

# One Year of Long-Acting Cabotegravir and Rilpivirine in People With Human Immunodeficiency Virus and Long Exposure to Antiretroviral Therapy: Data From the SCohoLART Study

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**Background.** The aim of the study was to evaluate the 12-month cumulative probability of treatment discontinuation (TD) in people with human immunodeficiency virus (HIV; PWH) and a long exposure to antiretroviral therapy (ART) switching to long-acting cabotegravir and rilpivirine (CAB/RPV).

**Methods.** SCohoLART is a single-center, prospective, cohort study designed to collect both samples and clinical data from PWH with virological suppression who switched to bimonthly long-acting CAB/RPV. TD occurred at switch to another regimen for any reason including virological failure (VF); VF was defined as HIV RNA levels  $\geq 50$  copies/mL at 2 consecutive measurements or a single HIV RNA level  $\geq 1000$  copies/mL. Results were reported as median (interquartile range [IQR]) or frequency (percentage). Cumulative probabilities of TD were estimated using Kaplan-Meier curves.

**Results.** We evaluated 514 participants; 467 (90.9%) were male, and their median age (IQR) was 49 (40–56) years. At the time of switching, the median time from HIV diagnosis and the median duration of ART were 14.0 (IQR, 8.8–20.5) and 11.4 (7.9–17.4) years, respectively; before starting CAB/RPV, the median number of antiretroviral regimens was 3 (2–4). During a median study follow-up (IQR) of 13.1 (9.1–15.5) months, 52 PWH (10.1%) experienced TD, including 4 (0.8%) for VF. The 12-month cumulative probability of TD was 11% (95% confidence interval, 8%–14%). The main cause of TD was injection site reaction (15 participants [28.8%]).

**Conclusions.** The 1-year cumulative probability of TD with long-acting CAB/RPV was quite low in this cohort of people with a median exposure to ART of 10 years, in whom injection site reaction was the leading cause of TD. VFs were rare during study follow-up.

**Keywords.** HIV; antiretroviral agents; cabotegravir; rilpivirine drug combination; long-acting drugs; virological suppression.

Antiretroviral therapy (ART) has dramatically changed the course of human immunodeficiency virus (HIV) infection, reducing the incidence of AIDS-defining events and death [1, 2]. Although current oral regimens are highly effective in achieving and maintaining virological suppression, the burden of daily pill administration, treatment adherence, and infection-associated stigma remain concrete issues in the management of people with HIV (PWH) [3].

Therefore, long-acting therapy in HIV infection represents an innovative strategy to address the aforementioned unmet need, thus positively affecting the quality of life. The combination of

cabotegravir (CAB), a novel integrase strand transfer inhibitor (INSTI) and rilpivirine (RPV), a nonnucleoside reverse-transcriptase inhibitor (NNRTI), has been shown to be effective and safe in phase 3 studies when administered as a monthly or bimonthly intramuscular injection [4–7].

Considering the promising results obtained from the trials, CAB/RPV was approved for medical use in December 2020 by the European Medicines Agency and in January 2021 by the US Food and Drug Administration [8, 9]. However, results from phase 3 trials are based on populations with a short exposure to antiretroviral drugs, which may not be generalizable to PWH with a decades-long history of ART, who represent the majority of patients in clinical practice in high-income countries [4–7].

Currently, there are no data to our knowledge on PWH with >10 years of ART receiving CAB/RPV for  $\geq 1$  year; therefore, it is very important to evaluate the impact of long-acting therapy on clinical outcomes, even in those with long ART exposure. The aim of the study was to evaluate the 12-month cumulative probability of treatment discontinuation (TD) in PWH with prolonged use of ART switching to long-acting CAB/RPV therapy.

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## METHODS

### Study Design and Participants

SCohoLART (cohort study of HIV-positive people treated with long-acting ART; NCT05663580) is a single-center, prospective, cohort study designed to collect both samples and clinical data from PWH on virological suppression who switched to bi-monthly long-acting CAB/RPV (600/900 mg), followed up at the Department of Infectious Diseases of IRCCS San Raffaele Scientific Institute in Milan, Italy. Adult PWH with HIV RNA levels <50 copies/mL on ART were enrolled at the start of CAB/RPV (baseline); the decision to start with oral lead-in or directly with CAB/RPV injections was made after consultation with the participant's physician. People with any contraindication to the use of  $\geq 1$  long-acting drugs, according to the data sheet of the study medications (including present or past evidence of viral resistance or prior virological failure to NNRTIs or INSTIs) [10, 11], were excluded from SCohoLART.

After initiation of CAB/RPV, HIV RNA testing were monitored at months 1, 3, and 6 and then every 6 months; the same schedule was used to monitor hepatitis B virus (HBV) DNA levels in those who are positive for antibodies to the HBV core antigen (HBcAbs). If HIV RNA was detected at >50 copies/mL, testing was repeated within the next 4 weeks. Routine blood tests were required every 6 months, including renal and metabolic assessment.

To ensure maximum adherence to scheduled injections, visits for CAB/RPV administration were managed via an app that could be freely downloaded from any mobile device, reminds patients of their appointments 48 hours in advance, and allows them to reschedule their visit for injections within the dosing period. Enrollment started on 15 July 2022, with a freeze date of 6 March 2024 for study analyses. Participants also remained in the cohort after stopping the long-acting regimen, to monitor the virological response to a rescue regimen (in case of virological failure [VF]) or toxic effects (in case of discontinuation due to adverse events).

All participants provided written informed consent before enrollment. The study protocol was approved by the Ethical Committee of IRCCS San Raffaele Scientific Institute (approved 20 June 2022; protocol 45/INT/2022). SCohoLART was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

### Outcomes

The primary end point of the study was the cumulative proportion of people experiencing TD over 12 months. TD was considered at the occurrence of VF, defined as 2 consecutive HIV RNA levels  $\geq 50$  copies/mL or a single level  $\geq 1000$  copies/mL after initiation of long-acting CAB/RPV or at switching to another regimen for any reason. Additional secondary end points were the proportion of participants with VF and viral blips, defined as an isolated HIV RNA value  $\geq 50$  and <1000

copies/mL with adjacent values <50 copies/mL. Safety end points included renal, weight, and metabolic changes during study follow-up.

### Statistical Analysis

Participant characteristics at baseline were reported as median (interquartile range [IQR]) or frequency (percentage). Linear mixed models with random intercept and slope were calculated to estimate crude mean changes in renal and metabolic parameters; slopes ( $\beta$  coefficient) were reported with the corresponding 95% confidence intervals (CIs). Overall, 26 participants starting/stopping a statin during follow-up were excluded.

Cumulative probabilities (and the corresponding 95% CIs) of TD were estimated using Kaplan-Meier curves. The analyses were conducted using 2-sided *t* tests (with significance defined at  $\alpha = .05$ ) and using R Statistical Software, version 4.2.2 (R Foundation for Statistical Computing).

## RESULTS

We included 514 participants: 467 (90.9%) were male, and the median age (IQR) was 49 (40–56) years. The median time from HIV diagnosis, duration of ART, and duration of virological suppression were 14.0 (IQR, 8.8–20.5), 11.4 (7.9–17.4), and 8.6 (5.1–12.8) years, respectively. At baseline, the median CD4<sup>+</sup> cell count (IQR) was 794/ $\mu$ L (602–994/ $\mu$ L), and the median CD4<sup>+</sup>/CD8<sup>+</sup> cell ratio 0.97 (0.69–1.28), while the median nadir CD4<sup>+</sup> cell count was 334/ $\mu$ L (214–512/ $\mu$ L).

The previous ART regimen was INSTI based in 313 participants (60.9%), NNRTI based in 130 (25.3%), and protease inhibitor based in 16 (3.1%); overall, 177 (34.4%) were on a 2-drug regimen, including 124 of 182 (68.1%) on dolutegravir (DTG)/lamivudine (3TC) and 45 of 182 (24.7%) on DTG/RPV. We also enrolled 122 PWH (30.2%) who were positive for HBcAb and negative for HBV surface antigen (HBsAg). At baseline, 55 participants (10.7%) received oral lead-in with CAB/RPV before starting injections. The main participant characteristics are reported in [Table 1](#).

During the SCohoLART study, 3438 ventrogluteal injections were administered. Excluding 514 first injections, 2924 injections were performed through the follow-up, and 2870 (98.2%) of the scheduled injections were administered within the dosing window of  $\pm 7$  days; in addition, 2 (0.01%) were received >7 days before the scheduled injection date and 52 (1.8%) >7 days after the scheduled injection date, as shown in [Figure 1](#).

During a median time study follow-up time (IQR) of 13.1 (9.1–15.5) months, 52 PWH (10.1%) experienced TD; the median time to TD was 5.1 (2.7–8.9) months. The main cause of TD was injection site reaction (ISR) in 15 participants (28.8%), followed by toxic effects (excluding gastrointestinal and central nervous system effects) in 10 (19.2%). All the reasons for TD are listed in [Table 2](#).

**Table 1. Participant Characteristics at Time of Switch to Cabotegravir and Rilpivirine**

Characteristic	Participants, No. (%) <sup>a</sup> (N = 514)
Age, median (IQR), y	49 (40–56)
Male sex	467 (90.9)
HIV risk group	
Men who have sex with men	364 (70.8)
Heterosexuals	58 (11.3)
People who inject drugs	11 (2.1)
Other	81 (15.8)
Time from HIV diagnosis, median (IQR), y	14.0 (8.8–20.5)
Duration of ART, median (IQR), y	11.4 (7.9–17.4)
Previous AIDS diagnosis	52 (10.3)
HIV RNA	
Target not detected	324 (63.0)
<50 copies/mL	190 (37.0)
CD4 <sup>+</sup> cell count, median (IQR), cells/ $\mu$ L	794 (602–994)
Nadir CD4 <sup>+</sup> cell count	
>200/ $\mu$ L	389 (76.4)
$\leq$ 200/ $\mu$ L	120 (23.6)
CD8 <sup>+</sup> cell count, median (IQR), cells/ $\mu$ L	850 (643–1114)
HBcAb positive	122 (30.2)
HCV Ab positive	56 (11.2)
Duration of ART regimen at CAB/RPV switch, median (IQR), y	3.4 (2.2–5.4)
No. of drugs in ART regimen at CAB/RPV switch, median (IQR)	3.00 (2.00–3.00)
Type of ART regimen at CAB/RPV switch	
2 NRTIs + 1 PI	14 (2.8)
2 NRTIs + 1 NNRTI	124 (24.6)
2 NRTIs + 1 INSTI	179 (35.5)
1 NRTI + 1 INSTI	124 (24.6)
1 INSTI + 1 NNRTI	45 (8.8)
PI monotherapy	5 (1.0)
Other	13 (2.5)

Abbreviations: ART, antiretroviral therapy; CAB/RPV, cabotegravir and rilpivirine; HBcAb, antibodies to hepatitis B virus core antigen; HCV Ab, hepatitis C virus antibody; HIV, immunodeficiency virus; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

<sup>a</sup>Data represent no. (%) of participants unless otherwise specified.

Overall, 1 of 122 participants positive for HBcAb discontinued treatment due to the acute exacerbation of chronic hepatitis B: at baseline, HBsAg and HBV DNA were negative for 6 years; the HBV genotype was A both before and after the start of the CAB/RPV regimen. After CAB/RPV interruption, the participant restarted the previous ART regimen with bicitegravir (BIC)/emtricitabine (F)/tenofovir alafenamide (TAF), which had been taken for almost 3 years before the injections; transaminase levels normalized after 4 weeks, and HBV DNA returned to negative at 24 weeks.

One participant died of complications secondary to a metastatic biliopancreatic adenocarcinoma, diagnosed 2 months after the start of long-acting therapy and considered unrelated to current antiretroviral drugs.

Among participants who experienced TD, 4 (0.8%) had VF and switched to CAB/RPV from an INSTI-based regimen (2 from BIC/F/TAF, 1 from DTG/3TC/abacavir, and 1 from DTG/RPV). The first participant met VF criteria at month 5 with HIV RNA levels of 371 copies/mL at the first and 436 copies/mL at the second measurement; virological suppression was achieved 4 weeks after initiation of darunavir/cobicistat (DRV/c)/F/TAF.

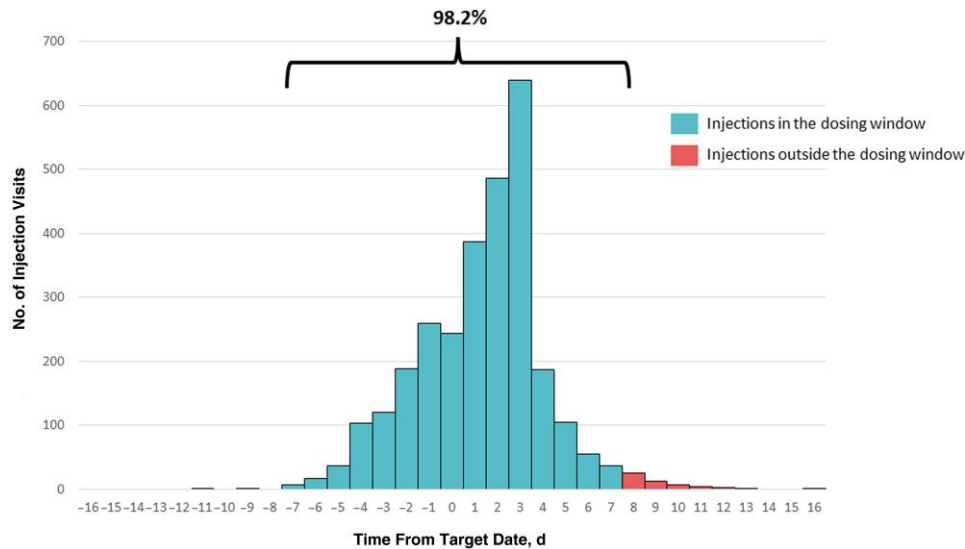
At month 5, the second participant's viral load reached 34 300 copies/mL, leading to discontinuation of the long-acting regimen in favor of DRV/c/F/TAF; an HIV RNA level <50 copies/mL was obtained again 32 weeks after the therapeutic switch. The third participant had an initial HIV RNA of 636 copies/mL at month 6, then 66 500 copies/mL 2 weeks later; after the stopping of CAB/RPV, DRV/c/F/TAF was started, and the viral load after 20 weeks was undetectable. Finally, at month 3, the fourth participant had 2 consecutive HIV RNA values >50 copies/mL, specifically 276 and 55 copies/mL; virological suppression was achieved 1 week after the switch to BIC/F/TAF.

The first 3 participants had a sexually transmitted infection concomitant with VF, 2 with gonococcal urethritis and 1 with primary syphilis, which were adequately treated at the time of symptom onset. Moreover, these 3 participants had received an NNRTI-based regimen in the past (RPV-containing ART in 2 people) for  $\geq$ 2 years and maintained virological suppression over the course of oral therapy; they had resistance-associated mutations to RPV and INSTIs on genotypic resistance testing (GRT) performed on both RNA and DNA at failure. For these participants, pretreatment genotypes were not available.

All the PWH experiencing VF received injections within the dosing window; detailed characteristics of participants with VFs are summarized in Table 3. The cumulative probabilities of TD were 3% (95% CI, 2%–5%) at month 3, 6% (4%–8%) at month 6, and 11% (8%–14%) at month 12, as illustrated in Figure 2.

At discontinuation of long-acting therapy, 16 participants (30.8%) started DTG/3TC, 15 (28.8%) BIC/F/TAF, 7 (13.5%) RPV/F/TAF, 4 (7.7%) DTG/RPV, 4 (7.7%) DRV/c/F/TAF, and 5 (9.6%) other drug regimens. After switching from long-acting therapy with CAB/RPV, all participants maintained or achieved HIV RNA levels <50 copies/mL. The proportion of PWH with viral blips throughout the study was 4.5% (23 of 514); before starting injections, 11 (47.8%) were on an INSTI plus 2 nucleoside reverse-transcriptase inhibitors, 7 (30.4%) on an NNRTI plus 2 nucleoside reverse-transcriptase inhibitors, and 5 on dual therapy (21.7%). VF did not develop in any participants with viral blips.

At CAB/RPV initiation, the median creatinine level (IQR) was 1.1 (1.0–1.2) mg/dL, and median estimated glomerular filtrate rate (eGFR; obtained using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) was 80



**Figure 1.** Proportion of injection visits occurring within the dosing window.

**Table 2. Reasons for Discontinuation of Long-Acting Treatment**

Reason for Discontinuation	Participants, No. (%) (n = 52)
Injection site reaction	15 (28.8)
Other toxic effects <sup>a</sup>	10 (19.2)
Other causes <sup>b</sup>	8 (15.4)
Participant's wish/decision	5 (9.6)
Virological failure	4 (7.7)
Central nervous system toxic effects	4 (7.7)
Gastrointestinal tract toxic effects	3 (5.8)
Hypersensitivity reaction/allergy	2 (3.8)
Death <sup>c</sup>	1 (1.9)

<sup>a</sup>Other toxic effects included pyrexia in 3 participants; fatigue, joint stiffness, and weight gain in 2 each; and polyarthralgia in 1.

<sup>b</sup>Other causes included personal commitments incompatible with scheduled injection visits in 2 participants and transfer to another country, hepatitis B virus reactivation, pregnancy, viral blip, enrollment in another study protocol, and chemotherapy-induced thrombocytopenia in 1 each.

<sup>c</sup>One participant died of complications secondary to a metastatic biliarypancreatic adenocarcinoma.

(70–89) mL/min/1.73 m<sup>2</sup>. Overall, the mean changes (95% CIs) in creatinine level and eGFR were –0.1 mg/dL/y (–.1 to –0.1) and +2.8 (1.9–3.8) mL/min/1.73 m<sup>2</sup> (both *P* < .001).

Regarding the metabolic profile, at baseline the median total cholesterol (TC) level (IQR) was 180 (159–202) mg/dL; the median high-density lipoprotein (HDL) cholesterol (HDL-C) level, 48 (41–57) mg/dL, and the median low-density lipoprotein cholesterol level, 113 (96–136) mg/dL; moreover, the median TC/HDL-C ratio was 3.7 (3.1–4.4). The median triglyceride level (IQR) was 99 (76–136) mg/dL, while median glucose level and homeostatic model assessment for insulin resistance were 89 (82–96) mg/dL and 1.7 (1.2–2.7), respectively; furthermore, the median weight was 76 (69–85) kg, and the median body mass index (BMI) 25 (23–27) (calculated as weight in kilograms

divided by height in meters squared). In participants switching to long-acting therapy, the mean changes in HDL-C and TC/HDL-C ratio were +3.0 mg/dL/y (95% CI, 1.9–4.1) and –0.2/y (–.3 to –0.1), respectively (both *P* < .001). Other changes are described in Table 4.

## DISCUSSION

In this cohort of PWH with a median exposure to ART of 10 years, the cumulative probability of TD during the first year of CAB/RPV was quite low, with few cases of VF, consistent with findings from previous trials. In the phase 3 SOLAR and FLAIR trials, rates of discontinuation for long-acting therapy at 48 weeks were slightly less than 10% (43 of 447 [9.6%] and 25 of 283 [8.8%], respectively), while in real-life studies TD rates are between 12% and 13% [12, 13]. The reasons for stopping regimen were heterogeneous; moreover, grade 4 drug-related adverse events were anecdotal [4–7]. ISRs were the most common clinical event reported in trials, mostly mild or moderate, but only a small number of patients discontinued long-acting therapy due to the appearance of pain, nodules, or edema. Indeed, the proportion of participants interrupting CAB/RPV for ISRs in most phase 3 trials (ATLAS, ATLAS-2 M, and FLAIR) was about 1% at 48 weeks [5–7, 12–16]; our results are comparable to those of the SOLAR study, which reported 10 of 447 discontinuations (2.2%) for ISRs in the first year of long-acting treatment [4].

Although our findings are in line with those of clinical trials, PWH enrolled in the SCohoLART study have different characteristics; in fact, our participants had a longer duration of ART exposure and a higher median age, with about 15% of PWH >60 years old included in the analysis. Phase 3 clinical trials

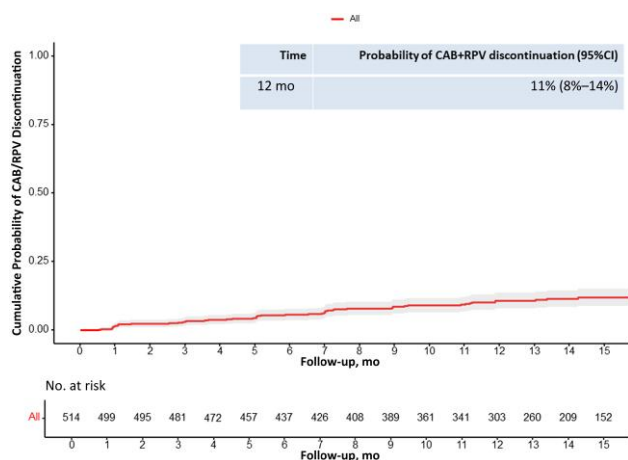
**Table 3. Characteristics of Participants Experiencing Virological Failure**

Participant/ Sex/Age, y	Year of HIV Diagnosis	Subtype	BMI <sup>a</sup>	Pre-CAB/ RPV Regimen	HIV RNA at VF, Copies/ mL	RPV at VF, ng/ mL	STI at VF	GRT at VF <sup>b</sup>	Post-CAB/ RPV Regimen	HIV RNA After CAB/ RPV Switch, Copies/mL
1/Male/50	2005	B	22.2	DTG/ABC/ 3TC	371; 436	121.8	Gonococcal urethritis	NNRTI (RNA): E138A NNRTI (DNA) E138EA INSTI (RNA): E138EK, Q148R; INSTI (DNA): Q148QR	DRV/c/F/ TAF	<50 (after 4 wk)
2/Male/41	2007	B	25.7	DTG/RPV	34 300	170.5	Gonococcal urethritis	NNRTI (RNA) K101PQ, E138A INSTI (RNA) E138K, Q148R	DRV/c/F/ TAF	<50 (after 32 wk)
3/Male/56	2012	B	24.6	BIC/F/TAF	636; 66 500	50.5	Primary syphilis	NNRTI (RNA) K101E, E138A NNRTI (DNA) K101KE, E138EA; INSTI (RNA/DNA): E157Q	DRV/c/F/ TAF	<50 (after 20 wk)
4/Male/57	2018	B	25.3	BIC/F/TAF	276; 55	70.8	/	WT for NNRTIs and INSTIs	BIC/F/TAF	<50 (after 1 wk)

Abbreviations: 3TC, lamivudine; ABC, abacavir; BIC, bictegravir; BMI, body mass index; CAB/RPV, cabotegravir and rilpivirine; DRV/c, darunavir/cobicistat; DTG, dolutegravir; F, emtricitabine; GRT, genotypic resistance testing; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse-transcriptase inhibitor; STI, sexually transmitted infection; TAF, tenofovir alafenamide; VF, virological failure; WT, wild type.

<sup>a</sup>BMI calculated as weight in kilograms divided by height in meters squared.

<sup>b</sup>Pretreatment GRT was available only for participant 4: HIV was WT for both NNRTIs and INSTIs. All participants received injections within the dosing window.



**Figure 2.** Cumulative probability of treatment failure. Abbreviations: CAB/RPV, cabotegravir and rilpivirine; CI, confidence interval.

have included PWH with a short history of ART; the median duration of antiretroviral drug use did not exceed 2.5 years or participants could not have received >2 antiretroviral regimens since HIV diagnosis to be included in the study [4–7]. In addition, the median age of participants receiving long-acting therapy in the clinical trials was approximately 7–15 years younger than in our study, with a maximum of 42 years [4–7].

Older people are typically underrepresented in phase 3 studies. They are a category to be considered because they have an increased incidence of comorbid conditions, and the impact of new antiretroviral drugs should be carefully evaluated in this population. Although real-world data have described PWH

**Table 4. Crude Mean Changes in Renal, Weight, and Metabolic Parameters After Switch to Cabotegravir and Rilpivirine**

Variable	Overall Crude Mean Change (Slope) per Year (95% CI)	P Value
Creatinine, mg/dL	−0.1 (−.1 to −.1)	<.001
eGFR, mL/min/1.73 m <sup>2</sup>	2.8 (1.9–3.8)	<.001
Weight, kg	0.4 (−.2 to 1.0)	.15
BMI <sup>a</sup>	0.1 (0–.3)	.12
Glucose, mg/dL	0.2 (−.2 to 2.4)	.88
HOMA index	0.1 (−.2 to .5)	.45
Triglycerides, mg/dL	−3.3 (−8.1 to 1.5)	.18
TC, mg/dL	0.5 (−2.4 to 3.3)	.75
HDL-C, mg/dL	3.0 (1.9–4.1)	<.001
LDL-C, mg/dL	0.5 (−1.9 to 2.9)	.70
TC/HDL-C ratio	−0.2 (−.3 to −.11)	.001

Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtrate rate; HDL, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment insulin resistance; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

<sup>a</sup>BMI calculated as weight in kilograms divided by height in meters squared.

with characteristics more similar to those in the SCohoLART study than in the trials, there are still no published data on participants >50 years old with at least a decade of ART history receiving CAB/RPV for >1 year. Therefore, it was crucial to observe a VF rate <1% even in a population with long-term antiretroviral exposure, with previous therapeutic switching studies reporting VFs ranging between 1% and 2% [4–7, 12–18]; this consistency was also found in the percentage of viral blips recorded [19].

Thus, it is important to identify PWH at highest risk for VF. According to a pooled analysis of 1651 participants, having ≥2

of the following significantly increased the risk of experiencing treatment failure: the presence of RPV resistance-associated mutations, HIV subtype A6/A1, and BMI  $\geq 30$  at the time of switching to CAB/RPV [20]. Indeed, higher BMI has been proved insufficient to decrease the efficacy of CAB/RPV in virologically suppressed individuals at the start of long-acting therapy, as shown in the OPERA cohort, where no differences in VF were found between 1022 PWH with a BMI  $< 30$  and 450 with a BMI  $\geq 30$  [21]. In our study, all 4 participants who experienced VF had a BMI  $< 30$  and were subtype B, and only 1 had an RPV concentration close to the threshold target of 50 ng/mL at treatment failure.

We also observed the concomitance of a sexually transmitted infection in 3 of the 4 participants in whom VF developed; the numbers are clearly too small to investigate a correlation, but we know that the onset of syphilis and gonorrhea can lead to viral blips in people who are virologically suppressed [22, 23]. Furthermore, 4 of 4 switched from an INSTI-based regimen and 3 of 4 previously received an NNRTI-based regimen, without ever recording a treatment failure and thus always maintaining undetectable viremia. Thus, VF with injectable CAB/RPV can also occur in the absence of known risk factors at baseline, similarly to what has been described in 3 of 5 PWH with treatment failure reported by van Welzen et al [24].

In our study, of the 3 participants who developed resistance-associated mutations to INSTIs and NNRTIs at VF, none had available pretreatment GRT. In fact, in people without failure of previous therapy containing INSTIs and/or NNRTIs, it is not currently indicated to require GRT on peripheral DNA before starting a long-acting CAB/RPV regimen. However, there are mutations in the reverse transcriptase gene, such as those at position 138 (particularly E138A), that can occur as natural polymorphisms in about 3%–4% of PWH, especially if harboring non-B subtype viruses [25]. Because mutations at codon 138 (K, Q/G, R) are associated with reduced susceptibility to RPV [26], GRT on peripheral DNA may be considered in patients without historical GRT to better identify candidates for long-acting therapy and to prevent VFs in those harboring drug-resistant variants.

In the SCohoLART study, 1 participant discontinued treatment due to the acute exacerbation of chronic hepatitis B, which resolved after starting BIC/F/TAF. Although cases of HBV reactivation during dual therapy, including CAB/RPV, are very rare in the literature [26, 27], it is important to check HBV serology before initiating long-acting therapy and monitor HBV DNA in patients who are HBcAb positive and HBsAg negative.

CAB/RPV is a regimen that has proved to be safe and well tolerated, with comparable results in real-world and phase 3 randomized clinical trials [4–7, 12–17]. The SOLAR study evaluated weight, BMI, and body composition measurements in 454 participants switching to CAB/RPV and 227 continuing on BIC/F/TAF in the first year of follow-up; changes in metabolic parameters were minimal and similar between the 2

groups, and there were no differences in the proportions of PWH with metabolic syndrome or insulin resistance [28].

In people switching to long-acting treatment enrolled in the SCohoLART study, HDL levels slightly increased; data on lipid profile in 2-drug regimens are often conflicting, showing either a decrease or an increase in HDL-C with treatment switching, depending on the study [29–32]. The simplification from 3 to 2 drugs in  $> 60\%$  of participants and the absence of drugs known to be associated with the development of dyslipidemia in long-acting therapy may have led to the improvement in lipid profile; however, longer follow-up is needed to confirm these changes over time and assess potential cardiovascular risk modification.

We also observed a decrease in serum creatinine and a consequent increase in eGFR after the switch to long-acting therapy. CAB does not appear to inhibit tubular secretion of creatinine, as it does not lead to inhibition of renal organic cation transporter 2 and multidrug and toxin extrusion transporter 1 [33]. The HPTN083 study, designed to compare the efficacy of CAB with that of tenofovir disoproxil fumarate/F for HIV preexposure prophylaxis, showed that CAB alone could reduce serum creatinine [34], and our study confirmed that combining CAB with RPV also results in this change.

One study limitation is the lack of assessment of CAB concentrations (data on RPV concentrations not shown), which would also allow us to better investigate the underlying causes of VFs. In addition, our cohort mainly included men with a good immunological profile. These results may not be generalizable to other populations, such as women or PWH with more advanced immunosuppression.

In conclusion, the 1-year cumulative probability of TD with CAB/RPV was quite low, and TDs were mostly due to ISRs. During the study follow-up, VFs were rare and must be managed with great care on a case-by-case basis. Based on our findings, switching to long-acting therapy is also a valid option in people with a long history of HIV infection and prolonged exposure to ART.

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