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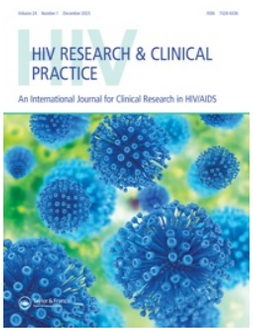

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Analytical description of adverse events with long-acting injectable cabotegravir and rilpivirine in people living with HIV: a large multicentre prospective observational cohort study (SCOLTA)

Gaia Cologgi[a,b], Elena Ricci[c], Antonio Di Biagio[a,b], Sergio Ferrara[d], Giancarlo Orofino[e], Nicola Squillace[f], Emanuele Pontali[g], Barbara Menzaghi[h], Eleonora Sarchi[i], Giovanni Cenderello[j], Giordano Madeddu[k], Giovanni Francesco Pellicanò[l], Olivia Bargiacchi[m], Filippo Lagi[n], Elena Salomoni[o], Teresa Bini[p], Paolo Bonfanti[q], and Lucia Taramasso[b], [1]on behalf of CISAI Group

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ABSTRACT

Introduction: Long-acting injectable cabotegravir plus rilpivirine (LA CAB+RPV) is a highly effective, well-tolerated antiretroviral regimen, but real-world adverse event (AE) data remain limited. We characterised the type and frequency of AEs associated with LA CAB+RPV in people with HIV in routine clinical practice.

Methods: This multicentre, prospective, observational study (SCOLTA project, Italy) enrolled people with HIV initiating LA CAB+RPV. Clinical characteristics, AEs and discontinuations were systematically collected. A centre-level survey assessed AE management and prevention practices.

Results: In our cohort 598 people with HIV were enrolled across 25 centres. Forty-two participants (7%) experienced overall 51 AEs, of which 37 (88%) led to discontinuation of LA injectable therapy. Injection site reactions (ISRs) were the most frequently reported AEs (29.4%). Central nervous system (CNS)-related AEs accounted for 7.8% of events and resulted in treatment discontinuation in 75% of cases. In multivariable analysis, unknown HIV acquisition mode was independently associated with an increased risk of AEs. Age ≥50 years showed a consistent trend across all models and was the only significant independent predictor in sensitivity analyses restricted to people with HIV with known HIV acquisition mode. Among the 23 centres responding to the survey, 15 (65.2%) reported a reduction in injection-related events following specific training of staff administering LA CAB+RPV.

Conclusions: LA CAB+RPV showed a lower AE rate than pivotal trials, despite more AE-related discontinuations. CNS-related AEs were uncommon, supporting good tolerability, but led to discontinuation when they occurred. Older age was independently associated with increased AE risk.

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Long-acting antiretroviral therapy; adverse events; cabotegravir/rilpivirine; pharmacovigilance; tolerability; injectable

Introduction

Long-acting injectable cabotegravir and rilpivirine (CAB + RPV) offers an effective and well-tolerated alternative to daily oral ART for people with HIV, representing an important advance in antiretroviral

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therapy. Early clinical trials have also shown high treatment satisfaction, improvements in adherence and quality of life [1–3]. While real-world studies confirmed the high effectiveness and favourable tolerability profile of LA CAB + RPV [4,5], observational data are still limited and frequently based on short follow-up periods. This limitation is evident in the characterisation of adverse events (AEs) during LA injectable therapy. Notably, some studies have reported substantial rates of treatment discontinuation attributable to AEs, underscoring the need for further investigation [4,5].

To address this gap, we conducted a multicentre, prospective, observational study across Italian centres to describe the AEs occurring among people with HIV receiving LA CAB + RPV. We further investigated clinical and demographic characteristics of individuals who developed AEs, with a focus on factors that may be associated with their occurrence. Additionally, a brief questionnaire was administered to participating centres to explore healthcare professionals perspectives toward AEs during LA injectable CAB + RPV, supporting the interpretation of clinical findings and providing insight into in real-world practice.

Methods

Aims and objectives

The primary objective of the study was to comprehensively characterise the incidence and nature of clinically relevant AEs occurring in individuals receiving LA injectable CAB + RPV over the treatment period. Attention was given to events with potential implications for treatment continuation.

Secondary objectives aimed to describe clinical and demographic characteristics of people with HIV who developed AEs and to identify individual- and treatment-related factors that may be associated with AEs occurrence, and to explore real-world clinical practices related to injection management and AEs during LA injectable CAB + RPV administration through a brief exploratory survey. The survey was developed specifically for this investigation, was not formally validated, and no pilot testing was performed. It was distributed to healthcare professionals involved in LA injectable CAB + RPV administration across all participating centres in July 2025 and remained open for 15 days. The full questionnaire is available as a Supplementary File.

Study design and ethical considerations

This is an observational, prospective, multicentre study including people with HIV participating to SCOLTA (Surveillance Cohort Long-Term Toxicity Antiretrovirals) study, who started LA injectable CAB + RPV, according to current European recommendations [6], between July 2022 and November 2024. Individuals who initiated LA CAB + RPV and had at least two recorded study visits were eligible for inclusion in the present analysis. The present analysis was based on data available up to November 2024, while enrolment and follow-up within the cohort remain ongoing.

The SCOLTA project is an Italian multicentre observational cohort comprising 25 infectious diseases centres and prospectively follows people with HIV starting new antiretroviral drugs in routine clinical practice to identify toxicities and adverse events in a real-world setting [7,8]. All individuals initiating LA CAB + RPV during the study period were eligible for inclusion, and no patients were excluded from the analysis.

The original study protocol for the SCOLTA project was approved on 18 September 2002 by the coordinating centre at the L. Sacco Hospital-University of Milan (CE18092002). New protocol amendments were approved on 13 June 2013, 20 December 2019, 12 May 2020, and 17 May 2023, by the coordinating all participating centres. Written consent for study participation was obtained from all participants, and the study was conducted in accordance with the ethical standards set out in the 1964 Declaration of Helsinki and subsequent amendments, as well as Italian national laws.

AEs were defined as any harmful and unintended effect, graded using the DAIDS Adverse Event Grading, resulting from the use of the LA injectable regimen [9].

Prior to data collection, we pre-specified the evaluation of psychiatric comorbidities and concurrent psychiatric medications as variables of interest, given the known CNS-related adverse effect profiles of the antiretroviral classes involved (INSTIs and NNRTIs).

Data were collected prospectively during routine clinical follow-up visits and entered into the web-based SCOLTA database at approximately six-month intervals. Baseline was defined as the date of the first CAB + RPV injection. Clinical, virological and treatment-related information, including AEs, were recorded at each study visit. Serious AEs were systematically reported, while the reporting of mild and moderate EAs reflected routine clinical practice and may have varied across participating centres, since no standardised active surveillance or systematic AE screening procedures were implemented.

Regarding the exploratory questionnaire, it was distributed electronically to study participants. One response per centre was collected, completed by the responsible physician. Survey data were analysed separately from clinical data. Feedback included closed-ended items.

Descriptive statistics were used to summarise results, including frequency distributions for categorical variables.

Statistical analysis

Data were described using mean ± standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQR) for not normally distributed continuous variables and percentage for categorical and ordinal variables. Cox regression models identified hazard ratio (HR) and 95% confidence intervals (95%CI) for AEs development. A multivariate model was run, using a stepwise selection model: all variables were included and selected for staying in the equation if their association with the outcome had a p value < 0.20.

Exploratory sensitivity analyses were conducted to assess the robustness of the findings. Kaplan–Meier analyses were performed to explore the time to first AE.

Results

Study population

A total of 683 people with HIV started LA injectable CAB + RPV during the study period. Of these, 598 (87.6%) individuals had at least two recorded study visits and were therefore included in the present analysis.

The median follow-up duration was 18 months (IQR 10–22). At enrolment, all people with HIV had HIV-RNA < 50 copies/ml and mean duration of previous ART was 10.5 year (SD 7.6). Further demographics and baseline characteristics are detailed in Table 1.

Sixty-one people with HIV (10.2%, 61/598) discontinued LA injectable treatment: 37/61 (60.7%) due to AEs, 10/61 (16.4%) due to scheduling issues, 8/61 (13%) due to virological failure, 3/61 (4.9%) changed city of residence, 1/61 (1.6%) lost to follow-up, 1/61(1.6%) for personal decision not further characterised. One out of 61 (1.6%) participants died, with the event deemed unrelated to the study drugs.

In the cohort, 42 (7%) participants developed at least one AE, of whom 37 (88.0%) discontinued treatment due to AEs. Of the 42 individuals who experienced at least one AE, eight (19.0%) reported two AEs, while one participant experienced three.

Overall, a total of 51 events were documented in the cohort. The demographic and clinical characteristics of people with HIV who experienced at least one AE were broadly similar to those of the overall cohort (Table 1), including sex (76.2% vs 76.4% male), ethnicity (95.2% vs 95.0% Caucasian ethnicity), and BMI (mean 25.2 vs 25.1 kg/m^2). Compared with the overall cohort, the AE subgroup was older (66.7% vs 49.7% aged ≥50 years), had longer prior ART exposure (mean 14.4 vs 10.5 years).

AEs descriptions and characteristics of people with HIV involved

The median time to AE occurrence was 2 months (IQR 0-5). In our cohort, injection site reactions (ISRs) were the most frequently reported AEs, constituting 29.4% of all AEs described (15/51). Musculoskeletal symptoms, including arthralgia and myalgia were observed in 17.6% (9/51), as well as fever (9/51). Central nervous system (CNS)-related symptoms were reported by four people with HIV, representing 7.8% of those who experienced an AE and 0.7% of the entire cohort; three people with HIV (3/4, 75.0%)

Table 1. Baseline characteristics of 598 people with HIV on CAB LA treatment.

Population Characteristics		Total people with HIV *N* = 598	People with HIV without AE(s) *N* = 556 (93.0%)	People with HIV with AE(s) *N* = 42 (7.0%)	*p*-value
Male sex, *N* (%)		457 (76.4)	425 (76.4)	32 (76.2)	0.97
Caucasian ethnicity, *N* (%)		568 (95.0)	528 (65.0)	40 (95.2)	0.94
Age (years), median (IQR)		49 (40–58)	49 (39.57)	54 (47–61)	0.01
Age ≥ 50 years, *N* (%)		297 (49.7)	269 (48.4)	28 (66.7)	0.022
BMI (kg/m^2), mean (SD) (56 missing)		25.1 (3.9)	25.1 (3.9)	25.2 (3.1)	0.85
BMI ≥ 30 (kg/m^2), *N* (%) (56 missing)		50 (8.4)	48 (8.6)	2 (4.8)	0.60
HIV acquisition mode, *N* (%)	Heterosexual	207 (34.6)	194 (34.9)	13 (31.0)	
	MSM	276 (46.5)	260 (46.8)	16 (38.1)	
	History of IDU	70 (11.7)	65 (11.7)	5 (11.9)	0.009
	Vertical	8 (1.3)	8 (1.4)	0	
	Unknown	37 (6.2)	29 (5.2)	8 (19.0)	
Polypharmacy, *N* (%)	No concomitant drug	270 (45.2)	254 (45.7)	16 (38.1)	
	1 concomitant drug	145 (24.2)	133 (23.9)	12 (28.6)	
	2 concomitant drugs	73 (12.2)	68 (12.2)	5 (11.9)	0.45
	≥3 concomitant drugs	110 (18.4)	101 (18.2)	9 (21.4)	
Psychiatric treatment, *N* (%)		58 (9.7)	52 (9.4)	6 (14.3)	0.30
Antiaggregant/anticoagulant treatment[a]**,** *N* (%)		32 (5.4)	29 (5.2)	3 (7.1)	0.59
CDC stage, *N* (%)	A	336 (56.2)	315 (56.7)	21 (50.0)	
	B	145 (24.3)	134 (24.1)	11 (26.2)	
	C	99 (16.6)	89 (16.0)	10 (23.9)	0.20
	missing	18 (3.0)	18 (3.2)	0	
Baseline T CD4+ count (cells/mm^3), median (IQR)		780 (567–1031)	783 (570–1029)	704 (497–1074)	0.55
Year of previous ART duration mean (SD)		10.5 (7.6)	10.3 (6.5–16.6)	14.4 (9.0)	0.11
Previous ART duration > 10 years, *N* (%)		313 (52.3)	287 (51.6)	26 (61.9)	0.20
Prior NNRTI treatment, *N* (%)		257 (43.0)	257 (46.2)	18 (42.8)	0.67
Prior INSTI treatment, *N* (%)		409 (68.4)	409 (73.6)	33 (78.6)	0.48
Years since LA treatment started in the centre, *N* (%)	1 year	336 (56.2)	312 (56.1)	24 (57.1)	
	2 years	233 (39.0)	215 (38.7)	18 (42.8)	0.51
	3 years	29 (4.8)	29 (5.2)	0	
Comorbidities, *N* (%)	Hypertension	116 (19.4)	102 (18.3)	2 (4.8)	0.018
	Diabetes	23 (4.4)	21 (3.8)	14 (3.3)	0.75
	Dyslipidaemia	138 (23.1)	127 (22.8)	11 (26.2)	0.62
	Renal function (eGFR ≥ 60)	551 (92.1)	515 (92.6)	36 (85.7)	0.09
	Psychiatric disorder	44 (7.4)	44 (7.9)	4 (9.5)	0.71

Data are presented as mean ± standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQR) for non-normally distributed continuous variables, and number (percentage) for categorical variables. Statistical analysis: continuous variables were compared using the Mann–Whitney U test, and categorical variables using the chi-square test. All tests were two-sided.

Abbreviations: AE: adverse event; ART: antiretroviral therapy; BMI: Body Mass Index; eGFR: estimated glomerular filtration; IDU: intravenous drug use; INSTI: integrase strand transferase inhibitors; MSM: men who have sex with men; NNRTI: non-nucleoside reverse transcriptase inhibitors.

[a] Acetylsalicylic acid (n = 26), clopidogrel (n = 1), ticagrelor (n = 1), oral anticoagulants (n = 2).

discontinued treatment for this reason. Several other isolated events, including hepatitis B reactivation (2/51–3.9%) and serious cardiovascular events (2/51–3.9%) are detailed in Table 2.

Most of the people with HIV who had at least one AE (Table 1) were male (32/42, 76.2%), most of them were older than 50 years (28/42, 66.7%) and of Caucasian ethnicity (40/42, 95.2%), with a mean BMI of 25.2 kg/m^2 (SD 3.1). At baseline, the median CD4+ count was 704 cells/mm^3 (IQR 497-1074), and the mean duration of prior ART was 14.4 years (SD 9.0). Twenty-six out of 42 (26/42, 61.9%) participants reported at least one concomitant medication at baseline. Among these, we focused on concomitant psychiatric therapy, as within this subgroup, six (6/42, 14.3%) people with HIV developed at least one AE.

In univariate Cox regression analyses, as shown in Table 1, age ≥50 years was associated with a significantly increased risk of AEs (HR 2.05, 95%CI: 1.08–3.90, $p = 0.028$). Participants with an unknown mode of HIV acquisition had a higher hazard of AEs than MSM (HR 4.28, 95% CI 1.83–10.03, $p = 0.009$), while no association was observed for other acquisition categories.

The experience of medical and nursing staff at each centre, measured by the length of time the centre had been using LA injectable CAB+ RPV, did not affect the occurrence of AEs (HR 1.16, 95% CI 0.63–2.14 for the second year compared to the first). Among the comorbidities evaluated (Table 3), only hypertension was associated with the development of any AEs in univariate analysis (HR 2.16; 95% CI: 1.14–4.1; $p = 0.019$). Neither psychiatric comorbidities nor concurrent psychiatric treatment were associated with the occurrence of AE.

Table 2. Characterisation of 51 AEs occurring in 42 people on long-acting CAB + RPV.

People with HIV who experienced at least 1 AE	*N* = 42 (%)
Months at AE, median (IQR)	2 (0-5)
Discontinuation due to AE, *N* (%)	37 (88.1)
Adverse Events Observed During Treatment	***N* = 51 (%)**
AEs grade 1-2, *N* (%)	26 (51.0)
AEs grade ≥3, *N* (%)	20 (39.2)
AE grade undefined, *N* (%)	5 (9.8)
ISRs, *N* (%)	15 (29.4)
Arthralgia/myalgia, *N* (%)	9 (17.6)
Fever, *N* (%)	9 (17.6)
Central nervous system symptoms, *N* (%)	4 (7.8)
• Mood alteration	1
• Headache	2
• Depression	1
Hepatitis B reactivation, *N* (%)	2 (3.9)
Cutaneous rash, *N* (%)	2 (3.9)
Cardiovascular disorders	2 (3.9)
• Myocardial infarction	1
Aortic dissection	1
Asthenia, *N* (%)	1 (2.0)
Acute pancreatitis, *N* (%)	1 (2.0)
Glycaemic dysregulation, *N* (%)	1 (2.0)
Weight gain, *N* (%)	1 (2.0)
Pericarditis	1 (2.0)
Gastrointestinal perforation	1 (2.0)
Impaired walking	1 (2.0)
Ankle fracture	1 (2.0)

Abbreviations: AE: adverse event; ISR: injection site reaction.

Isolated fever (2), gastrointestinal perforation (1), cardiovascular disorders (2), pericarditis (1), ankle fracture (1), weight gain (1), impaired walking (1) were deemed as unlikely related to treatment.

Table 3. Univariate and multivariate Cox regression analysis of AE first onset.

Population Characteristics		Crude HR	P	Adjusted HR*	P
Female, ref. Male		1.02 (0.50–2.07)	0.96	–	
Not Caucasian ethnicity, ref. Caucasian		0.94 (0.23–3.91)	0.94	–	
Age (per 1 year increase)		1.04 (1.01–1.06)	0.013	1.03 (1.00–1.06)	0.076
Age ≥ 50 years, ref. < 50 years		2.05 (1.08–3.90)	0.028	1.79 (0.90–3.58)	0.099
BMI (kg/m^2), (by 1 unit increase)		1.01 (0.93–1.10)	0.80	–	
BMI ≥ 30 (kg/m^2), ref. < 30.0		0.58 (0.14–2.39)	0.45	–	
HIV acquisition mode, ref. MSM	Heterosexual	1.09 (0.53–2.27)	0.81	0.96 (0.46–2.02)	0.92
	History of IDU	1.26 (0.46–3.45)	0.65	0.81 (0.28–2.30)	0.69
	Vertical	0.00 (n.e.)	0.98	0 (n.e.)	0.99
	Unknown	4.28 (1.83–10.03)	0.0008	3.92 (1.67–9.20)	0.0017
Polypharmacy, ref. 0	1	1.44 (0.68–3.03)	0.34	–	
	2	1.15 (0.42–3.14)	0.79	–	
	≥3	1.38 (0.61–3.12)	0.60	–	
Psychiatric treatment, ref. No		1.59 (0.67–3.78)	0.29	–	
Antiaggregant/anticoagulant treatment[a], *N* (%)		1.40 (0.43–4.53)	0.57	–	
CDC stage, ref. A	B	1.23 (0.59–2.55)	0.69	excluded	
	C	1.68 (0.79–3.57)	0.18	excluded	0.66
	missing	0 (n.e.)	0.99	excluded	
Baseline T CD4 + count (cells/mm^3) (by 100 cell/mm^3 increase)		0.99 (0.91–1.09	0.91	–	
Year of previous ART duration (by 1 year increase)		1.04 (1.00–1.08)	0.044	excluded	0.56
Previous ART duration > 10 years, ref. < 10 years		1.50 (0.81–2.80)	0.20	1.04 (0.99–1.08)	0.13
Prior NNRTI treatment, ref. No		0.87 (0.47–1.61)	0.66	–	
Prior INSTI treatment, ref. No		1.27 (0.61–2.65)	0.53	–	
Years since LA treatment started in the centre, ref. 1	2	1.16 (0.63–2.14)	0.63	–	
	3	0.00	0.99	–	
Comorbidities, ref. No	Hypertension	2.16 (1.14–4.10)	0.019	1.80 (0.91–3.56)	0.09
	Diabetes	1.28 (0.31–5.28)	0.74	–	
	Dyslipidaemia	1.16 (0.58–2.30)	0.68	–	
	Renal function (eGFR <60)	0.49 (0.20–1.16)	0.10	excluded	0.90
	Psychiatric disorder	1.23 (0.44–3.43)	0.70	–	

Age and ART duration were included as categorical variables in one model (main model), and as continuous variables in another. Abbreviations: n.e.: not estimable.

* Variable with p<0.20 in the univariate analysis were included in the multivariate model.

Given ISRs frequency, we explored whether the use of antiaggregant ($n = 30$) or anticoagulant ($n = 2$) therapy was associated with an increased risk of AEs (specifically ISRs) due to the risk of bleeding or haematoma formation. Only one out of 32 of them developed an ISR (3.1%), compared to 14 out of 566 participants not taking antiaggregant/anticoagulant agents (2.5%). This corresponds to an HR of 1.37 (95% CI 0.42–4.44) for the development of any adverse event, and an HR of 1.28 (95% CI 0.16–9.70) for an ISR.

In the exploratory multivariable model (Table 3), fitted as described in the Methods due to the limited number of AEs, the retained variables were age ≥50 years (aHR 1.79, 95% CI 0.90–3.58, $p = 0.099$), unknown mode of HIV acquisition (aHR 3.92, 95% CI 1.67–9.20, $p = 0.0017$), hypertension (aHR 1.80, 95% CI 0.91–3.56, $p = 0.09$), and prior ART duration >10 years (aHR 1.04, 95% CI 0.99–1.08, $p = 0.13$).

After the exclusion of 9 AEs unlikely related to the treatment, as these events were attributable to other concurrent clinical conditions, we found that 36 people with HIV had 42 AEs possibly/probably/certainly related with the treatment. Repeating the analyses, the same variables were retained, with minimal differences in the risk estimates: age ≥50 years (aHR, 1.63, 95% CI 0.78-3.39, $p = 0.19$), 'unknown' risk factors for HIV acquisition (aHR 3.88, 95% CI 1.56-9.65, $p = 0.004$) and hypertension (aHR, 1.64, 95% CI 0.77-3.50, $p = 0.19$).

To address the potential bias linked to the mode of HIV acquisition 'unknown', we limited the analyses to people with HIV with known risk factors, resulting in a restricted cohort of 561 individuals: age ≥50 years was significantly associated with AEs (HR 2.45, 95% CI 1.17–5.12, $p = 0.018$). No other demographic or clinical characteristics were associated with AEs.

Kaplan–Meier methods were used to estimate the cumulative incidence of first AEs over time (Figures 1 and 2). In the entire cohort ($n = 598$), participants aged ≥ 50 years had a higher cumulative incidence of AEs compared with those <50 years (Log-Rank $\chi^2 = 5.07$, $p = 0.0243$). In the restricted cohort excluding participants classified as 'unknown' ($n = 561$), age ≥50 years remained the only factor significantly associated with a higher cumulative incidence of AEs (Log-Rank $\chi^2 = 5.69$, $p = 0.0171$).

AEs management: investigation results

Among the 25 participating centres that enroled at least one people with HIV in the study period, feedback was obtained from 23 centres. All responding centres (23/23, 100%) reported that AEs related to LA injectable

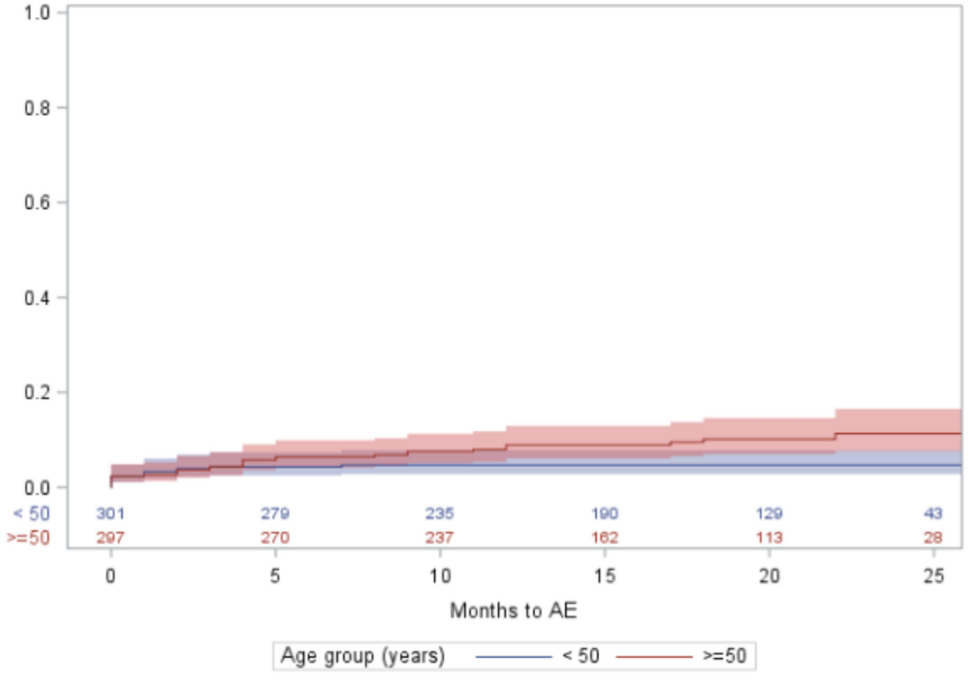

Figure 1. Cumulative Incidence of Adverse Events by Age Group in the Whole Cohort. Cumulative incidence of adverse events stratified by age group (<50 years vs. ≥ 50 years) in the whole cohort ($n = 598$). Shaded bands represent the 95% confidence intervals. Differences between groups were assessed using a two-sided log-rank test (log-rank $p = 0.0243$).

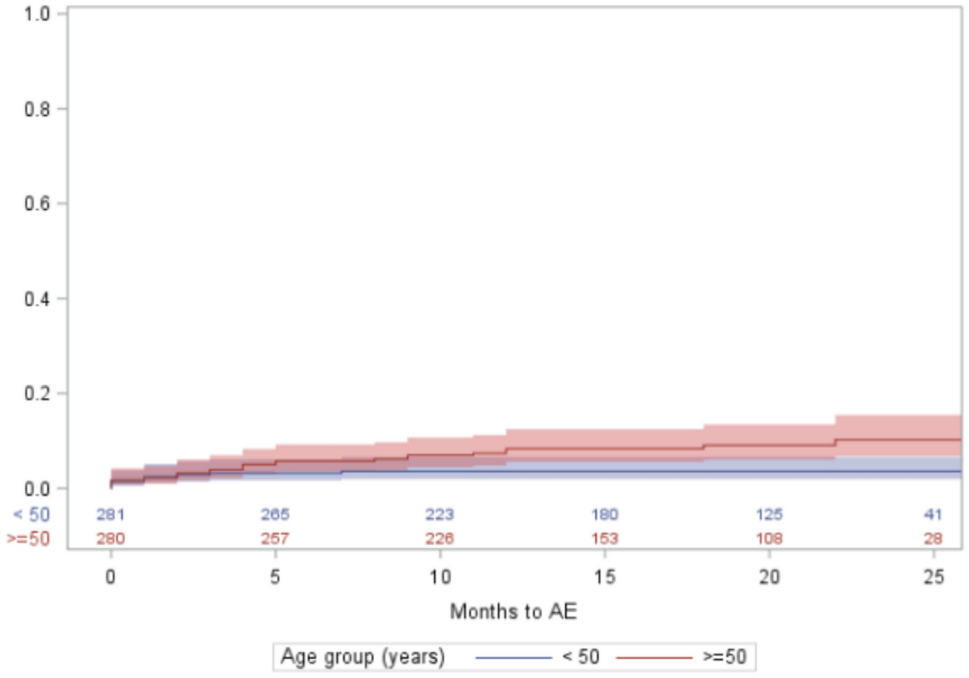

Figure 2. Cumulative Incidence of Adverse Events by Age Group in the Restricted Cohort. Cumulative incidence of adverse events stratified by age group (<50 years vs. ≥ 50 years) in the restricted cohort excluding participants with unknown HIV acquisition mode ($n = 561$). Shaded bands represent the 95% confidence intervals. Differences between groups were assessed using a two-sided log-rank test (log-rank $p = 0.0171$).

regimen were actively collected during routine clinical follow-up. Despite this approach, only 5 centres (21.7%) reported systematically recording all AEs, including grade 1–2 events. Meanwhile, 14 centres (60.9%) stated that AEs were recorded if recurrent and/or persisting across follow-up visits. A minority of centres (5/23, 21.7%) reported that mild to moderate AEs may be underreported or underestimated by people with HIV receiving LA injectable regimen.

Furthermore, 15 centres (65.2%) reported in our survey a perceived reduction in injection-related events following training of staff administering LA injectable CAB + RPV skills. Several centres also implemented post-injection measures to improve tolerability, including more accurate control of product temperature (10 centres, 43.5%), use of the dorso-gluteal injection site (13 centres, 56.5%), continuation of the prone position after injection (6 centres, 26.1%), and premedication with anti-inflammatory (1 centre, 4.3%).

Discussion

In this study, we provide an analysis of the incidence and spectrum of AEs observed in a large, prospective, real-world cohort.

The overall frequency of AEs in our cohort was lower than observed in clinical trials (7% compared to approximately 96%) [1–3]. Variability in AEs rates was also observed across real-world cohorts, ranging from rates comparable to clinical trials—such as CUSTOMISE-III [10] and CARISEL [11] which reported rates of up to 90%—to much lower rates, as in the JABS study [12] where no additional AEs beyond ISRs were observed.

To explore the lower incidence of AEs in our cohort, we examined the perspectives of healthcare personnel at the participating centres. This discrepancy is likely attributable to underreporting of mild and moderate events in routine clinical settings: only a minority of participating centres systematically recorded grade 1–2 events, and some clinicians reported that people with HIV may themselves under-report AEs, possibly motivated by the perceived benefit of reduced pill burden, as highlighted by Vinay et al; [13] however, this perception was not uniformly shared across centres.

On the other hand, we observed a high frequency of treatment discontinuation due to AEs, reaching 88% in our cohort, compared to an average of 4% reported in pivotal trials [1–3]. Heterogeneous rates are also emerging from real-life cohorts: AE-related discontinuations accounted for 73.2% of all discontinuations in the Icona cohort [4] and 48% in SCohoLART [14], while lower rates were observed in LONGITUDE (10.5%) [5].

The most frequently reported AE in our cohort were ISRs (29%): despite the prevalence, such events tended to be limited in severity and duration. The survey distributed to participating centres suggests that improving staff injection skills, alongside practical measures such as selecting the dorsogluteal site and controlling product temperature, may contribute to reducing ISRs.

In contrast to the findings reported by Teichner et al. [15], we found no significant difference in AEs occurrence between the first and second year of LA injectable CAB+ RPV use at each centre, and although the number of people with HIV receiving these medications in our cohort was small, no association between antiaggregant or anticoagulant therapy and ISR risk.

Another key point in our study is the close investigation of CNS-related symptoms, given the documented association of CAB and RPV with central nervous system effects [16]. CNS-related symptoms in our cohort were reported by only 4/51 (7.8%) people with HIV, a rate lower than that observed in approval studies (11–13%) [1–3] with variable rates reported across real-world cohorts [11,17].

Despite the limited numbers, the discontinuation rate in this subgroup was notably high (3/4, 75%); larger studies are needed to better characterise the clinical relevance of CNS-related AEs in this setting.

In our cohort, multivariate analyses of the overall cohort, HIV acquisition categorised as 'unknown' was associated with a higher risk of AEs; however, this category is heterogeneous and includes missing data, limiting the robustness of the analysis. Age ≥50 years showed a consistent trend towards higher AE risk across all models, though it did not reach statistical significance in the multivariable analysis of the overall cohort (aHR 1.79, 95% CI 0.90–3.58, $p = 0.099$).

Sensitivity analyses excluding the 'unknown' HIV acquisition mode group confirmed that age ≥50 years was the only significant independent predictor of AEs (HR 2.45, 95% CI 1.17–5.12, $p = 0.018$), supported by Kaplan–Meier analyses showing shorter AE-free survival in this age group. This association is clinically relevant and should be considered when counselling patients prior to LA CAB+ RPV initiation. Several biological mechanisms may underlie this finding: as aging-related sarcopenia and altered muscle blood flow may affect drug release, together with the greater burden of multimorbidity and polypharmacy typical of this population, may increase the risk of AEs [18].

No other demographic or clinical factors were associated with AEs occurrence.

Overall, these findings suggest that older age may identify people with HIV at higher risk of AEs during LA injectable CAB+ RPV, while the association with HIV acquisition category 'unknown' should be interpreted with caution, and warrants further investigation.

Among the study limitations, the relatively short follow-up period may have limited the identification of long-term AEs, and the restricted demographic diversity within the cohort may limit the generalisability of our findings. Additionally, AEs were not systematically collected, which should be considered when comparing the observed incidence with data from clinical trials. Due to the observational design of the study, some variables were found to have missing data, such as HIV acquisition mode. Moreover, as this analysis aimed to explore both AEs incidence and related potential risk factors in a real-world setting, we did not have a main intervention/exposure to include in a formal power calculation.

Finally, the exploratory questionnaire administered to participating centres was not formally validated, therefore, the responses should be interpreted with caution. As this was a purely observational study that did not address people with HIV selection for LA injectable CAB + RPV initiation or management strategies the findings should be interpreted as descriptive rather than prescriptive for clinical decision-making.

Conclusions

In this large real-life cohort of people with HIV receiving LA injectable CAB+ RPV, the overall incidence of AEs was lower than that reported in pivotal clinical trials, yet a comparatively higher proportion of events led to treatment discontinuation. This discrepancy likely reflects differences between trial settings

and routine clinical practice in the absence of systematic assessment, where mild or transient AEs may be underreported.

Age ≥50 years emerged as the only independent predictor of AEs, suggesting that older people with HIV may require closer monitoring and tailored counselling prior to LA CAB+ RPV initiation. These findings underscore the importance of AE collection in real-world settings to better inform clinical decision-making.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AI statement

During the preparation of this work, the authors utilised AI tools to assist exclusively with language editing. The authors have carefully reviewed the content and take full responsibility for the final version of the manuscript.

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