Received: 21 March 2024 | Accepted: 17 May 2024

DOI: 10.1111/hiv.13679

ORIGINAL ARTICLE

Multicentre service evaluation of injectable cabotegravir and rilpivirine delivery and outcomes across 12 UK clinics (SHARE LAI-net)

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Abstract

Introduction: Long-acting injectable cabotegravir + rilpivirine (CAB + RPV LAI) was approved for use in virally suppressed adults in the England and Wales national health service in November 2021. We describe a service evaluation of delivery processes and outcomes in 12 clinics.

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Methods: Centres populated a database using information from local policies and clinical records. Services were asked to describe approval processes, clinic pathways, and adherence to national guidelines. Additional data were collected on reasons for regimen choice, treatment discontinuations, and management of viraemia.

Results: In total, 518 adults from 12 clinics were approved for CAB + RPV LAI between February 2022 and December 2023. Of the 518 people approved for CAB + RPV LAI, 423 received at least one injection. Median duration on CAB + RPV was 7.5 months (interquartile range 3.7–11.3). In total, 97% of injections were administered within the ±7-day window. Virological failure occurred in 0.7%, and 6% discontinued CAB + RPV.

Conclusion: In this large UK-based cohort, robust approval processes and clinic protocols facilitated on-time injections and low rates of both discontinuation and virological failure.

KEYWORDS

Cabotegravir, capacity, discontinuation, effectiveness, HIV, long-acting injectable, real-world evidence, Rilpivirine, Virologic suppression

INTRODUCTION

Cabotegravir and rilpivirine (CAB + RPV) is the first complete long-acting injectable (LAI) treatment and has been approved for 2-monthly use in Europe and the UK as a switch option for virally suppressed people living with HIV-1 infection [1]. In the UK, HIV care is free at the point of delivery and mostly co-delivered as integrated care together with sexual health services within outpatient clinics. CAB + RPV was approved for use in the England and Wales national health service (NHS) in November 2021 based on its efficacy, safety, favourable treatment satisfaction, and a cost-effectiveness analysis performed by the National Institute for Health and Care Excellence (NICE) [2–9]. NICE modelling of cost effectiveness was based on assumptions about the seniority of staff needed to deliver injectables and appointment duration with no extra funding allocated to cover these costs. The assessment was that a junior-level (band 5) nurse would be able to deliver the injectable within a 15-min appointment [9].

CAB + RPV LAI was preferred by over 90% of trial participants across four randomized controlled trials (RCTs) [2–8, 10]. Improved treatment satisfaction compared with daily oral therapy has been consistently demonstrated using validated patient-reported outcome measures such as the HIV Treatment Satisfaction Questionnaire [10, 11]. The benefit has been shown to be most pronounced in people experiencing psycho-social or treatment challenges with daily oral therapy, including internalized and interpersonal stigma, inconvenience, adherence difficulties, swallowing difficulties, and pill fatigue [10, 11].

At 48 weeks, virological efficacy in RCTs ranges between 90% and 94.3%, and CAB + RPV LAI has been consistently non-inferior to the oral comparator with and without the use of an oral lead in (OLI) [2–8, 10]. However, it is also clear that CAB + RPV LAI demonstrates a lower genetic barrier to resistance than most second-generation integrase inhibitor-based oral regimens [12, 13]. In the context of suppressed switch, virological failure (VF) is uncommon, and the small number of cases of VF in the RCTs were all in people with on-time injections. Although VF is a rare event (<2%), most people who experience VF will accumulate one or two class resistance, thereby reducing future options [4, 8]. Consequently, a multivariable analysis including participants who received CAB + RPV LAI over 152 weeks found that the presence of at least two of three baseline factors (pre-existing RPV resistance-associated mutations, A6 subtype, and body mass index > 30 kg m^{-2}) was associated with VF [14]. A predictive model was developed to guide clinicians based on the relative weighting of each associated factor with confirmed VF (CVF). The model identified that the presence of two or more baseline factors is associated with a 19.3% risk of CVF [14]. Based on the summary of product characteristics (SmPC) licence and the findings of the multivariable analysis, the British HIV Association (BHIVA) guidelines have taken a more restrictive position than the European Medicines Agency (EMA) licence and the SmPC label and have added

various good practice suggestions such as ensuring an individual has an undetectable viral load (VL) for at least 6 months before starting, no history of unplanned treatment interruption on a non-nucleoside reverse transcriptase inhibitor (NNRTI) or integrase strand transfer inhibitor (INSTI)-containing regimen, no history of INSTI monotherapy, a mandatory OLI, and 2-monthly VL monitoring [1, 15, 16]. The guidelines also predict concerns about the capacity of services to accommodate the additional work and steer clinicians to focus on those with the greatest psychological need or who are unable to take oral medication [15].

We performed a service evaluation to assess CAB + RPV processes and pathways, adherence to national guidelines, and management of viraemia in 12 UK HIV clinics.

METHODS

Ethical and data considerations

Clinical researchers within the London-based Sexual Health and HIV All East Research (SHARE) Collaborative contacted peers through informal clinical and research networks to form a clinical collaborative network (SHARE LAI-net) with the aim of describing a real-world cohort within the NHS system. The SHARE LAI-net real-world cohort consists of a convenience sample from 12 participating NHS clinics across two nations in the UK. Data were retrospectively captured from routinely collected clinical data from electronic health records. Service evaluations fall outside of the research ethics system, but use of patient data does involve ethical considerations. The research team ensured that all data were managed according to Caldicott principles and, on review, felt that the benefits of the evaluation outweighed any risks to patients [17]. To further ensure that we were not overlooking any ethical issues, the research team reached out to the Health Research Authority for guidance and received confirmation that our use of data at a service level did not require any additional approvals beyond local registration. Service evaluations were registered at each participating centre with respective clinical-effectiveness teams and approved by clinical governance leads. Reporting of demographic data and outcomes is aggregated to prevent identifiability at smaller centres.

Cohort-specific data

We retrospectively reviewed electronic patient records for adults approved by a multidisciplinary team (MDT) for CAB + RPV LAI at each hospital between February 2022 and December 2023. We describe individual characteristics (demographics, prior antiretroviral therapy [ART] regimen, number of comorbidities, and concomitant medications) and reason for referral (multiple reasons could be selected). Approval processes were evaluated against SmPC licence criteria, local screening criteria, and BHIVA guidelines. We summarized clinical processes such as use of OLI, time from MDT approval to starting CAB + RPV, VL monitoring, and processes for management of viraemia. We summarized outcomes, including adherence to the 7-day window for injection receipt, and reasons for discontinuation. We described the frequency of viraemia and subsequent clinical management. Viraemia was categorized into either viral blips (single VL 50–200 c/mL preceded and followed by VL <50 c/mL), confirmed viraemia (two or more consecutive VL >50 c/mL), or VF (two consecutive HIV VL ≥200 c/mL). Individuals who received CAB + RPV before UK licensing (i.e. on compassionate use) were not included. Descriptive statistics were used to summarize data with median and range or interquartile range (IQR) where appropriate. Therapeutic drug monitoring was not performed, and pharmacokinetic data were not evaluated as this is not part of routine clinical care.

Clinic-specific data

Each clinic was provided with a de-identified structured case-report spreadsheet that included drop-down menus and free-text fields. The case-report spreadsheet routinely collected clinical data only and was not based on a research protocol. Variables of interest were focused on clinical outcomes, approval processes (criteria used for screening, frequency of approval meetings), and clinical care delivery logistics (e.g. recall systems, management of abnormal results, staff capacity, appointment duration, and number of people seen per injectable clinic).

RESULTS

Cohort characteristics

In our analysis, 518 people were approved to receive CAB + RPV. Of these, 365 (71%) were cisgender men, 150 (29%) were cisgender women, and three (0.6%) were transgender women. In total, 252 (48%) were White and 206 (40%) were heterosexual. Median age was 46 years (IQR 37–54) (Table 1). Of the 518 participants, 433 (84%) have commenced CAB + RPV to date; 37 people approved for treatment went on to decline CAB + RPV

TABLE 1 Baseline characteristics.

Total number of people approved for CAB + RPV LAI	$N = 518$
Age (years)	518 (100%)
Median (IQR)	46 (37–54)
Race and ethnicity	518 (100%)
White	252 (48.6)
Black or Black British	190 (36.6)
Asian or Asian British	35 (6.7)
Mixed	12 (2.3)
Other ethnic groups	26 (5.0)
Not recorded	3 (0.6)
Gender	518 (100%)
Cisgender men	365 (70.5)
Cisgender women	150 (28.9)
Non-binary people	0 (0.0)
Transgender women	3 (0.6)
Transgender men	0 (0.0)
Sexuality	518 (100%)
Homosexual	292 (56.4)
Heterosexual	206 (39.8)
Bisexual	12 (2.3)
Not stated	7 (1.4)
Other	1 (0.2)
ART regimen before switch	518 (100%)
Three-drug regimen	433 (83.6)
Backbone	
TDF-based	186 (42.9)
TAF-based	149 (34.4)
ABC-based	98 (22.6)
Third agent	
First-generation INSTI	63 (14.5)
Second-generation INSTI	161 (37.1)
Non-RPV NNRTI	92 (21.2)
RPV	62 (14.3)
PI-based	55 (12.7)
Two-drug regimen	79 (15.3)
DTG/3TC	67 (84.8)
DTG/RPV	10 (12.6)
PI-based	2 (2.5)
Non-standard regimen	6 (1.2)
PI monotherapy	3 (50.0)
Other	2 (33.3)
ART naïve	1 (16.7)
Proportion with comorbidities	242 (46.7%)
Number of comorbidities	
1	96 (39.7)
2	59 (24.4)
3	41 (16.9)
4	17 (7.0)
5	11 (4.6)
>5	18 (7.4)
Proportion on concomitant medications	153 (29.5%)
Number of drugs	
1	42 (27.5)
2	31 (20.3)
3	26 (17.0)
4	9 (6.0)
5	6 (4.0)
>5	39 (25.5)

Abbreviations: 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; CAB, cabotegravir; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; LAI, long-acting injectable; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil.

LAI at the initial treatment visit, and 48 are yet to start for reasons such as clinic capacity, concurrent clinical issues, or individual preference. Regarding current treatment, 84% switched from a three-drug regimen, 87% of whom were on either an NNRTI or an INSTI as their third agent (Table 1). According to healthcare providers, the commonest reasons for referral were inconvenience of oral medication (82%), followed by HIV stigma (31%) and fear of disclosure (27%) (Figure 1). A total of 153 (30%) people were taking concomitant medication and 242 (47%) had at least one other comorbidity (see Table 1). Most (92%) people met EMA licensing criteria, and 74% met both EMA licensing criteria and 2022 BHIVA guidance. The majority (78%) had no factors predictive of VF, 106 people (21%) had one baseline risk factor for failure, and six (1%) had two factors; none had all three factors.

Treatment and monitoring

A total of 433 individuals received at least one dose of CAB + RPV, 423 of whom received at least one injection of CAB + RPV LAI, six discontinued during OLI,

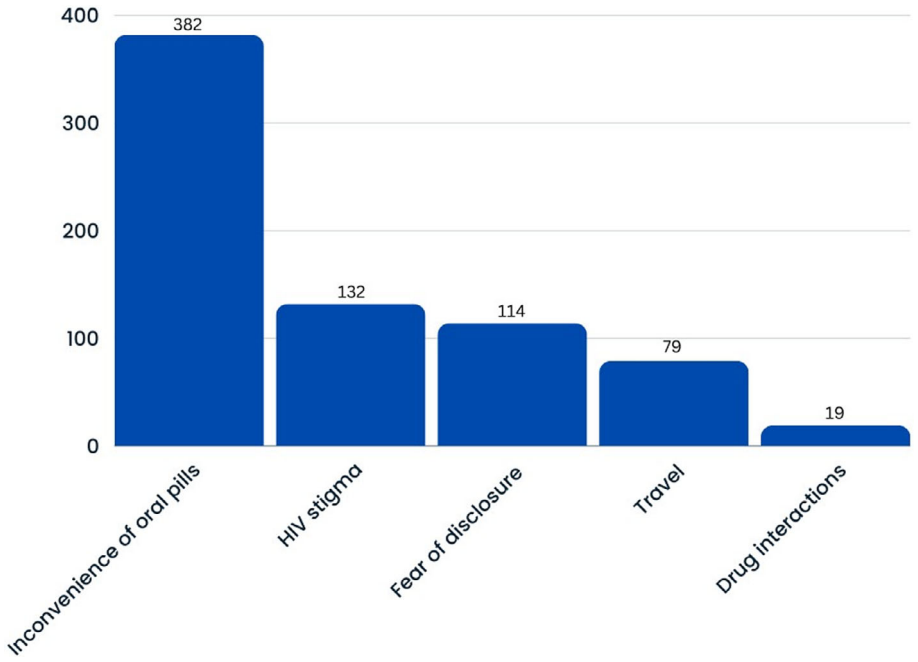

FIGURE 1 Reason for switch according to healthcare professional.

and four were receiving OLI at the time of analysis. OLI was used in 74% of individuals. Median time from approval to the first CAB + RPV LAI planning appointment was 23 days (IQR 5–61) and to the date of start of CAB + RPV was 35 days (IQR 14–78). The median time on CAB + RPV LAI to date is 7.5 months (IQR 3.7–11.3), and 97% (2072 of 2133) of injections were received within the 7-day window. Oral bridging was used on 16 occasions. HIV VL was monitored at 96% (2038/2133) of injection visits as per BHIVA guidelines, which are based on the VL monitoring frequency in registrational RCTs.

Clinic processes

Criteria for approval of CAB + RPV LAI differed between clinics, although all clinics used an MDT meeting to make decisions. (Table 2). Appointment durations ranged from 30 to 60 min, and injections were provided by senior nurses (band 6 and above) or pharmacists at all clinics. One HIV service delivered CAB + RPV LAI via their hospital's outpatient antimicrobial therapy service. A range of systems were used to remind people of upcoming appointments, including text messages or mobile phone app push notifications, and telephone calls. Most services had standardized processes to manage detectable VL and safety bloods, although these differed between clinics.

Discontinuations and management of viraemia

Of the 423 people who received CAB + RPV LAI, 25 (6%) discontinued, three of whom (0.7%) experienced confirmed CVF (Table 3). Of those with CVF, one developed resistance to NNRTIs, and all three were switched to three-drug oral therapy: one each on INSTI-, NNRTI-, and protease inhibitor-based ART. All achieved viral suppression on subsequent regimens. The main reasons for discontinuation were injection-site reactions (16%) or other side effects (32%) (Figure 2). One individual became pregnant following their third injection; they were switched back to oral ART (dolutegravir/emtricitabine/abacavir) and maintained an undetectable VL throughout the pregnancy. The baby was delivered at 39/40 weeks with a normal birthweight and no birth defects reported. There were 24 blip events in 21 people, of whom 19 continued CAB + RPV LAI and remained virally suppressed. Three people experienced two blips, one of whom subsequently experienced VF. One person switched treatment following two consecutive VLs 50–200 c/mL (i.e. low-level viraemia).

DISCUSSION

Women, racially minoritised people, and older people are historically underrepresented in HIV treatment trials, resulting in cohorts that are not equitably representative

TABLE 2 Clinic processes.

Clinic number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Participants (N)	**9**	**106**	**34**	**38**	**40**	**65**	**20**	**26**	**126**	**37**	**10**	**7**
Screening tool criteria												
EMA licensing criteria												
HIV-1 RNA < 50c/mL	X	X	X	X	X	X	X	X	X	X	X	X
NNRTI/INSTI resistance	X	X	X	X	X	X	X	X	X	X	X	X
VF on NNRTI/INSTI	X	X	X	X	X	X	X	X	X	X	X	X
HBsAg	X	X	X	X	X	X	X	X	X	X	X	X
Additional BHIVA criteria												
Likelihood to attend	X	X					X		X	X		X
BMI <30 kg/m^2	X	X				X	X	X	X	X		X
Non-A1/6 subtype	X	X				X	X	X	X	X		X
Other criteria												
Hep B immunity					X	X	X		X			
Pregnancy risk					X		X		X			X
Psychological issues					X							
MDT[a]												
MDT approval required?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Frequency of meeting	1×/wk	2 × /mo	2 ×/wk	2 ×/mo	1 ×/mo	1 ×/wk	1 ×/wk	3 ×/mo	1 ×/mo	1 ×/mo	1 ×/wk	2 ×/mo
SOP[b] in place?	Yes	Yes	Yes	Yes	Yes	Draft	Draft	Yes	Yes	Yes	Draft	Draft
Appointment reminder system?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Method of reminder	2 × SMS	2 × SMS	Call + 2 × SMS	Email or SMS	NA	Mobile app	SMS	SMS	Call + SMS	SMS	SMS	SMS
Abnormal results system	Nurse + clinic recall system	Nurse B6/7[c] + consultant	MDT review	Consultant	Pharmacist	Clinic recall system	Nurse B7/8 recall	Nurse B7 recall	Nurse B6/7 recall	Consultant	Consultant	Nurse B7/8 + consultant
Staff delivering LAI	Nurse B6/7	Nurse B5/6/7/8	Nurse B7	Nurse B6/7	Nurse B6	Nurse B6/7	Nurse B6/7/8	Nurse B7/8a	Nurse B6/7/8	Nurse B6/7	Nurse B5/6 + pharmacist	Nurse B6/7/8
Appointment length (min)	30	30	30	40	30	30	45	45–60	40	30	45–60	30

TABLE 2 (Continued)

Clinic number	1	2	3	4	5	6	7	8	9	10	11	12
Participants (N)	9	106	34	38	40	65	20	26	126	37	10	7
No. of patients/ session	2–4	2–4	3–6	4	N/a OPAT	4–13	4	4	5–9	6	2–3	6

Abbreviations: BHIVA, British HIV Association; BMI, body mass index; EMA, European Medicines Agency; HBsAg, hepatitis B surface antigen; INSTI, integrase strand transfer inhibitors ; LAI, long-acting injectable; MDT, multidisciplinary team; mo, month; NA, not applicable; NNRTI, non-nucleoside reverse transcriptase inhibitor ; SMS, short message service (text); SOP, standard operating procedure; VF, virological failure; wk, week

[a]An MDT is a group of healthcare staff with different professions (e.g. doctors, nurses, pharmacists) who work together to make decisions regarding the treatment of individual patients.

[b]An SOP is a set of written instructions describing the step-by-step process by which the LAI medications are stored, delivered, and administered and providing detail on patient monitoring and management of missed doses.

[c]Nurses are placed in pay-scale bands based on experience and seniority. Band 5: newly qualified or staff nurse. Band 6: senior nurse or nursing specialist. Band 7: advanced nurse or nurse practitioner. Band 8: modern matron, chief or head nurse.

of all people who might receive the most benefit from CAB + RPV LAI medication [18]. A scoping review of real-world cohorts and implementation studies of CAB + RPV LAI has so far highlighted that females were underrepresented relative to the country prevalence of females living with HIV in ~80% of studies [19]. In 2022, 35.3% of people living with HIV and accessing care in the UK were Black, 31.7% were women, and 49.8% were aged >50 years [20]. The UK-based implementation science study of CAB + RPV LAI (ILANA), which enrolled at the same time as the SHARE LAI-net cohort, was based in hospital and community settings and sought to redress inequitable inclusion in clinical trials through an intentionally anti-sexist, anti-racist, and anti-ageist protocol design [21]. Sites were intentionally selected based on agreement to adhere to recruitment targets, and recruitment caps were enforced to deliver the enrolment of at least 50% women, 50% people from racially minoritised backgrounds, and 30% people aged >50 years. The study exceeded its inclusive recruitment targets and enrolled 53% female, 51% Black, and 40% people aged >50 years within the projected recruitment period [22].

In the absence of an intentional approach to inclusion, the SHARE LAI-net real-world cohort comprised a lower proportion of cisgender women (29%) and Black people (36.6%) than were included in the ILANA study. However, encouragingly, the cohort is broadly representative of the UK epidemic with respect to race, ethnicity, and gender, suggesting that clinicians offered the therapy more equitably than in countries such as France, Germany, Canada, and the USA [19]. However, only 35% of our cohort were aged >50 years, which is lower than the UK demographic; this may reflect more treatment experience, and hence a greater likelihood of contraindications to CAB + RPV, in older people. Also of note, a higher proportion of this cohort were gay or bisexual men who have sex with men compared with overall UK figures (58% vs. 47%) [20]; this may reflect underrecruitment of other groups or variations in demographics of the populations attending the recruiting sites.

Participants receiving oral ART in CAB + RPV LAI phase III drug trials and in implementation science studies have reported psychosocial challenges at baseline, including fear of disclosure, adherence anxiety, and the daily reminder of HIV [10, 13]. HIV stigma and fear of disclosure are frequently recorded as reasons for switch in our cohort; however, inconvenience of oral ART is cited most commonly (82%). This suggests that many UK clinicians recognize the broader benefit of injectable therapy and prescribed the drug outside of the restrictive BHIVA recommendations that people with psychological need should be prioritized for CAB + RPV. This is also evidenced by the fact that, although 92% of people

approved for CAB + RPV LAI met the EMA criteria, only 74% met the BHIVA guidance for approval.

Considering outcomes, the VF rate of 0.7% at 7.5 months conforms to that of other recently described real-world cohorts with >500 participants [23–25]. Blips were infrequent, and all people with VF re-suppressed on oral ART. Discontinuation rates were low at 6%, suggesting high levels of persistence. Most discontinuations were related to treatment side effects. Notably, there were withdrawals during the OLI, emphasizing its utility in allowing participants to experience adverse events with an oral preparation.

Our evaluation of clinic processes found that the seniority of nurse that delivered CAB + RPV LAI differed markedly from what was modelled within the NHS cost-effectiveness assessment. Junior nurses (band 5) delivered injectable therapy at only 2 of 12 services and in both cases were supported by more senior nurses (band 6+) or pharmacists. We also found that appointment times ranged from 30 to 60 min. Both findings suggest a complexity that far exceeds the cost-effectiveness assessment performed by NICE, which was modelled on appointments of 15 min delivered by a band 5 nurse. Capacity was mentioned as an issue in both large and small centres, highlighting a

TABLE 3 Summary of virological failure events.

Individual details	Prescribed in accordance with EMA licence?	Baseline risk factors for VF?[a]	OLI?	Timing and VL (c/mL) at time of VF	Viral blips (c/mL) on CAB + RPV	Resistance at VF	Subsequent ART regimen	Suppressed post-switch?
45 Black woman	Yes	No	Yes	Injection 4 (5 months) VL 75 Repeat 278, then 479	None	None	Bictegravir/ emtricitabine/ tenofovir alafenamide	Yes
63 White man	Yes	BMI 40 kg/m^2	Yes	Injection 3 (3 months) VL 437 Repeat 271	None	None	Doravirine/ lamivudine/ tenofovir disoproxil	Yes
40 White man	Yes	No	Yes	Injection 7 (11 months) VL 109000 Repeat 15 300	Yes, at injection 1 (VL 64) and injection 5 (VL 194)	NNRTI RAM (K101E)	Darunavir/ cobicistat/ emtricitabine/ tenofovir alafenamide	Yes

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CAB, cabotegravir; EMA, European Medicines Agency; OLI, oral lead-in; RAM, resistance-associated mutation; RPV, rilpivirine; VF, virological failure; VL, viral load.
[a]BMI > 30 kg/m^2, Clade A6, RPV RAMs.

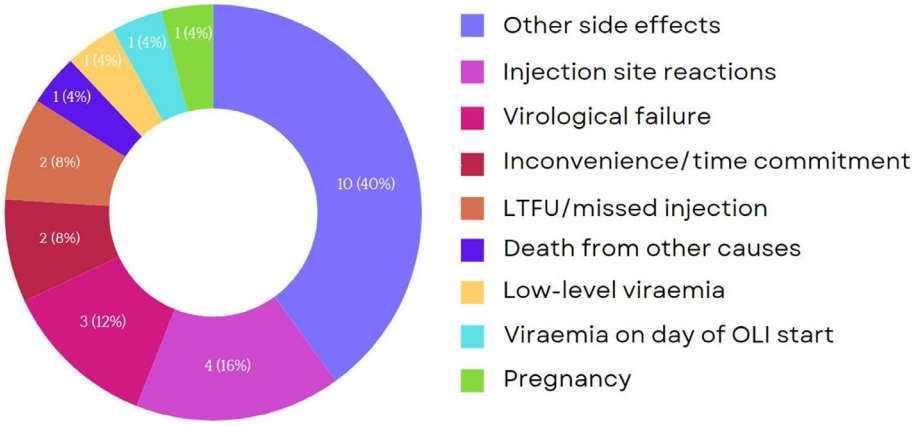

FIGURE 2 Reason for discontinuation of long-acting injectable cabotegravir + rilpivirine. LTFU = loss to follow-up; OLI = oral lead-in.

need for further resource within the NHS to ensure equitable access to this new mode of treatment.

As recommended in the BHIVA guidance, all clinics have developed standard operating procedure documents to govern the storage and administration of CAB + RPV LAI; however, the inclusion of sections on management of missed appointments and abnormal results varied. Despite this, all clinics have robust systems for appointment reminders and recall following abnormal blood results, resulting in 97% of injections being received within the 7-day window and all detectable VLs being repeated in line with local protocol. Clinics also conformed to 2-monthly HIV VL monitoring, as recommended in BHIVA guidelines.

The time from MDT approval to start of CAB + RPV was 35 days but with a wide range (IQR 14–78). There were various reasons for this, including clinical issues, patient preference, or the decision to avoid wastage and to complete current ART supplies before switching.

Several limitations are important to highlight in our study. We employed convenience sampling and, although we have relatively large numbers, our cohort is not representative of all four nations of the UK. We have a relatively short duration of follow-up, including many patients who have only recently been initiated on CAB + RPV, which could lead to an underestimation of both discontinuation and VF rates in the longer term. The reasons for switching to CAB + RPV were reported by healthcare professionals according to patient notes and may not accurately reflect the patient perspective. Future steps to improve speed of delivery could include coordination with BHIVA to gather information on nurse perspectives regarding challenges of delivery.

We describe excellent clinical outcomes using carefully designed local pathways and protocols in the largest and only real-world cohort of people on CAB + RPV LAI in England and Wales. Clear differences between the time and seniority of staff needed to deliver CAB + RPV LAI within the NHS system indicates that further funding for HIV and sexual health services is needed to maximize the potential opportunities of injectable therapy in the UK.

AUTHOR CONTRIBUTIONS

KR, CO, MoS and LO conceptualised and designed the service evaluation. KR, MeS and CO analysed the results. KR, LO, NEM, SA, TJB, JA, FF, DC, EH, BH, WB, AA, SD, GW, EC, FC, BA, GQ, MB, RB, NN, SL, AU, BT, DB, CM, JF and LW contributed data to the project. KR, CO, MeS drafted the manuscript. All authors reviewed the manuscript and approved it for publication, we thank LW for the careful review of the BHIVA guideline discussion.

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How to cite this article: Ring K, Smuk M, Shongwe M, et al. Multicentre service evaluation of injectable cabotegravir and rilpivirine delivery and outcomes across 12 UK clinics (SHARE LAI-net). *HIV Med*. 2024;1-10. doi:10.1111/hiv.13679