH). This study was aimed at evaluating participants switching from daily oral therapy to CAB + RPV LA dosed every 2 months (Q2M). However, the Spanish sites participating in the trial were only hospitals and no alternative outpatient centre were considered (CARISEL; NCT04399551).

In the CARISEL study, sites were randomized to standard implementation (Arm-S) or enhanced implementation (Arm-E), including additional implementation strategies. These enhancements were mainly focused on meetings that introduce CAB + RPV LA to clinic staff and discuss what might make implementation easier, and/or what might make it difficult, prior to first injection at the site; and meetings started to discuss an implementation plan, how to work through challenges, and introduce a continuous quality improvement plan, for 6 out of the 12 months of study. At Month 12, regardless of implementation arm, CAB + RPV LA was highly effective and well tolerated, consistent with clinical outcomes in the Phase 3 clinical program (De Wit S, et al. 2022).

Although HOLA has some similarity to CARISEL with respect to study outcomes, HOLA aims to examine differences between clinic settings (urban and rural) in Spain as well as hospital and community-based settings for administering CAB + RPV LA through a set of three questionnaires that had been previously developed under the Proctor framework, as four-item measures of implementation outcomes that indicate implementation success (Proctor et al., 2011): the AIM, IAM, and FIM questionnaires (Weiner et al., 2017). The importance of implementation research in HIV healthcare relies in its potential to generate the knowledge required for policymakers, healthcare mediators and the community to modify the current models of care in PWH in order to improve their quality of life. The HOLA study may provide the required outcomes that will help bridge the gap towards a patient-centered approach in HIV care.

Enrolment completion in the study is expected by the end of May 2024, with an end of study expected in May 2025. Pending end of enrolment, some of the limitations we have encountered in recruitment are patients opting not to enter in the study due to concerns regarding the confidentiality of their HIV status at their primary care center, specifically in the case of rural areas; or due to preference for in-hospital treatment exclusively due to distance to the clinic and time availabilities. It is also important to note that the intervention is not exempt from certain risks, such as staff strikes or logistic inconveniences, so it is important to plan for these in advance.

Competing interests

None of the authors have competing interests to declare in relation to this research. *VF, EN* and *JO* have received fees for educational activities and/or consultancies and/or financial support for attending conferences from Gilead Science, Janssen-Cilag, Merck Sharp & Dohme and ViiV Healthcare outside of the submitted work. *PAL* has received fees for educational activities from Janssen-Cilag and ViiV Healthcare outside of the submitted work.

Author contributions

EN and JO are the principal investigators of the study, initiated the conceptualization of the study, and coauthored the protocol with all the other authors. *DHS* is a clinical research fellow, and she converted the protocol into its publishable format. *JO* is coprincipal investigator of the study, participating in the conceptualization of the study and protocol writing. *VF, PAL, CBC, LB, AR, JJ, MAC, ABF,* and *JMP* are coinvestigators of the participating centers, and helped with implementation and patient recruitment. *NL, DC,* and *VF* are the hospital pharmaceutics and have contributed to implementation and protocol design. *EN, DHS, LB, CM, JP, DR,* and *NL* belong to the Coordinating Team at Hospital Germans Trias I Pujol and have helped in protocol design, trainings, and procedures of implementation, as well as in implementation support for other centers. *JO, DA* and *FR* belong to the Coordinating Team at Hospital Costa del Sol and have helped in trainings and procedures of implementation, as well as in implementation support for other centers.

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Tables

Table 1. List of affiliated primary care or community centers and its hospitals of reference

Reference hospital	Primary care center / Community center
Hospital Universitari Germans Trias i Pujol (Catalonia)	BCN Checkpoint
	CAP Dr. Robert
Hospital Universitari General de la Vall d'Hebron (Catalonia)	Centre de Salut Internacional i Malalties
	Transmissibles Drassanes - Vall d'Hebron
Hospital Costa del Sol (Andalucia)	CS San Pedro Alcántara
	CS San Luis de Sabinillas
	CS Leganitos

BMJ Open

Study protocol: the HOLA Study – Exploring the acceptability, appropriateness, feasibility and satisfaction of an implementation strategy for out-of-HOspital administration of the Long-Acting combination of cabotegravir and rilpivirine as an optional therapy in HIV patients from Spain – a hybrid implementation-effectiveness, phase IV, double arm, open label, multicentric study.

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Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	HIV/AIDS, Patient-centred medicine
Keywords:	Implementation Science, HIV & AIDS < INFECTIOUS DISEASES, Patient-Centered Care

Title: Study protocol: the **HOLA** Study – Exploring the acceptability, appropriateness, feasibility and satisfaction of an implementation strategy for out-of-**HO**spital administration of the **L**ong-**A**cting combination of cabotegravir and rilpivirine as an optional therapy in HIV in Spain – a hybrid implementation-effectiveness, phase IV, double arm, open label, multicentric study.

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Abstract

Introduction: The HOLA Study is a 12-month randomized, hybrid implementation-effectiveness, phase IV, double arm, open label, multicentric study including virologically suppressed people living with HIV (PWH). HOLA, which started in September 2023, evaluates acceptability, appropriateness, feasibility and satisfaction of out-of-hospital administration of cabotegravir and rilpivirine long-acting (CAB+RPV LA).

Methods: A total of 110 PWH who are already under treatment with CAB+RPV LA or switch their antiretroviral therapy to CAB+RPV LA will be recruited from two main hospitals in Barcelona (Germans Trias I Pujol and Vall d'Hebrón) and Costa del Sol Hospital, in Marbella. The patients will be randomized 1:1 into a Hospital Group (administration of CAB+RPV LA in the hospital) and the Outpatient Group (Out-of-hospital administration) including community or primary care centers. The main

objectives of the study are to compare the acceptability at month 12 of the administration of CAB+RPV LA in and out-of-hospital centers from the perspective of patients, and to assess and compare the safety and tolerability of CAB+RPV LA. The study takes place at 9 clinical units in Catalonia, and Andalusia, [3 tertiary hospitals (recruiting centers), 1 community center, 1 STI clinic, and 4 primary care centers].

Ethics and dissemination: The current publication refers to version 3.0. of the protocol, with issue date on the 14th April 2024, as approved by the Comité de Ética de la Investigación con medicamentos del Hospital Universitari Germans Trias i Pujol (approval number AC-23-042-HGT-CEIM). The clinical trial will be conducted according to the principles of the Declaration of Helsinki, Fortaleza, Brazil, October 2013. This study will be conducted according to Spanish regulations regarding clinical trials (Royal Decree 1090/2015) and biomedical investigations (Organic Law 14/2007 of biomedical investigation and the Royal Decree 1716/2011), and the Clinical Trial Regulation (Regulation EU No 536/2014). Confidentiality requirements will follow the required Data Protection legislation. Enrolment completion in the study is expected by the end of May 2024, with an end of study expected in May 2025. Results emerging from this study will be reported in HIV national and international meetings as well as published in international journals with high impact factor. If the outcome deems positive, we will also develop and propose policy guidelines for integration of the administration of CAB+RPV LA in alternative outpatient facilities into the standard of care in the HIV care pathway.

Trial registration number: NCT06185452 / 2023-503963-41-00

Keywords: implementation science, cabotegravir and rilpivirine long acting, CAB+RPV LA, HIV, patient-centered care

Number of words: 382

Strengths and limitations

Strengths:

- The HOLA study utilized verified implementation research methods in HIV healthcare that will generate the knowledge required for policymakers, healthcare mediators and the community to modify the current models of care in PWH towards a patient-centered approach.
- The study includes the participation of community centers and ITS clinics due to their proximity with PWH and their implication in PrEP implementation and rapid HIV diagnosis.
- The study addresses not only urban tertiary centers but also rural centers.

Limitations:

- It is important to note that the intervention is not exempt from certain risks, such as staff changes or logistic inconveniences, and planning for these in advance is at the expense of investigator criteria from each center.
- Per protocol, a medical visit at the hospital at months 6 and 12 had to be included for routine medical care. For those participants who have been randomized to receive treatment at the out-of-hospital center, this is a limitation since it implies duplicating the visit in two centers.

1

Introduction

UNAIDS is a strategic program aimed at guiding and coordinating governments and structures that are responsible for providing HIV services in order to save lives [1]. Until 2020, the objectives were to ensure that 90% of people with HIV (PWH) were diagnosed, 90% of them on antiretroviral treatment (ART), and 90% of them virally suppressed, and these have been updated to 95-95-95 for 2025. With this purpose, "Treat All" policies in many regions worldwide have favored access to ART, consequently reducing HIV-related morbidity and mortality, and increasing life expectancy in PWH. Thus, HIV treatment has shifted to a chronic care model of disease management [2]. Currently, there are many potent, convenient, and well tolerated antiretroviral combinations available. However, ART should be prescribed as early as possible and, for the moment, in a life-lasting manner.

Nevertheless, stigma is still present, and recent goals by the UNAIDS include a novel target of quality-of-life improvement [1–3]. In line with this, inclusion of PROs is becoming a preference in the development of the latest clinical trials, as these may shed light into which factors related to ART and patient care are of utmost importance in improving health-related quality of life, patient satisfaction, and in reducing stigma. In particular, a recent study carried out in Germany found out that the frequency of dosing and the risk of long-term side effects have a major influence on the acceptance of novel therapy regimens and should be considered to increase patient adherence and satisfaction [4].

Considering these reasons, there is a need for more convenient, less frequent treatment, to help address challenges associated with posology, psychosocial issues and adherence in PWH. Long-acting (LA) injectable regimens are emerging as a treatment option that may simplify therapy for PWH and anticipate a shift in the treatment paradigm for these people [5]. There are data confirming the non-inferiority of the LA intramuscular (IM) cabotegravir (CAB) and rilpivirine (RPV) compared with continuing a standard of care regimen in antiretroviral-naive adults with HIV-1 suppressed after 20 weeks in oral ARV with DTG/ABC/3TC (FLAIR study) [6] and for the maintenance of viral suppression (ATLAS, ATLAS-2M and LATTE-2 studies) [7,8]. Additionally, the use of CAB + RPV LA reduces the frequency of dosing from daily to every two months, and may aid in addressing fear of disclosure, anxiety around medication adherence, and daily reminders of the HIV status and the chronicity of disease [9].

Nonetheless, in Spain, this LA regimen must be administered in the hospital by a trained health team every 2 months, supposing a change in the dynamics of HIV units, which were previously reserved for a medical visit every 6 months. For these reasons, this option could be less convenient than conventional daily oral therapy for some people, since it implies visits to the hospital every 2 months for the administration of the injections. A shared approach for the treatment administration with primary care or community centers may be appropriate to improve the patient's satisfaction while maintaining high-quality care for PWH. However, there is still insufficient evidence regarding the feasibility of decentralizing treatment for PWH, in particular in the context of Spain.

Given these considerations, the proposed study seeks to address these issues by implementing the out-of-hospital CAB + RPV LA administration. Alternative settings to receive CAB + RPV LA will offer new options to PWH that may increase their quality of life and improve psychosocial challenges. Together with primary care centers, we are also interested in including community centers and STI clinics due to their proximity with PWH and their implication in PrEP and rapid HIV diagnosis. Furthermore, centers belong

to two different regions from Spain, including not only urban tertiary centers but also rural centers.

Research questions

To assess the implementability of this approach in Spain, first, we propose a comparison of the acceptability, appropriateness, and feasibility of the administration of CAB + RPV LA between out-of-hospital settings and the local standard of care (hospital administration), as well as the patient's satisfaction. The study is also focused on the identification of the PWH profile who are the best candidates to this strategy and whose satisfaction is higher. Finally, we will distinguish patients who are naïve to CAB+RPV LA from those who are not to evaluate potential intra-group differences.

The study is utilizing Proctor's research framework for measuring the success of especific implementation outcomes [10], according to which acceptability is defined as the perception among implementation stakeholders that a given treatment, service, practice, or innovation (the administration of CAB + RPV LA in alternative injection sites) is satisfactory. Appropriateness is defined as the perceived compatibility of the innovation or evidence-based practice for a given practice setting, provider, or consumer; and/or to address a particular issue. Finally, feasibility is defined as the extent to which the innovation can be successfully carried out within a given setting. Validity of these tools has been scientifically proven [11].

Aims and objectives

The primary objective of this post-approval study is to assess and compare the acceptability by the patient of the implementation of CAB+RPV LA from the perspective of participants receiving outside-hospital injections versus the participants receiving hospital injections by month 12, in order to support future scale up efforts. A co-primary objective of the study will be to assess and compare the safety and tolerability of CAB+RPV LA between the out-of-hospital administration and the in-hospital administration groups.

Secondary objectives are to assess and compare acceptability, appropriateness, and feasibility of the administration of CAB+RPV LA as perceived by patients and HCP/non-clinical staff, as well as patient's satisfaction, and expectations throughout all timepoints of the study; retention, engagement, and compliance; and to identify those patients in which the out-of-hospital administration is more suitable. Tertiary objectives are to assess and compare between groups the virological effectiveness; the change at month 12 vs baseline in patient's acceptability, satisfaction, and expectations among the subgroup of participants with previous experience with CAB+RPV LA; and to compare these to those patients who have never received CAB+RPV LA.

Methods and analysis

Study design

This is a 12-month, randomized, hybrid implementation-effectiveness, phase IV, double arm, open label, multicentric study including virologically suppressed PWH who start or are currently under treatment with CAB+RPV LA, to evaluate the out-of-hospital versus in-hospital administration of this combination in terms of acceptability, appropriateness, feasibility and satisfaction. Here, "hospital" refers to HIV specialty outpatient clinics within

tertiary care centers, while "out-of-hospital" refers to other medical settings such as community-based care facilities, STI centers or primary care centers.

The study began in the **preparation stage**, where healthcare staff were engaged, informed, and trained about CAB+RPV LA and the delivery strategies. All processes and protocols were ensured to be in place before the first patient was enrolled, and adequate material and human resources were provided. Community and primary care healthcare workers were trained to help deliver the injections to patients.

The study then transitioned into the **initial implementation stage** when the first patients were recruited and enrolled. Patients were randomized 1:1 into a in-hospital group or out-of-hospital group and stratified according to age (<50 years old or ≥50), gender (male or female), as well as according to whether participants are already receiving CAB + RPV LA. Rural and non-rural options were only considered in the out-of-hospital setting and the choice was made by the participant. As of October 2023, the first participant was enrolled. PWH naïve to CAB + RPV LA, during the oral treatment lead-in phase are attended at the reference hospital, to rule out adverse events, and the first injection is administered in the hospital. They start receiving CAB + RPV LA injection doses at their in-hospital or out-of-hospital assigned center from the next CAB + RPV LA administration (month 2). For patients previously receiving CAB + RPV LA, the first study injection is given in the randomized center, at month 2.

No changes in treatment regimens are foreseen during the study period. In case of failure of one of the regimens, a new regimen will be decided using a resistance test as clinical routine. In case adverse events to the medication occur, the investigator will decide if it is necessary to replace it.

Investigators may provide oral CAB and/or RPV as a short-term “bridging” strategy for participants who have begun LA CAB + RPV in case a patient cannot attend an appointment. Should a participant need “oral bridging”, sites must contact the coordinating investigators for guidance on treatment strategies prior to a missed LA CAB+ PV dose and the missed dose should be accurately noted in the registry. Bridge to oral therapy with CAB+RPV is permitted if a patient misses an injection. However, no more than two missing injections will be allowed as part of the study.

At the end of the study, the change of treatment will be done at the discretion of the physician.

Study setting

The study takes place at 9 clinical units in two regions of Spain, Catalonia, and Andalusia, [3 tertiary hospitals (recruiting centers), 1 community center, 1 STI clinic, and 4 primary care centers] (**Table 1**); and spans two implementation stages: preparation and initial implementation.

Outcome measures

The study includes both participant outcomes and staff outcomes, divided between primary, secondary and exploratory outcome measures:

Primary outcomes measures:

1. To assess and compare between groups the number of participants that show a mean score ≥ 4 across the Acceptability of Intervention Measure (AIM) questionnaire at month 12 [11–13].
2. To assess and compare between groups the proportion of participants with an mean score ≥ 4 across the AIM questionnaires at month 12.
3. To assess and compare between groups the mean score across the AIM questionnaires at month 12.
4. To assess and compare between groups the incidence and severity of CAB + RPV LA-related adverse events (AEs), all Serious Adverse Events (SAEs), injection site reactions (ISRs) or post-injection reactions through study completion, and the proportion of patients who presented grade 3 or 4 CAB + RPV LA-related adverse events.
5. To assess and compare between groups the proportion of participants who discontinue CAB + RPV LA due to AEs/SAEs and due to CAB+RPV LA-related adverse events.

Secondary outcomes measures:

1. To assess and compare between groups the proportion of participants with a mean score ≥ 4 across the AIM questionnaires at months 1 and 6.
2. To assess and compare between groups the proportion of participants with a mean score ≥ 4 across the Intervention Appropriateness Measure (IAM) and Feasibility of Intervention Measure (FIM) questionnaires, at months 1, 6 and 12 [11–13].
3. To assess and compare between groups the proportion of healthcare professionals and/or non- clinical staff that show an mean score ≥ 4 across the AIM, IAM and FIM questionnaires at months 1, 6 and 12.
4. To assess and compare between groups the proportion of patients who report high satisfaction at each study time-points using the HIV Treatment Satisfaction Questionnaire "status" (HIVTSQs12[14].
5. To assess and compare between groups changes in satisfaction derived from HIVTSQs12, in the overall sample from baseline to months 1, 6 and 12.
6. To assess and compare between groups changes in satisfaction derived from the HIV Treatment Satisfaction Questionnaire "change" (HIVTSQc12) [14] in the overall sample from baseline to month 12.
7. To assess and compare between groups the expectations of the CAB + RPV LA regarding the following areas: adherence to treatment, follow-up of medical visits, illness perception, physical and emotional quality of life, family and social relationships and work; at baseline and month 6 and 12. Expectations will be assessed through 5-likert scales developed *ad hoc* for the study.
8. To assess and compare between groups the Patient Reported Outcome Measures (PROMs) at each study time-points using the Patient Reported Outcome Measures HIV Clinic Screening Tool (PROMS-CST- HIV) questionnaire [15], at baseline and months 1, 6 and 12. This questionnaire assesses PRO regarding anticipated stigma, emotional distress, sexuality, social support, material deprivation, sleep and fatigue, cognitive problems, physical symptoms.
9. To assess and compare between groups changes in PROMs throughout the time points in each group in the overall sample using the PROMS-CST- HIV questionnaire.
10. To assess and compare between groups changes in the health professionals' expectations using a 5-likert Health Professional Expectations Questionnaire developed *ad hoc* for the study through study completion.

11. To assess and compare between groups the perception of injection, using the perception of injection (PIN) questionnaire [16] at months 1, 2, 4, 6, 8, 10 and 12.
12. To assess and compare between groups the proportion and number of patients who miss their appointment for the CAB + RPV LA administration (out of the window period ±7 days) from baseline to month 6 and 12.
13. To assess and compare between groups the number and proportion of patients who early interrupt CAB + RPV LA, at month 6 and 12.
14. To compare among groups the proportion of patients who adopt oral bridging therapy.
15. To identify those patients in which the out-of-hospital administration is more suitable by comparing the previous endpoints, stratifying according to: age (<50 vs ≥50 years old), gender (male vs female), as well as according to if the participant is already receiving or not CAB + RPV LA.

Exploratory outcomes measures:

1. To assess and compare between groups the virological effectiveness of CAB + RPV LA at month 6 and 12:
   - Proportion of subjects who are virologically suppressed (plasma HIV-1 RNA ≤50 copies/mL).
   - Proportion of participants with confirmed virologic failure/rebound (2 consecutive HIV-1 RNA greater than or equal to 200 copies/mL).
   - Proportion of participants with blips.
2. To assess the average change from baseline to month 12 in patient's acceptability, satisfaction, and expectations (AIM, HIVTSQs12, HIVTSQc12, expectations and PROMS-CST-HIV), as mentioned above, among the subgroup of participants with previous experience with CAB + RPV LA.
3. To compare patient's acceptability, satisfaction, and expectations at month 12 (AIM, HIVTSQs12, HIVTSQc12, expectations and PROMS-CST-HIV), as mentioned above, between patients under prior treatment with CAB + RPV LA and those patients who have never received CAB + RPV LA.

Patient and Public Involvement statement

Patients were not directly involved in the design or conduct of this study. However, the study addresses priorities relevant to patient care and outcomes, aligning with broader public health needs identified in previous research and clinical guidelines. In the dissemination phase, the results are planned to be shared with local community health organizations to inform future strategies and policies that directly impact patient care.

Sample size

A total of 110 virologically suppressed PWH will be included in this study and will receive CAB + RPV LA in the hospital and/or out-of-hospital alternative facilities. A period of enrolment of 8 months was considered.

Sample size justification

The sample size was calculated accepting an alpha error of 5%, for a statistical power of 80% in a bilateral contrast, and an expected acceptability of 45% in the hospital group

and of 75% for the outpatient group, at the end-of-study. Fixing the type I error at 5%, 55 subjects per group will be necessary to reject the equal null hypothesis with a power of 80%. Assuming a maximum loss of 25%, the required sample size is of 110 patients, 55 in each arm.

Participant identification

Potential participants who will be receiving or are receiving CAB + RPV LA within their routine clinical care are referred to the study team by their physicians within the HIV clinics of the three main hospitals. The local HIV teams then inform participants of the trial and provide patient information leaflets with contact details of the study team. Participants are scheduled for a screening visit, during which inclusion and exclusion criteria are revised and informed consent forms are signed as guided by the study nurses. Once the participants have signed the informed consent, they are randomized.

Inclusion and exclusion criteria

Adult PWH (age ≥18 years) will be invited to participate if they have capacity to consent with the following criteria:

- Chronic HIV-1 infection
- Will receive CAB+RPV LA as part of their routine clinical care.
- Recommended triple or dual therapy for at least 12 months, including CAB+RPV LA.
- Virological suppression for at least 6 months (2 consecutive determinations of undetectable viral load).
- Post-menopausal or fertile females that agree to avoid pregnancy during the study. If sexually active female; using an effective method of contraception (hormonal contraception, intra-uterine device (IUD), or anatomical sterility in self or partner from 14 days prior to the first IMP administration until at least 13 months after the last IMP administration; all female participants must be willing to undergo urine pregnancy tests at time points specified in the protocol.
- Patients which have access to an out-of-hospital center without inconvenience.
- Patient who agrees to participate in the study and signs the informed consent. An example of the informed consent form is attached as Supplementary Materials (Spanish language).

Exclusion criteria include:

- Active Hepatitis B infection
- History of virological failure or mutations to INSTI or NNRTI.
- Previous antiretroviral treatment interruption during the last 6 months or treatment interruptions for more than a month.
- Contraindication for intramuscular injections
- Pregnant or breastfeeding women or desiring to become pregnant in the near future.
- Current use of the following concomitant treatment: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampicin / rifampin, rifapentine, St. John's wort

Data collection

All participating sites will be assessed using a mixed-methods approach including questionnaires, templated data collection instruments and primary data sources (clinic records).

Treatment compliance and concomitant treatment

CAB + RPV LA compliance is guaranteed because study medication is to be administered by a designated study nurse at the clinical site. If the participant does not attend any visit, this information will be documented in the CRF.

All other treatments taken, apart from the study medication administered during the study period, will be considered concomitant treatments and should be documented in the CRF. Patients who participate in the study will be remembered that they should not start any new or continue any concomitant treatment without the knowledge and permission of the investigator. If discomfort following injection occurs, dosing with paracetamol 1g every 8 hours for a total of 24 hours will be allowed, but never as a prophylaxis treatment. If discomfort persists, the patient must seek medical attention.

The following medications must not be administered concurrently: Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin, Rifabutin, Rifampicin / Rifampin, Rifapentine, St. John's wort, Dexamethasone. In addition, the following treatments must be discontinued: proton pump inhibitors and systemic dexamethasone (more than a single dose). Use of anticoagulation agents greater than 14 days is prohibited and systemic anticoagulation on the day of an IM injection should be avoided where possible.

Questionnaires

Participant questionnaires

Questionnaires will be provided to participants by nursing staff involved in the study during their scheduled clinic visit, at baseline, months 1, 6 and 12, except for the perception of injection (PIN) questionnaire which is to be filled in by the patient 2 days after injection, electronically.

Healthcare staff questionnaires

Staff will complete at baseline and at the end of the study (final test) a Health Professional Expectations Questionnaire. At months 1, 6 and 12, healthcare professionals and non-clinical staff will fill in the AIM / IAM / FIM health professional/ non-clinical staff questionnaires.

Data analysis

Study data is collected through a study-specific /electronic Case Report Form (eCRF). All questionnaire data is collected directly on the eCRF by patients using an electronic device (tablets). All participants who passed screening and entered the study (ie, completed baseline electronic case report form - eCRF) will be included in the analysis population. The staff who complete the study questionnaires will also be considered part of the study and they will have an identification number and their role in the study (investigator, nurse, pharmacist, administrative staff).

The primary complete analyses will be conducted when the last study participant has completed their CAB + RPV LA study treatment up to month 12. All study staff participant (site-level) questionnaire, survey data, and all study participant (subject-level) data will be included in the analysis. For the primary analysis on the primary endpoint at month 12, we will use the ITT-E population. The ITT-E and Per-Protocol populations will be used for the secondary analyses and those on secondary aims. All the analyses on the primary and secondary objectives will be performed on the overall (total sample)

population and by study arm. To evaluate the main objective, a comparison of the percentages of acceptability with a Chi2 test will be made and both the differences in percentages and the quotient of these percentages in the form of relative risk will be reported. Regarding some of the secondary and the exploratory objectives, a descriptive analysis will be performed.

Ethics and dissemination

The clinical trial will be conducted according to the principles of the Declaration of Helsinki, Fortaleza, Brazil, October 2013. This study will be conducted according to Spanish regulations regarding clinical trials (Royal Decree 1090/2015) and biomedical investigations (Organic Law 14/2007 of biomedical investigation and the Royal Decree 1716/2011), which develop the Clinical Trial Regulation (Regulation EU No 536/2014). Confidentiality requirements will follow the required Data Protection legislation. The current publication refers to version 3.0. of the protocol, with issue date on the 14th April 2024, as approved by the Comité de Ética de la Investigación con medicamentos del Hospital Universitari Germans Trias i Pujol (approval number AC-23-042-HGT-CEIM).

Final data exportation is scheduled for June 2025; until then, data is stored in a secured database where only selected investigators have access for purely assistance reasons. Following data exportation, statistical analyses will follow, with complete datasets expected for the first quarter of 2026. After finishing the study, the Coordinating Teams of the study will discuss results and strategies for the future, as well as the data dissemination plan, in order to maximize the impact of this work on clinical care and policy. At least one manuscript is expected to be sent for publication covering the main results of the HOLA study. Subsequent sub-analyses will be considered by the investigators if they deem appropriate. Once data is made available to the researchers participating in the study, data generated that supports the final results article will be made available as soon as possible, wherever legally and ethically possible, upon request. The publication of the trial results shall meet the requirements set out in Article 42 of Royal Decree 1090/2015. Results emerged from this study will be reported in the HIV national and international meetings as well as published in international journals with high impact factor. If the outcome deems positive, we will also develop and propose policy guidelines for integration of the administration of CAB+RPV LA in alternative outpatient facilities into the standard of care in the HIV care pathway. In addition to this study, a qualitative substudy, with a different study code (NCT: NCT06643897), has been conducted. The objective of the substudy is to assess the barriers and solutions for the implementation by interviewing the staff participating in the HOLA study. The substudy analyses are underway and will be published as well.

Discussion

In the current clinical programs in Spain, the CAB+RPV LA formulation must be administered by a trained health team every 2 months in the hospital. Bringing treatment closer to patients may bring benefits to them in terms of satisfaction and reduction of stigma. However, evidence in the feasibility of the out-of-hospital delivery of CAB + RPV LA in Spain in non-existent. Implementation outcome measures are essential for monitoring and evaluating the feasibility of a change in procedures, such as the one described [11]. Prior evidence in implementation science for this treatment comes mainly from the CARISEL (Cabotegravir and Rilpivirine Implementation Study in European

Locations) study, a hybrid Phase III implementation-effectiveness trial implementing CAB + RPV LA for PWH). This study was aimed at evaluating participants switching from daily oral therapy to CAB + RPV LA dosed every 2 months (Q2M). However, the Spanish sites participating in the trial were only hospitals and no alternative outpatient centre were considered (CARISEL; NCT04399551).

In the CARISEL study, sites were randomized to standard implementation (Arm-S) or enhanced implementation (Arm-E), including additional implementation strategies. These enhancements were mainly focused on meetings that introduce CAB + RPV LA to clinic staff and discuss what might make implementation easier, and/or what might make it difficult, prior to first injection at the site; and meetings started to discuss an implementation plan, how to work through challenges, and introduce a continuous quality improvement plan, for 6 out of the 12 months of study. At Month 12, regardless of implementation arm, CAB + RPV LA was highly effective and well tolerated, consistent with clinical outcomes in the Phase 3 clinical program [17].

Although HOLA has some similarity to CARISEL with respect to study outcomes, HOLA aims to examine differences between clinic settings (urban and rural) as well as hospital and community-based settings for administering CAB + RPV LA through a set of three questionnaires that had been previously developed under the Proctor framework, as four-item measures of implementation outcomes that indicate implementation success [10] : the AIM, IAM, and FIM questionnaires [11]. Enrolment completion in the HOLA study took place by the end of May 2024, with an end of study expected in May 2025. It is important to note that the intervention is not exempt from certain risks, such as logistic inconveniences, so it is important to plan for these in advance.

The importance of implementation research in HIV healthcare relies in its potential to generate the knowledge required for policymakers, healthcare mediators and the community to modify the current models of care in PWH in order to improve their quality of life. The HOLA study may provide the required outcomes that will help bridge the gap towards a patient-centered approach in HIV care. The tools and methodology used for assessing implementation success have been validated and described previously as part of the Proctor framework [10], which gives value to decision makers to consider the success of the intervention of study. In addition, a qualitative substudy, aiming to identify barriers and facilitators of implementation of the administration of CAB+RPV LA in alternative facilities from the perspective of staff participating in the HOLA study, has been conducted. Data generated from both studies will contribute to the development of guidelines for implementation supporting governments and healthcare decision-makers in formulating successful implementation strategies.

Competing interests

None of the authors have competing interests to declare in relation to this research. *VF, EN* and *JO* have received fees for educational activities and/or consultancies and/or financial support for attending conferences from Gilead Science, Janssen-Cilag, Merck Sharp & Dohme and ViiV Healthcare outside of the submitted work. *PAL* has received fees for educational activities from Janssen-Cilag and ViiV Healthcare outside of the submitted work. All other authors have no competing interest to declare.

Author contributions

EN (guarantor) and JO are the principal investigators of the study, initiated the conceptualization of the study, and coauthored the protocol with all the other authors. *DHS* is a clinical research fellow, and she converted the protocol into its publishable format. *JO* is coprincipal investigator of the study, participating in the conceptualization of the study and protocol writing. *VF, PAL, CBC, LB, AR, JJ, MAC, ABF,* and *JMP* are coinvestigators of the participating centers, and helped with implementation and patient recruitment. *NL, DC,* and *VF* are the hospital pharmaceutics and have contributed to implementation and protocol design. *EN, DHS, LB, CM, JP, DR,* and *NL* belong to the Coordinating Team at Hospital Germans Trias I Pujol and have helped in protocol design, trainings, and procedures of implementation, as well as in implementation support for other centers. *JO, DA* and *FR* belong to the Coordinating Team at Hospital Costa del Sol and have helped in trainings and procedures of implementation, as well as in implementation support for other centers.

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Tables

Table 1. List of affiliated primary care or community centers and its hospitals of reference

Reference hospital	Primary care center / Community center
Hospital Universitari Germans Trias i Pujol (Catalonia)	BCN Checkpoint
	CAP Dr. Robert
Hospital Universitari General de la Vall d'Hebron (Catalonia)	Centre de Salut Internacional i Malalties Transmissibles Drassanes - Vall d'Hebron
Hospital Costa del Sol (Andalucia)	CS San Pedro Alcántara
	CS San Luis de Sabinillas
	CS Leganitos

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PARTICIPANT INFORMATION SHEET AND INFORMED CONSENT

STUDY TITLE	" Implementation of the out-of-hospital administration of long-acting Cabotegravir+Rilpivirine as optional therapy in HIV-infected patients in Spain. Acceptability, appropiateness, feasibility, and satisfaction. The HOLA Study. ".
STUDY CODE	Out-of-hospital LA CAB+RPV
PROMOTER	Fundació FLS de Lluita contra la Sida, les Malalties Infectioses i la Promoció de la Salut i La Ciència
PRINCIPAL INVESTIGATOR	
CENTER	

Introduction

We are writing to inform you about a research study in which you are invited to participate, promoted by Fundació FLS de Lluita contra la Sida, les Malalties Infectioses i la Promoció de la Salut i La Ciència. The study has been approved by a Drug Research Ethics Committee and by the Spanish Agency for Medicines and Health Products (AEMPS), in accordance with current legislation, Royal Decree 1090/2015 of December 4 and European Regulation 536/2014 of April 16, which regulates clinical trials with drugs.

Our intention is that you receive the correct and sufficient information so that you can decide whether or not to agree to participate in this study. To do this, read this information sheet carefully and we will clarify any doubts that may arise. In addition, you can consult with the people you consider appropriate.

We invite you to participate in the study because you are diagnosed with HIV, have been prescribed long-acting treatment with Cabotegravir and Rilpivirine and have an undetectable viral load.

The long-acting treatment is a combination of two antiretroviral drugs called Cabotegravir and Rilpivirine. Both act to suppress HIV (human immunodeficiency virus) in a similar way to other antiretrovirals, with the difference that this treatment consists of two injections every two months instead of a daily oral treatment.

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This treatment is only allowed be administered in the hospital and the aim of this study is to see if the administration of Cabotegravir and Rilpivirine for the treatment of HIV in alternative facilities outside the hospital setting, for example, in primary care centres or in community centres, is acceptable.

Voluntary participation

you should know that your participation in this study is voluntary and that you can choose NOT to participate. If you choose to participate, you can change your decision and withdraw your consent at any time, without altering your relationship with your doctor or harming your health care.

Objective of the study

The main objective of this study is to see if it is acceptable and safe to administer the injections for patients living with HIV that are treated with long-acting Cabotegravir and rilpivirine intramuscularly every 2 months outside the hospital.

The findings of this study will help us understand how the administration of the drugs outside of a hospital setting can be implemented and to see if it is acceptable, appropriate, feasible and satisfactory to administer Cabotegravir and Rilpivirine injections every 2 months in primary care centers or in community centers, as well as to evaluate the safety of the administration of Cabotegravir and Rilpivirine injections.

Study Description

This study will involve 110 adults living with HIV who have controlled disease (undetectable viral load) with their current HIV medication.

The medications that will be administered are injections of Cabotegravir and Rilpivirine. Participants will be divided into two groups:

- Group I: You will be given the dose of Cabotegravir and Rilpivirine in the hospital
- Group II: You will be given the dose of Cabotegravir and Rilpivirine outside the hospital, in a community center, or in a primary care center already assigned by the study.

Neither do you nor will the researcher know which group will be assigned before being included in the study. It will be decided at random (like flipping a coin) to which group you will belong. This is done to get reliable data from the results of the study.

Every 2 months you will receive 2 injections; each contains one of the two drugs that make up the treatment. You will be given an injection on each side of the upper outer part of the gluteus.

These medicines are approved by the AEMPS under the name Vocabria® (Cabotegravir) and Rekambys® (Rilpivirine).

If you have not been given Cabotegravir and Rilpivirine injections before, you will take the same oral medication for 28 days and, on the last day of oral medication, you will receive the first dose of Cabotegravir and Rilpivirine in the hospital. From the following month, the injections of Cabotegravir and Rilpivirine will be administered every 2 months at the center where you have been randomly assigned.

These oral medications are also approved by the AEMPS. In Spain, Rilpivirine is marketed under the name Edurant® and Cabotegravir under the name Vocabria®. The aim of this first phase of oral treatment is to ensure tolerance of the drugs.

Study activities

The study will last 12 months of treatment, in which 7 face-to-face visits will be carried out.

In the case of patients who have not previously been administered intramuscular cabotegravir and rilpivirine, they should make an additional visit after 28 days of oral antiretroviral treatment, to confirm good tolerance to the treatment.

Before starting the study:

Selection/baseline visit:

If you decide to participate in the study, we will ask you to sign this **informed consent before** you are enrolled, we will ask you some questions, and we will collect some data to confirm that you meet all the selection criteria to participate in the study. On this visit we will do:

- A review of your medical history
- A physical exam
- A review of your medication
- A test with determination of HIV viral load
- A pregnancy test

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- Questionnaires

During the study: *Study visits:*

Visits will be made every 2 months in which you will be given injections of Cabotegravir and Rilpivirine and questionnaires will be completed during the visits to assess whether the treatment is acceptable, appropriate and feasible, as well as your degree of satisfaction and expectations of the treatment and a questionnaire that will measure the perception of the injection, which you will have to fill out two days after the administrations.

A visit will be made in month 1 in the hospital if it is the first time that the medication Cabotegravir and intramuscular Rilpivirine is administered. At this visit, a blood draw will be performed for the determination of the HIV viral load, and the questionnaires will be completed. A questionnaire that will measure the perception of the injection will have to be filled in two days after the administration.

At the 6th month and 12th month visits, you will go to the hospital where you will have a blood draw to determine the HIV viral load and other tests, similar to those carried out for the monitoring of HIV infection in routine clinical practice (blood count, basic biochemistry and CD4/CD8 lymphocyte count).

In the visits of month 2, month 4, month 8 and month 10, only the questionnaire that will measure the perception of the injection will be completed, which will have to be filled out two days after the administration.

Procedure	Selection/Basal	Month 1	Month 2	Month 4	Month 6	Month 8	Month 10	Month 12
Informed Consent	X							
Clinic Visit (Medical History/Physical Exam)	X	X			X			X
Blood Draw	X	X			X			X

Pregnancy test (if applicable)	X	X			X			X
Study Questionnaires	X	X			X			X
Injection Perception Questionnaire		X	X	X	X	X	X	X
Oral Administration of Cabotegravir and Rilpivirine	X							
Intramuscular Administration of Cabotegravir and Rilpivirine		X	X	X	X	X	X	X

Blood Sample Collection:

Blood drawings will be routinary and will be carried out by the nursing staff of the HIV Unit of your Hospital. The amount of blood that will be drawn at each of the study visits will be approximately 30 mL.

Risks and discomforts arising from your participation in the study

In previous trials of Cabotegravir and rilpivirine it well tolerated, and serious adverse reactions were very rare.

The adverse reactions described are:

Frequency	Adverse Effect
Very common (at least 1 in 10 people)	Headache
	Injection site reactions. They are usually mild to moderate and their frequency decreases over time. Symptoms may include:- Very common: pain and discomfort, hard lumps or masses- Common: redness, itching, swelling, warmth, or bruising (which may include a change in color or a collection of blood under the skin).- Uncommon: numbness, light bleeding, abscess formation (accumulation of pus) or cellulitis (with a feeling of warmth, swelling, or redness).
	Feeling warm (pyrexia), which may occur in the first week after injections
Common (affects less	Depression
	Anxiety
	Abnormal dreams

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than 1 in 10 people)	Difficulty sleeping (insomnia)
	Dizziness
	Feeling unwell (nausea)
	Vomiting
	Abdominal pain
	Gases
	Diarrhoea
	Rash
	Muscle pain
	Tiredness (fatigue)
	Feeling weak (asthenia)
	Malaise
	Weight gain
Rare (affects less than 1 in 100 people)	Numbness (drowsiness)
	Feeling dizzy during or after an injection. This can lead to fainting.
	Liver damage (signs may include yellowing of the skin and whites of the eye, loss of appetite, itching, tenderness of the belly, light-colored stools, or abnormally dark urine).
	Changes in laboratory levels of liver function (increased transaminases)
	Increased bilirubin (a substance produced by the liver) in the blood.

Injection site reactions

You may experience local reactions at the site where you received the injections. Very common side effects can include pain or discomfort, which is usually mild or moderate. You may also have redness, swelling, itching, bruising, lumps, complications such as infection (cellulitis or abscess), and irritation where the injection(s) are given. In most cases, the reactions are mild (75%), while 4% of participants in previous clinical trials had a severe reaction at the injection site. Most reactions go away in a week or less, but sometimes they can last a long time. Most people find these reactions acceptable and rarely stop the injections due to adverse effects.

Possible side effects of the injection procedure

Symptoms of the post-injection reaction have occurred in some people within a few minutes of receiving the rilpivirine injection. Post-injection reactions are rare and occurred in less than 0.5% of participants in clinical trials. Most symptoms resolved within a few minutes of the injection. Symptoms of post-injection reactions may include: shortness of breath, stomach cramps, rash,

sweating, numbness in the mouth, anxious feeling, feeling warm, feeling dizzy or light-headed, changes in blood pressure, and back and/or chest pain. Tell your study doctor if you experience these symptoms after receiving the injections. These cases may be due to an accidental injection of part of the medication into a blood vessel instead of the muscle. Not all patients in whom accidental injection into a blood vessel was suspected reported such symptoms. Most symptoms resolved within minutes. Your doctor may need to give treatment to help resolve these symptoms. The study health care staff will observe you briefly (about 10 minutes) after the injection.

The injections will be given into the muscles of the buttocks. The injection may not reach the muscle or be given too far, not reaching the muscle and penetrating the skin, blood vessels, or nerves. The consequences of this are not well understood, but it could cause the levels of Cabotegravir and Rilpivirine to be too low or high. If they are too low, the medicine may not work properly against HIV. If the levels of Rilpivirine are too high, your heart rate could be altered, which very rarely, in severe cases, can be life-threatening and lead to sudden death; however, to date, no such severe changes in heart rate or sudden deaths have been observed in clinical studies with rilpivirine in any of its forms of administration (oral or intramuscular). Every effort will be made to decrease this risk, including ensuring that the correct size needle and proper injection technique are used. The staff is trained for it. You will also be monitored after each injection and during the test, as appropriate. If your doctor thinks the injection was not given correctly, you may be asked to stay at the center for up to 2 hours after the injection to monitor your progress, and additional tests may be needed to make sure there are no risks. If you are concerned about this issue, talk to your study doctor.

Hypersensitivity

Hypersensitivity reactions (also known as allergic reactions) have been reported with other medicines in the same class as Cabotegravir, with signs and symptoms of general feeling of malaise, rash, high fever, lack of energy, swelling (sometimes of the face or mouth, causing difficulty breathing), blisters, mouth ulcers, conjunctivitis, and muscle or joint aches. If you develop any of these signs and/or symptoms during the study, you should immediately call the study team to decide if any testing is required and/or to tell them to stop taking Cabotegravir and Rilpivirine. If you are told to stop taking your medications, you should do so immediately.

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Rash

Treatment with Cabotegravir and rilpivirine may cause a rash. Most are mild or moderate, but some types can be severe and treatment will need to be stopped. If you have any type of rash, itching, or other skin problems during treatment, you should tell the study team right away. You may be asked to come in for a scan, analysis, and/or tell you to stop taking Cabotegravir and/or Rilpivirine.

Impaired liver tests

A small number of participants in research studies who took Cabotegravir with rilpivirine developed impaired liver tests that forced them to stop treatment. In some cases, abnormal liver tests were explained by other causes (e.g., a new infection with a virus), while a smaller number (less than 1% of participants) had no alternative explanations, suggesting a mild form of liver damage suspected to be due to Cabotegravir and/or Rilpivirine. Liver tests improved after stopping the medication, suggesting that any possible damage was temporary. Blood tests will be carried out to check the health of the liver during this study, as part of your routine check-ups and you will be informed if any alterations occur and, if so, the steps to follow. If a liver problem occurs, you may be asked to stop taking the study treatment.

What if the side effects are intolerable?

If you experience side effects that are intolerable and need to change your HIV medications, you will need to stop the study**.**

What other possible risks are there?

Risk of HIV becoming resistant to treatment

With any drug used to treat HIV, there is a risk that the virus will become drug resistant, which means that the drug will lose its activity. The risk of developing resistance will depend on whether the treatment manages to keep the viral load undetectable, and this, in turn, will depend on you following the instructions on how to take the study medicines.

Therefore, it is very important that you attend your study visits on your scheduled dates and that you always take your treatment exactly as prescribed. Talk to your study doctor each time you stop

taking any tablets or if you think you will need to delay or advance your visits to receive injections due to work, vacation, travel, etc., that may interfere with your scheduled visits.

If you need to delay injections for more than a few days, you may be offered the option to take tablets for a short period of time, which is known as an 'oral bridge'. Your study doctor will be able to advise you on whether this is right for you.

Do not change or skip any doses of any of the study drugs unless your study doctor tells you to. Missing doses of medication (tablets or an injection) can lead to HIV becoming resistant to the drugs and these not working. This could also limit the possibilities of using other HIV medicines related to drug resistance in the future.

On the other hand, if stopping the long-acting treatment, it is important to start taking another HIV medication, as recommended by your study doctor, to maintain HIV control and prevent acquiring drug resistance.

Side effects after receiving long-acting injections

After an injection of Cabotegravir and Rilpivirine, these drugs will stay in your body for a long time. In some people, low levels of Cabotegravir and Rilpivirine may be present in the body for more than a year after the last injection. If you develop a side effect of the study drug after an injection, there will be no way to remove the drug from your body. If this happens, your doctor will do everything possible to treat the symptoms.

When you stop long-acting injections, the amount of medication in your body will decrease over time and go away.

Feeling faint after the injection

When receiving the injections, some people may feel dizzy or like they might pass out. This reaction, also called a "vasovagal reaction," may occur with many medical procedures, however resolves quickly, and is not a threat to your health.

Blood draw

When your blood is drawn, you may feel dizzy or experience mild pain, bruising, irritation, or redness at the puncture site. In rare cases, you can get an infection.

Mental health issues

Some people with chronic health problems, including HIV, sometimes have feelings of depression or may have thoughts of harming themselves or taking their own life (suicide). A small number of people taking Cabotegravir and Rilpivirine have had suicidal thoughts and actions, particularly those with a history of depression or mental health problems.

Tell the study doctor if you have a history of mental health problems. If you have thoughts of self-harm or suicide or have other unusual or uncomfortable thoughts or feelings during this study, you should tell the study doctor or go to the nearest hospital right away.

This list of side effects is not complete. You may experience side effects that are different from those described in this informed consent form or that are not currently known.

Medication NOT allowed during the study

The use of some other drugs is contraindicated or should be done with caution when administered concomitantly with Cabotegravir and/or Rilpivirine. For this reason, the following drugs are not allowed to be used during the study:

- Carbamazepine, oxcarbazepine, phenobarbital, phenytoin (medicines to treat epilepsy and prevent seizures)
- Rifabutin, rifampicin, rifapentine (medicines to treat bacterial infections such as tuberculosis)
- Dexamethasone (a corticosteroid used to treat a variety of conditions, such as inflammation and allergic reactions) given in an oral or injectable course of treatment
- Products that contain St. John's wort or St. John's wort (Hypericum perforatum, a medicinal plant used for depression).

Do not use medications (prescription and over-the-counter) without first talking to the study medical staff. The study medical staff will explain the need to avoid certain medications during the study, including those that are contraindicated. New drugs may be identified later that need to be added to the list of drugs you should not take during the study.

Can a pregnant person participate in the study?

Because there is no information available about the safety of long-acting cabotegravir and rilpivirine for the fetus, pregnant people are not allowed to participate in the study.

For this reason, as part of the tests planned at the screening visit and at the study visits, urine pregnancy tests will be performed on all menstruating people of childbearing potential* who wish to participate in the study or have been included in the study. The result must be confirmed as negative prior to administration of the first dose of study drugs. Pregnancy tests will also be done at any time during the study when pregnancy is suspected.

If you are a person who is able to have children, you should use birth control while participating in the study. Effective birth control should be used, as agreed with your study doctor, from at least 14 days prior to the start of your first dose of Cabotegravir and Rilpivirine and for as long as you are taking the study medication. It is recommended that you continue to use effective contraception until at least 14 days after your last oral dose of Cabotegravir and Rilpivirine, and at least 13 months after your last long-acting injection(s), as the study drugs may still be present in the body during this time. Your study doctor will talk with you about this recommendation and the potential risks of pregnancy during this time. You should tell your primary care physician and your HIV Unit doctor if you have a pregnancy within 12 months of the last Cabotegravir and Rilpivirine injection even if you are no longer in the study.

Therefore, at the screening visit and during the study, the use of one of the following contraceptive methods considered highly effective in preventing pregnancy should be accepted:

- hormonal contraception or intrauterine device [IUD]
- one's own or the partner's anatomical sterility

If the pregnancy test result is positive or equivocal, intramuscular injections should be postponed until a valid serum pregnancy test is obtained. If the test is positive, you will stop taking the study medication and the medical staff responsible for the study will inform you about the next actions to take (see next section).

What will happen if a person becomes pregnant during the study?

You should inform the study research team immediately if you suspect that there is a possibility of pregnancy during the study. If their participation in the study has ended, they should inform their usual doctor during HIV follow-up.

If your pregnancy is confirmed during the study, you will be given the option to switch to alternative antiretroviral therapy during pregnancy. An alternative antiretroviral treatment that is considered suitable for use during pregnancy will be initiated in accordance with local guidelines. The deadline for starting this treatment will be the expected date for the next injection of Cabotegravir and Rilpivirine.

After the study

When your participation ends, you will receive the best available treatment, the one that your doctor considers most appropriate for your disease, at your hospital. Because the study medication will already be marketed, you may still be able to be given the study medication, but neither the investigator nor the sponsor makes any commitment to maintain the treatment outside of this study.

What are the expected benefits of this study?

Possible benefits:

By participating in this study, you will receive antiretroviral treatment that has been shown to be highly effective and tolerable in different clinical trials. It is hoped that this study will be able to analyze whether the administration of the treatment is acceptable, appropriate and feasible to carry out outside the hospital setting and can be implemented in primary care centers and community centers, which may benefit other people infected with HIV in the future.

Costs:

You will not have to pay for medications or specific tests from the study. Your participation in the study will not incur any additional costs to your usual clinical practice. The study will be funded by the pharmaceutical company ViiV Healthcare in collaboration with Lluita Foundation against AIDS and Infectious Diseases.

Confidentiality and legal information

The sponsor of the study and the participating centres, as independent data controllers, will guarantee the confidentiality of the personal information of the participating subjects in accordance with current legal regulations (Organic Law 3/2018, on the Protection of Personal Data and Guarantee of Digital Rights, and Regulation [EU] 2016/679 of the European Parliament and of the Council, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data). During this study, the study medical team will record information about you, your health, and your participation in the study on forms called data collection notebooks.

To ensure that the data collected during the study are treated confidentially, your data will be identified by a code; your name or any other information that allows you to be directly identified will not be included in the data collection notebooks. Therefore, the identity will not be revealed to any other person except to the health authorities, when required or in cases of medical emergency. The ethics committees, the representatives of the Health Authority in matters of inspection and the personnel authorised by the sponsor may only access to check the personal data, the procedures of the clinical study and compliance with the rules of good clinical practice (always maintaining the confidentiality of the information).

Only the study medical staff/collaborators will be able to relate this data to you and your medical history. The sponsor will only have access to information relating to the general results of the study. Under no circumstances will you access your personal data.

To carry out this clinical trial, we will also need access to the medical information contained in your medical record and we will record your participation and safety aspects throughout the study in the electronic medical record system of the participating centers, so you must expressly authorize us to do so.

The data controllers are the sponsor, the Lluita Foundation against AIDS and Infectious Diseases, as well as the centres where this study will be carried out, belonging to the Catalan Health Institute and the Regional Government of Andalusia

- Data Protection Officer within the scope of the Department of Health contact email: dpd@ticsalutsocial.cat.

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- Data Protection Officer in the field of the Junta de Andalucía contact email **********
- Data Protection Officer of Fundació FLS de Lluita contra la Sida, les Malalties Infectioses i la Promoció de la Salut i La Ciència (developer), with address Ctra. de Canyet s/n, Hosp. Univ. Germans Trias i Pujol, 2a planta Maternal, 08916 Badalona (Barcelona): lopd@flsida.org.

Legal basis for data processing: The consent granted by means of this document and the general interest in the treatment of the disease.

Recipients: The recipients of the data are the research team and the personnel authorised by the data controllers, the suppliers that are necessary for the purpose of the processing (laboratories, software and hosting provider companies) and, where appropriate, the relevant administrative authorities. Although the data will be kept pseudonymized during the study, we inform you that your information will be hosted on a secure server located in the European Union under current regulations with the highest quality and specific security. The encrypted data may be transmitted to third parties and other countries, but in no case will it contain information that can identify you directly or indirectly, and contracts will be established with the recipients of the information that expressly prohibit re-identification, by cross-referencing with other databases or any technology that attempts to re-identify the data. In the event that this transfer occurs, it will be for the same purposes as the study described or for use in scientific publications, but always maintaining the confidentiality of these, in accordance with current legislation.

Rights: You can exercise your rights of access, rectification, cancellation, opposition, limitation of the processing of data that are incorrect, request a copy or that they be transferred to a third party (portability) of the patient on the data you have provided for the study (PARSOL Rights). To exercise their rights, the participant may contact the team of researchers or the data protection officer of the institutions

Data retention: The sponsor will retain records of the clinical trial for a period of at least 25 years after completion. Thereafter, your personal information will only be retained by your health care facility. The promoter will keep data that at no time will contain personal data.

We remind you that the data cannot be deleted, even if you stop participating in the study, to ensure the validity of the research and comply with legal duties and drug authorization

requirements. Therefore, if you decide to withdraw consent to participate in this study, no new data will be added to the database, but any data that has already been collected will be used.

Right to complain: You can exercise your right to lodge a complaint with the competent authority (the Catalan Data Protection Authority or the Spanish Data Protection Authority), if you consider that your data protection rights have been violated.

Sure:

The promoter of the study has taken out a civil liability insurance policy with the company Zurich Insurance PLC branch in Spain in accordance with the requirements established in RD 1090/2015, which covers the possible damages that they may experience as a result of their participation in the trial, provided that they are not a consequence of the disease under study itself or of the evolution of their disease as a result of the ineffectiveness of the treatment.

It is also possible that your participation in this clinical trial may modify the general and particular conditions (coverage) of your insurance policies (life, health, accident) and, therefore, we recommend that you contact your insurance company and inform them of your participation in it to determine if it could affect your current insurance policy or in the event that you are going to take out a new policy.

For more information regarding this section, please consult with the principal investigator of the study at your center.

Study Participation:

You do not need to make the decision at this time to participate in this study, you can take this Information Sheet home and think about it long enough and discuss your participation with your family or regular doctor.

You participate in this study on a voluntary basis and may withdraw from the study at any time without having to explain yourself or your subsequent attendance at our Consultation being affected.

Once the Informed Consent is signed, you will keep a copy of this document.

There is the possibility of exclusion from the trial by the sponsor or the research team, in the event of safety problems or non-compliance with the procedures established in the study.

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In the event of cancellation of the trial by the sponsor, the participants will be informed of the reasons.

Any new information regarding the drugs used in the study that may affect your decision to continue in the study will be communicated to you by your doctor as soon as possible and, if necessary, a new consent will be signed.

Contact for information

If you have any questions or problems related to your infection or the treatment given, outside of working hours, you can contact the principal investigator of the study:

Dr/a.....

Tel.....

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INFORMED CONSENT

STUDY TITLE	"Implementation of out-of-hospital administration of the long-acting combination Cabotegravir+Rilpivirine as optional therapy in HIV-infected patients in Spain. Acceptability, appropiateness, feasibility and satisfaction. The HOLA Study".
STUDY CODE	Out-of-hospital LA CAB+RPV
PROMOTER	Fundació FLS de Lluita contra la Sida, les Malalties Infectioses i la Promoció de la Salut i La Ciència
PRINCIPAL INVESTIGATOR	
CENTER	

I, (name and surname)....., after having read the information sheet that has been given to me and asking the clarifying questions about it to Dr./Dr.....

I confirm that I have received enough information about the study and that I have understood the objectives of the study and what it entails.

I understand that my participation is voluntary.

I understand that I can withdraw from the study:

- Whenever.
- Without having to give explanations.
- Without this having an impact on my medical care.

And I consent:

- That the clinical data collected during the study be stored in an automated file whose information may be handled exclusively for scientific purposes, provided that the information concerning me is dissociated (this means that the information obtained cannot be related to the person from whom it comes).
- I understand that I have the possibility of exercising the rights of access, rectification, cancellation, opposition, limitation of processing, data portability and not to be subject to automatic individualized decisions (profiling), by writing to the Data Protection Officer

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within the scope of the Department of Health (dpd@ticsalutsocial.cat), Junta de Andalucía (**********), or the promoter (LOPD@flsida.org)

I agree with everything related to this study and freely agree to participate in it and that my data can be used for research purposes as stated in the patient information sheet.

Patient signature

Signature of the Researcher

Date

Date

You will receive a copy of this document, once you have signed it, to keep with your records.

FOR ADULTS WHO ARE UNABLE TO GIVE CONSENT

.....,
Witness/interpreter at the consent interview

As of the date signed, I have been a witness in the consent interview for the research study named at the beginning of this document. I confirm that the information contained in this consent form was properly explained to the subject, and the subject has confirmed that all of their questions have been adequately answered.

Name of witness

Signature of the witness

Signature of the Researcher

Date

Date

The study subject will receive a completed fact sheet, along with a signed version of the consent form

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HOJA DE INFORMACIÓN AL PARTICIPANTE Y CONSENTIMIENTO INFORMADO

TÍTULO DEL ESTUDIO	"Implementación de la administración extrahospitalaria de la combinación de acción prolongada Cabotegravir+Rilpivirina como terapia opcional en pacientes de España infectados por el VIH. Aceptabilidad, idoneidad, viabilidad y satisfacción Estudio HOLA".
CÓDIGO DEL ESTUDIO	Out-of-hospital LA CAB+RPV
PROMOTOR	Fundació FLS de Lluita contra la Sida, les Malalties Infeccioses i la Promoció de la Salut i La Ciència
INVESTIGADOR PRINCIPAL	Eugenia Negredo Puigmal
CENTRO	Hospital Universitari Germans Trias i Pujol

Introducción

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar, promovido por Fundació FLS de Lluita contra la Sida, les Malalties Infeccioses i la Promoció de la Salut i La Ciència. El estudio ha sido aprobado por un Comité de Ética de la Investigación con medicamentos y por la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), de acuerdo a la legislación vigente, el Real Decreto 1090/2015 de 4 de diciembre y el Reglamento Europeo 536/2014 de 16 de abril, por los que se regulan los ensayos clínicos con medicamentos.

Nuestra intención es que usted reciba la información correcta y suficiente para que pueda decidir si acepta o no participar en este estudio. Para ello lea esta hoja informativa con atención y nosotros le aclararemos las dudas que le puedan surgir. Además, puede consultar con las personas que considere oportuno.

Le invitamos a participar en el estudio porque está diagnosticado de VIH, se le ha prescrito un tratamiento de acción prolongada con Cabotegravir y Rilpivirina y se encuentra con carga viral indetectable.

El tratamiento de acción prolongada es una combinación de dos medicamentos antirretrovirales llamados Cabotegravir y Rilpivirina. Ambos actúan para suprimir el VIH (virus de

inmunodeficiencia humana) de modo similar a otros antirretrovirales, con la diferencia que este tratamiento son dos inyecciones cada dos meses en lugar del tratamiento oral diario.

Este tratamiento solo puede ser administrado en el hospital y el objetivo de este estudio es ver si es aceptable la administración de Cabotegravir y Rilpivirina para el tratamiento del VIH en centros alternativos fuera del entorno hospitalario, por ejemplo, en centros de atención primaria o en centros comunitarios.

Participación voluntaria

Debe saber que su participación en este estudio es voluntaria y que puede decidir NO participar. Si decide participar, puede cambiar su decisión y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su atención sanitaria.

Objetivo del estudio

Este estudio tiene como objetivo principal ver si es aceptable y segura la administración de las inyecciones para los pacientes con infección por VIH tratados con Cabotegravir y Rilpivirina de acción prolongada vía intramuscular cada 2 meses fuera del hospital.

Las conclusiones de este estudio nos ayudarán a entender cómo se puede implementar la administración de los medicamentos fuera de un entorno hospitalario y ver si es aceptable, apropiado, factible y satisfactorio administrar las inyecciones de Cabotegravir y Rilpivirina cada 2 meses en centros de atención primaria o en centros comunitarios, así como evaluar la seguridad de la administración de las inyecciones de Cabotegravir y Rilpivirina.

Descripción del estudio

En este estudio participarán 110 adultos que viven con VIH y tienen la enfermedad controlada (carga viral indetectable) con su medicación actual para el VIH.

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Los medicamentos que se van a administrar son inyecciones de Cabotegravir y Rilpivirina. Los participantes serán distribuidos en dos grupos:

- Grupo I: se le administrará la dosis de Cabotegravir y Rilpivirina en el hospital
- Grupo II: se le administrará la dosis de Cabotegravir y Rilpivirina fuera del hospital, en un centro comunitario o en un centro de atención primaria ya asignado por el estudio.

Ni usted. ni el investigador sabrán a qué grupo será asignado antes de ser incluido en el estudio. Se decidirá al azar (como tirando una moneda al aire) a qué grupo pertenecerá. Esto se hace para obtener datos confiables de los resultados del estudio.

Cada 2 meses recibirá 2 inyecciones; cada una contiene uno de los dos medicamentos que forman el tratamiento. Se le administrarán en la parte superior externa del glúteo, una inyección a cada lado.

Estos medicamentos están aprobados por la AEMPS con el nombre Vocabria® (Cabotegravir) y Rekambys® (Rilpivirina).

Si no le han administrado Cabotegravir y Rilpivirina en inyecciones anteriormente, tomará la misma medicación oral durante 28 días y, el último día de medicación por vía oral, recibirá la primera dosis de Cabotegravir y Rilpivirina en el hospital. A partir del mes siguiente las inyecciones de Cabotegravir y Rilpivirina le serán administradas cada 2 meses en el centro donde le haya tocado.

Estos medicamentos orales también están aprobados por la AEMPS. En España Rilpivirina esta comercializado bajo el nombre de Edurant® y Cabotegravir bajo el nombre de Vocabria®. El objetivo de esta primera fase de tratamiento por vía oral es asegurar la tolerancia de los fármacos.

Actividades del estudio

El estudio tendrá una duración de 12 meses de tratamiento, en el que se realizarán 7 visitas presenciales.

En el caso de los pacientes que no se le haya administrado previamente Cabotegravir y Rilpivirina intramuscular deberán hacer una visita adicional después de 28 días de tratamiento antirretroviral oral, para confirmar la buena tolerancia al tratamiento.

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Antes de empezar el estudio:

Visita de selección/basal:

Si decide participar en el estudio, le pediremos que firme este **consentimiento informado** antes de ser incluido, le haremos algunas preguntas y recogeremos algunos datos para confirmar que cumple todos los criterios de selección para participar en el estudio. En esta visita realizaremos:

- Una revisión de su historia médica
- Una exploración física
- Una revisión de su medicación
- Una analítica con determinación de carga viral de VIH
- Un test de embarazo
- Unos cuestionarios

Durante el estudio: *Visitas de estudio:*

Se realizarán visitas cada 2 meses en las que se le administrarán inyecciones de Cabotegravir y Rilpivirina y se cumplimentarán unos cuestionarios durante las visitas para valorar si es aceptable, apropiado y viable el tratamiento, así como su grado de satisfacción y expectativas del tratamiento y un cuestionario que medirá la percepción de la inyección, que tendrá que rellenar dos días más tarde de las administraciones.

Se realizará una visita en el mes 1 en el hospital, si es la primera vez que se le administra la medicación Cabotegravir y Rilpivirina intramuscular y en esta visita se realizará una extracción de sangre para la determinación de la carga viral del VIH y se cumplimentarán los cuestionarios durante la visita y un cuestionario que medirá la percepción de la inyección, que tendrá que rellenar dos días más tarde de las administraciones.

En las visitas del mes 6 y las visitas del mes 12 acudirá al hospital donde se le realizará una extracción de sangre para la determinación de la carga viral del VIH y otros análisis, similares a los que se llevan a cabo para el seguimiento de la infección por VIH en la práctica clínica habitual (hemograma, bioquímica básica y recuento de linfocitos CD4/CD8).

En las visitas del mes 2, mes 4, mes 8 y mes 10 se rellenará solo el cuestionario que medirá la percepción de la inyección, que tendrá que rellenar dos días más tarde de las administraciones.

Procedimiento	Selección/Basal	Mes 1	Mes 2	Mes 4	Mes 6	Mes 8	Mes 10	Mes 12
Consentimiento Informado	X							
Visita clínica (Historial Médico/Examen Físico)	X	X			X			X
Extracción de Sangre	X	X			X			X
Test de embarazo (si aplica)	X	X			X			X
Cuestionarios del estudio	X	X			X			X
Cuestionario percepción de la inyección		X	X	X	X	X	X	X
Administración Oral de Cabotegravir y Rilpivirina	X							
Administración Intramuscular de Cabotegravir y Rilpivirina		X	X	X	X	X	X	X

Obtención de las muestras de sangre:

Las extracciones de sangre serán las de rutina y serán efectuadas por el personal de enfermería de la Unidad de VIH de su Hospital. La cantidad de sangre que se extraerá en cada una de las visitas del estudio será aproximadamente 30 mL.

Riesgos y molestias derivados de su participación en el estudio

En los ensayos previos de Cabotegravir y Rilpivirina ha sido bien tolerado, las reacciones adversas graves fueron muy poco frecuentes.

Las reacciones adversas descritas que pueden afectar son:

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Frecuencia	Efecto Adverso
Muy frecuentes (al menos a 1 de cada 10 personas)	Dolor de cabeza
	Reacciones en el lugar de inyección. Habitualmente son de leves a moderadas y su frecuencia disminuye con el tiempo. Sus síntomas pueden incluir: - Muy frecuentes: dolor y molestias, masas o bultos duros - Frecuentes: enrojecimiento, picor, hinchazón, calor o hematomas (que pueden incluir un cambio de color o una acumulación de sangre bajo la piel). - Poco frecuentes: entumecimiento, sangrado leve, formación de absceso (acumulación de pus) o celulitis (con sensación de calor, hinchazón o enrojecimiento).
	Sensación de calor (pirexia), que puede ocurrir en la primera semana tras las inyecciones
Frecuentes (afectan a menos de 1 de cada 10 personas)	Depresión
	Ansiedad
	Sueños anormales
	Dificultad para dormir (insomnio)
	Mareos
	Sensación de malestar (náuseas)
	Vómitos
	Dolor abdominal
	Gases
	Diarrea
	Sarpullido
	Dolor muscular
	Cansancio (fatiga)
	Sensación de debilidad (astenia)
	Malestar general
	Aumento de peso
Poco frecuentes (afectan a menos de 1 de cada 100 personas)	Adormecimiento (somnolencia)
	Sensación de mareo durante o después de una inyección. Esto puede provocar desvanecimientos.
	Daño hepático (sus signos pueden incluir coloración amarilla de la piel y la parte blanca del ojo, pérdida del apetito, picor, dolor a la palpación de la tripa, heces de color claro u orina de un color anormalmente oscuro).
	Cambios en los niveles analíticos de función hepática (aumento de las transaminasas)

	Aumento de la bilirrubina (una sustancia producida por el hígado) en sangre.

Reacciones en el lugar de la inyección

Puede experimentar reacciones locales en el lugar donde recibió las inyecciones. Los efectos secundarios muy frecuentes pueden incluir dolor o malestar, que suelen ser leves o moderados. También puede tener enrojecimiento, hinchazón, picor, hematomas, bultos, complicaciones en forma de infección (celulitis o absceso) e irritación en el lugar donde se aplica la(s) inyección(es). En la mayoría de los casos las reacciones son leves (75 %), mientras que el 4 % de los participantes en ensayos clínicos previos tuvo una reacción grave en el lugar de la inyección. La mayoría de las reacciones desaparecen en una semana o menos, pero a veces pueden durar mucho tiempo. La mayoría de las personas encuentran aceptables estas reacciones y rara vez suspender las inyecciones por efectos adversos.

Posibles efectos secundarios del procedimiento de inyección

Los síntomas de la reacción posterior a la inyección han ocurrido en algunas personas pocos minutos después de recibir la inyección de Rilpivirina. Las reacciones posteriores a la inyección son poco frecuentes y ocurrieron en menos del 0,5 % de los participantes en los ensayos clínicos. La mayoría de los síntomas se resolvieron unos minutos después de la inyección. Los síntomas de las reacciones posteriores a la inyección pueden incluir: dificultad para respirar, calambres estomacales, erupción cutánea, sudoración, entumecimiento de la boca, sensación de ansiedad, sensación de calor, sensación de mareo o sensación de que se va a desmayar, cambios en la presión arterial, y dolor en la espalda y/o el pecho. Informe a su médico/a del estudio si experimenta estos síntomas después de recibir las inyecciones. Estos casos pueden deberse a una inyección accidental de parte del medicamento en un vaso sanguíneo en lugar del músculo. No todos los pacientes en los que se sospechó una inyección accidental en un vaso sanguíneo informaron tales síntomas. La mayoría de los síntomas se resolvieron en minutos. Es posible que su médico/a necesite administrar un tratamiento para ayudar a resolver estos síntomas. El personal sanitario del estudio lo/la observará brevemente (aproximadamente 10 minutos) después de la inyección.

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Las inyecciones se administrarán en los músculos de las nalgas. La inyección podría no llegar al músculo o aplicarse demasiado lejos, sin llegar al músculo y penetrando en la piel, los vasos sanguíneos o los nervios. Las consecuencias de esto no se conocen bien, pero podría hacer que los niveles de Cabotegravir y Rilpivirina sean demasiado bajos o altos. Si son demasiado bajos, es posible que el medicamento no funcione adecuadamente contra el VIH. Si los niveles de Rilpivirina son demasiado elevados, podría alterarse su frecuencia cardíaca, que muy raramente, en casos graves, puede poner en peligro la vida y provocar la muerte súbita; sin embargo, hasta la fecha, no se han observado cambios tan graves en la frecuencia cardíaca ni muertes súbitas en estudios clínicos con Rilpivirina en ninguna de sus formas de administración (oral o intramuscular). Se hará todo lo posible para disminuir este riesgo, lo que incluye garantizar que se use la aguja del tamaño correcto y la técnica de inyección adecuada. El personal está entrenado para ello. También se le controlará después de cada inyección y durante el estudio, según corresponda. Si su médico/a cree que la inyección no se administró de la manera correcta, es posible que se le pida que permanezca en el centro hasta 2 horas después de la inyección para vigilar su evolución, y es posible que se necesiten pruebas adicionales para asegurarse de que no hay riesgos. Si le preocupa este tema, hable con su médico/a del estudio.

Hipersensibilidad

Se han notificado reacciones de hipersensibilidad (también conocidas como reacciones alérgicas) con otros medicamentos de la misma clase que Cabotegravir, con signos y síntomas que incluyen sensación general de malestar, erupción cutánea, fiebre alta, falta de energía, hinchazón (a veces de la cara o boca, causando dificultad para respirar), ampollas, úlceras bucales, conjuntivitis y dolores musculares o articulares. Si desarrolla cualquiera de estos signos y/o síntomas durante el estudio, debe llamar inmediatamente al equipo del estudio, para decidir si se requiere realizar algún tipo de análisis y/o e indicarle que deje de tomar Cabotegravir y Rilpivirina. Si se le indica que deje de tomar sus medicamentos, debe hacerlo de inmediato.

Erupción cutánea

El tratamiento con Cabotegravir y Rilpivirina podría ocasionar erupción cutánea. La mayoría son leves o moderadas, pero algunos tipos pueden ser graves y se deberá interrumpir el tratamiento. Si tiene algún tipo de erupción, picor u otros problemas en la piel durante el tratamiento, debe

informar al equipo del estudio de inmediato. Se le puede pedir que venga para realizar una exploración, análisis y/o decirle que deje de tomar Cabotegravir y/o Rilpivirina.

Alteración de las pruebas hepáticas

Un pequeño número de participantes en estudios de investigación que tomaron Cabotegravir con Rilpivirina desarrollaron alteración de las pruebas hepáticas que les obligaron a interrumpir el tratamiento. En algunos casos, las pruebas hepáticas anormales se explicaron por otras causas (p. ej., una nueva infección por un virus), mientras que un número menor (menos del 1 % de participantes) no tuvo explicaciones alternativas, lo que sugiere una forma leve de daño hepático sospechoso de ser debido a Cabotegravir y/o Rilpivirina. Las pruebas hepáticas mejoraron después de suspender la medicación, lo que sugiere que cualquier posible daño fue temporal. Se realizarán análisis de sangre para verificar la salud del hígado durante este estudio, dentro de sus controles rutinarios y se le informará si se produce alguna alteración y, si fuera el caso, los pasos a seguir. Si ocurre un problema hepático, es posible que se le pida que deje tomar el tratamiento del estudio.

¿Qué pasa si los efectos secundarios son intolerables?

Si experimenta efectos secundarios que son intolerables y necesita cambiar los medicamentos para el VIH, deberá suspender el estudio**.**

¿Qué otros posibles riesgos existen?

Riesgo de que el VIH se vuelva resistente al tratamiento

Con cualquier medicamento utilizado para tratar el VIH, existe el riesgo de que el virus adquiera resistencia a los fármacos, lo que significa que el medicamento perderá su actividad. El riesgo de adquirir resistencia dependerá de si el tratamiento consigue mantener la carga viral indetectable y esto, a su vez, dependerá de que usted siga las instrucciones sobre cómo tomar los medicamentos del estudio.

Por lo tanto, es muy importante que asista a sus visitas del estudio en las fechas programadas y que siempre tome su tratamiento exactamente como fue recetado. Hable con su médico/a del estudio cada vez que deje de tomar algún comprimido o si cree que deberá retrasar o adelantar

las visitas para recibir las inyecciones por motivos de trabajo, vacaciones, viajes, etc, que puedan interferir con sus visitas programadas.

Si necesita retrasar las inyecciones más de unos pocos días, se le puede ofrecer la opción de volver a tomar comprimidos durante un periodo corto de tiempo, lo cual se conoce como «puente oral». Su médico/a del estudio le podrá aconsejar de si esto es adecuado para usted.

No cambie ni omita ninguna dosis de ninguno de los medicamentos del estudio a menos que su médico/a del estudio se lo indique. Omitir dosis de la medicación (comprimidos o una inyección) puede favorecer que el VIH adquiera resistencia a los fármacos y estos dejen de actuar. Esto podría limitar, además, las posibilidades de utilizar en el futuro otros medicamentos contra el VIH relacionados con estos.

Por otro lado, al suspender el tratamiento de acción prolongada, es importante comenzar a tomar otro medicamento contra el VIH, según lo recomendado por su médico/a del estudio, para mantener el control del VIH y evitar que el VIH adquiera resistencia a los fármacos.

Efectos secundarios después de recibir inyecciones de acción prolongada

Después de una inyección de Cabotegravir y Rilpivirina, estos medicamentos permanecerán en su cuerpo durante mucho tiempo. En algunas personas, niveles bajos de Cabotegravir y Rilpivirine pueden estar presentes en el cuerpo durante más de un año después de la última inyección. Si desarrolla un efecto secundario del medicamento del estudio después de una inyección, no habrá forma de eliminar el medicamento de su cuerpo. Si esto sucede, su médico/a hará todo lo posible para tratar los síntomas.

Cuando suspende las inyecciones de acción prolongada, la cantidad de medicamento en su cuerpo disminuirá con el tiempo y desaparecerá.

Sensación de desmayo después de la inyección

Al recibir las inyecciones algunas personas pueden sentirse mareadas o con la sensación de que se pueden desmayar. Esta reacción, también llamada "reacción vasovagal", puede ocurrir con muchos procedimientos médicos, se resuelve rápidamente y no es una amenaza para su salud.

Extracción de sangre

Al extraerle sangre, puede sentirse mareado/a o experimentar un dolor leve, hematomas, irritación o enrojecimiento en el sitio de la punción. En casos raros, puede contraer una infección.

Problemas de salud mental

Algunas personas con problemas de salud crónicos, incluido el VIH, a veces tienen sentimientos de depresión o pueden tener pensamientos de hacerse daño o quitarse la vida (suicidio). Un pequeño número de personas en tratamiento con Cabotegravir y Rilpivirina han tenido pensamientos y acciones suicidas, en particular aquellas con antecedentes de depresión o problemas de salud mental.

Informe al médico/a del estudio si tiene antecedentes de problemas de salud mental. Si tiene pensamientos de autolesionarse o suicidarse o tiene otros pensamientos o sentimientos inusuales o incómodos durante este estudio, debe informar al médico/a del estudio o acudir al hospital más cercano de inmediato.

Esta lista de efectos secundarios no está completa. Puede experimentar efectos secundarios diferentes a los descritos en este formulario de consentimiento informado o que no se conocen actualmente.

Medicación NO permitida durante el estudio

El uso de algunos otros fármacos está contraindicado o debe realizarse con precaución cuando se administran de forma simultánea con Cabotegravir y/o Rilpivirina. Por este motivo, no está permitido el uso de los siguientes fármacos durante el estudio:

- Carbamazepina, oxcarbazepina, fenobarbital, fenitoína (medicamentos para tratar la epilepsia y prevenir las convulsiones)
- Rifabutina, rifampicina, rifapentina (medicamentos para tratar infecciones bacterianas como la tuberculosis)
- Dexametasona (un corticosteroide que se emplea para tratar diversas patologías, tales como la inflamación y las reacciones alérgicas) administrada en un ciclo de tratamiento por vía oral o inyectable
- Productos que contienen Hierba de San Juan o Hipérico (Hypericum perforatum, una planta medicinal que se emplea para la depresión).

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No utilice medicamentos (de venta con y sin receta) sin consultar antes con el personal médico del estudio. El personal médico del estudio le explicará la necesidad de evitar ciertos medicamentos durante el estudio, incluidos los contraindicados. Es posible que más adelante se identifiquen nuevos medicamentos que tengan que añadirse a la lista de fármacos que no debe tomar durante el estudio.

¿Puede participar en el estudio una persona embarazada?

Debido a que no se dispone de información acerca de la seguridad para el feto de Cabotegravir y Rilpivirina de acción prolongada, no se permite la participación en el estudio a personas embarazadas.

Por este motivo, dentro de las pruebas previstas en la visita de selección y en las visitas del estudio se realizarán pruebas de embarazo en orina a todas las personas que menstrúan en edad fértil* que deseen participar en el estudio o hayan sido incluidas en el estudio. El resultado debe confirmarse como negativo antes de la administración de la primera dosis de los fármacos del estudio. Las pruebas de embarazo también se realizarán en cualquier momento durante el estudio cuando se sospeche un embarazo.

Si usted es una persona que puede tener hijos, debe usar métodos anticonceptivos mientras participe en el estudio. Se debe usar un método anticonceptivo eficaz, según lo acordado con su médico/a del estudio, desde al menos 14 dias antes del inicio de su primera dosis de Cabotegravir y Rilpivirina y durante el tiempo que esté tomando el medicamento del estudio. Se recomienda que continúe usando un método anticonceptivo efectivo hasta al menos 14 días después de su última dosis oral de Cabotegravir y Rilpivirina, y al menos 13 meses después de su última(s) inyección(es) de acción prolongada, ya que los medicamentos del estudio aún pueden estar presentes en el cuerpo durante este tiempo. Su médico/a del estudio hablará con usted sobre esta recomendación y sobre los riesgos potenciales del embarazo durante este tiempo. Debe informar a su médico/a de atención primaria y su médico/a de la Unidad de VIH si tuviera un embarazo dentro de los 12 meses posteriores a la última inyección de Cabotegravir y Rilpivirina aunque ya no esté en el estudio.

Por lo tanto, en la visita de selección y durante el estudio, se deberá aceptar el uso de alguno de los siguientes métodos anticonceptivos considerados altamente efectivos para evitar el embarazo:

- anticoncepción hormonal o dispositivo intrauterino [DIU]
- esterilidad anatómica propia o de la pareja

Si el resultado de la prueba de embarazo es positivo o equívoco, las inyecciones intramusculares deberán posponerse hasta que se obtenga una prueba de embarazo en suero válida. Si la prueba es positiva, dejará de tomar la medicación del estudio y el personal médico responsable del estudio le informará sobre las siguientes acciones a seguir (ver apartado siguiente).

¿Qué sucederá si una persona queda embarazada durante el estudio?

Debe informar al equipo investigador del estudio de forma inmediata si sospecha que hay posibilidad de embarazo durante el estudio. Si su participación en el estudio ha terminado, deberán informar a su médico/a habitual en el seguimiento del VIH.

Si se confirma su embarazo durante el estudio se le dará la opción de cambiar a una terapia antirretroviral alternativa durante el embarazo. Se iniciará un tratamiento antirretroviral alternativo que se considere adecuado para su uso durante el embarazo de acuerdo con las directrices locales. La fecha límite para iniciar este tratamiento será la fecha prevista para la siguiente inyección de Cabotegravir y Rilpivirina.

Después del estudio

Cuando acabe su participación recibirá el mejor tratamiento disponible, el que su médico considere el más adecuado para su enfermedad, en su hospital. Debido a que la medicación del estudio ya estará comercializada es posible que se le pueda seguir administrando la medicación del estudio pero ni el investigador ni el promotor adquieren compromiso alguno de mantener dicho tratamiento fuera de este estudio.

¿Cuáles son los beneficios esperables de este estudio?

Posibles beneficios:

Al participar en este estudio, usted recibirá un tratamiento antirretroviral que ha demostrado una alta eficacia y una excelente tolerabilidad en diferentes ensayos clínicos. Es esperable que con

este estudio se pueda analizar si la administración del tratamiento es aceptable, apropiado y viable llevarlo a cabo fuera del ámbito hospitalario y se puede implementar en los centros de atención primaria y centros comunitarios, lo cual puede beneficiar en el futuro a otras personas infectadas por el VIH.

Costes:

Usted no tendrá que pagar por los medicamentos ni por pruebas específicas del estudio. Su participación en el estudio no le supondrá ningún gasto adicional a la práctica clínica habitual. El estudio será financiado por la compañía farmacéutica ViiV Healthcare en colaboración con la Fundació Lluita contra la SIDA i les Malalties Infeccioses.

Confidencialidad e información legal

El promotor del estudio y los centros participantes, como responsables independientes del tratamiento de datos, garantizarán la confidencialidad de la información personal de los sujetos participantes de acuerdo con la normativa legal vigente (Ley Orgánica 3/2018, de Protección de Datos Personales y Garantía de los Derechos Digitales, y Reglamento [UE] 2016/679 del Parlamento Europeo y del Consejo, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos).Durante este estudio, el equipo médico del estudio registrará información referente a usted, a su salud y a su participación en el estudio en impresos denominados cuadernos de recogida de datos.

Para garantizar que los datos recogidos durante el estudio se tratan de forma confidencial, sus datos estarán identificados mediante un código, no se incluirá su nombre ni ninguna otra información que permita identificarle directamente en los cuadernos de recogida de datos. Por lo tanto, su identidad no será revelada a ninguna otra persona salvo a las autoridades sanitarias, cuando así lo requieran o en casos de urgencia médica. Los comités éticos, los representantes de la Autoridad Sanitaria en materia de inspección y el personal autorizado por el promotor, únicamente podrán acceder para comprobar los datos personales, los procedimientos del estudio clínico y el cumplimiento de las normas de buena práctica clínica (siempre manteniendo la confidencialidad de la información).

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Solo el personal médico del estudio / colaboradores podrán relacionar dichos datos con usted y con su historia clínica. El promotor sólo tendrá acceso a la información relativa a los resultados generales del estudio. En ningún caso accederá a sus datos personales.

Para llevar a cabo este ensayo clínico, necesitaremos asimismo acceder a la información médica contenida en su historia clínica y registraremos su participación y aspectos de seguridad a lo largo del estudio en el sistema electrónico de historia clínica de los centros participantes, por lo que usted nos deberá autorizar para ello expresamente.

Los responsables del tratamiento de los datos son el promotor, Fundació Lluita contra la Sida y enfermedades infecciosas, así como también los centros donde se llevará a cabo este estudio perteneciente al Institut Català de la Salut y la Junta de Andalucia

- Delegado de Protección de Datos en el ámbito del Departamento de Salud mail de contacto: dpd@ticsalutsocial.cat.
- Delegado de Protección de datos en el ámbito de la Junta de Andalucía mail de contacto **********
- Delegado de Protección de Datos de Fundació FLS de Lluita contra la Sida, les Malalties Infeccioses i la Promoció de la Salut i La Ciència (promotor), con domicilio en la Ctra. de Canyet s/n, Hosp. Univ. Germans Trias i Pujol, 2a planta Maternal, 08916 Badalona (Barcelona): lopd@flsida.org.

Base Jurídica del tratamiento de los datos: El consentimiento que otorga mediante este documento y el interés general en el tratamiento de la enfermedad.

Destinatarios: Son destinatarios de los datos el equipo investigador y el personal autorizado por los responsables del tratamiento de datos, los proveedores necesarios para la finalidad del tratamiento (laboratorios, empresa proveedoras de software y alojamiento) y en su caso, las autoridades administrativas pertinentes. Aunque los datos se conservarán pseudoanonimizados durante el estudio, le informamos que su información estará alojada en un servidor seguro ubicado en la Unión Europea bajo normativa actual con la más alta calidad y seguridad especifica. Los datos codificados pueden ser transmitidos a terceros y a otros países, pero en ningún caso contendrán información que le pueda identificar directamente, ni indirectamente, y se establecerán contratos con los destinatarios de la información que prohíban expresamente la reidentificación, mediante el cruce con otras bases de datos o cualquier tecnología que intente reidentificar los datos. En el caso de que se produzca esta cesión, será para

los mismos fines del estudio descrito o para su uso en publicaciones científicas, pero siempre manteniendo la confidencialidad de estos, de acuerdo a la legislación vigente.

Derechos: Usted puede ejercer sus derechos de acceso, rectificación, cancelación, oposición, limitación del tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) del paciente sobre los datos que ha facilitado para el estudio (Derechos PARSOL). Para ejercer sus derechos al participante podrá dirigirse al equipo de investigadores o bien al delegado de protección de datos de las instituciones

Conservación de los datos: El promotor conservará los registros del ensayo clínico durante un período de al menos 25 años tras su finalización. Posteriormente, su información personal sólo se conservará por el centro para el cuidado de su salud. El promotor conservará datos que en ningún momento contendrán datos personales.

Le recordamos que los datos no se pueden eliminar, aunque deje de participar en el estudio para garantizar la validez de la investigación y cumplir con los deberes legales y los requisitos de autorización de medicamentos. Por lo tanto, si usted decide retirar el consentimiento para participar en este estudio, ningún dato nuevo será añadido a la base de datos, pero sí se utilizarán los que ya se hayan recogido.

Derecho de reclamación: Puede ejercer su derecho a presentar una reclamación ante la Autoridad competente (la Autoritat Catalana de Protecció de Dades o bien, la Autoridad Española de Protección de Datos), si considera que se han vulnerado sus derechos en materia de protección de datos.

Seguro:

El promotor del estudio ha suscrito una póliza de seguro de responsabilidad civil con la compañía Zurich Insurance PLC sucursal en España de acuerdo con los requerimientos establecidos en el RD 1090/2015, que cubre los posibles daños y perjuicios que puedan experimentar derivados de su participación en el ensayo, siempre que no sean consecuencia de la propia enfermedad que se estudia o de la evolución propia de su enfermedad como consecuencia de la ineficacia del tratamiento.

Así mismo, es posible que su participación en este ensayo clínico pueda modificar las condiciones generales y particulares (cobertura) de sus pólizas de seguros (vida, salud, accidente) y, por ello, le recomendamos que se ponga en contacto con su compañía de seguros y le informe de su

participación en el mismo para determinar si podría afectar a su póliza de seguro actual o en el caso de que vaya a contratar una póliza nueva.

Si desea más información relativa a este apartado, consulte con el investigador principal del estudio en su centro.

Participación en el estudio:

Para participar en este estudio no es necesario que tome la decisión en este momento, puede llevarse esta Hoja de Información a casa y meditar sobre ello el tiempo suficiente y consultar su participación con su familia o médico/a habitual.

Usted participa en este estudio de forma voluntaria y podrá retirarse del estudio cuando lo desee sin por ello tener que dar explicaciones ni verse afectada su asistencia posterior en nuestra Consulta.

Una vez firmado el Consentimiento Informado, usted se quedará con una copia de este documento.

Existe la posibilidad de exclusión del ensayo por parte del promotor o el equipo investigador, en caso de producirse problemas de seguridad o incumplimiento con los procedimientos establecidos en el estudio.

En caso de cancelación del ensayo por parte del promotor, se informará a las personas participantes de los motivos.

Cualquier información nueva referente a los fármacos utilizados en el estudio que puedan afectar a su decisión para continuar en el estudio se la comunicará su médico/a lo antes posible y, si es necesario, se firmará un nouvo consentimiento.

Contacto para información

En caso de cualquier duda o problema relacionados con su infección o con el tratamiento administrado, fuera del horario laboral, usted puede contactar con el investigador principal del estudio:

Dr/a…….

Tel ……

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CONSENTIMIENTO INFORMADO

TÍTULO DEL ESTUDIO	"Implementación de la administración extrahospitalaria de la combinación de acción prolongada Cabotegravir+Rilpivirina como terapia opcional en pacientes de España infectados por el VIH. Aceptabilidad, idoneidad, viabilidad y satisfacción Estudio HOLA".
CÓDIGO DEL ESTUDIO	Out-of-hospital LA CAB+RPV
PROMOTOR	Fundació FLS de Lluita contra la Sida, les Malalties Infeccioses i la Promoció de la Salut i La Ciència
INVESTIGADOR PRINCIPAL	Eugenia Negredo Puigmal
CENTRO	Hospital Universitari Germans Trias i Pujol

Yo, (nombre y apellido)....., después de haber leído la hoja de información que se me ha entregado y hacer las preguntas aclaratorias al respecto al Dr./Dra.....

Confirmo haber recibido suficiente información sobre el estudio y haber entendido los objetivos del estudio y lo que implica.

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:

- Cuando quiera.
- Sin tener que dar explicaciones.
- Sin que esto repercuta en mis cuidados médicos.

Y consiento:

- Que los datos clínicos recogidos durante el estudio sean guardados en un fichero automatizado cuya información podrá ser manejada exclusivamente con fines científicos, siempre que la información referente a mi persona sea disociada (esto significa que la información que se obtiene no puede ser relacionada con la persona de la que proviene).
- Comprendo que tengo la posibilidad de ejercitar los derechos de acceso, rectificación, cancelación, oposición, limitación de tratamiento, portabilidad de datos y a no ser objeto

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de decisiones individualizadas automáticas (elaboración de perfiles), dirigiéndome por escrito al delegado de Protección de Datos en el ámbito del Departamento de Salud (dpd@ticsalutsocial.cat) Junta de Andalucía (**********) o del promotor (LOPD@flsida.org)

Estoy de acuerdo con todo lo referido a este estudio y presto libremente mi conformidad para participar en el mismo y que mis datos puedan ser utilizados con fines de investigación según consta en la hoja de información al paciente.

Firma de paciente Firma de/la Investigador/a

Fecha Fecha

Recibirá una copia de este documento, una vez la haya firmado, para que la conserve con sus registros.

PARA LOS ADULTOS QUE NO PUEDEN DAR SU CONSENTIMIENTO

....,
Testigo/interprete en la entrevista de consentimiento

En la fecha suscrita, yo he sido testigo en la entrevista de consentimiento para el estudio de investigación nombrado al principio de este documento. Yo confirmo que la información contenida en este formulario de consentimiento fue debidamente explicada al sujeto, y el sujeto ha confirmado que todas sus dudas han sido contestadas adecuadamente.

Nombre del testigo

Firma del testigo Firma de/la Investigador/a

Fecha Fecha

El sujeto del estudio recibirá una hoja informativa completa, junto a una versión firmada del formulario de consentimiento

BMJ Open

Study protocol: the HOLA Study – Exploring the acceptability, appropriateness, feasibility and satisfaction of an implementation strategy for out-of-HOspital administration of the Long-Acting combination of cabotegravir and rilpivirine as an optional therapy in HIV patients from Spain – a hybrid implementation-effectiveness, phase IV, double arm, open label, multicentric study.

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Title: Study protocol: the **HOLA** Study – Exploring the acceptability, appropriateness, feasibility and satisfaction of an implementation strategy for out-of-**HO**spital administration of the **L**ong-**A**cting combination of cabotegravir and rilpivirine as an optional therapy in HIV in Spain – a hybrid implementation-effectiveness, phase IV, double arm, open label, multicentric study.

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Abstract

Introduction: The HOLA Study is a 12-month randomized, hybrid implementation-effectiveness, phase IV, double arm, open label, multicentric study including virologically suppressed people living with HIV (PWH). HOLA, which started in September 2023, evaluates acceptability, appropriateness, feasibility and satisfaction of out-of-hospital administration of cabotegravir and rilpivirine long-acting (CAB+RPV LA).

Methods: A total of 110 PWH who are already under treatment with CAB+RPV LA or switch their antiretroviral therapy to CAB+RPV LA will be recruited from two main hospitals in Barcelona (Germans Trias I Pujol and Vall d'Hebrón) and Costa del Sol Hospital, in Marbella. The patients will be randomized 1:1 into a Hospital Group (administration of CAB+RPV LA in the hospital) and the Outpatient Group (Out-of-hospital administration) including community or primary care centers. The main

objectives of the study are to compare the acceptability at month 12 of the administration of CAB+RPV LA in and out-of-hospital centers from the perspective of patients, and to assess and compare the safety and tolerability of CAB+RPV LA. The study takes place at 9 clinical units in Catalonia, and Andalusia, [3 tertiary hospitals (recruiting centers), 1 community center, 1 STI clinic, and 4 primary care centers].

Ethics and dissemination: The current publication refers to version 3.0. of the protocol, with issue date on the 14th April 2024, as approved by the Comité de Ética de la Investigación con medicamentos del Hospital Universitari Germans Trias i Pujol (approval number AC-23-042-HGT-CEIM). The clinical trial will be conducted according to the principles of the Declaration of Helsinki, Fortaleza, Brazil, October 2013. This study will be conducted according to Spanish regulations regarding clinical trials (Royal Decree 1090/2015) and biomedical investigations (Organic Law 14/2007 of biomedical investigation and the Royal Decree 1716/2011), and the Clinical Trial Regulation (Regulation EU No 536/2014). Confidentiality requirements will follow the required Data Protection legislation. Enrolment completion in the study is expected by the end of May 2024, with an end of study expected in May 2025. Results emerging from this study will be reported in HIV national and international meetings as well as published in international journals with high impact factor. If the outcome deems positive, we will also develop and propose policy guidelines for integration of the administration of CAB+RPV LA in alternative outpatient facilities into the standard of care in the HIV care pathway.

Trial registration number: NCT06185452 / EUCT number: 2023-503963-41-00

Keywords: implementation science, cabotegravir and rilpivirine long acting, CAB+RPV LA, HIV, patient-centered care

Number of words: 382

Strengths and limitations

Strengths:

- The HOLA study utilized verified implementation research methods in HIV healthcare that will generate the knowledge required for policymakers, healthcare mediators and the community to modify the current models of care in PWH towards a patient-centered approach.
- The study includes the participation of community centers and ITS clinics due to their proximity with PWH and their implication in PrEP implementation and rapid HIV diagnosis.
- The study addresses not only urban tertiary centers but also rural centers.

Limitations:

- It is important to note that the intervention is not exempt from certain risks, such as staff changes or logistic inconveniences, and planning for these in advance is at the expense of investigator criteria from each center.
- Per protocol, a medical visit at the hospital at months 6 and 12 had to be included for routine medical care, including those participants who have been randomized to receive treatment at the out-of-hospital center.

Introduction

The Joint United Nations Programme on HIV/AIDS (UNAIDS) is a strategic program aimed at guiding and coordinating governments and structures that are responsible for providing HIV services in order to save lives [1]. Until 2020, the objectives were to ensure that 90% of people with HIV (PWH) were diagnosed, 90% of them on antiretroviral treatment (ART), and 90% of them virally suppressed, and these have been updated to 95-95-95 for 2025. With this purpose, “Treat All” policies in many regions worldwide have favored access to ART, consequently reducing HIV-related morbidity and mortality, and increasing life expectancy in PWH. Thus, HIV treatment has shifted to a chronic care model of disease management [2]. Currently, there are many potent, convenient, and well tolerated antiretroviral combinations available. However, ART should be prescribed as early as possible and, for the moment, in a life-lasting manner.

Nevertheless, stigma is still present, and recent goals by the UNAIDS include a novel target of quality-of-life improvement [1–3]. In line with this, inclusion of Patient Reported Outcomes (PROs) is becoming a preference in the development of the latest clinical trials, as these may shed light into which factors related to ART and patient care are of utmost importance in improving health-related quality of life, patient satisfaction, and in reducing stigma. In particular, a recent study carried out in Germany found out that the frequency of dosing and the risk of long-term side effects have a major influence on the acceptance of novel therapy regimens and should be considered to increase patient adherence and satisfaction [4].

Considering these reasons, there is a need for more convenient, less frequent treatment, to help address challenges associated with posology, psychosocial issues and adherence in PWH. Long-acting (LA) injectable regimens are emerging as a treatment option that may simplify therapy for PWH and anticipate a shift in the treatment paradigm for these people [5]. There are data confirming the non-inferiority of the LA intramuscular (IM) cabotegravir (CAB) and rilpivirine (RPV) compared with continuing a standard of care regimen in antiretroviral-naive adults with HIV-1 suppressed after 20 weeks in oral ARV with DTG/ABC/3TC (FLAIR study) [6] and for the maintenance of viral suppression (ATLAS, ATLAS-2M and LATTE-2 studies) [7,8]. Additionally, the use of CAB+RPV LA reduces the frequency of dosing from daily to every two months, and may aid in addressing fear of disclosure, anxiety around medication adherence, and daily reminders of the HIV status and the chronicity of disease [9].

Nonetheless, in Spain, this LA regimen must be administered in the hospital by a trained health team every 2 months, supposing a change in the dynamics of HIV units, which were previously reserved for a medical visit every 6 months. For these reasons, this option could be less convenient than conventional daily oral therapy for some people, since it implies visits to the hospital every 2 months for the administration of the injections. A shared approach for the treatment administration with primary care or community centers may be appropriate to improve the patient’s satisfaction while maintaining high-quality care for PWH. However, there is still insufficient evidence regarding the feasibility of decentralizing treatment for PWH, in particular in the context of Spain.

Given these considerations, the proposed study seeks to address these issues by implementing the out-of-hospital CAB+RPV LA administration. Alternative settings to receive CAB+RPV LA will offer new options to PWH that may increase their quality of life and improve psychosocial challenges. Together with primary care centers, we are also interested in including community centers and STI clinics due to their proximity with

PWH and their implication in Pre-exposure Prophylaxis (PrEP) and rapid HIV diagnosis. Furthermore, centers belong to two different regions from Spain, including not only urban tertiary centers but also rural centers.

Research questions

To assess the implementability of this approach in Spain, first, we propose a comparison of the acceptability, appropriateness, and feasibility of the administration of CAB+RPV LA between out-of-hospital settings and the local standard of care (hospital administration), as well as the patient's satisfaction. The study is also focused on the identification of the PWH profile who are the best candidates to this strategy and whose satisfaction is higher. Finally, we will distinguish patients who are naïve to CAB+RPV LA from those who are not to evaluate potential intra-group differences.

The study is utilizing Proctor's research framework for measuring the success of specific implementation outcomes [10], according to which acceptability is defined as the perception among implementation stakeholders that a given treatment, service, practice, or innovation (the administration of CAB+RPV LA in alternative injection sites) is satisfactory. Appropriateness is defined as the perceived compatibility of the innovation or evidence-based practice for a given practice setting, provider, or consumer; and/or to address a particular issue. Finally, feasibility is defined as the extent to which the innovation can be successfully carried out within a given setting. Validity of these tools has been scientifically proven [11].

Aims and objectives

The primary objective of this post-approval study is to assess and compare the acceptability by the patient of the implementation of CAB+RPV LA from the perspective of participants receiving outside-hospital injections versus the participants receiving hospital injections by month 12, in order to support future scale up efforts. A co-primary objective of the study will be to assess and compare the safety and tolerability of CAB+RPV LA between the out-of-hospital administration and the in-hospital administration groups.

Secondary objectives are to assess and compare acceptability, appropriateness, and feasibility of the administration of CAB+RPV LA as perceived by patients and HCP/non-clinical staff, as well as patient's satisfaction, and expectations throughout all timepoints of the study; retention, engagement, and compliance; and to identify those patients in which the out-of-hospital administration is more suitable. Tertiary objectives are to assess and compare between groups the virological effectiveness; the change at month 12 vs baseline in patient's acceptability, satisfaction, and expectations among the subgroup of participants with previous experience with CAB+RPV LA; and to compare these to those patients who have never received CAB+RPV LA.

Methods and analysis

Study design

This is a 12-month, randomized, hybrid implementation-effectiveness, phase IV, double arm, open label, multicentric study including virologically suppressed PWH who start or are currently under treatment with CAB+RPV LA, to evaluate the out-of-hospital versus in-hospital administration of this combination in terms of acceptability, appropriateness,

feasibility and satisfaction. Here, "hospital" refers to HIV specialty outpatient clinics within tertiary care centers, while "out-of-hospital" refers to other medical settings such as community-based care facilities, STI centers or primary care centers.

The study began in the **preparation stage**, where healthcare staff were engaged, informed, and trained in CAB+RPV LA and the delivery strategies. All processes and protocols were ensured to be in place before the first patient was enrolled, and adequate material and human resources were provided. Community and primary care healthcare workers were trained to help deliver the injections to patients.

The study then transitioned into the **initial implementation stage** when the first patients were recruited and enrolled. Patients were randomized 1:1 into a in-hospital group or out-of-hospital group and stratified according to age (<50 years old or ≥50), gender (male or female), as well as according to whether participants are already receiving CAB+RPV LA. Rural and non-rural options were only considered in the out-of-hospital setting and the choice was made by the participant. As of October 2023, the first participant was enrolled. PWH naïve to CAB+RPV LA, during the oral treatment lead-in phase are attended at the reference hospital, to rule out adverse events, and the first injection is administered in the hospital. They start receiving CAB+RPV LA injection doses at their in-hospital or out-of-hospital assigned center from the next CAB+RPV LA administration (month 2). For patients previously receiving CAB+RPV LA, the first study injection is given in the randomized center, at month 2.

No changes in treatment regimens are foreseen during the study period. In case of failure of one of the regimens, a new regimen will be decided using a resistance test as clinical routine. In case adverse events to the medication occur, the investigator will decide if it is necessary to replace it.

Investigators may provide oral CAB and/or RPV as a short-term “bridging” strategy for participants who have begun CAB + RPV LA in case a patient cannot attend an appointment. Should a participant need “oral bridging”, sites must contact the coordinating investigators for guidance on treatment strategies prior to a missed CAB+RPV LA dose and the missed dose should be accurately noted in the registry. Bridge to oral therapy with CAB+RPV is permitted if a patient misses an injection. However, no more than two missing injections will be allowed as part of the study.

At the end of the study, the change of treatment will be done at the discretion of the physician.

Study setting

The study takes place at 9 clinical units in two regions of Spain, Catalonia, and Andalusia, [3 tertiary hospitals (recruiting centers), 1 community center, 1 sexually transmitted infection (STI) clinic, and 4 primary care centers] (**Table 1**); and spans two implementation stages: preparation and initial implementation.

Outcome measures

The study includes both participant outcomes and staff outcomes, divided between primary, secondary and exploratory outcome measures:

Primary outcomes measures:

1. To assess and compare between groups the number of participants that show a mean score ≥ 4 across the Acceptability of Intervention Measure (AIM) questionnaire at month 12 [11–13].
2. To assess and compare between groups the proportion of participants with a mean score ≥ 4 across the AIM questionnaires at month 12.
3. To assess and compare between groups the mean score across the AIM questionnaires at month 12.
4. To assess and compare between groups the incidence and severity of CAB+RPV LA-related adverse events (AEs), all Serious Adverse Events (SAEs), injection site reactions (ISRs) or post-injection reactions through study completion, and the proportion of patients who presented grade 3 or 4 CAB+RPV LA-related adverse events.
5. To assess and compare between groups the proportion of participants who discontinue CAB+RPV LA due to AEs/SAEs and due to CAB+RPV LA-related adverse events.

Secondary outcomes measures:

1. To assess and compare between groups the proportion of participants with a mean score ≥ 4 across the AIM questionnaires at months 1 and 6.
2. To assess and compare between groups the proportion of participants with a mean score ≥ 4 across the Intervention Appropriateness Measure (IAM) and Feasibility of Intervention Measure (FIM) questionnaires, at months 1, 6 and 12 [11–13].
3. To assess and compare between groups the proportion of healthcare professionals and/or non- clinical staff that show an mean score ≥ 4 across the AIM, IAM and FIM questionnaires at months 1, 6 and 12.
4. To assess and compare between groups the proportion of patients who report high satisfaction at each study time-points using the HIV Treatment Satisfaction Questionnaire "status" (HIVTSQs12[14].
5. To assess and compare between groups changes in satisfaction derived from HIVTSQs12, in the overall sample from baseline to months 1, 6 and 12.
6. To assess and compare between groups changes in satisfaction derived from the HIV Treatment Satisfaction Questionnaire "change" (HIVTSQc12) [14] in the overall sample from baseline to month 12.
7. To assess and compare between groups the expectations of the CAB+RPV LA regarding the following areas: adherence to treatment, follow-up of medical visits, illness perception, physical and emotional quality of life, family and social relationships and work; at baseline and month 6 and 12. Expectations will be assessed through 5-likert scales developed *ad hoc* for the study.
8. To assess and compare between groups the Patient Reported Outcome Measures (PROMs) at each study time-points using the Patient Reported Outcome Measures HIV Clinic Screening Tool (PROMS-CST- HIV) questionnaire [15], at baseline and months 1, 6 and 12. This questionnaire assesses PROs regarding anticipated stigma, emotional distress, sexuality, social support, material deprivation, sleep and fatigue, cognitive problems, physical symptoms.
9. To assess and compare between groups changes in PROMs throughout the time points in each group in the overall sample using the PROMS-CST- HIV questionnaire.
10. To assess and compare between groups changes in the health professionals' expectations using a 5-likert Health Professional Expectations Questionnaire developed *ad hoc* for the study through study completion.

11. To assess and compare between groups the perception of injection, using the perception of injection (PIN) questionnaire [16] at months 1, 2, 4, 6, 8, 10 and 12.
12. To assess and compare between groups the proportion and number of patients who miss their appointment for the CAB+RPV LA administration (out of the window period ±7 days) from baseline to month 6 and 12.
13. To assess and compare between groups the number and proportion of patients who early interrupt CAB+RPV LA, at month 6 and 12.
14. To compare among groups the proportion of patients who adopt oral bridging therapy.
15. To identify those patients in which the out-of-hospital administration is more suitable by comparing the previous endpoints, stratifying according to: age (<50 vs ≥50 years old), gender (male vs female), as well as according to if the participant is already receiving or not CAB+RPV LA.

Exploratory outcomes measures:

1. To assess and compare between groups the virological effectiveness of CAB+RPV LA at month 6 and 12:
   - Proportion of subjects who are virologically suppressed (plasma HIV-1 RNA ≤50 copies/mL).
   - Proportion of participants with confirmed virologic failure/rebound (2 consecutive HIV-1 RNA greater than or equal to 200 copies/mL).
   - Proportion of participants with blips.
2. To assess the average change from baseline to month 12 in patient's acceptability, satisfaction, and expectations (AIM, HIVTSQs12, HIVTSQc12, expectations and PROMS-CST-HIV), as mentioned above, among the subgroup of participants with previous experience with CAB+RPV LA.
3. To compare patient's acceptability, satisfaction, and expectations at month 12 (AIM, HIVTSQs12, HIVTSQc12, expectations and PROMS-CST-HIV), as mentioned above, between patients under prior treatment with CAB+RPV LA and those patients who have never received CAB+RPV LA.

Patient and Public Involvement statement

Patients were not directly involved in the design or conduct of this study. However, the study addresses priorities relevant to patient care and outcomes, aligning with broader public health needs identified in previous research and clinical guidelines. In the dissemination phase, the results are planned to be shared with local community health organizations to inform future strategies and policies that directly impact patient care.

Sample size

A total of 110 virologically suppressed PWH will be included in this study and will receive CAB+RPV LA in the hospital and/or out-of-hospital alternative facilities. A period of enrolment of 8 months was considered.

Sample size justification

The sample size was calculated accepting an alpha error of 5%, for a statistical power of 80% in a bilateral contrast, and an expected acceptability of 45% in the hospital group

and of 75% for the outpatient group, at the end-of-study. Fixing the type I error at 5%, 55 subjects per group will be necessary to reject the equal null hypothesis with a power of 80%. Assuming a maximum loss of 25%, the required sample size is 110 patients, 55 in each arm.

Participant identification

Potential participants who will be receiving or are receiving CAB+RPV LA within their routine clinical care are referred to the study team by their physicians within the HIV clinics of the three main hospitals. The local HIV teams then inform participants of the trial and provide patient information leaflets with contact details of the study team. Participants are scheduled for a screening visit, during which inclusion and exclusion criteria are revised and informed consent forms are signed as guided by the study nurses. Once the participants have signed the informed consent, they are randomized by a study nurse.

The randomization list will be created using a uniform distribution and assigning a range of values to each group. The distribution between the branches A and B will be 1:1. The assignment will be made by the electronic Case Report Form (eCRF). It will be impossible for the investigators to know which group will be assigned to a patient before his/her inclusion in the study. Stratification will be made according to age (<50 years old or ≥50), gender (male or female), and according to if the participant is already receiving or not CAB+RPV LA.

Inclusion and exclusion criteria

Adult PWH (age ≥18 years) will be invited to participate if they have capacity to consent with the following criteria:

- Chronic HIV-1 infection
- Will receive CAB+RPV LA as part of their routine clinical care.
- Recommended triple or dual therapy for at least 12 months, including CAB+RPV LA.
- Virological suppression for at least 6 months (2 consecutive determinations of undetectable viral load).
- Post-menopausal or fertile females that agree to avoid pregnancy during the study. If sexually active female; using an effective method of contraception (hormonal contraception, intra-uterine device (IUD), or anatomical sterility in self or partner from 14 days prior to the first IMP administration until at least 13 months after the last Investigational Medicinal Product (IMP) administration; all female participants must be willing to undergo urine pregnancy tests at time points specified in the protocol.
- Patients which have access to an out-of-hospital center without inconvenience.
- Patient who agrees to participate in the study and signs the informed consent. An example of the informed consent form is attached as Supplementary Materials (Spanish language).

Exclusion criteria include:

- Active Hepatitis B infection
- History of virological failure or mutations to integrase strand transfer inhibitors (INSTI) or nucleoside reverse transcriptase inhibitors (NNRTI).
- Previous antiretroviral treatment interruption during the last 6 months or treatment interruptions for more than a month.

- Contraindication for intramuscular injections
- Pregnant or breastfeeding women or desiring to become pregnant in the near future.
- Current use of the following concomitant treatment: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampicin / rifampin, rifapentine, St. John's wort

Data collection

All participating sites will be assessed using a mixed-methods approach including questionnaires, templated data collection instruments and primary data sources (clinic records). Blinding is not applicable since it is an open clinical trial.

Data management and monitorization is under ScienHub. A data management system will be set up and procedures will be implemented to warrant homogenization, traceability, and data quality. Data will be entered in a study-specific eCRF. Quality control procedures will be put in place for data checking. Rigorous consistency checks will be created in order to reduce errors during data entry. In the study eCRF codified data will be collected and stored, without including any personal data. The eCRF will be accessible to the sponsor, the data management team, the investigators, and the study staff with data entry permissions. Investigators and institutions will allow monitoring and audits by the Health Authorities or the Sponsor giving direct access to data and original source documents. Access to personal patient information will be restricted to the Study physician/staff. To allow monitoring, audits and inspections, access to data to Health Authorities (Spanish Agency for Medicines and Health Products), the Ethics Committee and personnel authorized by the Sponsor, is guaranteed while maintaining the confidentiality thereof according to current legislation.

Treatment compliance and concomitant treatment

CAB + RPV LA compliance is guaranteed because study medication is to be administered by a designated study nurse at the clinical site. If the participant does not attend any visit, this information will be documented in the CRF.

All other treatments taken, apart from the study medication administered during the study period, will be considered concomitant treatments and should be documented in the CRF. Patients who participate in the study will be remembered that they should not start any new or continue any concomitant treatment without the knowledge and permission of the investigator. If discomfort following injection occurs, dosing with paracetamol 1g every 8 hours for a total of 24 hours will be allowed, but never as a prophylaxis treatment. If discomfort persists, the patient must seek medical attention.

The following medications must not be administered concurrently: Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin, Rifabutin, Rifampicin/Rifampin, Rifapentine, St. John's wort, Dexamethasone. In addition, the following treatments must be discontinued: proton pump inhibitors and systemic dexamethasone (more than a single dose). Use of anticoagulation agents greater than 14 days is prohibited and systemic anticoagulation on the day of an IM injection should be avoided where possible.

Questionnaires

Participant questionnaires

Questionnaires will be provided to participants by nursing staff involved in the study during their scheduled clinic visit, at baseline, months 1, 6 and 12, except for the

perception of injection (PIN) questionnaire which is to be filled in by the patient 2 days after injection, electronically.

Healthcare staff questionnaires

Staff will complete at baseline and at the end of the study (final test) a Health Professional Expectations Questionnaire. At months 1, 6 and 12, healthcare professionals and non-clinical staff will fill in the AIM/IAM/FIM health professional/non-clinical staff questionnaires.

Data analysis

Study data is collected through a study-specific/electronic Case Report Form (eCRF). All questionnaire data is collected directly on the eCRF by patients using an electronic device (tablets). All participants who passed screening and entered the study (ie. completed baseline electronic case report form - eCRF) will be included in the analysis population. The staff who complete the study questionnaires will also be considered part of the study and they will have an identification number and their role in the study (investigator, nurse, pharmacist, administrative staff).

The primary complete analyses will be conducted when the last study participant has completed their CAB+RPV LA study treatment up to month 12. All study staff participant (site-level) questionnaire, survey data, and all study participant (subject-level) data will be included in the analysis. For the primary analysis on the primary endpoint at month 12, we will use the intention-to-treat (ITT-E) population. The ITT-E and Per-Protocol populations will be used for the secondary analyses and those on secondary aims. All the analyses on the primary and secondary objectives will be performed on the overall (total sample) population and by study arm. To evaluate the main objective, a comparison of the percentages of acceptability with a Chi2 test will be made and both the differences in percentages and the quotient of these percentages in the form of relative risk will be reported. Regarding some of the secondary and the exploratory objectives, a descriptive analysis will be performed.

Ethics and dissemination

The clinical trial will be conducted according to the principles of the Declaration of Helsinki, Fortaleza, Brazil, October 2013. This study will be conducted according to Spanish regulations regarding clinical trials (Royal Decree 1090/2015) and biomedical investigations (Organic Law 14/2007 of biomedical investigation and the Royal Decree 1716/2011), which develop the Clinical Trial Regulation (Regulation EU No 536/2014). Confidentiality requirements will follow the required Data Protection legislation. The current publication refers to version 3.0. of the protocol, with issue date on the 14th April 2024, as approved by the Comité de Ética de la Investigación con medicamentos del Hospital Universitari Germans Trias i Pujol (approval number AC-23-042-HGT-CEIM).

Final data exportation is scheduled for June 2025; until then, data is stored in a secured database where only selected investigators have access for purely assistance reasons. Following data exportation, statistical analyses will follow, with complete datasets expected for the first quarter of 2026. After finishing the study, the Coordinating Teams of the study will discuss results and strategies for the future, as well as the data dissemination plan, in order to maximize the impact of this work on clinical care and

policy. At least one manuscript is expected to be sent for publication covering the main results of the HOLA study. Subsequent sub-analyses will be considered by the investigators if they deem appropriate. Once data is made available to the researchers participating in the study, data generated that supports the final results article will be made available as soon as possible, wherever legally and ethically possible, upon request. The publication of the trial results shall meet the requirements set out in Article 42 of Royal Decree 1090/2015. An individual personal statement (IPD) according to the ICMJE guidelines is available in the clinical trial registry (NCT06185452). Results emerged from this study will be reported in the HIV national and international meetings as well as published in international journals with high impact factor. If the outcome deems positive, we will also develop and propose policy guidelines for integration of the administration of CAB+RPV LA in alternative outpatient facilities into the standard of care in the HIV care pathway. In addition to this study, a qualitative substudy, with a different study code (NCT: NCT06643897), has been conducted. The objective of the substudy is to assess the barriers and solutions for the implementation by interviewing the staff participating in the HOLA study. The substudy analyses are underway and will be published as well.

Discussion

In the current clinical programs in Spain, the CAB+RPV LA formulation must be administered by a trained health team every 2 months in the hospital. Bringing treatment closer to patients may bring benefits to them in terms of satisfaction and reduction of stigma. However, evidence in the feasibility of the out-of-hospital delivery of CAB + RPV LA in Spain in non-existent. Implementation outcome measures are essential for monitoring and evaluating the feasibility of a change in procedures, such as the one described [11]. Prior evidence in implementation science for this treatment comes mainly from the CARISEL (Cabotegravir and Rilpivirine Implementation Study in European Locations) study, a hybrid Phase III implementation-effectiveness trial implementing CAB + RPV LA for PWH). This study was aimed at evaluating participants switching from daily oral therapy to CAB + RPV LA dosed every 2 months (Q2M). However, the Spanish sites participating in the trial were only hospitals and no alternative outpatient centre was considered (CARISEL; NCT04399551).

In the CARISEL study, sites were randomized to standard implementation (Arm-S) or enhanced implementation (Arm-E), including additional implementation strategies. These enhancements were mainly focused on meetings that introduce CAB + RPV LA to clinic staff and discuss what might make implementation easier, and/or what might make it difficult, prior to first injection at the site; and meetings started to discuss an implementation plan, how to work through challenges, and introduce a continuous quality improvement plan, for 6 out of the 12 months of study. At Month 12, regardless of implementation arm, CAB + RPV LA was highly effective and well tolerated, consistent with clinical outcomes in the Phase 3 clinical program [17].

Although HOLA has some similarity to CARISEL with respect to study outcomes, HOLA aims to examine differences between clinic settings (urban and rural) as well as hospital and community-based settings for administering CAB+RPV LA through a set of three questionnaires that had been previously developed under the Proctor framework, as four-item measures of implementation outcomes that indicate implementation success [10] : the AIM, IAM, and FIM questionnaires [11]. Enrolment completion in the HOLA study took place by the end of May 2024, with an end of study expected in May 2025. It is important

to note that the intervention is not exempt from certain risks, such as logistic inconveniences, so it is important to plan for these in advance.

The importance of implementation research in HIV healthcare relies in its potential to generate the knowledge required for policymakers, healthcare mediators and the community to modify the current models of care in PWH in order to improve their quality of life. The HOLA study may provide the required outcomes that will help bridge the gap towards a patient-centered approach in HIV care. The tools and methodology used for assessing implementation success have been validated and described previously as part of the Proctor framework [10], which gives value to decision makers to consider the success of the intervention of study. In addition, a qualitative substudy, aiming to identify barriers and facilitators of implementation of the administration of CAB+RPV LA in alternative facilities from the perspective of staff participating in the HOLA study, has been conducted. Data generated from both studies will contribute to the development of guidelines for implementation supporting governments and healthcare decision-makers in formulating successful implementation strategies.

Competing interests

None of the authors have competing interests to declare in relation to this research. *VF, EN* and *JO* have received fees for educational activities and/or consultancies and/or financial support for attending conferences from Gilead Science, Janssen-Cilag, Merck Sharp & Dohme and ViiV Healthcare outside of the submitted work. *PAL* has received fees for educational activities from Janssen-Cilag and ViiV Healthcare outside of the submitted work. All other authors have no competing interest to declare.

Author contributions

EN (guarantor) and *JO* are the principal investigators of the study, initiated the conceptualization of the study, and coauthored the protocol with all the other authors. *DHS* is a clinical research fellow, and she converted the protocol into its publishable format. *EN* and *DHS* contributed equally to this paper. *VF, PAL, CBC, LB, AR, JJ, MAC, ABF,* and *JMP* are coinvestigators of the participating centers, and helped with implementation and patient recruitment. *NL, DC,* and *VF* are the hospital pharmaceutics and have contributed to implementation and protocol design. *EN, DHS, LB, CM, JP, DR,* and *NL* belong to the Coordinating Team at Hospital Germans Trias I Pujol and have helped in protocol design, trainings, and procedures of implementation, as well as in implementation support for other centers. *JO, DA* and *FR* belong to the Coordinating Team at Hospital Costa del Sol and have helped in trainings and procedures of implementation, as well as in implementation support for other centers.

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Tables

Table 1. List of affiliated primary care or community centers and its hospitals of reference

Reference hospital	Primary care center / Community center
Hospital Universitari Germans Trias i Pujol (Catalonia)	BCN Checkpoint
	CAP Dr. Robert
Hospital Universitari General de la Vall d'Hebron (Catalonia)	Centre de Salut Internacional i Malalties
	Transmissibles Drassanes - Vall d'Hebron

Hospital Costa del Sol (Andalucia)	Centro de Salud San Pedro Alcántara
	Centro de Salud San Luis de Sabinillas
	Centro de Salud Leganitos

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PARTICIPANT INFORMATION SHEET AND INFORMED CONSENT

STUDY TITLE	" Implementation of the out-of-hospital administration of long-acting Cabotegravir+Rilpivirine as optional therapy in HIV-infected patients in Spain. Acceptability, appropiateness, feasibility, and satisfaction. The HOLA Study. ".
STUDY CODE	Out-of-hospital LA CAB+RPV
PROMOTER	Fundació FLS de Lluita contra la Sida, les Malalties Infectioses i la Promoció de la Salut i La Ciència
PRINCIPAL INVESTIGATOR	
CENTER	

Introduction

We are writing to inform you about a research study in which you are invited to participate, promoted by Fundació FLS de Lluita contra la Sida, les Malalties Infectioses i la Promoció de la Salut i La Ciència. The study has been approved by a Drug Research Ethics Committee and by the Spanish Agency for Medicines and Health Products (AEMPS), in accordance with current legislation, Royal Decree 1090/2015 of December 4 and European Regulation 536/2014 of April 16, which regulates clinical trials with drugs.

Our intention is that you receive the correct and sufficient information so that you can decide whether or not to agree to participate in this study. To do this, read this information sheet carefully and we will clarify any doubts that may arise. In addition, you can consult with the people you consider appropriate.

We invite you to participate in the study because you are diagnosed with HIV, have been prescribed long-acting treatment with Cabotegravir and Rilpivirine and have an undetectable viral load.

The long-acting treatment is a combination of two antiretroviral drugs called Cabotegravir and Rilpivirine. Both act to suppress HIV (human immunodeficiency virus) in a similar way to other antiretrovirals, with the difference that this treatment consists of two injections every two months instead of a daily oral treatment.

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This treatment is only allowed be administered in the hospital and the aim of this study is to see if the administration of Cabotegravir and Rilpivirine for the treatment of HIV in alternative facilities outside the hospital setting, for example, in primary care centres or in community centres, is acceptable.

Voluntary participation

you should know that your participation in this study is voluntary and that you can choose NOT to participate. If you choose to participate, you can change your decision and withdraw your consent at any time, without altering your relationship with your doctor or harming your health care.

Objective of the study

The main objective of this study is to see if it is acceptable and safe to administer the injections for patients living with HIV that are treated with long-acting Cabotegravir and rilpivirine intramuscularly every 2 months outside the hospital.

The findings of this study will help us understand how the administration of the drugs outside of a hospital setting can be implemented and to see if it is acceptable, appropriate, feasible and satisfactory to administer Cabotegravir and Rilpivirine injections every 2 months in primary care centers or in community centers, as well as to evaluate the safety of the administration of Cabotegravir and Rilpivirine injections.

Study Description

This study will involve 110 adults living with HIV who have controlled disease (undetectable viral load) with their current HIV medication.

The medications that will be administered are injections of Cabotegravir and Rilpivirine. Participants will be divided into two groups:

- Group I: You will be given the dose of Cabotegravir and Rilpivirine in the hospital
- Group II: You will be given the dose of Cabotegravir and Rilpivirine outside the hospital, in a community center, or in a primary care center already assigned by the study.

Neither do you nor will the researcher know which group will be assigned before being included in the study. It will be decided at random (like flipping a coin) to which group you will belong. This is done to get reliable data from the results of the study.

Every 2 months you will receive 2 injections; each contains one of the two drugs that make up the treatment. You will be given an injection on each side of the upper outer part of the gluteus.

These medicines are approved by the AEMPS under the name Vocabria® (Cabotegravir) and Rekambys® (Rilpivirine).

If you have not been given Cabotegravir and Rilpivirine injections before, you will take the same oral medication for 28 days and, on the last day of oral medication, you will receive the first dose of Cabotegravir and Rilpivirine in the hospital. From the following month, the injections of Cabotegravir and Rilpivirine will be administered every 2 months at the center where you have been randomly assigned.

These oral medications are also approved by the AEMPS. In Spain, Rilpivirine is marketed under the name Edurant® and Cabotegravir under the name Vocabria®. The aim of this first phase of oral treatment is to ensure tolerance of the drugs.

Study activities

The study will last 12 months of treatment, in which 7 face-to-face visits will be carried out.

In the case of patients who have not previously been administered intramuscular cabotegravir and rilpivirine, they should make an additional visit after 28 days of oral antiretroviral treatment, to confirm good tolerance to the treatment.

Before starting the study:

Selection/baseline visit:

If you decide to participate in the study, we will ask you to sign this **informed consent before** you are enrolled, we will ask you some questions, and we will collect some data to confirm that you meet all the selection criteria to participate in the study. On this visit we will do:

- A review of your medical history
- A physical exam
- A review of your medication
- A test with determination of HIV viral load
- A pregnancy test

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- Questionnaires

During the study: *Study visits:*

Visits will be made every 2 months in which you will be given injections of Cabotegravir and Rilpivirine and questionnaires will be completed during the visits to assess whether the treatment is acceptable, appropriate and feasible, as well as your degree of satisfaction and expectations of the treatment and a questionnaire that will measure the perception of the injection, which you will have to fill out two days after the administrations.

A visit will be made in month 1 in the hospital if it is the first time that the medication Cabotegravir and intramuscular Rilpivirine is administered. At this visit, a blood draw will be performed for the determination of the HIV viral load, and the questionnaires will be completed. A questionnaire that will measure the perception of the injection will have to be filled in two days after the administration.

At the 6th month and 12th month visits, you will go to the hospital where you will have a blood draw to determine the HIV viral load and other tests, similar to those carried out for the monitoring of HIV infection in routine clinical practice (blood count, basic biochemistry and CD4/CD8 lymphocyte count).

In the visits of month 2, month 4, month 8 and month 10, only the questionnaire that will measure the perception of the injection will be completed, which will have to be filled out two days after the administration.

Procedure	Selection/Basal	Month 1	Month 2	Month 4	Month 6	Month 8	Month 10	Month 12
Informed Consent	X							
Clinic Visit (Medical History/Physical Exam)	X	X			X			X
Blood Draw	X	X			X			X

Pregnancy test (if applicable)	X	X			X			X
Study Questionnaires	X	X			X			X
Injection Perception Questionnaire		X	X	X	X	X	X	X
Oral Administration of Cabotegravir and Rilpivirine	X							
Intramuscular Administration of Cabotegravir and Rilpivirine		X	X	X	X	X	X	X

Blood Sample Collection:

Blood drawings will be routinary and will be carried out by the nursing staff of the HIV Unit of your Hospital. The amount of blood that will be drawn at each of the study visits will be approximately 30 mL.

Risks and discomforts arising from your participation in the study

In previous trials of Cabotegravir and rilpivirine it well tolerated, and serious adverse reactions were very rare.

The adverse reactions described are:

Frequency	Adverse Effect
Very common (at least 1 in 10 people)	Headache
	Injection site reactions. They are usually mild to moderate and their frequency decreases over time. Symptoms may include:- Very common: pain and discomfort, hard lumps or masses- Common: redness, itching, swelling, warmth, or bruising (which may include a change in color or a collection of blood under the skin).- Uncommon: numbness, light bleeding, abscess formation (accumulation of pus) or cellulitis (with a feeling of warmth, swelling, or redness).
	Feeling warm (pyrexia), which may occur in the first week after injections
Common (affects less	Depression
	Anxiety
	Abnormal dreams

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than 1 in 10 people)	Difficulty sleeping (insomnia)
	Dizziness
	Feeling unwell (nausea)
	Vomiting
	Abdominal pain
	Gases
	Diarrhoea
	Rash
	Muscle pain
	Tiredness (fatigue)
	Feeling weak (asthenia)
	Malaise
	Weight gain
Rare (affects less than 1 in 100 people)	Numbness (drowsiness)
	Feeling dizzy during or after an injection. This can lead to fainting.
	Liver damage (signs may include yellowing of the skin and whites of the eye, loss of appetite, itching, tenderness of the belly, light-colored stools, or abnormally dark urine).
	Changes in laboratory levels of liver function (increased transaminases)
	Increased bilirubin (a substance produced by the liver) in the blood.

Injection site reactions

You may experience local reactions at the site where you received the injections. Very common side effects can include pain or discomfort, which is usually mild or moderate. You may also have redness, swelling, itching, bruising, lumps, complications such as infection (cellulitis or abscess), and irritation where the injection(s) are given. In most cases, the reactions are mild (75%), while 4% of participants in previous clinical trials had a severe reaction at the injection site. Most reactions go away in a week or less, but sometimes they can last a long time. Most people find these reactions acceptable and rarely stop the injections due to adverse effects.

Possible side effects of the injection procedure

Symptoms of the post-injection reaction have occurred in some people within a few minutes of receiving the rilpivirine injection. Post-injection reactions are rare and occurred in less than 0.5% of participants in clinical trials. Most symptoms resolved within a few minutes of the injection. Symptoms of post-injection reactions may include: shortness of breath, stomach cramps, rash,

sweating, numbness in the mouth, anxious feeling, feeling warm, feeling dizzy or light-headed, changes in blood pressure, and back and/or chest pain. Tell your study doctor if you experience these symptoms after receiving the injections. These cases may be due to an accidental injection of part of the medication into a blood vessel instead of the muscle. Not all patients in whom accidental injection into a blood vessel was suspected reported such symptoms. Most symptoms resolved within minutes. Your doctor may need to give treatment to help resolve these symptoms. The study health care staff will observe you briefly (about 10 minutes) after the injection.

The injections will be given into the muscles of the buttocks. The injection may not reach the muscle or be given too far, not reaching the muscle and penetrating the skin, blood vessels, or nerves. The consequences of this are not well understood, but it could cause the levels of Cabotegravir and Rilpivirine to be too low or high. If they are too low, the medicine may not work properly against HIV. If the levels of Rilpivirine are too high, your heart rate could be altered, which very rarely, in severe cases, can be life-threatening and lead to sudden death; however, to date, no such severe changes in heart rate or sudden deaths have been observed in clinical studies with rilpivirine in any of its forms of administration (oral or intramuscular). Every effort will be made to decrease this risk, including ensuring that the correct size needle and proper injection technique are used. The staff is trained for it. You will also be monitored after each injection and during the test, as appropriate. If your doctor thinks the injection was not given correctly, you may be asked to stay at the center for up to 2 hours after the injection to monitor your progress, and additional tests may be needed to make sure there are no risks. If you are concerned about this issue, talk to your study doctor.

Hypersensitivity

Hypersensitivity reactions (also known as allergic reactions) have been reported with other medicines in the same class as Cabotegravir, with signs and symptoms of general feeling of malaise, rash, high fever, lack of energy, swelling (sometimes of the face or mouth, causing difficulty breathing), blisters, mouth ulcers, conjunctivitis, and muscle or joint aches. If you develop any of these signs and/or symptoms during the study, you should immediately call the study team to decide if any testing is required and/or to tell them to stop taking Cabotegravir and Rilpivirine. If you are told to stop taking your medications, you should do so immediately.

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Rash

Treatment with Cabotegravir and rilpivirine may cause a rash. Most are mild or moderate, but some types can be severe and treatment will need to be stopped. If you have any type of rash, itching, or other skin problems during treatment, you should tell the study team right away. You may be asked to come in for a scan, analysis, and/or tell you to stop taking Cabotegravir and/or Rilpivirine.

Impaired liver tests

A small number of participants in research studies who took Cabotegravir with rilpivirine developed impaired liver tests that forced them to stop treatment. In some cases, abnormal liver tests were explained by other causes (e.g., a new infection with a virus), while a smaller number (less than 1% of participants) had no alternative explanations, suggesting a mild form of liver damage suspected to be due to Cabotegravir and/or Rilpivirine. Liver tests improved after stopping the medication, suggesting that any possible damage was temporary. Blood tests will be carried out to check the health of the liver during this study, as part of your routine check-ups and you will be informed if any alterations occur and, if so, the steps to follow. If a liver problem occurs, you may be asked to stop taking the study treatment.

What if the side effects are intolerable?

If you experience side effects that are intolerable and need to change your HIV medications, you will need to stop the study**.**

What other possible risks are there?

Risk of HIV becoming resistant to treatment

With any drug used to treat HIV, there is a risk that the virus will become drug resistant, which means that the drug will lose its activity. The risk of developing resistance will depend on whether the treatment manages to keep the viral load undetectable, and this, in turn, will depend on you following the instructions on how to take the study medicines.

Therefore, it is very important that you attend your study visits on your scheduled dates and that you always take your treatment exactly as prescribed. Talk to your study doctor each time you stop

taking any tablets or if you think you will need to delay or advance your visits to receive injections due to work, vacation, travel, etc., that may interfere with your scheduled visits.

If you need to delay injections for more than a few days, you may be offered the option to take tablets for a short period of time, which is known as an 'oral bridge'. Your study doctor will be able to advise you on whether this is right for you.

Do not change or skip any doses of any of the study drugs unless your study doctor tells you to. Missing doses of medication (tablets or an injection) can lead to HIV becoming resistant to the drugs and these not working. This could also limit the possibilities of using other HIV medicines related to drug resistance in the future.

On the other hand, if stopping the long-acting treatment, it is important to start taking another HIV medication, as recommended by your study doctor, to maintain HIV control and prevent acquiring drug resistance.

Side effects after receiving long-acting injections

After an injection of Cabotegravir and Rilpivirine, these drugs will stay in your body for a long time. In some people, low levels of Cabotegravir and Rilpivirine may be present in the body for more than a year after the last injection. If you develop a side effect of the study drug after an injection, there will be no way to remove the drug from your body. If this happens, your doctor will do everything possible to treat the symptoms.

When you stop long-acting injections, the amount of medication in your body will decrease over time and go away.

Feeling faint after the injection

When receiving the injections, some people may feel dizzy or like they might pass out. This reaction, also called a "vasovagal reaction," may occur with many medical procedures, however resolves quickly, and is not a threat to your health.

Blood draw

When your blood is drawn, you may feel dizzy or experience mild pain, bruising, irritation, or redness at the puncture site. In rare cases, you can get an infection.

Mental health issues

Some people with chronic health problems, including HIV, sometimes have feelings of depression or may have thoughts of harming themselves or taking their own life (suicide). A small number of people taking Cabotegravir and Rilpivirine have had suicidal thoughts and actions, particularly those with a history of depression or mental health problems.

Tell the study doctor if you have a history of mental health problems. If you have thoughts of self-harm or suicide or have other unusual or uncomfortable thoughts or feelings during this study, you should tell the study doctor or go to the nearest hospital right away.

This list of side effects is not complete. You may experience side effects that are different from those described in this informed consent form or that are not currently known.

Medication NOT allowed during the study

The use of some other drugs is contraindicated or should be done with caution when administered concomitantly with Cabotegravir and/or Rilpivirine. For this reason, the following drugs are not allowed to be used during the study:

- Carbamazepine, oxcarbazepine, phenobarbital, phenytoin (medicines to treat epilepsy and prevent seizures)
- Rifabutin, rifampicin, rifapentine (medicines to treat bacterial infections such as tuberculosis)
- Dexamethasone (a corticosteroid used to treat a variety of conditions, such as inflammation and allergic reactions) given in an oral or injectable course of treatment
- Products that contain St. John's wort or St. John's wort (Hypericum perforatum, a medicinal plant used for depression).

Do not use medications (prescription and over-the-counter) without first talking to the study medical staff. The study medical staff will explain the need to avoid certain medications during the study, including those that are contraindicated. New drugs may be identified later that need to be added to the list of drugs you should not take during the study.

Can a pregnant person participate in the study?

Because there is no information available about the safety of long-acting cabotegravir and rilpivirine for the fetus, pregnant people are not allowed to participate in the study.

For this reason, as part of the tests planned at the screening visit and at the study visits, urine pregnancy tests will be performed on all menstruating people of childbearing potential* who wish to participate in the study or have been included in the study. The result must be confirmed as negative prior to administration of the first dose of study drugs. Pregnancy tests will also be done at any time during the study when pregnancy is suspected.

If you are a person who is able to have children, you should use birth control while participating in the study. Effective birth control should be used, as agreed with your study doctor, from at least 14 days prior to the start of your first dose of Cabotegravir and Rilpivirine and for as long as you are taking the study medication. It is recommended that you continue to use effective contraception until at least 14 days after your last oral dose of Cabotegravir and Rilpivirine, and at least 13 months after your last long-acting injection(s), as the study drugs may still be present in the body during this time. Your study doctor will talk with you about this recommendation and the potential risks of pregnancy during this time. You should tell your primary care physician and your HIV Unit doctor if you have a pregnancy within 12 months of the last Cabotegravir and Rilpivirine injection even if you are no longer in the study.

Therefore, at the screening visit and during the study, the use of one of the following contraceptive methods considered highly effective in preventing pregnancy should be accepted:

- hormonal contraception or intrauterine device [IUD]
- one's own or the partner's anatomical sterility

If the pregnancy test result is positive or equivocal, intramuscular injections should be postponed until a valid serum pregnancy test is obtained. If the test is positive, you will stop taking the study medication and the medical staff responsible for the study will inform you about the next actions to take (see next section).

What will happen if a person becomes pregnant during the study?

You should inform the study research team immediately if you suspect that there is a possibility of pregnancy during the study. If their participation in the study has ended, they should inform their usual doctor during HIV follow-up.

If your pregnancy is confirmed during the study, you will be given the option to switch to alternative antiretroviral therapy during pregnancy. An alternative antiretroviral treatment that is considered suitable for use during pregnancy will be initiated in accordance with local guidelines. The deadline for starting this treatment will be the expected date for the next injection of Cabotegravir and Rilpivirine.

After the study

When your participation ends, you will receive the best available treatment, the one that your doctor considers most appropriate for your disease, at your hospital. Because the study medication will already be marketed, you may still be able to be given the study medication, but neither the investigator nor the sponsor makes any commitment to maintain the treatment outside of this study.

What are the expected benefits of this study?

Possible benefits:

By participating in this study, you will receive antiretroviral treatment that has been shown to be highly effective and tolerable in different clinical trials. It is hoped that this study will be able to analyze whether the administration of the treatment is acceptable, appropriate and feasible to carry out outside the hospital setting and can be implemented in primary care centers and community centers, which may benefit other people infected with HIV in the future.

Costs:

You will not have to pay for medications or specific tests from the study. Your participation in the study will not incur any additional costs to your usual clinical practice. The study will be funded by the pharmaceutical company ViiV Healthcare in collaboration with Lluita Foundation against AIDS and Infectious Diseases.

Confidentiality and legal information

The sponsor of the study and the participating centres, as independent data controllers, will guarantee the confidentiality of the personal information of the participating subjects in accordance with current legal regulations (Organic Law 3/2018, on the Protection of Personal Data and Guarantee of Digital Rights, and Regulation [EU] 2016/679 of the European Parliament and of the Council, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data). During this study, the study medical team will record information about you, your health, and your participation in the study on forms called data collection notebooks.

To ensure that the data collected during the study are treated confidentially, your data will be identified by a code; your name or any other information that allows you to be directly identified will not be included in the data collection notebooks. Therefore, the identity will not be revealed to any other person except to the health authorities, when required or in cases of medical emergency. The ethics committees, the representatives of the Health Authority in matters of inspection and the personnel authorised by the sponsor may only access to check the personal data, the procedures of the clinical study and compliance with the rules of good clinical practice (always maintaining the confidentiality of the information).

Only the study medical staff/collaborators will be able to relate this data to you and your medical history. The sponsor will only have access to information relating to the general results of the study. Under no circumstances will you access your personal data.

To carry out this clinical trial, we will also need access to the medical information contained in your medical record and we will record your participation and safety aspects throughout the study in the electronic medical record system of the participating centers, so you must expressly authorize us to do so.

The data controllers are the sponsor, the Lluita Foundation against AIDS and Infectious Diseases, as well as the centres where this study will be carried out, belonging to the Catalan Health Institute and the Regional Government of Andalusia

- Data Protection Officer within the scope of the Department of Health contact email: dpd@ticsalutsocial.cat.

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- Data Protection Officer in the field of the Junta de Andalucía contact email **********
- Data Protection Officer of Fundació FLS de Lluita contra la Sida, les Malalties Infectioses i la Promoció de la Salut i La Ciència (developer), with address Ctra. de Canyet s/n, Hosp. Univ. Germans Trias i Pujol, 2a planta Maternal, 08916 Badalona (Barcelona): lopd@flsida.org.

Legal basis for data processing: The consent granted by means of this document and the general interest in the treatment of the disease.

Recipients: The recipients of the data are the research team and the personnel authorised by the data controllers, the suppliers that are necessary for the purpose of the processing (laboratories, software and hosting provider companies) and, where appropriate, the relevant administrative authorities. Although the data will be kept pseudonymized during the study, we inform you that your information will be hosted on a secure server located in the European Union under current regulations with the highest quality and specific security. The encrypted data may be transmitted to third parties and other countries, but in no case will it contain information that can identify you directly or indirectly, and contracts will be established with the recipients of the information that expressly prohibit re-identification, by cross-referencing with other databases or any technology that attempts to re-identify the data. In the event that this transfer occurs, it will be for the same purposes as the study described or for use in scientific publications, but always maintaining the confidentiality of these, in accordance with current legislation.

Rights: You can exercise your rights of access, rectification, cancellation, opposition, limitation of the processing of data that are incorrect, request a copy or that they be transferred to a third party (portability) of the patient on the data you have provided for the study (PARSOL Rights). To exercise their rights, the participant may contact the team of researchers or the data protection officer of the institutions

Data retention: The sponsor will retain records of the clinical trial for a period of at least 25 years after completion. Thereafter, your personal information will only be retained by your health care facility. The promoter will keep data that at no time will contain personal data.

We remind you that the data cannot be deleted, even if you stop participating in the study, to ensure the validity of the research and comply with legal duties and drug authorization

requirements. Therefore, if you decide to withdraw consent to participate in this study, no new data will be added to the database, but any data that has already been collected will be used.

Right to complain: You can exercise your right to lodge a complaint with the competent authority (the Catalan Data Protection Authority or the Spanish Data Protection Authority), if you consider that your data protection rights have been violated.

Sure:

The promoter of the study has taken out a civil liability insurance policy with the company Zurich Insurance PLC branch in Spain in accordance with the requirements established in RD 1090/2015, which covers the possible damages that they may experience as a result of their participation in the trial, provided that they are not a consequence of the disease under study itself or of the evolution of their disease as a result of the ineffectiveness of the treatment.

It is also possible that your participation in this clinical trial may modify the general and particular conditions (coverage) of your insurance policies (life, health, accident) and, therefore, we recommend that you contact your insurance company and inform them of your participation in it to determine if it could affect your current insurance policy or in the event that you are going to take out a new policy.

For more information regarding this section, please consult with the principal investigator of the study at your center.

Study Participation:

You do not need to make the decision at this time to participate in this study, you can take this Information Sheet home and think about it long enough and discuss your participation with your family or regular doctor.

You participate in this study on a voluntary basis and may withdraw from the study at any time without having to explain yourself or your subsequent attendance at our Consultation being affected.

Once the Informed Consent is signed, you will keep a copy of this document.

There is the possibility of exclusion from the trial by the sponsor or the research team, in the event of safety problems or non-compliance with the procedures established in the study.

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In the event of cancellation of the trial by the sponsor, the participants will be informed of the reasons.

Any new information regarding the drugs used in the study that may affect your decision to continue in the study will be communicated to you by your doctor as soon as possible and, if necessary, a new consent will be signed.

Contact for information

If you have any questions or problems related to your infection or the treatment given, outside of working hours, you can contact the principal investigator of the study:

Dr/a.....

Tel.....

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INFORMED CONSENT

STUDY TITLE	"Implementation of out-of-hospital administration of the long-acting combination Cabotegravir+Rilpivirine as optional therapy in HIV-infected patients in Spain. Acceptability, appropiateness, feasibility and satisfaction. The HOLA Study".
STUDY CODE	Out-of-hospital LA CAB+RPV
PROMOTER	Fundació FLS de Lluita contra la Sida, les Malalties Infectioses i la Promoció de la Salut i La Ciència
PRINCIPAL INVESTIGATOR	
CENTER	

I, (name and surname)....., after having read the information sheet that has been given to me and asking the clarifying questions about it to Dr./Dr.....

I confirm that I have received enough information about the study and that I have understood the objectives of the study and what it entails.

I understand that my participation is voluntary.

I understand that I can withdraw from the study:

- Whenever.
- Without having to give explanations.
- Without this having an impact on my medical care.

And I consent:

- That the clinical data collected during the study be stored in an automated file whose information may be handled exclusively for scientific purposes, provided that the information concerning me is dissociated (this means that the information obtained cannot be related to the person from whom it comes).
- I understand that I have the possibility of exercising the rights of access, rectification, cancellation, opposition, limitation of processing, data portability and not to be subject to automatic individualized decisions (profiling), by writing to the Data Protection Officer

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within the scope of the Department of Health (dpd@ticsalutsocial.cat), Junta de Andalucía (**********), or the promoter (LOPD@flsida.org)

I agree with everything related to this study and freely agree to participate in it and that my data can be used for research purposes as stated in the patient information sheet.

Patient signature

Signature of the Researcher

Date

Date

You will receive a copy of this document, once you have signed it, to keep with your records.

FOR ADULTS WHO ARE UNABLE TO GIVE CONSENT

.....,
Witness/interpreter at the consent interview

As of the date signed, I have been a witness in the consent interview for the research study named at the beginning of this document. I confirm that the information contained in this consent form was properly explained to the subject, and the subject has confirmed that all of their questions have been adequately answered.

Name of witness

Signature of the witness

Signature of the Researcher

Date

Date

The study subject will receive a completed fact sheet, along with a signed version of the consent form

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HOJA DE INFORMACIÓN AL PARTICIPANTE Y CONSENTIMIENTO INFORMADO

TÍTULO DEL ESTUDIO	"Implementación de la administración extrahospitalaria de la combinación de acción prolongada Cabotegravir+Rilpivirina como terapia opcional en pacientes de España infectados por el VIH. Aceptabilidad, idoneidad, viabilidad y satisfacción Estudio HOLA".
CÓDIGO DEL ESTUDIO	Out-of-hospital LA CAB+RPV
PROMOTOR	Fundació FLS de Lluita contra la Sida, les Malalties Infeccioses i la Promoció de la Salut i La Ciència
INVESTIGADOR PRINCIPAL	Eugenia Negredo Puigmal
CENTRO	Hospital Universitari Germans Trias i Pujol

Introducción

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar, promovido por Fundació FLS de Lluita contra la Sida, les Malalties Infeccioses i la Promoció de la Salut i La Ciència. El estudio ha sido aprobado por un Comité de Ética de la Investigación con medicamentos y por la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), de acuerdo a la legislación vigente, el Real Decreto 1090/2015 de 4 de diciembre y el Reglamento Europeo 536/2014 de 16 de abril, por los que se regulan los ensayos clínicos con medicamentos.

Nuestra intención es que usted reciba la información correcta y suficiente para que pueda decidir si acepta o no participar en este estudio. Para ello lea esta hoja informativa con atención y nosotros le aclararemos las dudas que le puedan surgir. Además, puede consultar con las personas que considere oportuno.

Le invitamos a participar en el estudio porque está diagnosticado de VIH, se le ha prescrito un tratamiento de acción prolongada con Cabotegravir y Rilpivirina y se encuentra con carga viral indetectable.

El tratamiento de acción prolongada es una combinación de dos medicamentos antirretrovirales llamados Cabotegravir y Rilpivirina. Ambos actúan para suprimir el VIH (virus de

inmunodeficiencia humana) de modo similar a otros antirretrovirales, con la diferencia que este tratamiento son dos inyecciones cada dos meses en lugar del tratamiento oral diario.

Este tratamiento solo puede ser administrado en el hospital y el objetivo de este estudio es ver si es aceptable la administración de Cabotegravir y Rilpivirina para el tratamiento del VIH en centros alternativos fuera del entorno hospitalario, por ejemplo, en centros de atención primaria o en centros comunitarios.

Participación voluntaria

Debe saber que su participación en este estudio es voluntaria y que puede decidir NO participar. Si decide participar, puede cambiar su decisión y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su atención sanitaria.

Objetivo del estudio

Este estudio tiene como objetivo principal ver si es aceptable y segura la administración de las inyecciones para los pacientes con infección por VIH tratados con Cabotegravir y Rilpivirina de acción prolongada vía intramuscular cada 2 meses fuera del hospital.

Las conclusiones de este estudio nos ayudarán a entender cómo se puede implementar la administración de los medicamentos fuera de un entorno hospitalario y ver si es aceptable, apropiado, factible y satisfactorio administrar las inyecciones de Cabotegravir y Rilpivirina cada 2 meses en centros de atención primaria o en centros comunitarios, así como evaluar la seguridad de la administración de las inyecciones de Cabotegravir y Rilpivirina.

Descripción del estudio

En este estudio participarán 110 adultos que viven con VIH y tienen la enfermedad controlada (carga viral indetectable) con su medicación actual para el VIH.

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Los medicamentos que se van a administrar son inyecciones de Cabotegravir y Rilpivirina. Los participantes serán distribuidos en dos grupos:

- Grupo I: se le administrará la dosis de Cabotegravir y Rilpivirina en el hospital
- Grupo II: se le administrará la dosis de Cabotegravir y Rilpivirina fuera del hospital, en un centro comunitario o en un centro de atención primaria ya asignado por el estudio.

Ni usted. ni el investigador sabrán a qué grupo será asignado antes de ser incluido en el estudio. Se decidirá al azar (como tirando una moneda al aire) a qué grupo pertenecerá. Esto se hace para obtener datos confiables de los resultados del estudio.

Cada 2 meses recibirá 2 inyecciones; cada una contiene uno de los dos medicamentos que forman el tratamiento. Se le administrarán en la parte superior externa del glúteo, una inyección a cada lado.

Estos medicamentos están aprobados por la AEMPS con el nombre Vocabria® (Cabotegravir) y Rekambys® (Rilpivirina).

Si no le han administrado Cabotegravir y Rilpivirina en inyecciones anteriormente, tomará la misma medicación oral durante 28 días y, el último día de medicación por vía oral, recibirá la primera dosis de Cabotegravir y Rilpivirina en el hospital. A partir del mes siguiente las inyecciones de Cabotegravir y Rilpivirina le serán administradas cada 2 meses en el centro donde le haya tocado.

Estos medicamentos orales también están aprobados por la AEMPS. En España Rilpivirina esta comercializado bajo el nombre de Edurant® y Cabotegravir bajo el nombre de Vocabria®. El objetivo de esta primera fase de tratamiento por vía oral es asegurar la tolerancia de los fármacos.

Actividades del estudio

El estudio tendrá una duración de 12 meses de tratamiento, en el que se realizarán 7 visitas presenciales.

En el caso de los pacientes que no se le haya administrado previamente Cabotegravir y Rilpivirina intramuscular deberán hacer una visita adicional después de 28 días de tratamiento antirretroviral oral, para confirmar la buena tolerancia al tratamiento.

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Antes de empezar el estudio:

Visita de selección/basal:

Si decide participar en el estudio, le pediremos que firme este **consentimiento informado** antes de ser incluido, le haremos algunas preguntas y recogeremos algunos datos para confirmar que cumple todos los criterios de selección para participar en el estudio. En esta visita realizaremos:

- Una revisión de su historia médica
- Una exploración física
- Una revisión de su medicación
- Una analítica con determinación de carga viral de VIH
- Un test de embarazo
- Unos cuestionarios

Durante el estudio: *Visitas de estudio:*

Se realizarán visitas cada 2 meses en las que se le administrarán inyecciones de Cabotegravir y Rilpivirina y se cumplimentarán unos cuestionarios durante las visitas para valorar si es aceptable, apropiado y viable el tratamiento, así como su grado de satisfacción y expectativas del tratamiento y un cuestionario que medirá la percepción de la inyección, que tendrá que rellenar dos días más tarde de las administraciones.

Se realizará una visita en el mes 1 en el hospital, si es la primera vez que se le administra la medicación Cabotegravir y Rilpivirina intramuscular y en esta visita se realizará una extracción de sangre para la determinación de la carga viral del VIH y se cumplimentarán los cuestionarios durante la visita y un cuestionario que medirá la percepción de la inyección, que tendrá que rellenar dos días más tarde de las administraciones.

En las visitas del mes 6 y las visitas del mes 12 acudirá al hospital donde se le realizará una extracción de sangre para la determinación de la carga viral del VIH y otros análisis, similares a los que se llevan a cabo para el seguimiento de la infección por VIH en la práctica clínica habitual (hemograma, bioquímica básica y recuento de linfocitos CD4/CD8).

En las visitas del mes 2, mes 4, mes 8 y mes 10 se rellenará solo el cuestionario que medirá la percepción de la inyección, que tendrá que rellenar dos días más tarde de las administraciones.

Procedimiento	Selección/Basal	Mes 1	Mes 2	Mes 4	Mes 6	Mes 8	Mes 10	Mes 12
Consentimiento Informado	X							
Visita clínica (Historial Médico/Examen Físico)	X	X			X			X
Extracción de Sangre	X	X			X			X
Test de embarazo (si aplica)	X	X			X			X
Cuestionarios del estudio	X	X			X			X
Cuestionario percepción de la inyección		X	X	X	X	X	X	X
Administración Oral de Cabotegravir y Rilpivirina	X							
Administración Intramuscular de Cabotegravir y Rilpivirina		X	X	X	X	X	X	X

Obtención de las muestras de sangre:

Las extracciones de sangre serán las de rutina y serán efectuadas por el personal de enfermería de la Unidad de VIH de su Hospital. La cantidad de sangre que se extraerá en cada una de las visitas del estudio será aproximadamente 30 mL.

Riesgos y molestias derivados de su participación en el estudio

En los ensayos previos de Cabotegravir y Rilpivirina ha sido bien tolerado, las reacciones adversas graves fueron muy poco frecuentes.

Las reacciones adversas descritas que pueden afectar son:

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Frecuencia	Efecto Adverso
Muy frecuentes (al menos a 1 de cada 10 personas)	Dolor de cabeza
	Reacciones en el lugar de inyección. Habitualmente son de leves a moderadas y su frecuencia disminuye con el tiempo. Sus síntomas pueden incluir: - Muy frecuentes: dolor y molestias, masas o bultos duros - Frecuentes: enrojecimiento, picor, hinchazón, calor o hematomas (que pueden incluir un cambio de color o una acumulación de sangre bajo la piel). - Poco frecuentes: entumecimiento, sangrado leve, formación de absceso (acumulación de pus) o celulitis (con sensación de calor, hinchazón o enrojecimiento).
	Sensación de calor (pirexia), que puede ocurrir en la primera semana tras las inyecciones
Frecuentes (afectan a menos de 1 de cada 10 personas)	Depresión
	Ansiedad
	Sueños anormales
	Dificultad para dormir (insomnio)
	Mareos
	Sensación de malestar (náuseas)
	Vómitos
	Dolor abdominal
	Gases
	Diarrea
	Sarpullido
	Dolor muscular
	Cansancio (fatiga)
	Sensación de debilidad (astenia)
	Malestar general
	Aumento de peso
Poco frecuentes (afectan a menos de 1 de cada 100 personas)	Adormecimiento (somnolencia)
	Sensación de mareo durante o después de una inyección. Esto puede provocar desvanecimientos.
	Daño hepático (sus signos pueden incluir coloración amarilla de la piel y la parte blanca del ojo, pérdida del apetito, picor, dolor a la palpación de la tripa, heces de color claro u orina de un color anormalmente oscuro).
	Cambios en los niveles analíticos de función hepática (aumento de las transaminasas)

	Aumento de la bilirrubina (una sustancia producida por el hígado) en sangre.

Reacciones en el lugar de la inyección

Puede experimentar reacciones locales en el lugar donde recibió las inyecciones. Los efectos secundarios muy frecuentes pueden incluir dolor o malestar, que suelen ser leves o moderados. También puede tener enrojecimiento, hinchazón, picor, hematomas, bultos, complicaciones en forma de infección (celulitis o absceso) e irritación en el lugar donde se aplica la(s) inyección(es). En la mayoría de los casos las reacciones son leves (75 %), mientras que el 4 % de los participantes en ensayos clínicos previos tuvo una reacción grave en el lugar de la inyección. La mayoría de las reacciones desaparecen en una semana o menos, pero a veces pueden durar mucho tiempo. La mayoría de las personas encuentran aceptables estas reacciones y rara vez suspender las inyecciones por efectos adversos.

Posibles efectos secundarios del procedimiento de inyección

Los síntomas de la reacción posterior a la inyección han ocurrido en algunas personas pocos minutos después de recibir la inyección de Rilpivirina. Las reacciones posteriores a la inyección son poco frecuentes y ocurrieron en menos del 0,5 % de los participantes en los ensayos clínicos. La mayoría de los síntomas se resolvieron unos minutos después de la inyección. Los síntomas de las reacciones posteriores a la inyección pueden incluir: dificultad para respirar, calambres estomacales, erupción cutánea, sudoración, entumecimiento de la boca, sensación de ansiedad, sensación de calor, sensación de mareo o sensación de que se va a desmayar, cambios en la presión arterial, y dolor en la espalda y/o el pecho. Informe a su médico/a del estudio si experimenta estos síntomas después de recibir las inyecciones. Estos casos pueden deberse a una inyección accidental de parte del medicamento en un vaso sanguíneo en lugar del músculo. No todos los pacientes en los que se sospechó una inyección accidental en un vaso sanguíneo informaron tales síntomas. La mayoría de los síntomas se resolvieron en minutos. Es posible que su médico/a necesite administrar un tratamiento para ayudar a resolver estos síntomas. El personal sanitario del estudio lo/la observará brevemente (aproximadamente 10 minutos) después de la inyección.

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Las inyecciones se administrarán en los músculos de las nalgas. La inyección podría no llegar al músculo o aplicarse demasiado lejos, sin llegar al músculo y penetrando en la piel, los vasos sanguíneos o los nervios. Las consecuencias de esto no se conocen bien, pero podría hacer que los niveles de Cabotegravir y Rilpivirina sean demasiado bajos o altos. Si son demasiado bajos, es posible que el medicamento no funcione adecuadamente contra el VIH. Si los niveles de Rilpivirina son demasiado elevados, podría alterarse su frecuencia cardíaca, que muy raramente, en casos graves, puede poner en peligro la vida y provocar la muerte súbita; sin embargo, hasta la fecha, no se han observado cambios tan graves en la frecuencia cardíaca ni muertes súbitas en estudios clínicos con Rilpivirina en ninguna de sus formas de administración (oral o intramuscular). Se hará todo lo posible para disminuir este riesgo, lo que incluye garantizar que se use la aguja del tamaño correcto y la técnica de inyección adecuada. El personal está entrenado para ello. También se le controlará después de cada inyección y durante el estudio, según corresponda. Si su médico/a cree que la inyección no se administró de la manera correcta, es posible que se le pida que permanezca en el centro hasta 2 horas después de la inyección para vigilar su evolución, y es posible que se necesiten pruebas adicionales para asegurarse de que no hay riesgos. Si le preocupa este tema, hable con su médico/a del estudio.

Hipersensibilidad

Se han notificado reacciones de hipersensibilidad (también conocidas como reacciones alérgicas) con otros medicamentos de la misma clase que Cabotegravir, con signos y síntomas que incluyen sensación general de malestar, erupción cutánea, fiebre alta, falta de energía, hinchazón (a veces de la cara o boca, causando dificultad para respirar), ampollas, úlceras bucales, conjuntivitis y dolores musculares o articulares. Si desarrolla cualquiera de estos signos y/o síntomas durante el estudio, debe llamar inmediatamente al equipo del estudio, para decidir si se requiere realizar algún tipo de análisis y/o e indicarle que deje de tomar Cabotegravir y Rilpivirina. Si se le indica que deje de tomar sus medicamentos, debe hacerlo de inmediato.

Erupción cutánea

El tratamiento con Cabotegravir y Rilpivirina podría ocasionar erupción cutánea. La mayoría son leves o moderadas, pero algunos tipos pueden ser graves y se deberá interrumpir el tratamiento. Si tiene algún tipo de erupción, picor u otros problemas en la piel durante el tratamiento, debe

informar al equipo del estudio de inmediato. Se le puede pedir que venga para realizar una exploración, análisis y/o decirle que deje de tomar Cabotegravir y/o Rilpivirina.

Alteración de las pruebas hepáticas

Un pequeño número de participantes en estudios de investigación que tomaron Cabotegravir con Rilpivirina desarrollaron alteración de las pruebas hepáticas que les obligaron a interrumpir el tratamiento. En algunos casos, las pruebas hepáticas anormales se explicaron por otras causas (p. ej., una nueva infección por un virus), mientras que un número menor (menos del 1 % de participantes) no tuvo explicaciones alternativas, lo que sugiere una forma leve de daño hepático sospechoso de ser debido a Cabotegravir y/o Rilpivirina. Las pruebas hepáticas mejoraron después de suspender la medicación, lo que sugiere que cualquier posible daño fue temporal. Se realizarán análisis de sangre para verificar la salud del hígado durante este estudio, dentro de sus controles rutinarios y se le informará si se produce alguna alteración y, si fuera el caso, los pasos a seguir. Si ocurre un problema hepático, es posible que se le pida que deje tomar el tratamiento del estudio.

¿Qué pasa si los efectos secundarios son intolerables?

Si experimenta efectos secundarios que son intolerables y necesita cambiar los medicamentos para el VIH, deberá suspender el estudio**.**

¿Qué otros posibles riesgos existen?

Riesgo de que el VIH se vuelva resistente al tratamiento

Con cualquier medicamento utilizado para tratar el VIH, existe el riesgo de que el virus adquiera resistencia a los fármacos, lo que significa que el medicamento perderá su actividad. El riesgo de adquirir resistencia dependerá de si el tratamiento consigue mantener la carga viral indetectable y esto, a su vez, dependerá de que usted siga las instrucciones sobre cómo tomar los medicamentos del estudio.

Por lo tanto, es muy importante que asista a sus visitas del estudio en las fechas programadas y que siempre tome su tratamiento exactamente como fue recetado. Hable con su médico/a del estudio cada vez que deje de tomar algún comprimido o si cree que deberá retrasar o adelantar

las visitas para recibir las inyecciones por motivos de trabajo, vacaciones, viajes, etc, que puedan interferir con sus visitas programadas.

Si necesita retrasar las inyecciones más de unos pocos días, se le puede ofrecer la opción de volver a tomar comprimidos durante un periodo corto de tiempo, lo cual se conoce como «puente oral». Su médico/a del estudio le podrá aconsejar de si esto es adecuado para usted.

No cambie ni omita ninguna dosis de ninguno de los medicamentos del estudio a menos que su médico/a del estudio se lo indique. Omitir dosis de la medicación (comprimidos o una inyección) puede favorecer que el VIH adquiera resistencia a los fármacos y estos dejen de actuar. Esto podría limitar, además, las posibilidades de utilizar en el futuro otros medicamentos contra el VIH relacionados con estos.

Por otro lado, al suspender el tratamiento de acción prolongada, es importante comenzar a tomar otro medicamento contra el VIH, según lo recomendado por su médico/a del estudio, para mantener el control del VIH y evitar que el VIH adquiera resistencia a los fármacos.

Efectos secundarios después de recibir inyecciones de acción prolongada

Después de una inyección de Cabotegravir y Rilpivirina, estos medicamentos permanecerán en su cuerpo durante mucho tiempo. En algunas personas, niveles bajos de Cabotegravir y Rilpivirine pueden estar presentes en el cuerpo durante más de un año después de la última inyección. Si desarrolla un efecto secundario del medicamento del estudio después de una inyección, no habrá forma de eliminar el medicamento de su cuerpo. Si esto sucede, su médico/a hará todo lo posible para tratar los síntomas.

Cuando suspende las inyecciones de acción prolongada, la cantidad de medicamento en su cuerpo disminuirá con el tiempo y desaparecerá.

Sensación de desmayo después de la inyección

Al recibir las inyecciones algunas personas pueden sentirse mareadas o con la sensación de que se pueden desmayar. Esta reacción, también llamada "reacción vasovagal", puede ocurrir con muchos procedimientos médicos, se resuelve rápidamente y no es una amenaza para su salud.

Extracción de sangre

Al extraerle sangre, puede sentirse mareado/a o experimentar un dolor leve, hematomas, irritación o enrojecimiento en el sitio de la punción. En casos raros, puede contraer una infección.

Problemas de salud mental

Algunas personas con problemas de salud crónicos, incluido el VIH, a veces tienen sentimientos de depresión o pueden tener pensamientos de hacerse daño o quitarse la vida (suicidio). Un pequeño número de personas en tratamiento con Cabotegravir y Rilpivirina han tenido pensamientos y acciones suicidas, en particular aquellas con antecedentes de depresión o problemas de salud mental.

Informe al médico/a del estudio si tiene antecedentes de problemas de salud mental. Si tiene pensamientos de autolesionarse o suicidarse o tiene otros pensamientos o sentimientos inusuales o incómodos durante este estudio, debe informar al médico/a del estudio o acudir al hospital más cercano de inmediato.

Esta lista de efectos secundarios no está completa. Puede experimentar efectos secundarios diferentes a los descritos en este formulario de consentimiento informado o que no se conocen actualmente.

Medicación NO permitida durante el estudio

El uso de algunos otros fármacos está contraindicado o debe realizarse con precaución cuando se administran de forma simultánea con Cabotegravir y/o Rilpivirina. Por este motivo, no está permitido el uso de los siguientes fármacos durante el estudio:

- Carbamazepina, oxcarbazepina, fenobarbital, fenitoína (medicamentos para tratar la epilepsia y prevenir las convulsiones)
- Rifabutina, rifampicina, rifapentina (medicamentos para tratar infecciones bacterianas como la tuberculosis)
- Dexametasona (un corticosteroide que se emplea para tratar diversas patologías, tales como la inflamación y las reacciones alérgicas) administrada en un ciclo de tratamiento por vía oral o inyectable
- Productos que contienen Hierba de San Juan o Hipérico (Hypericum perforatum, una planta medicinal que se emplea para la depresión).

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No utilice medicamentos (de venta con y sin receta) sin consultar antes con el personal médico del estudio. El personal médico del estudio le explicará la necesidad de evitar ciertos medicamentos durante el estudio, incluidos los contraindicados. Es posible que más adelante se identifiquen nuevos medicamentos que tengan que añadirse a la lista de fármacos que no debe tomar durante el estudio.

¿Puede participar en el estudio una persona embarazada?

Debido a que no se dispone de información acerca de la seguridad para el feto de Cabotegravir y Rilpivirina de acción prolongada, no se permite la participación en el estudio a personas embarazadas.

Por este motivo, dentro de las pruebas previstas en la visita de selección y en las visitas del estudio se realizarán pruebas de embarazo en orina a todas las personas que menstrúan en edad fértil* que deseen participar en el estudio o hayan sido incluidas en el estudio. El resultado debe confirmarse como negativo antes de la administración de la primera dosis de los fármacos del estudio. Las pruebas de embarazo también se realizarán en cualquier momento durante el estudio cuando se sospeche un embarazo.

Si usted es una persona que puede tener hijos, debe usar métodos anticonceptivos mientras participe en el estudio. Se debe usar un método anticonceptivo eficaz, según lo acordado con su médico/a del estudio, desde al menos 14 dias antes del inicio de su primera dosis de Cabotegravir y Rilpivirina y durante el tiempo que esté tomando el medicamento del estudio. Se recomienda que continúe usando un método anticonceptivo efectivo hasta al menos 14 días después de su última dosis oral de Cabotegravir y Rilpivirina, y al menos 13 meses después de su última(s) inyección(es) de acción prolongada, ya que los medicamentos del estudio aún pueden estar presentes en el cuerpo durante este tiempo. Su médico/a del estudio hablará con usted sobre esta recomendación y sobre los riesgos potenciales del embarazo durante este tiempo. Debe informar a su médico/a de atención primaria y su médico/a de la Unidad de VIH si tuviera un embarazo dentro de los 12 meses posteriores a la última inyección de Cabotegravir y Rilpivirina aunque ya no esté en el estudio.

Por lo tanto, en la visita de selección y durante el estudio, se deberá aceptar el uso de alguno de los siguientes métodos anticonceptivos considerados altamente efectivos para evitar el embarazo:

- anticoncepción hormonal o dispositivo intrauterino [DIU]
- esterilidad anatómica propia o de la pareja

Si el resultado de la prueba de embarazo es positivo o equívoco, las inyecciones intramusculares deberán posponerse hasta que se obtenga una prueba de embarazo en suero válida. Si la prueba es positiva, dejará de tomar la medicación del estudio y el personal médico responsable del estudio le informará sobre las siguientes acciones a seguir (ver apartado siguiente).

¿Qué sucederá si una persona queda embarazada durante el estudio?

Debe informar al equipo investigador del estudio de forma inmediata si sospecha que hay posibilidad de embarazo durante el estudio. Si su participación en el estudio ha terminado, deberán informar a su médico/a habitual en el seguimiento del VIH.

Si se confirma su embarazo durante el estudio se le dará la opción de cambiar a una terapia antirretroviral alternativa durante el embarazo. Se iniciará un tratamiento antirretroviral alternativo que se considere adecuado para su uso durante el embarazo de acuerdo con las directrices locales. La fecha límite para iniciar este tratamiento será la fecha prevista para la siguiente inyección de Cabotegravir y Rilpivirina.

Después del estudio

Cuando acabe su participación recibirá el mejor tratamiento disponible, el que su médico considere el más adecuado para su enfermedad, en su hospital. Debido a que la medicación del estudio ya estará comercializada es posible que se le pueda seguir administrando la medicación del estudio pero ni el investigador ni el promotor adquieren compromiso alguno de mantener dicho tratamiento fuera de este estudio.

¿Cuáles son los beneficios esperables de este estudio?

Posibles beneficios:

Al participar en este estudio, usted recibirá un tratamiento antirretroviral que ha demostrado una alta eficacia y una excelente tolerabilidad en diferentes ensayos clínicos. Es esperable que con

este estudio se pueda analizar si la administración del tratamiento es aceptable, apropiado y viable llevarlo a cabo fuera del ámbito hospitalario y se puede implementar en los centros de atención primaria y centros comunitarios, lo cual puede beneficiar en el futuro a otras personas infectadas por el VIH.

Costes:

Usted no tendrá que pagar por los medicamentos ni por pruebas específicas del estudio. Su participación en el estudio no le supondrá ningún gasto adicional a la práctica clínica habitual. El estudio será financiado por la compañía farmacéutica ViiV Healthcare en colaboración con la Fundació Lluita contra la SIDA i les Malalties Infeccioses.

Confidencialidad e información legal

El promotor del estudio y los centros participantes, como responsables independientes del tratamiento de datos, garantizarán la confidencialidad de la información personal de los sujetos participantes de acuerdo con la normativa legal vigente (Ley Orgánica 3/2018, de Protección de Datos Personales y Garantía de los Derechos Digitales, y Reglamento [UE] 2016/679 del Parlamento Europeo y del Consejo, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos).Durante este estudio, el equipo médico del estudio registrará información referente a usted, a su salud y a su participación en el estudio en impresos denominados cuadernos de recogida de datos.

Para garantizar que los datos recogidos durante el estudio se tratan de forma confidencial, sus datos estarán identificados mediante un código, no se incluirá su nombre ni ninguna otra información que permita identificarle directamente en los cuadernos de recogida de datos. Por lo tanto, su identidad no será revelada a ninguna otra persona salvo a las autoridades sanitarias, cuando así lo requieran o en casos de urgencia médica. Los comités éticos, los representantes de la Autoridad Sanitaria en materia de inspección y el personal autorizado por el promotor, únicamente podrán acceder para comprobar los datos personales, los procedimientos del estudio clínico y el cumplimiento de las normas de buena práctica clínica (siempre manteniendo la confidencialidad de la información).

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Solo el personal médico del estudio / colaboradores podrán relacionar dichos datos con usted y con su historia clínica. El promotor sólo tendrá acceso a la información relativa a los resultados generales del estudio. En ningún caso accederá a sus datos personales.

Para llevar a cabo este ensayo clínico, necesitaremos asimismo acceder a la información médica contenida en su historia clínica y registraremos su participación y aspectos de seguridad a lo largo del estudio en el sistema electrónico de historia clínica de los centros participantes, por lo que usted nos deberá autorizar para ello expresamente.

Los responsables del tratamiento de los datos son el promotor, Fundació Lluita contra la Sida y enfermedades infecciosas, así como también los centros donde se llevará a cabo este estudio perteneciente al Institut Català de la Salut y la Junta de Andalucia

- Delegado de Protección de Datos en el ámbito del Departamento de Salud mail de contacto: dpd@ticsalutsocial.cat.
- Delegado de Protección de datos en el ámbito de la Junta de Andalucía mail de contacto **********
- Delegado de Protección de Datos de Fundació FLS de Lluita contra la Sida, les Malalties Infeccioses i la Promoció de la Salut i La Ciència (promotor), con domicilio en la Ctra. de Canyet s/n, Hosp. Univ. Germans Trias i Pujol, 2a planta Maternal, 08916 Badalona (Barcelona): lopd@flsida.org.

Base Jurídica del tratamiento de los datos: El consentimiento que otorga mediante este documento y el interés general en el tratamiento de la enfermedad.

Destinatarios: Son destinatarios de los datos el equipo investigador y el personal autorizado por los responsables del tratamiento de datos, los proveedores necesarios para la finalidad del tratamiento (laboratorios, empresa proveedoras de software y alojamiento) y en su caso, las autoridades administrativas pertinentes. Aunque los datos se conservarán pseudoanonimizados durante el estudio, le informamos que su información estará alojada en un servidor seguro ubicado en la Unión Europea bajo normativa actual con la más alta calidad y seguridad especifica. Los datos codificados pueden ser transmitidos a terceros y a otros países, pero en ningún caso contendrán información que le pueda identificar directamente, ni indirectamente, y se establecerán contratos con los destinatarios de la información que prohíban expresamente la reidentificación, mediante el cruce con otras bases de datos o cualquier tecnología que intente reidentificar los datos. En el caso de que se produzca esta cesión, será para

los mismos fines del estudio descrito o para su uso en publicaciones científicas, pero siempre manteniendo la confidencialidad de estos, de acuerdo a la legislación vigente.

Derechos: Usted puede ejercer sus derechos de acceso, rectificación, cancelación, oposición, limitación del tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) del paciente sobre los datos que ha facilitado para el estudio (Derechos PARSOL). Para ejercer sus derechos al participante podrá dirigirse al equipo de investigadores o bien al delegado de protección de datos de las instituciones

Conservación de los datos: El promotor conservará los registros del ensayo clínico durante un período de al menos 25 años tras su finalización. Posteriormente, su información personal sólo se conservará por el centro para el cuidado de su salud. El promotor conservará datos que en ningún momento contendrán datos personales.

Le recordamos que los datos no se pueden eliminar, aunque deje de participar en el estudio para garantizar la validez de la investigación y cumplir con los deberes legales y los requisitos de autorización de medicamentos. Por lo tanto, si usted decide retirar el consentimiento para participar en este estudio, ningún dato nuevo será añadido a la base de datos, pero sí se utilizarán los que ya se hayan recogido.

Derecho de reclamación: Puede ejercer su derecho a presentar una reclamación ante la Autoridad competente (la Autoritat Catalana de Protecció de Dades o bien, la Autoridad Española de Protección de Datos), si considera que se han vulnerado sus derechos en materia de protección de datos.

Seguro:

El promotor del estudio ha suscrito una póliza de seguro de responsabilidad civil con la compañía Zurich Insurance PLC sucursal en España de acuerdo con los requerimientos establecidos en el RD 1090/2015, que cubre los posibles daños y perjuicios que puedan experimentar derivados de su participación en el ensayo, siempre que no sean consecuencia de la propia enfermedad que se estudia o de la evolución propia de su enfermedad como consecuencia de la ineficacia del tratamiento.

Así mismo, es posible que su participación en este ensayo clínico pueda modificar las condiciones generales y particulares (cobertura) de sus pólizas de seguros (vida, salud, accidente) y, por ello, le recomendamos que se ponga en contacto con su compañía de seguros y le informe de su

participación en el mismo para determinar si podría afectar a su póliza de seguro actual o en el caso de que vaya a contratar una póliza nueva.

Si desea más información relativa a este apartado, consulte con el investigador principal del estudio en su centro.

Participación en el estudio:

Para participar en este estudio no es necesario que tome la decisión en este momento, puede llevarse esta Hoja de Información a casa y meditar sobre ello el tiempo suficiente y consultar su participación con su familia o médico/a habitual.

Usted participa en este estudio de forma voluntaria y podrá retirarse del estudio cuando lo desee sin por ello tener que dar explicaciones ni verse afectada su asistencia posterior en nuestra Consulta.

Una vez firmado el Consentimiento Informado, usted se quedará con una copia de este documento.

Existe la posibilidad de exclusión del ensayo por parte del promotor o el equipo investigador, en caso de producirse problemas de seguridad o incumplimiento con los procedimientos establecidos en el estudio.

En caso de cancelación del ensayo por parte del promotor, se informará a las personas participantes de los motivos.

Cualquier información nueva referente a los fármacos utilizados en el estudio que puedan afectar a su decisión para continuar en el estudio se la comunicará su médico/a lo antes posible y, si es necesario, se firmará un nouvo consentimiento.

Contacto para información

En caso de cualquier duda o problema relacionados con su infección o con el tratamiento administrado, fuera del horario laboral, usted puede contactar con el investigador principal del estudio:

Dr/a…….

Tel ……

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CONSENTIMIENTO INFORMADO

TÍTULO DEL ESTUDIO	"Implementación de la administración extrahospitalaria de la combinación de acción prolongada Cabotegravir+Rilpivirina como terapia opcional en pacientes de España infectados por el VIH. Aceptabilidad, idoneidad, viabilidad y satisfacción Estudio HOLA".
CÓDIGO DEL ESTUDIO	Out-of-hospital LA CAB+RPV
PROMOTOR	Fundació FLS de Lluita contra la Sida, les Malalties Infeccioses i la Promoció de la Salut i La Ciència
INVESTIGADOR PRINCIPAL	Eugenia Negredo Puigmal
CENTRO	Hospital Universitari Germans Trias i Pujol

Yo, (nombre y apellido)....., después de haber leído la hoja de información que se me ha entregado y hacer las preguntas aclaratorias al respecto al Dr./Dra.....

Confirmo haber recibido suficiente información sobre el estudio y haber entendido los objetivos del estudio y lo que implica.

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:

- Cuando quiera.
- Sin tener que dar explicaciones.
- Sin que esto repercuta en mis cuidados médicos.

Y consiento:

- Que los datos clínicos recogidos durante el estudio sean guardados en un fichero automatizado cuya información podrá ser manejada exclusivamente con fines científicos, siempre que la información referente a mi persona sea disociada (esto significa que la información que se obtiene no puede ser relacionada con la persona de la que proviene).
- Comprendo que tengo la posibilidad de ejercitar los derechos de acceso, rectificación, cancelación, oposición, limitación de tratamiento, portabilidad de datos y a no ser objeto

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de decisiones individualizadas automáticas (elaboración de perfiles), dirigiéndome por escrito al delegado de Protección de Datos en el ámbito del Departamento de Salud (dpd@ticsalutsocial.cat) Junta de Andalucía (**********) o del promotor (LOPD@flsida.org)

Estoy de acuerdo con todo lo referido a este estudio y presto libremente mi conformidad para participar en el mismo y que mis datos puedan ser utilizados con fines de investigación según consta en la hoja de información al paciente.

Firma de paciente Firma de/la Investigador/a

Fecha Fecha

Recibirá una copia de este documento, una vez la haya firmado, para que la conserve con sus registros.

PARA LOS ADULTOS QUE NO PUEDEN DAR SU CONSENTIMIENTO

....,
Testigo/interprete en la entrevista de consentimiento

En la fecha suscrita, yo he sido testigo en la entrevista de consentimiento para el estudio de investigación nombrado al principio de este documento. Yo confirmo que la información contenida en este formulario de consentimiento fue debidamente explicada al sujeto, y el sujeto ha confirmado que todas sus dudas han sido contestadas adecuadamente.

Nombre del testigo

Firma del testigo Firma de/la Investigador/a

Fecha Fecha

El sujeto del estudio recibirá una hoja informativa completa, junto a una versión firmada del formulario de consentimiento