

Switching to long-acting cabotegravir/rilpivirine: data from an Italian monocentric cohort

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Abstract

Background: Cabotegravir/Rilpivirine (CAB/RPV) is the first long-acting injectable (LAI) antiretroviral therapy approved for virologically suppressed adults with HIV-1.

Setting: Italian single centre cohort.

Methods: We conducted a retrospective observational study to assess the durability, adherence to the prescribed injection schedule, and reasons for discontinuation of CAB/RPV LAI administered every 8 weeks (Q8W).

Results: One hundred and thirty-eight patients were included with a median observation period of 43 weeks (IQR 34-47). Of these, 32 (23.2%) were female, and the median age was 51 years old (IQR 40-58). Twelve patients (8.7%) discontinued CAB/RPV LAI treatment with a median time to

discontinuation of 21 weeks (IQR 12-35). 92.8% of the injections occurred within the CAB/RPV LAI schedule. The most common reason for discontinuation was injection-related pain (5/12). No confirmed virological failure occurred during the period of observation with 3 individuals who experienced virological blips.

Conclusions: Our findings showed that CAB/RPV LAI Q8W is well-tolerated in clinical practice, with high adherence to the injection schedule and few discontinuations mainly related to injection site related pain.

Keywords:

Adherence

Long-acting Antiretroviral therapy

Cabotegravir

Discontinuation

HIV

Rilpivirine

1.0 Introduction

The continuous evolution of antiretroviral therapies (ART) has significantly changed the landscape of HIV treatment, offering improved efficacy, tolerability, and adherence. However, despite these advancements, long-term adherence to daily oral therapy remains challenging for people with HIV (PWH)¹. Recent years have seen a significant breakthrough with the introduction of long-acting injectable (LAI) regimens, offering an alternative to the conventional daily oral treatment

approach². Cabotegravir/Rilpivirine (CAB/RPV) is the first LAI antiretroviral therapy approved for virologically suppressed people with HIV-1³. This innovative approach marks a crucial step forward in addressing adherence issues and enhancing the overall efficacy of HIV treatment strategies.

Clinical trials, including LATTE-2⁴, ATLAS, and FLAIR⁵, have substantiated the efficacy and safety of CAB/RPV LAI administered every four weeks (Q4W). Furthermore, findings from the ATLAS-2M trial demonstrate that administering CAB/RPV LAI every eight weeks (Q8W) maintains non-inferiority compared to the Q4W schedule⁶.

While clinical trials provide essential information regarding the safety and efficacy of medical interventions, real-life scenarios introduce a variety of factors that can significantly impact patient adherence and, consequently, treatment outcomes.

Observational studies in real-world settings have corroborated the pharmacokinetic profiles and virological outcomes observed in clinical trials^{7,8}. Moreover, adherence to CAB/RPV LAI, both Q4W and Q8W, has shown promising results in these studies, with low rates of injection delays and regimen discontinuations noted^{8,9}. Despite these positive findings, real-life studies specifically focusing on the Q8W schedule are underrepresented. Additionally, these studies have observed that adverse events associated with CAB/RPV LAI are generally contained, with the most common being injection site-related pain, which rarely leads to discontinuation of the regimen^{9,10}.

Thus, there remains a need for further investigation, particularly focusing on the Q8W dosing schedule in routine clinical practice.

In this context, our study aims to assess the durability, adherence to the prescribed injection schedule, and reasons for discontinuation of CAB/RPV LAI Q8W in a single centre cohort of PWH in Italy.

2.0 Methods

2.1 Study design and setting

This is a retrospective observational study conducted at a third-level centre (Department of Infectious Diseases, ASST Fatebenefratelli Sacco, in Milan, Italy).

We included consecutive PWH who (i) switched to CAB/RPV LAI, (ii) started the LAI regimen between 1st November 2022 and 30th April 2023, and (iii) had a viral load (VL) <50 copies per mL (cp/mL) for at least 6 months before the switch. We followed the included patients until 31st December 2023 (end of study period). The switch to CAB/RPV LAI was pro-active and patient driven at our center in the absence of a documented previous regimen related toxicity. During the initial three months of the study, two physicians assessed eligibility by reviewing patient records. Subsequently, clinicians referred eligible patients directly to CAB/RPV LAI. Eligibility was determined based on comprehensive medical history review, assessment of genotype and virological failure, evaluation of previous antiretroviral therapy exposure, consideration of potential drug interactions, assessment of hepatitis B serostatus, confirmed undetectable viral load at baseline, no prior virological failure to cabotegravir or rilpivirine. For the purposes of this study, baseline (BL) is defined as the date of the first intramuscular injection of CAB/RPV, following any oral lead-in phase if applicable.

Following the commercial availability of this new treatment option, our center implemented a novel approach by establishing a nursing clinic adjacent to the medical clinics. Patients are referred by their HIV physician to the nursing clinic for injections, allowing for concurrent blood samples and follow-up visits. This approach aims to reduce hospital visits to six-per-year for clinically and virologically stable patients. Injections are scheduled in advance for a six-month period, and the nursing clinic staff provides the patient list.

All PWH with stable virological control who switched to CAB/RPV LAI followed an 8 week schedule. Eligible patients were given the opportunity to choose to switch to injectable treatment. Virological failure was defined as VL >50 cp/mL in two consecutive measurements taken four weeks apart or VL>1000 cp/mL in a single measurement, while virological blip as VL >50 and <1000 cp/mL in a single measurement followed by measurements less than 50 cp/mL without any change in treatment¹¹.

2.2 Data collection

Data were collected through manual review of clinical records. Baseline data were comprehensively collected, encompassing demographic and physiological characteristics, medical history, and details of any concomitant medical conditions or therapies including previous ART regimens and oral lead in. VL was performed at 4 weeks after the start of therapy and, since patients already had a VL<50 cp/mL at baseline, at 24 and 48 weeks after the first injection. If VL > 50 cp/mL was detected, a follow-up VL test was performed 4 weeks later to confirm virological status and to guide further clinical decisions. All VL measurements taken during the study period were included in the analysis. The appropriate time-window for CAB/RPV LAI injections was defined as 28 ± 7 days from the previous injection for the second injection and as 56 ± 7 days for the further administrations. For patients who discontinued treatment, the date of the last effective injection was considered the date of discontinuation. Reasons for discontinuation were collected by systematic analysis of medical records.

2.3 Outcomes of interest

The primary outcome was the discontinuation of CAB/RPV LAI for any reason.

The secondary outcome was adherence to the injection schedule.

2.4 Statistical analysis

Continuous variables were described using appropriate summary statistics such as mean or median (with standard deviation or interquartile range, as appropriate), while categorical variables were expressed as frequencies and percentages. All causes discontinuation was estimated by means of Kaplan Meier curves.

Study data were collected and managed using REDCap electronic data capture tools hosted at ASST-FBF-SACCO. Statistical analyses were performed with IBM SPSS Statistics, v. 28.0.

2.5 Ethical statement

The study protocol received approval from the Ethical Committee of Luigi Sacco Hospital (Protocol 0011903/2023–March 16, 2023), and no external funding was received for this research endeavor.

3.0 Results

We included 138 patients who received CAB/RPV LAI with a median time of observation of 43 weeks (IQR 34-47). Of these, 32 were female (23.2%), the median age was 51 years (IQR 40-58) and 64 (47%) were taking almost one comedication.

Out of 138 individuals, 88 (63.8%) had ever been exposed to INSTIs (Integrase Strand Transfer Inhibitors), 81 (58.7%) to NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors) and 60 (43.5%) to PIs (Protease Inhibitors). Before switching to CAB/RPV LAI, 107 patients (77.5%) were on an INSTI-containing regimen, 44 (31.9%) from a NNRTI-containing regimen and 5 (6.3%) from a PI-containing regimen. Median time of VL <50 cp/ml before the switch was 10 years (IQR: 6-16).

Other clinical characteristics of the cohort are resumed in Table 1.

In our study, 12 PWH (8.7%) discontinued the treatment (Figure 1), with a higher proportion of female PWH compared to male PWH (7/32, 21.7% versus 5/106, 4.7%; RR 5.7; p= 0.03). The median time to discontinuation was of 21 weeks (IQR 12-35) and the median number of injections

before discontinuation was 4 (IQR 3-5). The probability of adherence after 48 weeks of LAI was estimated at 89.4% (95% confidence interval 83.3%-95.5%). Reasons for discontinuation among these 12 individuals included injection-related pain (n=5), evidence of HBV infection retrospectively identified post-initiation of CAB/RPV LAI (n=1), clinical decision after an episode of major depression (n=1), pregnancy (n=1), implant of silicon prosthesis (n=1), drug-drug interactions (n=1), evidence of rilpivirine resistance-associated mutations (RAMs) after re-exam of genotypic resistance test (n=1), and logistic reasons (n=1). We recorded 3 (2.2%) virological blips (all < 200 cp/mL) and no virological failures during the study period.

Analysis of adequacy of time-window of injections showed that 92.8% (128/138) of patients did not experience delayed injections. Among the total injections, 629 (96.3%) were administered within the adequate ± 7 day window. Nine patients had one injection delay, while one patient experienced two delays. Most injections were administered within a few days of the target window, with only two patients experiencing significant delays greater than +13 days, including one instance of a +22 day delay (Figure 2).

Finally, a patient developed significant gluteal pain after the second injection of CAB/RPV LAI. To manage this pain, the patient was placed on oral bridging for 21 days, postponing the third injections. After this period, injections were resumed according to the original schedule, with the first two doses given 28 days apart. The patient did not experience a virological blip.

4.0 Discussion

CAB/RPV became available at our centre in November 2022. Over the following six months, 138 patients switched to CAB/RPV LAI Q8W. The discontinuation rate, particularly less than 10% within our monocentric cohort, underscores the overall positive outcome of the implementation

or pre-existing resistance-associated mutations (RAMs). Furthermore, the relatively small sample size limits the generalizability of our findings and may contribute to observed higher discontinuation rates among female patients. The median observation period of 43 weeks might not capture the long-term effects of CAB/RPV LAI adequately, given its intended use as a prolonged therapy. Moreover, focusing exclusively on CAB/RPV LAI limits our ability to compare its performance with other antiretroviral therapies, potentially overlooking alternative treatment considerations.

Future research with a longer observation period, multi-centre design and broader scope may provide a more comprehensive understanding of the performance of CAB/RPV LAI.

5.0 Conclusions

In conclusion, our findings showed that CAB/RPV LAI Q8W is well-tolerated in clinical practice, with high adherence to the injection schedule and few discontinuations mainly related to injection site related pain. Further studies about practical strategies to minimize injection-related pain are needed.

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Figure 1. The Kaplan-Meier curve depicts the probability of treatment continuation over time up to 48 weeks. Vertical dashes indicate censored data (end of observation while on therapy).

Figure 2. Distribution of injection delays beyond the ± 7 day window.

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Demographics	N = 138
Female (%)	32 (23.2)
Median Age (IQR)	51 (40-58)
MSM (%)	80 (58)
IVDU (%)	7 (5.1)
N° of comedications (%)	
0	72 (52.9)
1	23 (16.9)
2 or more	41 (30.1)
BMI > 30 kg/m ²	12 (8.7)
BMI > 35 kg/m ² and < 40 kg/m ²	1 (0.72)
BMI > 40 kg/m ²	0 (0)
Median time from diagnosis (IQR)	13.0 (8-20)
AIDS (%)	17 (12.8)
N° of previous TARV (IQR)	4 (3-5)
NNRTI Exposure (%)	81 (58.7)
INSTI Exposure (%)	88 (63.8)
PI Exposure (%)	60 (43.5)
No Oral Lead in (%)	23 (18.3)
BL CD4 (IQR)	755 (597-895)
BL CD4 < 500/mm ³ (%)	24 (17.4)
Results	
Median N of injections (IQR)	6 (5-7)
Discontinuation (%)	12 (8.7)
Injection in adequate window (%)	629 (96.3)
Individual N of delays (%)	
0	128 (92.8)
1	9 (6.5)
2 or 3	1 (0.7)

Figure 1. The Kaplan-Meier curve depicts the probability of treatment continuation over time up to 48 weeks. Vertical dashes indicate censored data (end of observation while on therapy).

Table 1. Description of the population. Continuous variables are described using appropriate summary statistics such as mean or median (with standard deviation or interquartile range, as appropriate), while categorical variables are expressed as frequencies and percentages.

IQR: interquartile range; MSM: men having sex with men; IVDU: intravenous drug users; BMI: body mass index; AIDS: acquired immunodeficiency syndrome; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitors; INSTI: Integrase Strand Transfer Inhibitors; PI: Protease Inhibitors; BL: blood lymphocytes; VL: viral load.

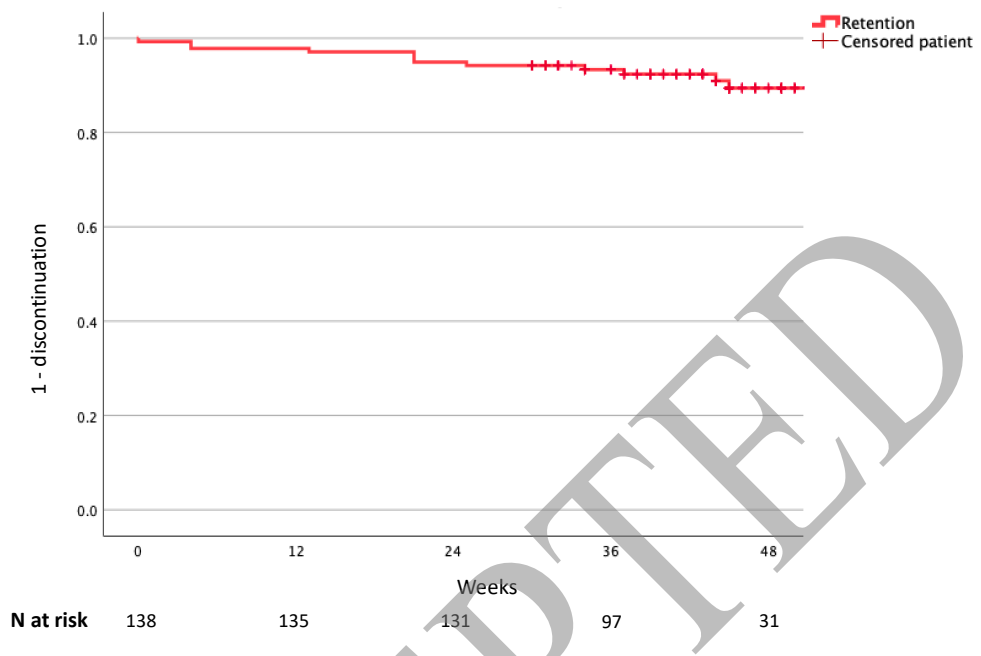


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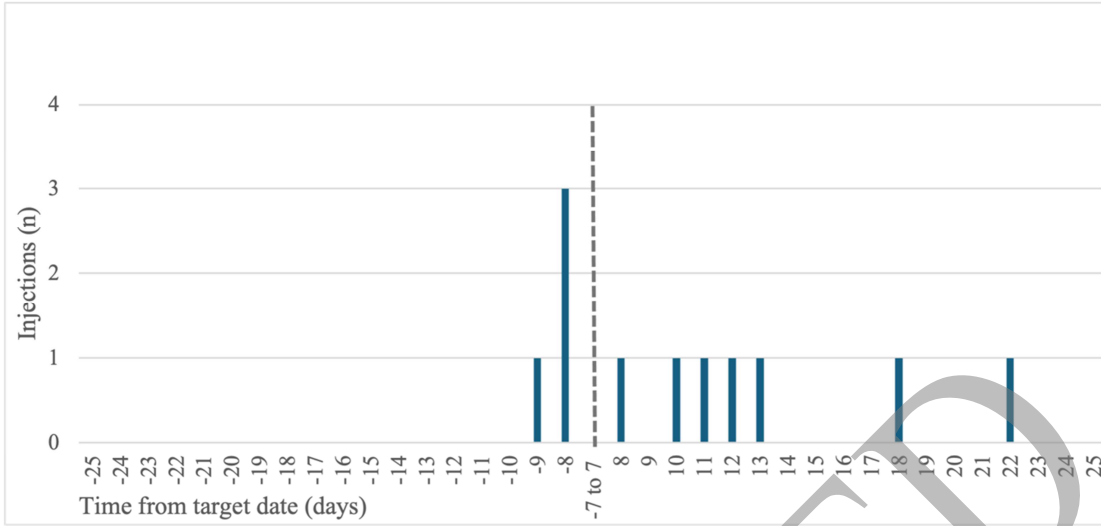


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