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Patient Participant Perspectives on Implementation of Long-Acting Cabotegravir and Rilpivirine: Results From the Cabotegravir and Rilpivirine Implementation Study in European Locations (CARISEL) Study

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Abstract

Introduction: CARISEL is an implementation–effectiveness "hybrid" study examining the perspectives of people living with HIV-1 (patient study participants [PSPs]) on cabotegravir (CAB) plus rilpivirine (RPV) long-acting (LA) dosed every 2 months (Q2M) across 5 European countries.

Methods: PSPs completed questionnaires on acceptability (Acceptability of Intervention Measure), appropriateness (Intervention Appropriateness Measure), and feasibility (Feasibility of Intervention Measure) at their first (Month [M] 1), third (M4), and seventh (M12) injection visits. Semistructured qualitative interviews were also conducted.

Results: Overall, 437 PSPs were enrolled, of whom 430 received treatment. Median (interquartile range) age was 44 (37-51) years, 25.3% (n = 109/430) were female (sex at birth), and 21.9% (n = 94/430) were persons of color. Across time points, PSPs found CAB + RPV LA highly acceptable, appropriate, and feasible (mean scores ≥4.47/5). Qualitative data supported these observations.

Conclusions: PSPs found CAB + RPV LA Q2M to be an acceptable, appropriate, and feasible treatment option.

Keywords

cabotegravir + rilpivirine, long-acting, acceptability, satisfaction, stigma, appropriateness

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Introduction

Daily oral dosing remains the dominant delivery method for antiretroviral therapy (ART) and, despite advances in effectiveness and convenience, can be associated with long-standing challenges for some people living with HIV (PWH). These include the fear of inadvertent disclosure and stigma, pill fatigue, anxiety related to staying adherent, and the daily reminder of living with HIV.[1,2] The development and approval of long-acting (LA) ART has provided a therapeutic alternative to daily oral ART for the maintenance of virological suppression and has been shown to address some of the challenges faced by some PWH while providing an option more suited to individual needs and preferences.[3–5]

Cabotegravir (CAB), a drug of the integrase strand transfer inhibitor (INSTI) ART class, plus rilpivirine (RPV), a drug of the non-nucleoside reverse transcriptase inhibitor (NNRTI) ART class, is the first and only complete LA regimen recommended by treatment guidelines for the maintenance of HIV-1 virological suppression.[6–15] Cabotegravir + RPV LA is administered every 2 months (Q2M) via 2 separate intramuscular gluteal injections administered by a healthcare professional (HCP), reducing dosing frequency compared with daily oral ART.[16–18] The efficacy and tolerability of CAB + RPV LA has previously been demonstrated in Phase 3/3b noninferiority trials (ATLAS, FLAIR, ATLAS-2 M, and SOLAR), with high treatment efficacy and patient satisfaction reported across the Phase 3 clinical program.[15,19,20]

As CAB + RPV LA represents a significant paradigm shift in the delivery of HIV care (oral to injectable), healthcare facilities may differ in their ability to implement the intramuscular injectable treatment, preventing CAB + RPV LA from being utilized to its full potential in the real world. For example, clinics may differ in their availability of physical space to administer injections (number of injection rooms), staff resource to accommodate an increased volume of visits, medication procurement and storage procedures, as well as having different training requirements for administering injections.[21] Consequently, refining strategies to support the introduction of this innovative LA injectable ART modality is fundamental for successful implementation and optimal delivery from a PWH and HCP perspective.[22]

Previously, CAB + RPV LA administered once monthly was shown to be successfully implemented across a range of US healthcare settings in the CUSTOMIZE (NCT04001803) clinical trial[23]; however, to date, no multicountry, European-specific implementation evaluations have been conducted with the CAB + RPV LA Q2M dosing regimen to our knowledge. The CAB and RPV Implementation Study in European Locations (CARISEL; NCT04399551) was a Phase 3b "hybrid" implementation–effectiveness study examining strategies to support the implementation of CAB + RPV LA dosed Q2M in 18 sites across 5 European countries (Belgium, France, Germany, the Netherlands, and Spain) and is the first study in which all participants switched from daily oral ART to CAB + RPV LA dosed Q2M. Efficacy and safety data from the CARISEL study, as well as perspectives on implementation from HCPs (the study's primary endpoint), will be published in full separately.[24,25] Here, we report the perspectives of PWH (patient study participants [PSPs]) after 12 months of CAB + RPV LA in CARISEL, including quantitative and qualitative data on perceived barriers and facilitators, to help inform strategies that enhance the implementation of CAB + RPV LA.

Methods

Study Design and Participants

CARISEL (NCT04399551) was a Phase 3b, multicenter, open-label, hybrid-type III implementation–effectiveness trial—a study that answers both implementation and clinical questions—conducted from September 2020 to March 2023; data collection for Month 12 was completed in February 2022. The goal of an implementation–effectiveness trial is to generate robust implementation evidence that will support the use of an intervention[26] and is not to compare the implementation of one intervention to another. Consequently, no comparator intervention arm was required. The implementation intervention, and randomization to study arm, occurred only at the level of the sites and impacted staff study participants (SSPs). As CARISEL was conducted during the height of the COVID-19 pandemic in Europe, additional measures and procedures were implemented to protect participant safety, as well as to ensure that there were no gaps in HIV-1 treatment for participants enrolled in this clinical study. Examples included direct-to-participant shipments of oral ART for when participants were unable to travel to the clinic, capturing COVID-19-specific protocol deviations and making adjustments to study visit procedures.[27]

CARISEL was conducted at 18 sites across Belgium (n = 4), France (n = 6), Germany (n = 2), the Netherlands (n = 2), and Spain (n = 4). Clinics with no prior experience with CAB + RPV LA were preferentially selected for study participation. Both SSPs and PSPs were enrolled to participate in this study; this publication focuses only on PSPs, with the SSP data presented separately.[24] For PSPs, CARISEL was designed as a single-arm, unblinded, interventional study in which all participants who fulfilled eligibility requirements were assigned to receive CAB + RPV LA Q2M and complete assessments as per the study protocol. The study design has been previously published.[25] Clinical sites were asked to recruit PSPs, which was completed in a manner deemed most appropriate by each site. Each site was also responsible for screening participants for eligibility. PSPs who were eligible were:

1. ≥18 years of age at the time of signing the informed consent
2. virologically suppressed (HIV-1 RNA <50 copies/mL) on guideline-recommended ART for ≥6 months prior to screening
3. Virologically suppressed at screening, as well as having documented evidence of at least 2 plasma HIV-1 RNA

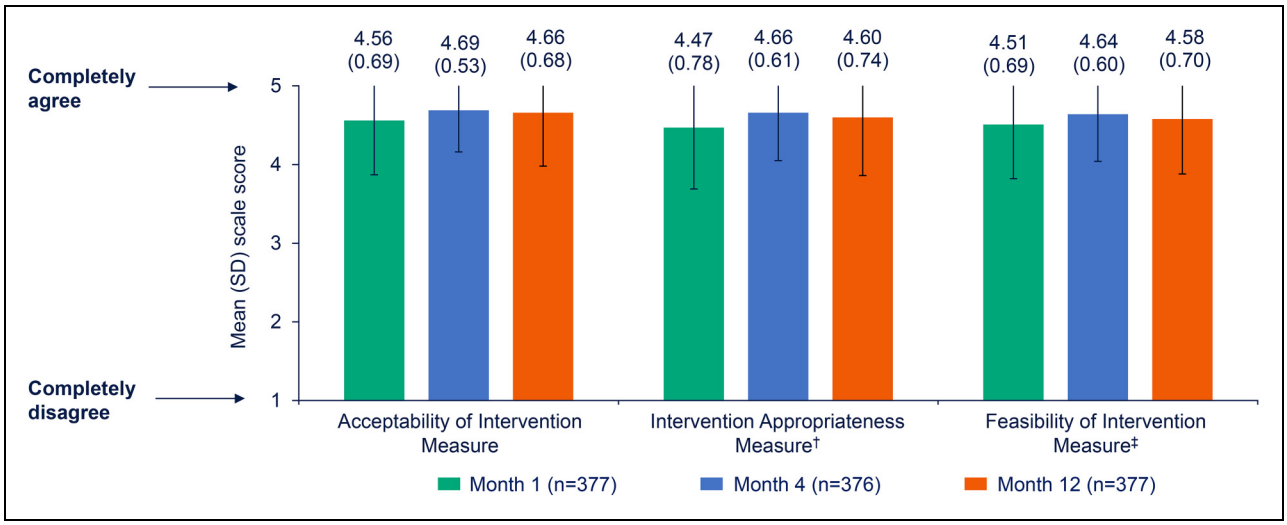

Figure 1. Acceptability, Appropriateness and Feasibility of CAB + RPV LA over time for PSPs*. *Acceptability, appropriateness, and feasibility measures are rated on a 1 to 5 Likert scale: 1 = "completely disagree"; 2 = "disagree"; 3 = "neither agree nor disagree"; 4 = "agree"; 5 = "completely agree." †Month 1, n = 376. ‡Month 1, n = 376; Month 4, n = 373; Month 12, n = 376. CAB, cabotegravir; LA, long-acting; PSP, patient study participant; RPV, rilpivirine; SD, standard deviation. "Abstract P123—Figure 1. Acceptability, appropriateness, and feasibility* of CAB + RPV LA over time." Lutz et al HIV Glasgow, October 23-26, 2022, Glasgow, UK / Virtual –https://onlinelibrary.wiley.com/doi/10.1002/jia2.26009. CC BY 4.0.

measurements <50 copies/mL in the 12 months prior: one within 6 months prior to screening and one within 6 to 12 months prior to screening

4. PWH who had not previously switched therapy due to virological failure (on-treatment HIV-1 RNA ≥200 copies/mL), defined as a change of a single drug or multiple drugs simultaneously
5. PWH with no primary resistance based on the presence of any major known INSTI or NNRTI resistance-associated mutations, in alignment with the European indication for CAB + RPV LA.[28,29] The K103N mutation was permitted as it is not associated with resistance to CAB or RPV.[30]

Ethical Approval and Informed Consent

The CARISEL study was conducted following the ethical principles of the Declaration of Helsinki. All participants provided written informed consent, the collection of which was unaffected by the COVID-19 pandemic. The study protocol, amendments, informed consent forms, and other study documents and information were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board (Belgium (20.81-infect20.08 - piloot 266), Jessa Ziekenhuis; France (2020/87), CPPIle de France IV; Germany (20053), Ethik-Kommission der Bayerischen Landesärztekammer; the Netherlands (R20.052), St. Antonius Ziekenhuis; Spain (local committee), General University Hospital of Alicante).

Clinical Intervention

The clinical intervention comprised an oral lead-in (OLI) phase and a maintenance phase.

- The OLI phase comprised oral CAB (30 mg) + RPV (25 mg) for 1 month to assess initial individual safety and tolerability.
- The maintenance phase comprised loading injections comprised 2 separate intramuscular gluteal injections of CAB LA (600 mg) and RPV LA (900 mg) at Month (M) 1 and 2, followed Q2M thereafter.

In the event of planned missed injection visits, CAB + RPV oral therapy was administered. If participants were unable to attend a visit and oral CAB + RPV could not be obtained, alternative oral ART was administered. After M12, CAB + RPV LA administration continued Q2M per current clinical practice during the extension phase of the study.

Outcomes and Procedures

The primary endpoint of CARISEL was to evaluate the perceived acceptability, appropriateness, and feasibility of the implementation of CAB + RPV LA in SSPs, the results of which are published separately.[24] For PSPs, CARISEL was designed as a single-arm, unblinded, interventional study. Key secondary endpoints, published here, were to evaluate PSP perspectives on perceived acceptability, appropriateness, and feasibility of CAB + RPV LA, perceived barriers, and facilitators for optimal implementation of CAB + RPV LA administration among PWH and patient preferences for HIV treatment (previous daily oral ART vs CAB + RPV LA Q2M). PSP satisfaction with CAB + RPV LA and levels of pain caused by the injections were also evaluated.

Quantitative data. Quantitative data were collected at day 1, M1, M4, and M12 (prior to CAB + RPV OLI, first, third, and seventh CAB + RPV LA injections, respectively). PSPs evaluated the acceptability, appropriateness, and feasibility of CAB + RPV LA using the previously validated Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM) questionnaires, respectively; each comprises 4 items rated on a 1 to 5 Likert scale (1 = "completely disagree" to 5 = "completely agree").[31] Additionally, data on barriers and facilitators for optimal implementation were collected using a bespoke 17-item study-specific questionnaire (CAB + RPV LA effects on stigmatization, convenience of scheduling injections, etc), with predetermined response choices to each question. Treatment satisfaction was assessed using the 12-item HIV Treatment Satisfaction Questionnaire status version (HIVTSQs),[32] with a rating scale for each item of 0 ("very dissatisfied") to 6 ("very satisfied"), measured at day 1 (evaluating prior daily oral ART), M1 (evaluating CAB + RPV OLI), M4, and M12 (evaluating CAB + RPV LA). For total HIVTSQs scores, a composite of items 1 to 11 was taken, with possible scores ranging from 0 ("very dissatisfied") to 66 ("very satisfied"); item 12 (discomfort/pain) is not included in total scores. To ascertain the level of pain caused by CAB + RPV LA, PSPs were presented with a visual analog scale (VAS) at M12 and asked to rate the pain they experienced during their most recent injection visit between 0 ("no pain") and 10 ("extreme pain"). PSPs were asked at M12 to assess whether they preferred their previous daily oral ART, CAB + RPV LA or if they had no preference between the 2 regimens. PSPs were also asked to indicate supporting reasons for their preference by multiple closed-format response options.

Qualitative data. Qualitative data were obtained from semistructured qualitative telephone interviews (60-90 min) on CAB + RPV LA experience at M1 and M12 with a subgroup of PSPs (each site [n = 18] was given a target recruitment of 7 PSPs). Purposive sampling was used to select PSPs for the semistructured qualitative interviews, with the goal of interviewing 7 PSPs per site (a minimum of 2 females [sex at birth] per site). Sites were instructed to ask the first 5 PSPs who attended study visits to participate in interviews. After 5 PSPs had consented, sites who had not interviewed at least 2 females were instructed to only offer interviews to female PSPs to ensure an adequate representation of females. Interview guides were informed by the Exploration, Preparation, Implementation, Sustainment (EPIS) framework, and the implementation outcomes taxonomy proposed by Proctor and colleagues, both of which have been previously used extensively.[33,34] The interview guides covered the acceptability, appropriateness, feasibility, and sustainability of treatment, as well as barriers to/facilitators of its implementation. Interview questions were open ended and designed to elicit discussions from PSPs on these topics. Owing to the nature of this data capture, PSPs did not necessarily discuss each theme, and instead discussed the themes most relevant to their experience. Therefore, the absence of a PSP discussing a specific topic cannot be interpreted as an indication as to whether they agreed or disagreed with certain aspects of the CAB + RPV LA experience.

Interviews were conducted and coded by 5-trained qualitative researchers. Interviews were recorded, transcribed, and analyzed for thematic trends (Supplemental Material: qualitative data analysis) using ATLAS.ti (version 8.4), a data analysis software used for qualitative research. The first 2 interviews were independently coded, and a reconciliation meeting was then held to review the coding in detail, and to compare, discuss, and reconcile any discrepancies. This process occurred until the rated agreement was consistent, after which one qualitative researcher would code each remaining transcript. The repetitive comparative method, an iterative coding approach moving between consecutive transcripts and new codes that emerged, was followed. Interview transcripts were analyzed in stages, with reconciliation occurring at the end of each week.

Strategies for ensuring trustworthiness in qualitative research, outlined by Ahmed,[35] were consulted to evaluate the overall quality of qualitative data collection and analysis. For example, confirmability was ensured by utilizing double coding methods, dependability was ensured by the rigorous documentation of coding transcripts and credibility through the triangulation of data sources in the study (ie, qualitative and quantitative data sources).

Statistical Analysis

The study population included all PSPs who successfully completed each questionnaire. For the change-over-time analyses, only those PSPs who completed the questionnaires at the relevant time points were included. The internal consistency of the validated questionnaires was assessed using Cronbach's alpha coefficients (Supplemental Table 1). The sample size was based on practical considerations in terms of the feasibility of enrolling an adequate number of sites balanced with the desire to have interventions tested across several types of investigative sites, as well as being able to obtain in-depth qualitative site-level feedback via interviews. Quantitative data were summarized using descriptive statistics.

Results

PSP Characteristics

In total, 437 PSPs were enrolled, of whom 430 entered the intervention phase and received study treatment. The total sample decreased throughout the study (Month 1, n = 424; Month 4, n = 408 [4.2% attrition]; Month 12, n = 379 [11% attrition]). PSP had a median (interquartile range) age of 44 (37-51) years (≥50 years, 30.0% [n = 129/430]), 25.3% (n = 109/430) were female (sex at birth), 74.7% (n = 321/430) were male (sex at birth), 1.4% (n = 6/430) were transgender women (participant-reported gender), 78.1% (n = 336/430) were of White race, and 17.7% (n = 76/430) were of Black race.

Demographics by country can be found in Supplemental Table 2. Full baseline demographics will be published separately in the clinical manuscript.[25] A total of 379 PSPs from France (38.8%, n = 147/379), Spain (23%, n = 87/379), Belgium (17.9%, n = 68/379), Germany (11.3%, n = 43/379), and the Netherlands (9.0%, n = 34/379) completed questionnaires through M12. For qualitative data analyses, a total of 110 PSPs from France (32.7%, n = 36/110), Belgium (24.5%, n = 27/110), Spain (20.9%, n = 23/110), Germany (10.9%, n = 12/110), and the Netherlands (10.9%, n = 12/110) participated in the qualitative semistructured interviews.

Acceptability, Appropriateness, and Feasibility of CAB + RPV LA

Across time points, PSPs found CAB + RPV LA to be highly acceptable, appropriate, and feasible with mean AIM, IAM, and FIM scores remaining high and stable from M1 to M4 and M12 (≥4.47/5) (Figure 1). No differences were observed between countries across time points, with M12 mean (standard deviation [SD]) scores ranging from 4.5 (0.92) (the Netherlands) to 4.9 (0.26) (Belgium) for AIM, 4.4 (0.91) (the Netherlands) to 4.8 (0.48) (Belgium) for IAM, and 4.4 (0.88) (the Netherlands) to 4.7 (0.41) (Belgium) for FIM (Supplemental Table 3). Qualitative data supported the acceptability, appropriateness, and feasibility demonstrated (Figure 2).

Barriers and Facilitators

Perception of CAB + RPV LA. PSP generally felt positive about receiving CAB + RPV LA (Supplemental Figure 1). At M1, 83.5% of PSPs felt either "extremely positive" (38.4%, n = 161/419) or "very positive" (45.1%, n = 189/419) about receiving CAB + RPV LA, with 0.2% (n = 1/419) feeling "not at all positive." By M12, 91.3% of PSPs reported that they were either "extremely positive" (61.7%, n = 234/379) or "very positive" (29.6%, n = 112/379) about receiving the treatment. No PSPs selected the "not at all positive" response and 6 (1.6%, n = 6/379) PSP responses from the total sample were missing. There were no notable variations by country. At least half of PSPs in each of the 5 countries were "extremely positive" about getting CAB + RPV LA at M12. High proportions of PSPs living in Spain (74.7%, n = 65/87), Belgium (72.1%, n = 49/68), and Germany (58.1%, n = 25/43) reported being "extremely positive" about receiving the treatment. Qualitative data reflected the quantitative data, with PSPs mentioning feeling informed about CAB + RPV LA (95.5%, n = 105/110) and having an overall positive experience with CAB + RPV LA (90.9%, n = 100/110) during M12 interviews. Additionally, approximately one-third of participants at both M4 (34.1% [n = 126/369]) and M12 (31.7% [n = 117/369]) reported that "nothing makes this treatment difficult" (Figure 3).

> Well, I thought let's give it a try and it might be handy. That was it. Then I started using it and I thought oh my goodness. I never realized the freedom aspect. That was so important for me. (Male, Month 12)

> I did not imagine it would be so convenient, but then you realize it is true. It is worth trying it. In the beginning you are always a bit afraid, but then you get the injection, and you can forget about it for two months. (Female, Month 12)

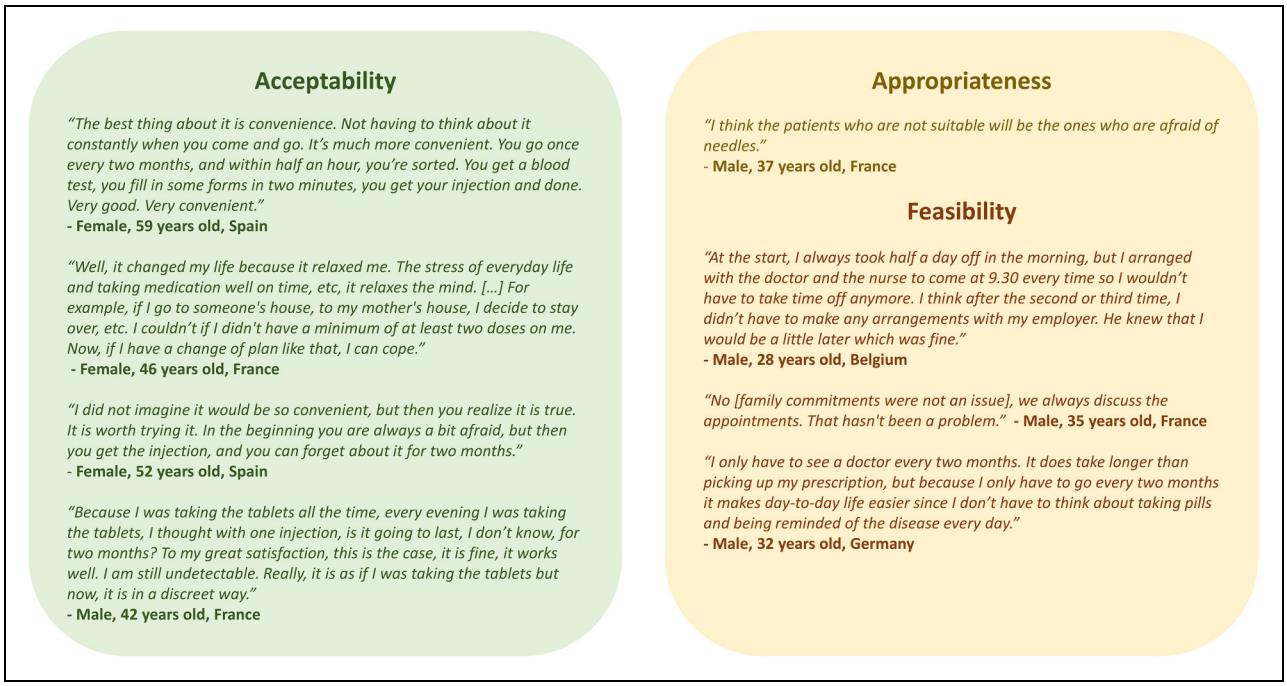

Figure 2. Direct participant quotations from Interviews at Month 12.

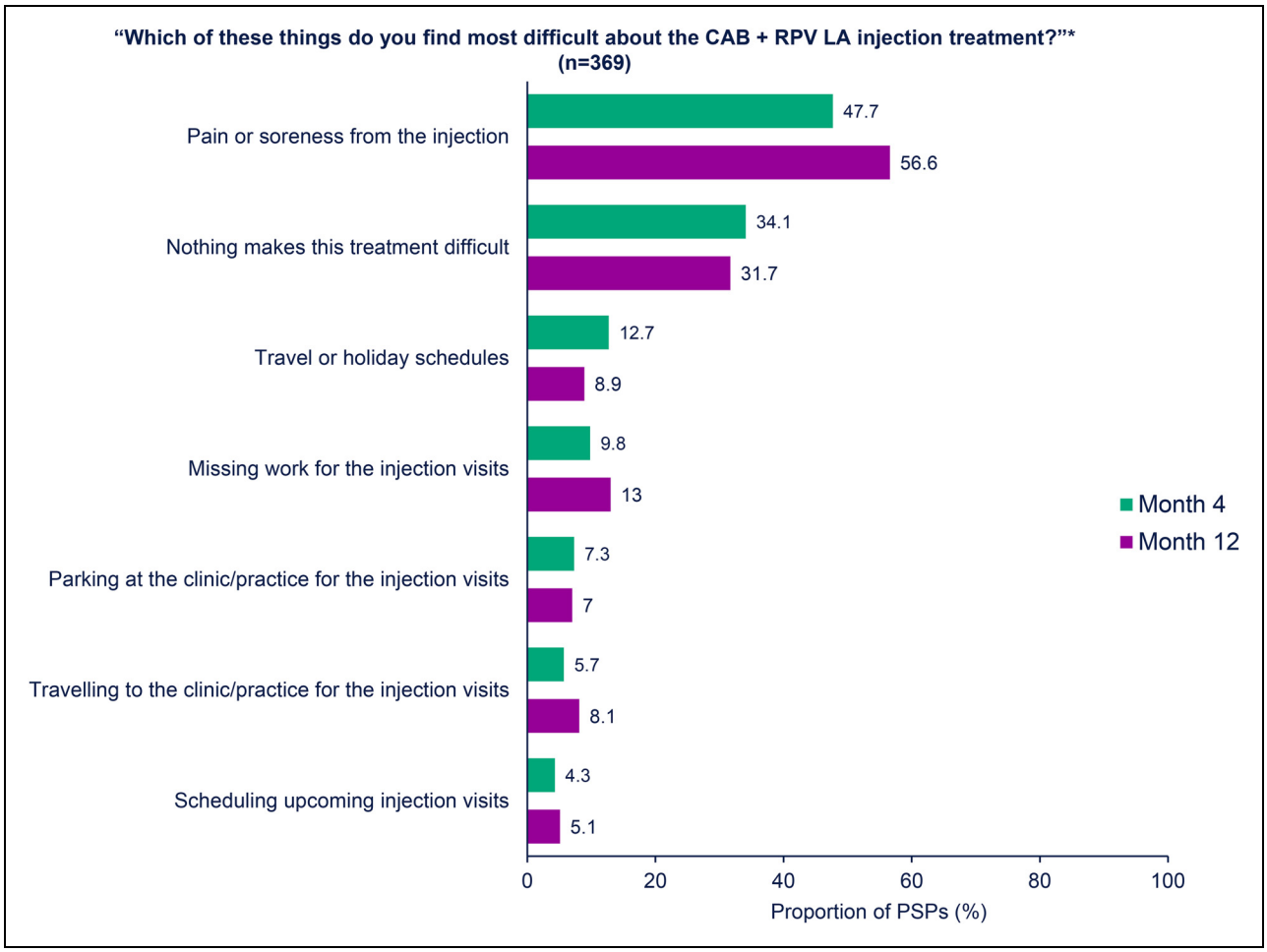

Figure 3. Summary of Difficulties Relating to CAB + RPV LA. *Only responses given by >5% of PSPs at either time point are shown. Responses are not mutually exclusive. CAB, cabotegravir; LA, long-acting; PSP, patient study participant; RPV, rilpivirine.

Perception of pain and injections. The most frequently reported difficulty PSPs had relating to CAB + RPV LA at M4 and M12 was "pain or soreness from the injection" (47.7% [n = 176/369] and 56.6% [n = 209/369], respectively) (Figure 3). Overall, 62.1% and 63.1% of PSPs reported a VAS score for pain experienced to be 3 or lower, on a 0 ("no pain") to 10 ("extremely painful") scale at M4 and M12, respectively (Supplemental Figure 2). The most common score at M4 (16.8%, n = 62/369) and M12 (19.2%, n = 71/369) was "1." A numerically larger number of PSPs reported having "no pain" (a score of "0") at M4 (14.9%, n = 55/369) compared with M12 (13.0%, n = 48/369). Few PSPs reported that their injection was "extremely painful" (a score of "10") at M4 (1.1%, n = 4/369), decreasing to 0.3% (n = 1/369) at M12. Mean (SD) pain scores were similar at M4 (3.1 ± 2.47, n = 369) and M12 (3.0 ± 2.29, n = 369), with a median score of 3.0 at both time points. Additionally, at M12, over three-quarters of PSPs reported that they had not needed to take time off from work, study, or daily activities to recover from any injection site reaction issues (77.6%, n = 294/379). For those who did report needing any time off, the most common response was that they had needed this time on the day they had received the treatment (11.9%, n = 45/379).

Pain or soreness was discussed in the qualitative interviews in a consistent manner. PSP mentioned 2 barriers related to injection side effects, including pain; this was cited both as a treatment component PSPs found difficult (60.9%, n = 67/110) and a challenge to receiving injections (30.0%, n = 33/110). Initial concerns about CAB + RPV LA largely resolved once PSPs had experience with the treatment:

> The injection itself isn't painful but I do have—I wouldn't call it pain but—discomfort 2 to 3 days afterwards. (Male, Month 12)

> [Pain] did not happen every time I got the injection. To tell you the truth, sometimes I felt the pain, and other times, I didn't. I believe it has to do with the way I am being injected. (Female, Month 12)

CAB + RPV LA effects on stigmatization. Quantitative data showed most PSPs perceived CAB + RPV LA as less stigmatizing than daily oral ART. At M4, when presented with the statement "*CAB + RPV LA is less stigmatizing than my oral*

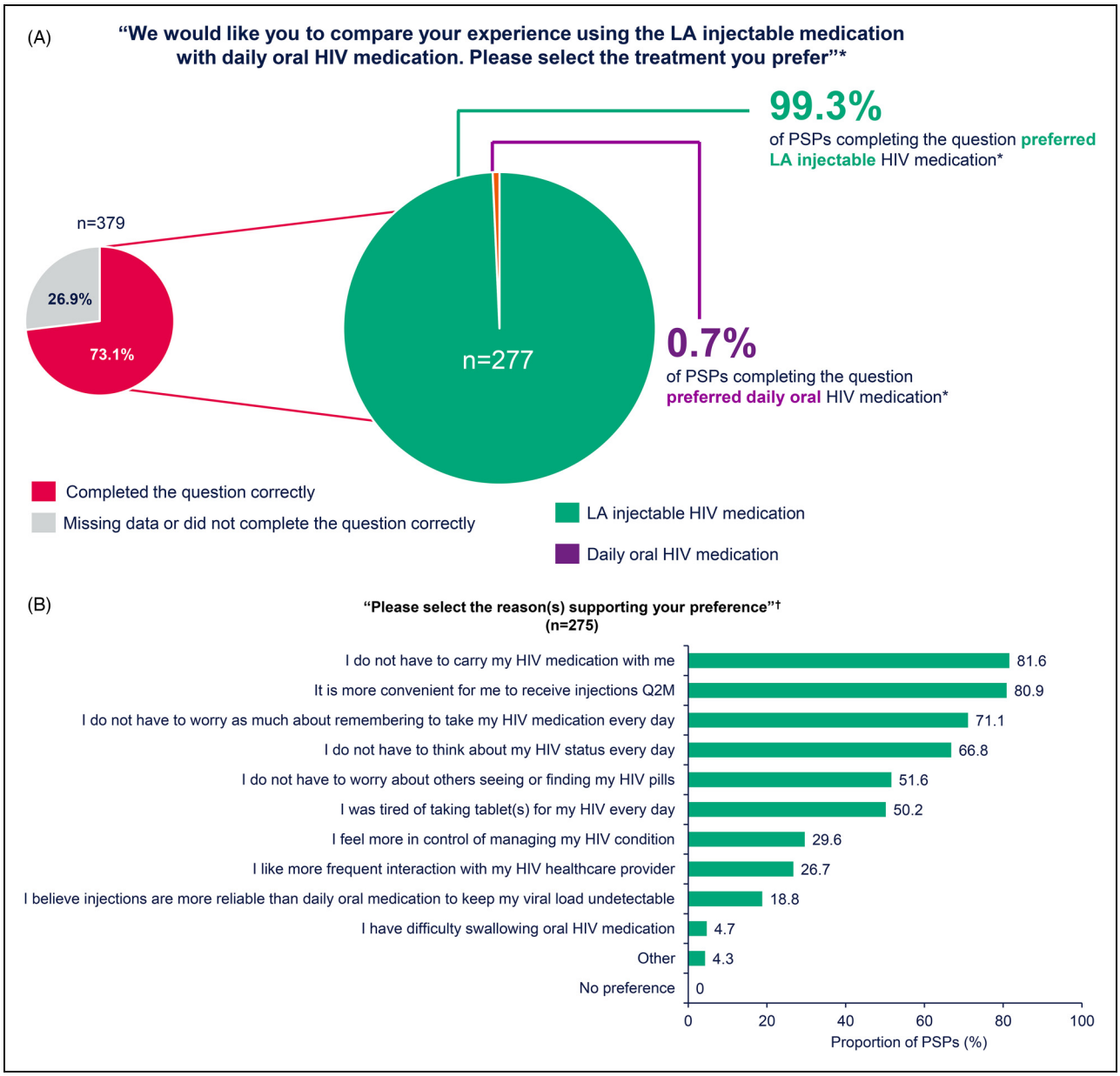

Figure 4. PSPs preferred HIV-1 Therapy at Month 12 (A) and Reasons for Preference (B). *Includes data from PSPs who selected only one leading checkbox (ie, "Daily oral HIV medication" or "Long-acting injectable HIV medication"). All erroneous and missing data were excluded. †Includes data from PSPs who selected only one leading checkbox (ie, "Daily oral HIV medication" or "LA injectable HIV medication"). All erroneous and missing data were excluded. Responses are not mutually exclusive. Two participants (0.7%) preferred daily oral medication. Both participants (0.7%) selected the reason: "It is more convenient for me to take my HIV medication every day." A single participant (0.4%) selected the reasons: "I want to avoid injection pain and side effects from the injection," "I am afraid of needles and injections," "It is inconvenient for me to visit the HIV clinic to receive injections," "I believe daily oral medication is more reliable than injections to keep my viral load undetectable," and "I feel more in control of managing my HIV condition." LA, long-acting; PSP, patient study participant; Q2M, every 2 months.

medication," the most frequent response selected was "completely agree" (55.6%, n = 208/374), followed by "agree" (25.7%, n = 96/374) and "neutral" (16.0%, n = 60/374); 2.6% (n = 9/374) of PSPs selected either "disagree" or "completely disagree" at M4. This response pattern was replicated at M12, when 81.0% (n = 307/379) of participants "agreed" or "completely agreed" that CAB + RPV LA was less stigmatizing than daily oral ART (Supplemental Figure 3). Some PSPs discussed the impact of CAB + RPV LA on stigma in their qualitative interviews in a consistent manner, with 20.0% of PSPs (n = 22/110) at M12 discussing that CAB + RPV LA reduced stigma around their HIV status during qualitative interviews:

> With tablets, you feel a bit of stigma in front of people. You hide… When you take tablets when there are people, you have to go in a corner to take the tablets, the pills. There is a bit of stigma. With the injection, you no longer need all this. (Male, Month 12)

Recommending CAB + RPV LA to other PWH. Almost all PSPs (95.4%, n = 356/373) "agreed" or "completely agreed" that they would recommend CAB + RPV LA to other PWH (Supplemental Figure 3). Two PSPs (0.5%, n = 2/373) from the total sample selected "disagree" or "completely disagree" at M12. In interviews, 58.2% (n = 64/110) of PSPs discussed characteristics that they felt may make CAB + RPV LA less appropriate for PWH. These included people fearing or being squeamish about injections (20.0%, n = 22/110) and people not tolerating intramuscular injections (10.9%, n = 12/110).

Scheduling and attending CAB + RPV LA appointments. When asked about how convenient the clinic's procedures for scheduling injections were, the most common response at M12 was that the clinic or practice's procedures were "extremely convenient" (46.2%, n = 175/379), followed by "very convenient" (40.6%, n = 154/379). No PSPs said that the clinic or practice's procedures were "not at all convenient." With respect to time spent in clinic, at M12, over three-quarters of PSPs (76.8%, n = 291/379) found the time spent in the clinic to be either "very" or "extremely acceptable" (Supplemental Figure 4A). Overall, PSPs at both M1 and M12 were accepting of the requirement to attend the clinic Q2M to receive CAB + RPV LA (Supplemental Figure 4B). Over half of PSPs reported that they did not need to take time off from work to attend their injection appointments at M12 (58.6%, n = 222/379). Most PSPs reported that they had not needed to seek additional care for a dependent to attend their appointment (83.9%, n = 318/379). The most common form of transportation to their appointments was by "private vehicle" (43.3%, n = 164/379), followed by public transport (36.4%, n = 138/379).

During M12 interviews, PSPs discussed having an acceptable overall experience at the clinic (74.5%, n = 82/110), with in-person communication with the HCP (69.1%, n = 76/110), calendar, diary, notes, and/or reminders for appointments (62.7%, n = 69/110) and not missing appointments and/or rescheduling (59.1%, n = 65/110) mentioned as facilitators of CAB + RPV LA. Common barriers discussed by a minority of PSPs at M12 were related to not being informed about the term "target date" (34.5%, n = 38/110), having to reschedule or miss injection appointments (20.9%, n = 23/110), issues due to work (19.1%, n = 21/110), and issues due to transportation and/or parking (12.7%, n = 14/110). Additionally, some PSPs discussed difficult components of CAB + RPV LA including "travel or holiday scheduled," which decreased from M4 (12.7%, n = 47/369) to M12 (8.9%, n = 33/369) as well as "missing work for the injection visits," which increased from M4 (9.8%, n = 36/369) to M12 (13.0%, n = 48/369). PSPs also discussed suggestions for improving appointments. While not discussed by the majority of PSPs, some suggested collecting the medication from the pharmacy prior to their injection appointment:

> I would like to be able to pick up the medication at the pharmacy before I go to the doctor. That would be easier. That is how we are doing it as of now. I already have the prescription for my next appointment now. (Female, Month 12)

Other Outcomes

Treatment satisfaction (HIVTSQs). On day 1, PSP satisfaction with their current treatment (prior daily oral ART) was high, with an overall (items 1-11) mean (SD) HIVTSQs score of 58.6 (7.01) (n = 359; maximum of 66 points). These scores had numerically improved by M12 (M1: 57.9 [7.84]; M4: 61.6 [5.05]; and M12: 61.4 [5.84]). During the OLI phase, a slight numerical decrease in total score (mean change [SD] −0.7 [6.1]; n = 359) was observed in M1 scores. With a switch to CAB + RPV LA, increases in satisfaction versus previous daily oral ART (day 1) were observed at M4 (+3.1 [7.0]; n = 359) and M12 (+2.8 [8.2]; n = 359) (Supplemental Figure 5).

Treatment preference. At M12, CAB + RPV LA was generally preferred by PSPs over previous daily oral ART; 72.6% (n = 275/379) reported that they preferred CAB + RPV LA, 0.5% (n = 2/379) preferred the daily oral ART and 26.4% (n = 100/379) selected more than one preference or reasons for a preference that did not match the preference selected. Data were missing for the remaining 2 PSPs (<1%). Among the 277 PSPs who completed the question correctly, 99.3% (n = 275/277) preferred CAB + RPV LA (Figure 4A). Reasons for this preference were mainly related to discretion, convenience, and not having to remember to take daily medication (Figure 4B).

Discussion

This phase 3b, hybrid-type III implementation–effectiveness trial was conducted in a diverse population being treated across varying healthcare settings across 5 European countries (Belgium, France, Germany, the Netherlands, and Spain). The study demonstrated that PSPs found CAB + RPV LA to be an acceptable, appropriate, and feasible treatment option. The most prominent drivers of this broad acceptability were the characteristics of CAB + RPV LA and how it complemented PSPs' daily lives, with information and communication playing an important role supporting this outcome. Qualitative data from semistructured interviews provided further context to observations from quantitative assessments. These findings are complemented by effectiveness data collected in CARISEL (reported separately), in which 87% of participants maintained virological suppression at the Month 12 Snapshot and only one PSP (0.23%, n = 1/430) met the confirmed virological failure criterion.[25]

Consistent with evaluations of the implementation of CAB + RPV LA administered monthly in US healthcare settings,[36] PSPs had a positive perception of CAB + RPV LA and found

the time spent waiting in the clinic and the frequency of visits to be highly acceptable, highlighting the potential ease of integrating the LA regimen into their lives. Although injection pain or soreness was cited as the most common concern and most difficult aspect of CAB + RPV LA by PSPs, patient-reported pain scores, as assessed by a VAS, remained low throughout the study (indicated by a median score of 3/10, as well as the most common response being 1/10). This observation is consistent with data collected during CAB + RPV LA development across all 4 phase 3/3b clinical trials,[6,7,9–12,15] demonstrating that injection site reactions were short lived (median duration of 3 days) and infrequently a cause of treatment discontinuation (<2%). The collected data are also aligned with specific patient-reported outcome analyses, which demonstrated that participants receiving CAB + RPV LA are very accepting of pain and local reactions (up to ~80% finding both "very" or "totally acceptable" in other studies).[19,20] Moreover, in the present study, almost a third of PSPs stated that they found nothing difficult about receiving CAB + RPV LA.

Both quantitative and qualitative data from CARISEL support the positive impact CAB + RPV LA can have for people experiencing psychological challenges with their current daily oral ART, a population that has been described in international surveys,[2] as well as in questionnaires and qualitative interviews carried out during CAB + RPV LA clinical development.[3,15,37] Addressing issues in HIV treatment such as stigma, adherence anxiety, and fears related to inadvertent disclosure will be important in attaining the Joint United Nations Programme on HIV/AIDS goal of ensuring that 95% of people with viral load suppression have good health-related quality of life.[38]

For data collected on barriers to and facilitators of CAB + RPV LA implementation, there was little variation between countries for the majority of the answers, and few changes in responses were observed over time. Although some barriers to implementation were noted, PSPs largely discussed facilitators in their interviews. In line with results obtained during the phase 3/3b clinical trials of CAB + RPV LA,[15,19,20] improvements in treatment satisfaction scores were observed over time. Furthermore, the majority of PSPs reported a preference for CAB + RPV LA compared with daily oral ART and would recommend the treatment to other PWH—observations that have been consistent across the clinical development program for CAB + RPV LA.[19,20]

Limitations

It should be noted that questionnaires and interviews were not captured at participant withdrawal; therefore, analyses that required participants to have data at each time point (ie, at M1, M4, and M12) do not include those participants who discontinued during the study (~12%). Furthermore, PSPs completed questionnaires relating to their previous injection, occurring 2 months prior to the assessment, which may have introduced recall bias into the data capture. It should also be noted that, as qualitative interviews were conducted by telephone, contextual cues and nonverbal data may have been lost.

Although CARISEL was designed to reflect real-world situations wherever possible, the study protocol was finalized prior to marketing approval of CAB + RPV LA. Therefore, some aspects of the study do not reflect real-world practice. Similarly, the enrolled patient population was interested in participating in research evaluating LA therapies. With respect to capturing patient-reported outcomes, the high treatment satisfaction scores at baseline may not have permitted the full magnitude of treatment effects to become apparent. It is also noteworthy that CARISEL was conducted during the COVID-19 pandemic, demonstrating that successful implementation can be achieved in challenging and unprecedented circumstances. However, subtle factors, such as decreased physical human interaction, may have impacted study outcomes.

Conclusions

Across 5 European countries, PWH participating in the CARISEL study found CAB + RPV LA to be an acceptable, appropriate, and feasible treatment option, with improvements in HIV treatment satisfaction scores observed over time. CAB + RPV LA was preferred to daily oral ART by most participants and was perceived as a less stigmatizing intervention. Qualitative data supported these observations and highlighted CAB + RPV LA as a therapeutic alternative to daily oral ART that can be readily incorporated into European clinical settings.

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Authors' Note

Contributors: All authors vouch for the accuracy and completeness of the data, data analyses, and interpretation and fidelity to the protocol. *Data Availability Statement:* Data sharing requests will be considered by the management group upon written request to the corresponding author. Deidentified participant data or other prespecified data may be available subject to a written proposal and a signed data sharing agreement.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: CAG, RM, RT, JS, MP-B, MA-K, BH, AdR, PM and MC are employees of ViiV Healthcare and may be stockholders of GSK. MvdV has received research grants and fees for participation in advisory boards from ViiV, MSD and Gilead. JP reports grants from Gilead and ViiV Healthcare and payments from lectures from Gilead and Janssen. EJ has received speaking fees or consulting activities from ViiV and Gilead laboratories and hospitality and congress registrations

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Supplemental Material

Supplemental material for this article is available online.

References

1. Altice F, Evuarherhe O, Shina S, Carter G, Beaubrun AC. Adherence to HIV treatment regimens: systematic literature review and meta-analysis. *Patient Prefer Adherence*. 2019;13:475-490. doi:10.2147/PPA.S192735
2. de Los Rios P, Okoli C, Castellanos E, et al. Physical, emotional, and psychosocial challenges associated with daily dosing of HIV medications and their impact on indicators of quality of life: findings from the positive perspectives study. *AIDS Behav*. 2021;25(3):961-972. doi:10.1007/s10461-020-03055-1
3. Mantsios A, Murray M, Karver TS, et al. Efficacy and freedom: patient experiences with the transition from daily oral to long-acting injectable antiretroviral therapy to treat HIV in the context of phase 3 trials. *AIDS Behav*. 2020;24(12):3473-3481. doi:10.1007/s10461-020-02918-x
4. Flexner C, Owen A, Siccardi M, Swindells S. Long-acting drugs and formulations for the treatment and prevention of HIV infection. *Int J Antimicrob Agents*. 2021;57(1):106220. doi:10.1016/j.ijantimicag.2020.106220
5. D'Amico R, Margolis DA. Long-acting injectable therapy: an emerging paradigm for the treatment of HIV infection. *Curr Opin HIV AIDS*. 2020;15(1):13-18. doi:10.1097/COH.0000000000000606
6. Orkin C, Arasteh K, Górgolas Hernández-Mora M, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. *N Engl J Med*. 2020;382(12):1124-1135. doi:10.1056/NEJMoa1909512
7. Orkin C, Bernal Morell E, Tan DHS, et al. Initiation of long-acting cabotegravir plus rilpivirine as direct-to-injection or with an oral lead-in in adults with HIV-1 infection: week 124 results of the open-label phase 3 FLAIR study. *Lancet HIV*. 2021;8(11):e668-e678. doi:10.1016/S2352-3018(21)00184-3
8. Orkin C, Oka S, Philibert P, et al. Long-acting cabotegravir plus rilpivirine for treatment in adults with HIV-1 infection: 96-week results of the randomised, open-label, phase 3 FLAIR study. *Lancet HIV*. 2021;8(4):e185-e196. doi:10.1016/S2352-3018(20)30340-4
9. Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. *N Engl J Med*. 2020;382(12):1112-1123. doi:10.1056/NEJMoa1904398
10. Swindells S, Lutz T, Van Zyl L, et al. Week 96 extension results of a phase 3 study evaluating long-acting cabotegravir with rilpivirine for HIV-1 treatment. *AIDS*. 2022;36(2):185-194. doi:10.1097/QAD.0000000000003025
11. Overton ET, Richmond G, Rizzardini G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2 M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet*. 2020;396(10267):1994-2005. doi:10.1016/S0140-6736(20)32666-0
12. Jaeger H, Overton ET, Richmond G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2 M), 96-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet HIV*. 2021;8(11):e679-e689. doi:10.1016/S2352-3018(21)00185-5
13. Saag MS, Gandhi RT, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the international antiviral society-USA panel. *JAMA*. 2020;324(16):1651-1669. doi:10.1001/jama.2020.17025
14. U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Accessed March 2023. https://clinicalinfo.hiv.gov/en/guidelines.
15. Ramgopal MN, Castagna A, Cazanave C, et al. Efficacy, safety, and tolerability of switching to long-acting cabotegravir plus rilpivirine versus continuing fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed adults with HIV, 12-month results (SOLAR): a randomised, open-label, phase 3b, non-inferiority trial. *Lancet HIV*. 2023;10(9):e566-e577.
16. European Medicines Agency. Vocabria Product Information. Accessed November 2022. https://www.ema.europa.eu/en/documents/product-information/vocabria-epar-product-information_en.pdf
17. ViiV Healthcare. Cabenuva PI. 2024. Accessed January 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/212888s005s006lbl.pdf
18. European AIDS Clinical Society. Guidelines Version 11.1 October 2022. Accessed November 2023. https://www.eacsociety.org/media/guidelines-11.1_final_09-10.pdf
19. Chounta V, Overton ET, Mills A, et al. Patient-Reported outcomes through 1 year of an HIV-1 clinical trial evaluating long-acting cabotegravir and rilpivirine administered every 4 or 8 weeks (ATLAS-2 M). *Patient*. 2021;14(6):849-862. doi:10.1007/s40271-021-00524-0
20. Murray M, Antela A, Mills A, et al. Patient-reported outcomes in ATLAS and FLAIR participants on long-acting regimens of cabotegravir and rilpivirine over 48 weeks. *AIDS Behav*. 2020;24(12):3533-3544. doi:10.1007/s10461-020-02929-8
21. Hickey MD, Grochowski J, Mayorga-Munoz F, et al. Identifying implementation determinants and strategies for long-acting injectable cabotegravir-rilpivirine in people with hiv who are virally unsuppressed. *J Acquir Immune Defic Syndr*. 2024;96(3):280-289. doi:10.1097/QAI.0000000000003421

22. Havlir D, Gandhi M. Implementation challenges for long-acting antivirals as treatment. *Curr Opin HIV AIDS*. 2015;10(4):282-289. doi:10.1097/coh.0000000000000158
23. Czarnogorski M, Garris CP, Dalessandro M, et al. Perspectives of healthcare providers on implementation of long-acting cabotegravir plus rilpivirine in US healthcare settings from a hybrid III implementation-effectiveness study (CUSTOMIZE). *J Int AIDS Soc*. 2022;25(9):e26003. doi:10.1002/jia2.26003
24. Gutner CA, Hocqueloux L, Jonsson-Oldenbüttel C, et al. Implementation of long-acting cabotegravir and rilpivirine: primary results from the perspective of staff study participants in the cabotegravir and rilpivirine implementation study in European Locations. *J Int AIDS Soc*. 2024;27(7):e26243. doi:10.1002/jia2.26243.
25. Jonsson-Oldenbüttel C, Ghosn J, van der Valk, M, et al. Safety and effectiveness from the cabotegravir and rilpivirine implementation study in European locations study: phase 3b hybrid type III implementation study integrating cabotegravir + rilpivirine long-acting into European clinical settings. *J Acquir Immune Defic Syndr*. 2024;96(5):472-480. doi:10.1097/QAI.0000000000003448.
26. Curran GM, Landes SJ, McBain SA, et al. Reflections on 10 years of effectiveness-implementation hybrid studies. Perspective. *Front Health Serv*. 2022;2. doi:10.3389/frhs.2022.1053496
27. Gutner C. Use of the FRAME-IS to Collect Provider Implementation Strategy Modifications in a Hybrid III Trial: Cabotegravir and Rilpivirine Implementation Study in European Locations (CARISEL). Presented at: Annual Conference on the Science of Dissemination and Implementation in Health; December 14-16, 2021; 2021; Virtual.
28. European Medicines Agency. Rekambys product information. Accessed November 2022. https://www.ema.europa.eu/en/documents/product-information/rekambys-epar-product-information_en.pdf
29. ViiV Healthcare. Vocabria Summary of Product Characteristics. *EU*. 2021.
30. Wensing AM, Calvez V, Ceccherini-Silberstein F, et al. 2019 Update of the drug resistance mutations in HIV-1. *Top Antivir Med*. 2019;27(3):111-121.
31. Weiner BJ, Lewis CC, Stanick C, et al. Psychometric assessment of three newly developed implementation outcome measures. *Implement Sci*. 2017;12(1):108. doi:10.1186/s13012-017-0635-3
32. Romaine J, Murray M, Bradley C. Psychometric evaluation of the revised HIV Treatment Satisfaction Questionnaire (HIVTSQ). *Value Health.* 2016;19(7):A420. doi:10.1016/j.jval.2016.09.426
33. Moullin JC, Dickson KS, Stadnick NA, Rabin B, Aarons GA. Systematic review of the Exploration, Preparation, Implementation, Sustainment (EPIS) framework. *Implement Sci*. 2019;14(1):1. doi:10.1186/s13012-018-0842-6
34. Proctor E, Silmere H, Raghavan R, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. *Adm Policy Ment Health*. 2011;38(2):65-76. doi:10.1007/s10488-010-0319-7
35. Ahmed SK. The pillars of trustworthiness in qualitative research. *J Med Surg Public Health*. 2024;2:100051. https://doi.org/10.1016/j.glmedi.2024.100051
36. Garris CP, Czarnogorski M, Dalessandro M, et al. Perspectives of people living with HIV-1 on implementation of long-acting cabotegravir plus rilpivirine in US healthcare settings: results from the CUSTOMIZE hybrid III implementation-effectiveness study. *J Int AIDS Soc*. 2022;25(9):e26006. doi:10.1002/jia2.26006
37. Mantsios A, Murray M, Karver TS, et al. "I feel empowered": women's perspectives on and experiences with long-acting injectable antiretroviral therapy in the USA and Spain. *Cult Health Sex.* 2021;23(8):1066-1078. doi:10.1080/13691058.2020.1752397
38. Bessong PO, Mavhandu-Ramarumo LG. Moving towards the global HIV 95% viral suppression target. *Lancet HIV*. 2021;8(12):e731-e732. doi:10.1016/S2352-3018(21)00273-3