EFFICACY, SAFETY, AND CLINICAL OUTCOMES OF LONG-ACTING CABOTEGRAVIR AND RILPIVIRINE FOR HIV-1 MANAGEMENT

S.Rabiniraj[1*], K.K.Senthilkumar[2], Armstrong Vinodraj[3], A.Ezhilarasi[4], S.Sivaraman[5], P.Thilagesh[6]

[1]Department of Pharmacy Practice, Sri Shanmugha College of Pharmacy
[2]Department of Pharmaceutical Analysis, Sri Shanmugha College of Pharmacy
[3]Department of Pharmacognosy, Sri Shanmugha College of Pharmacy
[4]Pharmaceutical Quality Assurance, Sri Shanmugha College of Pharmacy
[5]Department of Pharmaceutical Analysis, Sri Shanmugha College of Pharmacy
[6]Department of Pharmacy Practice, Sri Shanmugha College of Pharmacy

E-mail: rabuniraj31.98@gmail.com, kksenthil.a@gmail.com, armstrongvinodraj@gmail.com, ezhilarasiazhagasan4@gmail.com, sivaraman0216@gmail.com, thilakbabu811@gmail.com
[*]**Corresponding Author:** S.Rabiniraj

Abstract

Background*: Adherence to daily oral ART can be challenging for people living with HIV (PLHIV), influenced by factors such as pill fatigue, stigma, and lifestyle barriers. Long-acting injectable antiretroviral therapies, specifically Cabotegravir (CAB) and Rilpivirine (RPV), present a promising alternative, requiring administration monthly (Q4W) or bi-monthly (Q8W).*

Methods*: This study analyzed four clinical trials—ATLAS, ATLAS-2M, LATTE-2, and FLAIR—assessing the efficacy, safety, and adherence of CAB and RPV. Participants, virologically suppressed on ART, received either Q4W or Q8W injections. Data were collected on viral suppression rates, injection site reactions (ISRs), and patient-reported outcomes.*

Results*: Both dosing schedules achieved viral suppression rates comparable to daily ART, with ATLAS-2M showing a 94% suppression rate at 96 weeks in the Q8W group. Safety was favorable; ISRs, mainly mild to moderate, occurred in 82-88% of participants, with minimal severe ISRs. Adherence support measures, such as reminders and counseling, contributed to high adherence rates, and patient preference was notably strong for the Q8W regimen, which offered reduced visit frequency and minimized stigma.*

Conclusion*: Long-acting CAB and RPV are effective, safe, and patient-preferred alternatives to daily ART. While logistical challenges, including scheduling and provider training, must be addressed, these injectables hold potential for enhancing adherence and quality of life among PLHIV.*

Keywords: Long-acting antiretroviral therapy, Cabotegravir, Rilpivirine , HIV viral suppression, Patient adherence and quality of life

INTRODUCTION

HIV is now touching an estimated 38 million people in the world and over 2.3 million in India.[1] Since the advent of ART, HIV has transformed to go from being a fatal disease to one that can be managed as a chronic condition, thereby drastically improving life expectancy and quality of life for people living with HIV (PLHIV).[2] However, the success of ART hinges greatly on compliance with daily oral regimens. For many patients, adherence becomes very difficult due to factors, such as pill fatigue, stigma towards the intake of drugs, and the inconvenience of managing daily dosing.[3] Poor so-called suboptimal viral suppression increases the risk of virologic failure and the development of drug-resistant strains of the virus. New alternative treatment options that better fit the needs and lifestyles of patients are needed to maintain long-term success in ART by addressing the adherence barriers related to those issues.[4]

Long-acting injectable antiretroviral therapies may be a new alternative to daily oral medication. A long-acting INSTI, cabotegravir, in combination with a non-nucleoside reverse transcriptase inhibitor (NNRTI), Rilpivirine, has been developed and is currently assessed in studies like ATLAS, ATLAS-2M, and FLAIR as monthly or bimonthly injectable therapy.[5] This injectable regimen is shown in those studies to be not inferior to daily oral ART regarding viral suppression, while participants commonly preferred injectables over having to take daily pills.[6] Patients can record the advantages of it, such as more convenience, fewer reminders about their status, and minimized stigma with the use of medications. Considering the results of these long-acting injectables were promising, they might be considered a paradigm shift in HIV management, being more flexible and centered on the patient for it to address current problems in adherence.[7]

Despite these gains, there remain wide gaps in the understanding of the broader applicability and potential limitations of long-acting injectable ART.[8] Most studies restrict to a population already on stable ART and virologically suppressed, which does not improve understanding of how the treatment might work in the ART-naïve, those with previous challenge adherence or the comorbid patient.[9] Such logistical burdens of injectable ART, including requirements for healthcare visits, storage needs, and provider training, have been underaddressed thus far in the real world. To this end, this study aims to fill these gaps by assessing the effectiveness, safety, and adherence outcomes related to long-acting Cabotegravir and Rilpivirine in a variety of populations. Specific objectives included pharmacokinetic studies of the injectable regimen in varying patient demographics, potential in ART-naïve populations, and identifying barriers and facilitators to successful implementation.

Answers to these questions are hoped to contribute to a better understanding on how long-acting injectable ART can be optimized and scaled to meet the ever-changing needs of PLHIV for diverse healthcare environments.

METHODS AND METHODOLOGY

Study Design and Randomization

Design Phased:

The CAB-RPV study includes four late-stage trials: ATLAS, ATLAS-2M, LATTE-2, and FLAIR, all of which were designed to answer different questions regarding CAB and RPV as LAIs. The Induction Phase, Maintenance Phase, and Extension Phase for each of the four trials were designed to answer specific questions regarding adherence, patient satisfaction, and virologic suppression. For instance, the ATLAS-2M study is an extension of results from the ATLAS study, with a non-inferiority model conducted on a Q4W and a Q8W regimen for CAB and RPV.

Eligibility and Randomization Criteria:

The subjects were required to satisfy rigorous inclusion criteria. They had to be virologically suppressed with stable ART, which was going on for at least six months before inclusion into the study, and are characterized by an HIV-1 RNA level below 50 copies/mL. The exclusion criteria included previous exposure to CAB or RPV, ART-naïve status, or signs of virologic resistance, thus avoiding confounding by previous antiretroviral treatment or the presence of resistance. In ATLAS and ATLAS-2M, a 1:1 model was used to randomize the participants, whereas in LATTE-2, a 2:2:1 ratio for the bi-monthly, monthly, and control groups was used to ensure that demographics, adherence backgrounds, and baseline viral loads are well balanced across all the study arms.

Dosing and Administration Protocols

The pre-Phase to the Initial Oral Induction Phase:

All participants entered the pre-phase to the initial oral induction phase establishing tolerability. They were administered daily CAB 30 mg and RPV 25 mg for at least four weeks. This is an important induction phase to identify potential adverse events or issues with tolerability of the components before entering the long-acting injectable formulations.

Injectable Maintenance Phase:

Participants received intramuscular injections after the induction. A quarterly dosing schedule in the Q4W arm received 400 mg of CAB and 600 mg of RPV. The bi-monthly dosing schedule group or the Q8W group, in the LATTE-2 study, was optimized for sustained viral suppression with fewer appointments having received a loading dose of 600 mg of CAB and 900 mg of RPV. In the gluteal muscle, the injection was done using a 23-gauge, 1.5-inch needle, with alternative injections in the vastus lateralis (thigh muscle) being permitted in some studies as a way of ascertaining pharmacokinetic results from varying locations.

Switching and Extension Protocols:

The Extension Phase allowed patients to stay on their previously established regimen (monthly or bi-monthly) or to switch dosing intervals if clinically appropriate.

This flexible approach has proven very useful in assessing effectiveness and patient preference in the real world over longer durations, including adjustments to meet lifestyle needs and long-term views on adherence.

Missed Dose Management

In case of missed injections, additional seven-day buffer was considered in the management. It allowed the patient to receive the dose within seven days before or after the scheduled date. When an appointment was missed beyond that window, oral bridging therapy was used; and daily oral doses of CAB 25 mg and RPV 30 mg were used until the injections could be resumed again. This strategy was critical in minimizing virological failure and maintaining therapeutic drug levels in the interruption.

Collection of Data, Safety Monitoring and Pharmacokinetic Analysis

Monitoring of Virological and Pharmacokinetic Activities:

The HIV RNA levels of the subjects were periodically monitored to ascertain the level of chronic suppression throughout the study. PK samples were drawn for determining drug absorption, distribution, and elimination across a period. Important PK parameters monitored were steady-state plasma concentration, time to maximum concentration, Cmax, and Ctrough. This would ensure whether the Q4W and Q8W regimens maintain adequate levels in plasma for viral suppression.

Safety Monitoring and ADR:

The Safety profile was monitored, particularly Adverse Drug Reactions such as Injection Site Reactions (ISRs). Grading of ISRs was standardized by using a grading scale representing graded response including scores for severity and occurrence for pain, swelling, pruritis, nodules, and induration; laboratory abnormalities - elevations of ALT and AST - to determine systemic effects. In LATTE-2 and ATLAS-2M, high-grade ISRs were few, and most of them were mild to moderate. Patients were instructed on how to cope with expected ISR, and where serious ADRs occurred, the use should stop in some cases for consideration of safety of the patient.

Adherence Monitoring Support Structures:

An adherence support system that would help in sticking was not included in the study. Participants received alerts on the scheduled appointments, and adherence was checked through attendance and dosing logs. The research team made counseling available to those who may have raised concerns such that keeping up with the injection schedule posed a potential financial or logistical barrier. Counseling also covered strategy in the context of fears and worries associated with the injections and concerning perceived economic burden. The study design was to optimally retain and minimize the chance of viral rebound due to omitting doses by integrating adherence support with clinical care.

Patient Satisfaction and Quality of Life Metrics:

The study had included PROMs to assess the treatment satisfaction, the influence of lifestyle, and quality of life after changing to injectable therapy. Cross-sectional surveys and interviews were conducted at various times in the study to assess patients' perceptions of their treatment, such as preference for injectable or oral regimen, decrease in perceived stigma, and overall level of convenience.

PROMs revealed a general preference for the long-acting injectables as it permits less reminder of daily medications and less intruders in daily life. Suggests, therefore, a possible positive influence on the patient's adherence and mental.

Real-world feasibility challenges:

The research identified some of the potential challenges to the feasibility of injectable ART in real-world settings. Some of these challenges included practical issues such as scheduling regular appointments, supervising supply and storage of injectables, and establishing training for health providers on injection protocols. These are important features to enhance wide-scale adoption of long-acting injectables, primarily in low-resource or high-volume settings, and were monitored to gauge feasibility and scalability.

RESULTS:

Viral Suppression and Efficacy

The aim of this research was to determine whether the long-acting Cabotegravir (CAB) and Rilpivirine (RPV) was effective in maintaining viral suppression in HIV-1 patients, as shown in more than one clinical trial. In the ATLAS study, the Q4W dosing regimen resulted in 92.5% of participants reaching viral suppression at 48 weeks, who had HIV RNA <50 copies/mL. This was almost similar to the 95.5% suppression rate observed in participants on standard daily oral ART. This established that LAART was non-inferior to daily regimens in maintaining viral load suppression. The ATLAS-2M study further improved on these results by comparing monthly versus bi-monthly (Q8W) injection frequency, with 93% of the monthly group and 94% of the bi-monthly group maintaining viral suppression through to week 96. The FLAIR study also established the same by having 93.6% of those under LAART retain HIV RNA levels below 50 copies/mL that concurred with the 93.3% viral suppression rate among those on daily oral ART after 48 weeks. These high levels of viral suppression across differing dosing intervals affirm CAB and RPV's efficacy as an alternative remedy for patients seeking relief from the daily regimen burden of traditional ART.

Table 1: Maintenance and Extension Dosing Phases (Q4W and Q8W)

Phase	Dosing Interval	CAB Dosage (mg)	RPV Dosage (mg)	Administration Mode
Maintenance Phase	Q4W	400 mg	600 mg	IM Injection
	Q8W	600 mg	900 mg	IM Injection
Extension Phase	Q4W	400 mg	600 mg	IM Injection
	Q8W	600 mg	900 mg	IM Injection
Optimized Dosing	Q4W	400 mg	600 mg	IM Injection
	Q8W	600 mg	900 mg	IM Injection

This table outlines the dosing protocols used during the maintenance and extension phases of the study, comparing monthly (Q4W) and bi-monthly (Q8W) intervals for long-acting Cabotegravir (CAB) and Rilpivirine (RPV) injections. Dosage adjustments were made depending on patient response and interval schedule.

Injections were administered intramuscularly, typically in the gluteal muscle, with adjustments for body mass index (BMI) as needed to ensure proper administration depth.

Safety Profile and Injection Site Reactions (ISRs)

Safety was a key area of concern with ISRs forming the majority reported adverse event. While in the LATTE-2 study, ISRs were reported by 82% of participants in the bi-monthly group (Q8W) and 88% in the monthly group (Q4W), these were mostly mild (Grade I) or moderate (Grade II). Mild ISR symptoms included pain, which was reported in 67% of Q8W participants and 62% in Q4W participants; there were also nodules and pruritus, commonly associated with swelling, all of which were transient and resolved without interventions. The ATLAS-2M study experienced minimal severe reactions, with high-grade ISRs less than 1% Grade IV. Systemic side effects encompassing mild increases in liver enzymes (ALT and AST) were rare, occurring with such infrequency that they did not impact continuation of therapy. Only a few subjects discontinued due to adverse events; in general, the drug is tolerated well, ensuring that some discontinuations are unlikely to be necessary. The study therefore ascertains the safety of the injectable regimen that positions it at the forefront as a well-tolerated alternative for long-term HIV management.

Table 2: Injection Site Reactions, Common Adverse Events, and Laboratory Abnormalities

Category	**Specific Measure**	**Q8W Group (%)**	**Q4W Group (%)**
Injection Site Reactions (ISR) Grades	Grade I	71%	70%
	Grade II	27%	28%
	Grade III	<4%	<4%
	Grade IV	<1%	<1%
Common Adverse Events	Pain	72%	70%
	Nodule	10%	17%
	Induration	8%	8%
	Discomfort	7%	8%
	Swelling	6%	5%
	Pruritis	5%	5%
Laboratory Abnormalities	ALT (Grade 3 to 4)	<1%	1%
	AST (Grade 3 to 4)	1%	1%
	Total Bilirubin	<1%	<1%
	Triglycerides	1%	1%
	Total Cholesterol	<1%	1%
	LDL Cholesterol	2%	1%

This combined table provides a summary of injection site reactions (ISRs), common adverse events, and laboratory abnormalities recorded in the study for both bi-monthly (Q8W) and monthly (Q4W) dosing schedules. ISRs are categorized by severity, with common symptoms such as pain, nodules, and pruritis highlighted. Additionally, laboratory abnormalities, including levels of ALT, AST, and lipid profiles, were tracked to assess systemic tolerability and safety of the CAB and RPV regimens.

Satisfaction and Adherence Results

Patient satisfaction with the LAART regimen was significantly high particularly on the Q8W dosing schedule. The shift from daily oral ART to an injectable formulation was a welcome change in the opinion of patient-reported outcomes in the trials of ATLAS and FLAIR. Many said that their quality-of-life improvements by amounts considered considerable; they felt that stigma related to HIV had lessened, and they found injections far more convenient, as they required far fewer visits to healthcare providers and less disruption to routines. Participants who most appreciated not being required to visit healthcare providers as frequently preferred a bi-monthly injection regimen. In this study, reminder systems, educational sessions, and counseling were implemented to improve adherence, probably solving the barriers in retaining injection schedules. All these strategies towards adherence and the preferences of patients concerning less frequent injections led to the high rates of adherence recorded. A high satisfaction score for LAART brings out the potential for better patient experiences with a reduction in the burden associated with daily ART.

Table 3: Comparison of Other Adverse Events in ATLAS Study (Oral vs. LAART)

Adverse Event	**Oral Group**	**LAART Group**
Weight Gain	0.30 kg	1.80 kg
Lipase	Not Applicable	Grade 4 (n=1)
Alanine Amino Transference (ALT)	≥3 folds (n=1)	≥3 folds (n=5)

This table compares additional adverse events observed in the ATLAS study between participants on daily oral ART and those on long-acting injectable ART (LAART). Key metrics include differences in weight gain, lipase levels, and ALT elevation, providing insights into the physiological effects of injectable versus oral ART regimens. These findings contribute to understanding the long-term safety and metabolic impacts of transitioning from oral to injectable HIV treatment.

Management of Missed Dose and Oral Bridging Protocol

This oral bridging protocol was also established to prevent the otherwise inevitable virologic rebound following the possible missed injection in a real-life clinical setting. This protocol ensured that, if a participant could not attend to an injection, daily oral bridging therapy comprised of CAB (25 mg) and RPV (30 mg) maintained therapeutic drug levels until injections resumed. The protocol was flexible, allowing for an injection grace period of seven days whereby the injection was tolerated seven days before or after the planned date without affecting viral suppression.

This actually meant that this strategy worked well in maintaining viral control and showing how LAART could flex with the needs of the patients. Such successful implementation of the oral bridging protocol underscores the potential of long-acting injectables in actual practice settings, whose circumstances may prove unpredictable for scheduling. In summary, the study shows that with robust support systems, LAART can offer reliable and flexible long-term HIV treatment management.

DISCUSSION:

An important study, it demonstrates the potential of using long-acting injectable Cabotegravir (CAB) and Rilpivirine (RPV) to become an effective alternative in maintaining HIV suppression as a replacement for daily oral ART. In agreement with results from the ATLAS, ATLAS-2M, LATTE-2, and FLAIR studies, CAB/RPV Q4W and Q8W injection regimens are able to maintain viral suppression rates on par with those achieved through daily oral ART.[11] Such findings are very important, as they would demonstrate that a non-daily ART alternative is equal to its daily counterpart in terms of virologic control at best, thus relieving the daily burden for the people living with HIV and potentially improving adherence through fewer interruptions because of the missed daily doses.[12]

The ISRs in terms of safety were common but generally mild to moderate in severity; most resolved without intervention, thus indicating promising tolerability, as this aspect suggests that greater convenience in less frequent dosing does not come at the cost of patient comfort. Low incidence of grade IV more severe ISRs and relatively low incidence of systemic-related adverse findings like elevation in transaminases at ALT and AST also establish the safety profile of CAB and RPV injectables. Patients showed a marked preference for injectables over daily reminders and stigma in the clinical settings and greater flexibility in everyday life.[13]

Adherence was one of the significant advantages of the injectable regimen. Patients were able to keep scheduled appointments with adherence support strategies, such as reminding and counseling sessions. There is preference for Q8W, indicating potential to move bi-monthly dosing forward to even decrease more adherence burden related to HIV management. Success of the adherence support interventions, like oral bridging protocols for missed doses, also provides evidence for the feasibility of the implementation of long-acting injectables in different health care settings, provided there is appropriate support for adherence is in place.[14] The study also discovers challenges in the implantation of this regime. The major practical challenges are scheduling of the visit, safe storage, and educating the healthcare providers on the protocol. These are practical challenges that would need careful planning in order to be applied in the real world. This study therefore suggests that the afore-mentioned barriers can be overcome through tailored strategies and other options for administration, such as pharmacy-based injection scheduling, which may improve the access and scalability of CAB and RPV injectables for managing HIV.[15]

At the end, long-acting CAB/RPV could be of great interest to patients as a safer alternative to the daily implementation of ART with sizeable gains in quality of life and long-term treatment outcomes among PLHIV.

CONCLUSION:

This investigation proves both the efficacy and safety as well as patient preference for long-acting CAB and RPV as a transformative alternative to daily ART. Among the ATLAS, ATLAS-2M, LATTE-2, and FLAIR trials, the monthly (Q4W) and bi-monthly (Q8W) injectable regimens showed viral suppression comparably to that of daily ART with suppression rates over 92.5% and showing rate of suppression above 94% at week 96 in ATLAS-2M with Q8W regimen. Injection Site Reactions were the most common adverse events, occurring in 82-88% of patients as mild to moderate symptoms such as pain and swelling that usually resolved spontaneously. A low rate of severe ISRs (Grade IV) and minimal systemic effects such as elevation of the liver enzyme highly highlight the favorable safety profile of injectable CAB and RPV, which may constitute a well-tolerated long-term option in the treatment of PLHIV. Besides, the reminder system, counseling, and an oral bridging rule that would prevent virologic rebound when doses are missed, each promoting a high rate of adherence, made the Q8W regimen give the client a good reason to be satisfied, reduce number of visits for healthcare, and fewer daily reminders about their HIV status. This study underlines the potential of long-acting injectables to advance ART by combining effectiveness, safety, and patient-centered care and points out the need for addressing logistical factors, such as storage, training of providers, and scheduling, to be key elements in implementing the intervention successfully in the real world with long-term outcomes for PLHIV.

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