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Virological History Predicts Non-sustained Viral Suppression With Long-Acting Cabotegravir and Rilpivirine Therapy, Independent of Pharmacokinetic Parameters

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Background. This study aimed to investigate factors contributing to non-sustained viral suppression, including intermittent viremia and persistent low-level viremia, during cabotegravir (CAB) plus rilpivirine (RPV) long-acting (LA) injectable therapy, with a focus on pharmacokinetics (PK).

Methods. A prospective cohort study was conducted on people with human immunodeficiency virus (HIV, PWH) transitioning from stable oral antiretroviral therapy (ART) to bimonthly CAB + RPV LA. Standardized follow-up included close monitoring through blood sampling for plasma human immunodeficiency virus type 1 (HIV-1) viral load (VL) and multiple plasma drug concentrations measurements to analyze the connection between PK parameters and virologic outcomes.

Results. Among 173 patients with a median (interquartile range [IQR]) follow-up of 11.1(7.1–13.2) months and 789 pre-dose measurements, 38.7% experienced VL ≥ 20 copies/mL, and 16.2% had levels ≥50 copies/mL. Intermittent viremia occurred in 34.7% of patients, and persistent low-level viremia in 4%. Virological failure developed in 2 cases. Predictors of non-sustained viral suppression included VL at HIV diagnosis (adjusted hazard ratio [AHR]: 1.49 per log10 VL, 95% confidence interval [CI]: 1.04–2.12, $P = .027$), detectable viremia on oral ART (AHR: 2.45, 95% CI: 1.29–4.65, $P = .006$), and the level of viral suppression at transition (AHR: 0.38, 95% CI: .19–.75, $P = .004$). We found a significant association between low trough concentrations of CAB and RPV and episodes of detectable viremia exceeding 50 copies/mL. However, none of the assessed PK covariates predicted non-sustained viral suppression in multivariable models.

Conclusions. Non-sustained viral suppression in PWH transitioning from stable oral ART to CAB + RPV LA was linked to preexisting factors before transition. Higher VL pre-ART and incomplete suppression on oral therapy increased the risk, independent of PK parameters.

Keywords. long-acting cabotegravir and rilpivirine; pharmacokinetics; non-sustained viral suppression; viral blips; low-level viremia.

Cabotegravir (CAB) plus rilpivirine (RPV) is the first long-acting (LA) injectable antiretroviral therapy (ART) for human immunodeficiency virus type 1 (HIV-1) infection, demonstrating noninferiority to oral therapy in maintaining virologic suppression in patients with human immunodeficiency virus (HIV, PWH) [1–4]. Across phase 3 studies, virologic failure was infrequent, with an incidence of approximately 1% [1–7].

Pooling data from clinical trials identified baseline factors—RPV resistance-associated mutations (RAMs), HIV-1 subtype A6/A1, and body mass index (BMI) exceeding 30 kg/m^2—as increasing the risk of virologic failure. Although initial analyses linked low RPV and CAB trough concentrations (Ctrough) with virologic failure [8], multivariable models showed these factors did not enhance predictive accuracy beyond the presence of 2 or more baseline factors [9].

Real-world cohorts have corroborated the high efficacy rates observed in clinical trials but have also uncovered instances of

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virologic failure with RAMs, even without known risk factors [10–14]. Pharmacokinetic (PK) analyses revealed low drug levels in some individuals considered at low risk [15], highlighting the potential benefit of therapeutic drug monitoring to optimize outcomes.

A subset of PWH on ART experience mild, transient increases in plasma HIV-1 RNA levels, termed viral "blips" or "intermittent viremia" or "persistent low-level viremia" [16–18]. This phenomenon, associated with treatment failure and/or HIV drug resistance mutations in oral ART regimens [16, 18–22], was infrequent with CAB + RPV LA in phase 3 trials [23]. However, recent real-world data suggest higher prevalence rates in clinical practice [24]. Understanding the causes of non-sustained viral suppression and their potential relationship with suboptimal PK could clarify virological failures with CAB + RPV.

Our objective was to investigate factors contributing to non-sustained viral suppression, including HIV-1 RNA intermittent viremia and persistent low-level viremia, during CAB + RPV LA therapy, with a focus on PK.

METHODS

Study Population

A prospective cohort study was conducted among PWH initiating CAB + RPV LA as part of routine clinical care following European Medicines Agency (EMA) approval at Hospital General de Elche, Spain. All adults ≥18 years who started CAB + RPV from 23 January to 27 December 2023 were invited to participate.

Key inclusion criteria were initiating CAB + RPV with HIV-1 RNA viral load (VL) < 50 copies/mL on stable ART, no prior virological failure with non-nucleoside reverse transcriptase inhibitors (NNRTIs) or integrase strand transfer inhibitors (INSTIs), and receiving CAB + RPV LA for at least 3 months.

Treatment initiation options included an oral lead-in period (CAB 30 mg and RPV 25 mg QD for 1 month) or direct intramuscular loading injection followed by bimonthly injections (CAB 600 mg + RPV 900 mg) 1 month later. The choice of needle length was at the physician's discretion.

The study protocol involved standardized follow-up with specific timing for blood sampling to monitor VL and measure drug concentrations.

Ethics

The protocol received approval from the institutional review board of Hospital General de Elche. Written informed consent was obtained from all participants.

Procedures and Laboratory Measurements

Clinical and laboratory data, including demographic and HIV-related covariates, were collected. Study investigators reviewed medical records, focusing on virological and immunological history, previous ART, and RAMs to NNRTIs or INSTIs in historical genotypes.

Blood samples were collected before each injection to measure plasma VL and CAB and RPV trough concentrations. Plasma was separated by centrifugation and stored at −80°C.

VL was assessed using the COBAS® HIV-1 Test in an automated Cobas 6800 System (Roche Diagnostics SL, Barcelona, Spain). This assay quantifies VL within the range of 20–10 000 000 copies/mL and provides qualitative results (Target Detected/Target Not Detected) for VLs <20 copies/mL.

CAB and RPV trough concentrations were measured in plasma samples taken just before the first injection in participants receiving CAB + RPV oral lead-in, at week 4 post-first injection, and bimonthly thereafter.

The analyses were conducted using previously validated procedures [25] by liquid chromatography coupled with triple quadrupole mass spectrometry detection (LC–QqQ-MS) (Supplementary file).

Virological Definitions and Outcomes

VL profiles were classified into 4 categories: (1) Fully suppressed HIV-1 viremia: all VLs below the limit of detection of the assay (<20 copies/mL); (2) Viral blip or intermittent viremia: a single VL between 20–199 copies/mL (low-range) and 200–999 copies/mL (high-range), with adjacent values <20 copies/mL; (3) Persistent low-level viremia: at least 2 consecutive VL measurements of 20–199 copies/mL; and (4) Virological failure: at least 2 consecutive VL ≥200 copies/mL or a single VL ≥1000 copies/mL.

The primary outcome of interest was non-sustained viral suppression, defined as any episode of plasma VL ≥20 copies/mL after switching to CAB + RPV. This included low- and high-range intermittent viremia as well as persistent low-level viremia but excluded virological failures. Secondary analyses were conducted by selecting participants who had VL <20 copies/mL when they switched to CAB + RPV and by using a VL cutoff of 50 copies/mL instead of 20 copies/mL.

Statistical Analysis

Baseline covariates assessed as potential predictors of non-sustained viral suppression are shown in Supplementary Table 1, including past virological and immunological history, preexisting RAMs to INSTI or NNRTI, ART regimens, duration of viral suppression pre-switch, and the presence of intermittent or persistent low-level viremia before transitioning to CAB + RPV.

Additional covariates included the use of oral lead-in, the frequency of late injections, and CAB and RPV trough plasma concentrations. This included overall drug exposure (median of all available drug levels measured) and concentrations at specific time points: week 4 (4 weeks after the first injection) and week 12 (8 weeks after the second injection).

Proportions of participants with at least 1 VL ≥20 and ≥50 copies/mL before and after transitioning to CAB + RPV were summarized. Patient, viral, and PK variables were compared between those who did and did not experience non-sustained viral suppression after transitioning. This analysis included assessing the proportion of CAB and RPV trough plasma concentrations above or below previously reported thresholds from clinical trials: in vitro protein-adjusted inhibitory concentration required for 90% viral inhibition (PAIC90): 166 ng/mL for CAB, 12 ng/mL for RPV; 4xPAIC90: 664 ng/mL for CAB and 50 ng/mL for RPV; and Q1 Ctrough, twenty-fifth percentile:1120 ng/mL for CAB and 32 ng/mL for RPV [7, 8, 26–29].

Univariate analyses used Pearson χ^2 test or Fisher exact test for categorical variables, and Student *t* test or Mann-Whitney *U* test for continuous variables. Multivariable Cox proportional hazards regression models were performed to explore potential predictors of non-sustained viral suppression. Additionally, mixed-effects Cox regression was applied to analyse the added effect of repeated measures of PK covariates.

Regression models were constructed using the best set of baseline predictors, chosen based on their potential clinical impact and unadjusted associations ($P \leq .1$) with outcome measures. In cases of collinearity among predictors, priority was given to variables more likely to influence clinical decisions. Additional statistical modelling was performed by integrating PK covariates into the models. We compared the accuracy of the models in predicting non-sustained viral suppression to ascertain the contribution of PK factors.

All analyses were conducted using R software version 4.0.3 (R-Core Team 2020, R-4.1.2.1).

RESULTS

Study Population

Of 205 PWH who began CAB + RPV treatment post-EMA approval, 173 met the selection criteria and were analysed. Also, 26 were excluded for receiving only 1 dose, and 6 for starting with viremia due to non-adherence to oral ART. All received CAB + RPV LA bimonthly, with 53.8% (93/173) undergoing an oral lead-in. Baseline characteristics are provided in Supplementary Table 1.

The median age was 48 years, 76.3% were White Spanish, and 85.5% identified as male at birth. The median duration since HIV diagnosis was 11.3 years, with a median VL at diagnosis of 4.79 log10 copies/mL and a median nadir CD4 count of 272 cells/μL.

Only 18.3% (17/93) of participants with available data had HIV-1 non-B subtypes, with none having subtype A6/A1. All were on stable ART, 55.5% on an INSTI-based 2-drug regimen. The median time with VL <50 copies/mL before CAB + RPV was 5.1 years. Within the year before switching, 53.2%, 12.7%, and 4.1% had at least 1 VL measurement of ≥20, ≥50, and ≥200 copies/mL, respectively.

At the baseline visit for transitioning to CAB + RPV, 148 (85.5%) had VL < 20 copies/mL, and 166 (95.9%) had <50 copies/mL. Although only participants with VL < 50 copies/mL were selected for this study, 7 patients (4.0%) had VLs between 50 and 99 copies/mL at the baseline visit (which was after the selection visit). Of the 107 (61.8%) patients with previous resistance testing, none had major INSTI resistance mutations, and 8 (7.5%) had RPV-associated mutations conferring low-level resistance according to the Stanford University HIV Drug Resistance Database [30].

Virological Outcomes

The median follow-up duration of CAB + RPV therapy was 11.1 months. At the last observation carried forward, 154 (89.0%) participants had VL < 20 copies/mL, with 116 having the target not detected. Additionally, 167 (96.5%) had VL < 50 copies/mL and 6 (3.5%) had ≥50 copies/mL.

Throughout the observation period, 61.3%, 84.8%, and 95.9% maintained VLs below 20 copies/mL, 50 copies/mL, and 200 copies/mL, respectively.

The overall unadjusted incidence rate (95% confidence interval [CI]) of detectable viremia per 100 person-years was 45.8 (35.5–58.2) and the median (interquartile range [IQR]) time to detectable VL in those fully suppressed at switching was 14 [5–22] weeks.

In total, 67 (38.7%) of the 173 subjects had non-sustained viral suppression during CAB + RPV: 54 (31.2%) had low-range intermittent viremia, 6 (3.5%) high-range intermittent viremia, and 7 (4.0%) had persistent low-level viremia. Virological failure occurred in 2 cases (1.2%), detailed in Supplementary Table 2. Resistance testing at failure showed one case with RAMs to NNRTI and INSTI, conferring high-level resistance to CAB and intermediate resistance to RPV, while the other case retained full susceptibility to both RPV and CAB.

Pharmacokinetic Parameters

A total of 789 CAB and RPV pre-dose concentration measurements were performed in 173 PWH, with a median of 5 (range, 2–7) determinations per patient. Of these, 88 were performed during the oral lead-in phase (n = 93). Concentrations were significantly higher during the oral lead-in: 11431 [7723–14885] versus 2476 [1714–3565] ng/mL ($P < .001$) for CAB and 2346 [1488–3829] versus 879 [559–1362] ng/mL ($P < .001$) for RPV.

While receiving injectable CAB + RPV, CAB and RPV concentrations ranged from 231 ng/mL to 11184 ng/mL, and from 70 ng/mL to 9440 ng/mL, respectively. There was moderate intrapatient variability for both CAB (coefficient of variation, 40%) and RPV (45%), and large interpatient variability (58% and 78%, respectively).

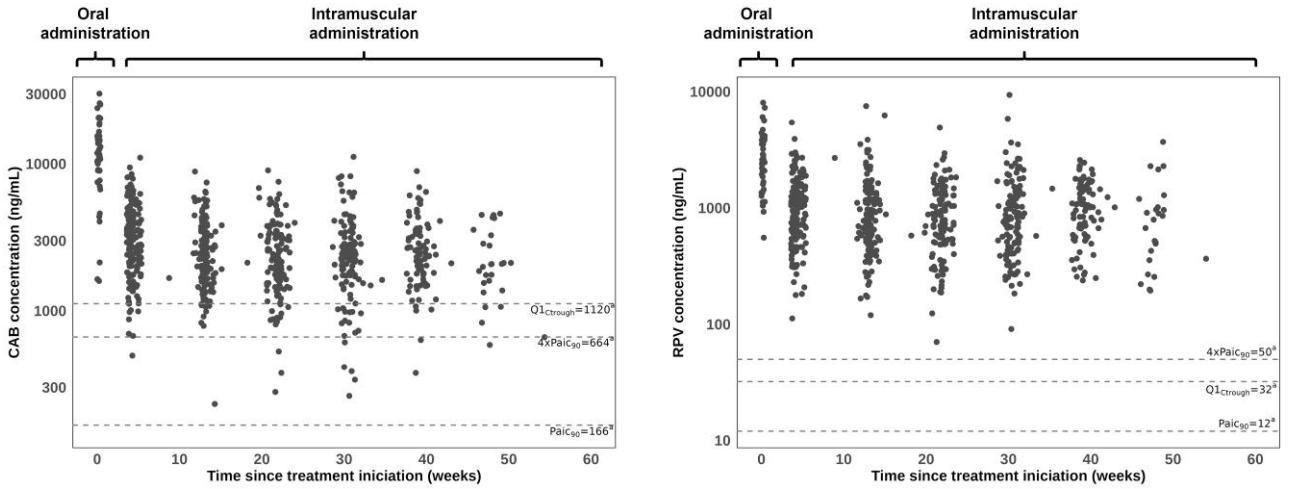

Figure 1. Distribution of all trough plasma concentrations of cabotegravir and rilpivirine determined in study participants. Abbreviations: CAB, cabotegravir; PAIC90, in vitro protein-adjusted inhibitory concentration required for 90% viral inhibition; Q1 Ctrough, 25th percentile in the pooled population from clinical trials; RPV, rilpivirine. [a]Trough concentrations thresholds reported in clinical trials [7, 8, 26–28].

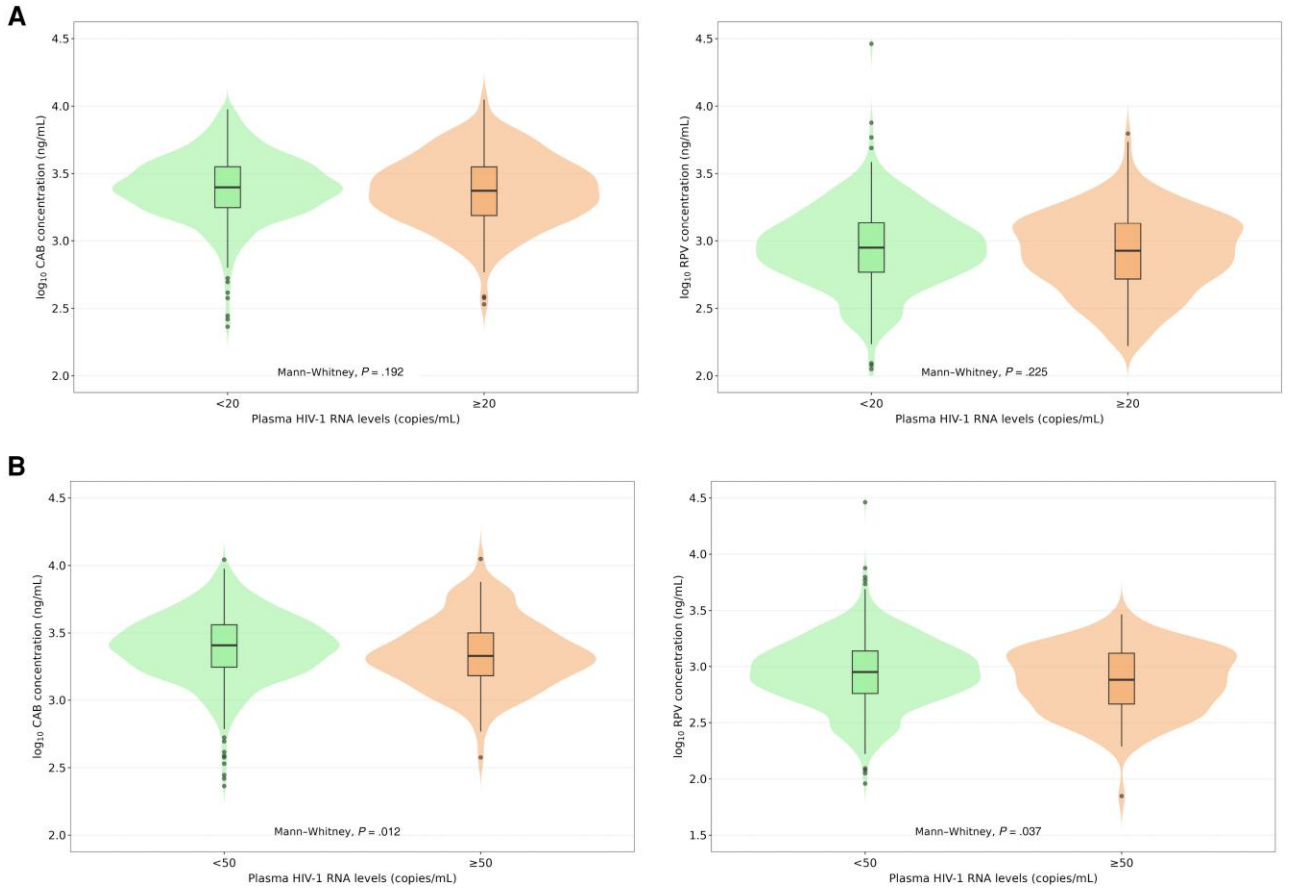

Figure 2. Distribution of trough plasma concentrations of cabotegravir and rilpivirine in study participants with non-sustained viral suppression compared to those with consistent viral suppression. *A*, Patients experiencing any episode of plasma HIV-1 RNA ≥20 copies/mL after switching to cabotegravir plus rilpivirine (65 patients/292 samples), versus those who maintained all HIV viral loads below 20 copies/mL during the observation period (106 patients/406 samples) (*B*) Patients experiencing any episode of plasma HIV-1 RNA ≥50 copies/mL after switching to cabotegravir plus rilpivirine (26 patients/121 samples), versus those who maintained all HIV viral loads below 50 copies/mL during the observation period (145 patients/577 samples). The violin plots represent the distribution of concentration data. The boxplots depict the median and interquartile range. Abbreviations: CAB, cabotegravir; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; RPV, rilpivirine.

Table 1. Cabotegravir and Rilpivirine Trough Plasma Concentrations in Participants With Non-sustained Viral Suppression Compared to Those With Consistent Viral Suppression[a]

Characteristic	Any Plasma HIV-1 RNA ≥20 copies/mL	All Plasma HIV-1 RNA <20 copies/mL	*P* Value	Any Plasma HIV-1 RNA ≥50 copies/mL	All Plasma HIV-1 RNA <50 copies/mL	*P* Value
No. Participants/No. samples	65/292	106/406	…	26/121	145/577	…
Ctrough, median (IQR), log10 ng/mL						
CAB	3.37 (3.19–3.55)	3.40 (3.25–3.55)	.192	3.33 (3.17–3.50)	3.41 (3.24–3.56)	.012
RVP	2.92 (2.71–3.13)	2.95 (2.76–3.14)	.225	2.89 (2.66–3.12)	2.95 (2.75–3.14)	.037
Week 4 Ctrough, median (IQR), log10 ng/mL						
CAB	3.51 (3.30–3.67)	3.44 (3.30–3.60)	.143	3.40 (3.26–3.57)	3.49 (3.32–3.64)	.289
RVP	3.03 (2.83–3.18)	3.02 (2.79–3.14)	.864	2.99 (2.78–3.15)	3.03 (2.81–3.17)	.615
Week 12 Ctrough, median(IQR), log10 ng/mL						
CAB	3.36 (3.21–3.52)	3.39 (3.23–3.54)	.549	3.31 (3.15–3.49)	3.39 (3.24–3.53)	.223
RVP	2.93 (2.75–3.12)	2.90 (2.74–3.12)	.745	2.85 (2.71–2.98)	2.92 (2.76–3.13)	.128
CAB Ctrough, n/N (%)						
<Q1 (<1714ng/mL)	84/292 (28.77)	90/406 (22.17)	.057	38/121 (31.40)	136/577 (23.57)	.089
<Q1 (<1120 ng/mL)[b]	30/292 (10.27)	29/406 (7.14)	.183	14/121 (11.57)	45/577 (7.80)	.239
4xPAIC90 (<664 ng/mL)[b]	5/292 (1.71)	9/406 (2.22)	.845	2/121 (1.65)	12/577 (2.08)	.999
PAIC90 (<166 ng/mL)[b]	0	0		0	0	
RPV Ctrough, n/N (%)						
<Q1 (<559 ng/mL)	80/290 (27.59)	94/406 (23.15)	.213	38/120 (31.67)	136/576 (23.61)	.082
<Q1 (<32 ng/mL)[b]	0	0		0	0	
4xPAIC90 (<50 ng/mL)[b]	0	0		0	0	
PAIC90 (<12 ng/mL)[b]	0	0		0	0	

Abbreviations: CAB, cabotegravir; Ctrough, trough concentrations; HIV-1, human immunodeficiency virus type 1; IQR, interquartile range; n/N (%), denotes number of samples below the threshold (n) out of the number of samples tested (N); PAIC90, in vitro protein-adjusted inhibitory concentration required for 90% viral inhibition; Q1 Ctrough, 25th percentile; RPV, rilpivirine.

[a]The 2 patients with virological failure were excluded.

[b]CAB and RPV trough plasma concentrations thresholds reported in the literature [7, 8, 26–28].

The distribution of all plasma concentrations determined during the study period compared to the ranges reported from clinical trials [7, 8, 26–28] is shown in Figure 1. Median CAB and RPV Ctrough throughout the study remained well above their respective in vitro inhibitory concentrations, being 14.9 times and 73.1 times greater than the PAIC90 of 166 ng/mL for CAB and 12 ng/mL for RPV against wild-type HIV-1. Moreover, more than 75% of CAB and RPV concentrations were above the Q1 trough thresholds reported of 1120 ng/mL and 32 ng/mL, respectively.

Virological Outcomes Relative to Cabotegravir and Rilpivirine Plasma Levels

Figure 2 depicts the distribution of CAB and RPV plasma concentrations based on the presence of non-sustained viral suppression during therapy, excluding the two patients with virological failure. Table 1 compares PK parameters between groups. The plasma concentrations of the two patients who developed virological failure are detailed in Supplementary Table 2, showing Ctrough levels well above the 4xPAIC90 threshold for both CAB and RPV in both cases.

Median trough plasma concentrations of CAB and RPV were slightly lower in participants with non-sustained viral suppression compared to those with consistent viral suppression. These differences were statistically significant in subjects who had any plasma VL ≥ 50 copies/mL during the observation period, as opposed to those who maintained all VLs below 50 copies/mL (Table 1). Additionally, the proportion of plasma CAB levels below the Q1Ctrough threshold of the study participants (ie, 1714 ng/mL) tended to be higher among those with episodes of detectable viremia, whether defined by VL ≥ 20 or ≥50 copies/mL.

All thresholds reported in the literature—PAIC90 for CAB and RPV, 4xPAIC90 for CAB and RPV, and Q1Ctrough for CAB and RPV [7, 8, 27, 28, 31, 32]—were similar across different categories of viral suppression (Table 1). Restricted analyses of participants who had VLs below 20 copies/mL when they switched to CAB + RPV LA also yielded consistent results.

Predictors of Non-sustained Viral Suppression

Overall, 65 (38%) and 26 (15.2%) participants experienced VL levels of ≥20 copies/mL and ≥50 copies/mL, respectively, excluding the 2 patients with virological failure. Characteristics of the participants according to virological outcomes are shown in Table 2.

Compared to those with all VLs below 20 copies/mL, participants with at least VL ≥ 20 copies/mL showed higher VL at HIV diagnosis (4.98 vs 4.58 log10 copies/mL, $P < .001$) and a trend toward having a nadir CD4 cell count below 200 cells/mm^3 (39.7% vs 27.6%, $P = .147$). They also had a higher incidence of detectable viremia episodes in the year prior to transitioning to CAB + RPV (72.3% vs 41.5%, $P < .001$) and a

Table 2. Characteristics of Patients With Non-sustained Viral Suppression Compared to Those With Consistent Viral Suppression During the Observation Period[a]

Characteristic	Any Plasma HIV-1 RNA ≥20 copies/mL (n = 65)		All Plasma HIV-1 RNA <20 copies/mL (n = 106)		*P* Value
Age, median (IQR), years	48	37–53	49	38–57	.320
Sex at birth, n (%)					.371
Female	7	10.77	18	16.98	
Male	58	89.23	88	83.02	
Race, n (%)					.999
Black	0	0	1	0.94	
Non-black	65	100	105	99.06	
Country of origin, n (%)					.105
Spain	52	80.00	78	73.58	
Other West European countries	3	4.62	0	0	
Eastern European countries	1	1.54	3	2.83	
Latin American countries	8	12.31	23	21.70	
Other	1	1.54	2	1.89	
HIV transmission route, n (%)					.362
Men having sex with men	42	64.62	59	55.66	
Heterosexual	7	10.77	20	18.87	
Injection drug use	9	13.85	11	10.38	
Other	7	10.77	16	15.09	
HIV-1 Non-B subtypes, n/N (%)	6/36	16.67	11/55	20.00	.857
Type B	30/36	83.33	44/55	80.00	
HIV-1 viral load at diagnosis (pre-ART), median(IQR), copies/mL	4.98	4.64–5.48	4.58	4.21–5.14	.001
≤4.9 log10 copies/mL, n/N (%)	19/49	38.78	47/73	64.38	.009
>4.9 log10 copies/mL, n/N (%)	30/49	61.22	26/73	35.62	
Nadir CD4 count, median(IQR), cells/μL	255	143–450	285	180–478	.331
>350 cells/μL, n/N (%)	20/63	31.75	43/105	40.95	.249
200–350 cells/μL, n/N (%)	18/63	28.57	33/105	31.43	
<200 cells/μL, n/N (%)	25/63	39.68	29/105	27.62	
Nadir CD4 < 200 cells/μL, n/N (%)	25/63	39.68	29/105	27.62	.147
Pre-transition ART regimen, n (%)					.623
INSTI + 2 NRTI	16	24.62	21	19.81	
NNRTI + 2 NRTI	11	16.92	16	15.09	
PI + 2 NRTI	2	3.08	9	8.49	
DTG + LMV	18	27.69	34	32.08	
DTG + RPV	13	20.00	21	19.81	
2-Drug regimen other than DTG + LMV or DTG + RPV	4	6.15	5	4.72	
Other	1	1.54	0	0.00	
Time since HIV diagnosis, median(IQR), years	10.2	4.2–20.3	11.6	5.3–23.1	.276
Time with HIV-1 viral load <50 copies/mL, median(IQR), years	4.6	2.0–13.5	6.5	1.7–13.5	.533
Episodes of detectable viremia in the year pre-transition, n (%)					
At least 1 viral load ≥20 copies/mL	47	72.31	44	41.51	.001
At least 1 viral load ≥50 copies/mL	14	21.54	8	7.55	.015
At least 1 viral load ≥200 copies/mL	6	9.23	1	0.94	.023
Episodes of detectable viremia in the 3-year pre-transition, n (%)					
At least 1 viral load ≥20 copies/mL	60	92.31	72	67.92	.001
At least 1 viral load ≥50 copies/mL	26	40.00	27	25.47	.068
At least 1 viral load ≥200 copies/mL	14	21.54	18	16.98	.589
HIV-1 viral load at transition, n (%)					
Target not detected	29	44.62	86	81.13	.001
<20 copies/mL	47	72.31	100	94.34	.001
20–49 copies/mL	14	21.54	4	3.77	.001
50–99 copies/mL	4	6.15	2	1.89	.296
CD4 cell count at transition, median (IQR), cells/μL	762	640–961	822	685–980	.417
CD4/CD8 ratio at transition, median (IQR)	0.93	0.74–1.38	0.97	0.68–1.34	.670
BMI at transition, median (IQR), Kg/m^2	24.8	22.3–27.1	24.9	22.7–27.9	.494

Table 2. Continued

Characteristic	Any Plasma HIV-1 RNA ≥20 copies/mL (n = 65)		All Plasma HIV-1 RNA <20 copies/mL (n = 106)		*P* Value
BMI ≥30 Kg/m^2 at transition, n (%)	5	7.69	17	16.04	.177
RPV-associated mutations in historical medical records, n/N (%)	4/43	9.30	4/64	6.25	.830
Completed oral lead in, n (%)	29	44.62	62	58.49	.108
Late injection or used oral bridge, n (%)	1	1.54	3	2.83	.983
Viral load at the last observation carried forward, n (%)					
Target not detected	29	44.62	87	82.08	.001
<20 copies/mL	48	73.85	106	100.00	.001
20–49 copies/mL	13	20.00	0	0.00	.001
50–199 copies/mL	3	4.62	0	0.00	.102
≥200 copies/mL	1	1.54	0	0.00	.804

Abbreviations: ART, antiretroviral therapy; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DTG, dolutegravir; HIV-1, human immunodeficiency virus type 1; IQR, interquartile range; INSTI, integrase strand transfer inhibitor; LMV, lamivudine; n/N (%), denotes number of patients with the characteristic (n) out of the total number of patients with data available (N); NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RPV, rilpivirine.

[a]The 2 patients with virological failure were excluded.

lower likelihood of having a VL < 20 copies/mL at the time of transition (72.3% vs 94.3%, $P < .001$) (Table 2). Similar trends were observed in secondary analyses for participants with VL <20 copies/mL at the time of switching and when using a VL cutoff of 50 copies/mL (Supplementary Tables 3 and 4).

Cox proportional hazards regression models of baseline predictors identified three factors significantly associated with the risk of non-sustained viral suppression: VL at HIV diagnosis (adjusted hazard ratio [AHR]: 1.49 per log10 VL, 95% CI: 1.04–2.12, $P = .027$), episodes of detectable viremia within the prior year (AHR: 2.45, 95% CI: 1.29–4.65, $P = .006$), and being fully suppressed at the time of transitioning to CAB + RPV LA (AHR:0.38, 95% CI: .19–.75, $P = .004$) (Table 3). Due to the correlation between the last 2 factors, a single model including both could not be fitted.

Additional statistical modeling was conducted including all baseline factors as well as plasma CAB and RPV trough levels measured before the viral rebound. None of the PK covariates were significantly associated with an increased risk of non-sustained viral suppression (Table 4). Consistent findings were observed in models for participants who switched to CAB + RPV with VLs below 20 copies/mL and when using a VL cutoff of 50 copies/mL (Supplementary Tables 5 and 6). Furthermore, integrating these covariates into the baseline predictor models did not improve their accuracy in predicting non-sustained viral suppression (Supplementary Table 7).

DISCUSSION

In our investigation of patients transitioning from oral antiretroviral regimens to injectable CAB + RPV therapy, we observed a notable occurrence of non-sustained viral suppression, primarily manifesting as intermittent low-level viremia. Virologic failures were limited to 2 patients, aligning with reported rates from clinical trials [9].

Several baseline factors were associated with an increased risk of non-sustained viral suppression, including higher VL at HIV diagnosis, episodes of detectable viremia during oral ART, and the level of viral suppression at the time of transitioning to CAB + RPV. Notably, PK parameters measured before viral rebound did not significantly predict non-sustained suppression, suggesting that baseline patient and virological factors might be more critical determinants of this outcome.

Although low plasma drug levels have been associated with virological failures in patients receiving CAB + RPV, the role of suboptimal PK in treatment failures remains debated [9–11, 13–15]. No documented link exists between lower plasma drug concentrations and the risk of persistent HIV-1 viremia or resistance development in individuals on CAB + RPV LA. However, clinical trials have shown a lower resistance emergence among those on monthly dosing versus a bimonthly, which has lower trough concentrations [7, 32]. Clinical observations also suggest transient viremia re-suppression in young adults shifting to a monthly schedule, indicating the potential impact of lower trough concentrations on sustained virological efficacy in bimonthly dosing [33].

This study systematically explored the potential link between suboptimal PK and non-sustained viral suppression during CAB + RPV treatment, addressing a hypothesis not previously covered in the literature. To enhance the precision of drug exposure assessment, we conducted multiple plasma concentration measurements and thoroughly analyzed the connection between PK parameters and virologic outcomes.

Our PK data reveal significant variability in CAB and RPV plasma concentrations, both within and between patients, suggesting potential benefits for individualized monitoring and dose adjustments. However, in line with phase III trials findings [4, 7], the study found that plasma concentrations were generally well above the inhibitory thresholds for HIV-1, supporting the regimen´s efficacy. Although participants

Table 3. Cox Proportional Hazards Regression Models of Baseline Predictors of Non-sustained Viral Suppression With Cabotegravir Plus Rilpivirine Long-acting Therapy

	Any Plasma HIV-1 RNA ≥20 copies/mL HR (95% CI) [*P* Value]					
	All Participants (N = 171)[a]			Participants Switching to CAB + RPV With HIV-1 RNA <20 copies/mL (N = 147)		
	Un-adjusted	Adjusted (N = 122)[b]	Adjusted (N = 122)[b]	Un-adjusted	Adjusted (N = 104)[b]	Adjusted (N = 104)[b]
HIV-1 viral load at diagnosis, log10 copies/mL	**1.59 (1.17–2.16) [.003]**	**1.49 (1.04–2.12) [.027]**	**1.48 (1.07–2.05) [.019]**	**1.59 (1.12–2.28) [.009]**	**1.67 (1.07–2.61) [.022]**	**1.62 (1.08–2.45) [.019]**
Episodes of detectable viremia within the prior year[c]: yes/no	**3.03 (1.75–5.24) [<.001]**	**2.45 (1.29–4.65) [.006]**	……[d]	**2.91 (1.59–5.32) [<.001]**	**2.17 (1.08–4.38) [.029]**	…[d]
Fully suppressed at the time of switching[e]: yes/no	**0.30 (0.17–0.53) [<.001]**	…[d]	**0.38 (0.19–0.75) [.004]**	**0.33 (0.18–0.60) [<.001]**	…[d]	0.72 (0.34–1.53) [.400]
Nadir CD4 cell count, cells/μL	0.98 (0.61–1.56) [.925]	…[d]	…[d]	0.87 (0.53–1.42) [.577]	…[d]	…[d]
Nadir CD4 cell count >350 cells/μL	Ref	…[d]	…[d]	Ref	Ref	Ref
Nadir CD4 cell count 200–350 cells/μL	0.99 (0.52–1.87) [.966]	…[d]	…[d]	1.59 (0.75–3.41) [.226]	2.05 (0.85–4.99) [.110]	2.09 (0.85–5.11) [.105]
Nadir CD4 < 200 cells/μL	1.49 (0.82–2.70) [.183]	…[d]	…[d]	1.99 (0.94–4.22) [.070]	1.48 (0.59–3.64) [.395]	1.66 (0.68–4.09) [.264]
RPV-associated mutations in historical medical records: yes/no	1.10 (0.38–3.12) [.864]	…[d]	…[d]	1.70 (0.64–4.49) [.285]	…[d]	…[d]

Bolded values represent statistically significant predictors ($P < .05$).

Abbreviations: CAB, cabotegravir; CI, confidence interval; HIV-1, human immunodeficiency virus type 1; HR, hazard ratio; RPV, rilpivirine.

[a]The 2 patients with virological failure were excluded.

[b]Models conducted using data from 122 and 104 participants with complete records, respectively. In total, 49 and 43 patients were excluded due to missing HIV-1 viral load at diagnosis, respectively.

[c]At least 1 HIV-1 viral load ≥20 copies/mL.

[d]Covariate eliminated from the selected model.

[e]HIV-1 viral load <20 copies/mL (all participants models) and target not detected (participants switching to CAB + RPV with HIV-1 RNA <20 copies/mL).

Table 4. Cox Proportional Hazards Regression Models of Baseline Predictors of Non-sustained Viral Suppression With Cabotegravir Plus Rilpivirine Long-acting Therapy, Including Pharmacokinetic Parameters

	Any Plasma HIV-1 RNA ≥20 copies/mL HR (95% CI) [*P* Value]							
	All Participants (171 Patients, 534 Samples)[a]				Participants Switching to CAB + RPV With HIV-1 RNA <20 copies/mL (147 Patients, 486 Samples)			
	Un-adjusted	Adjusted[b]	Adjusted[b]	Adjusted	Un-adjusted	Adjusted[b]	Adjusted[b]	Adjusted
No. Subjects/No. samples		121/380[c]	121/380[c]	120/120[c]		103/342[c]	103/342[c]	103/103[c]
HIV-1 viral load at diagnosis, copies/mL	**1.59 (1.16–2.16) [.003]**	**1.45 (1.02–2.07) [.036]**	**1.46 (1.05–2.02) [.022]**	**1.47 (1.05–2.06) [.026]**	**1.59 (1.12–2.28) [.009]**	**1.68 (1.06–2.67) [.027]**	**1.73 (1.08–2.77) [.022]**	**1.66 (1.06–2.59) [.026]**
Episodes of detectable viremia within the prior year[d]: yes/no	**3.03 (1.75–5.24) [<.001]**	**2.98 (1.56–5.67) [<.001]**	…[e]	…[e]	**2.80 (1.52–5.13) [<.001]**	**2.66 (1.26–5.61) [.010]**	…[e]	**2.18 (1.08–4.40) [.029]**
Fully suppressed at the time of switching[f]: yes/no	**0.30 (0.17–0.52) [<.001]**	…[e]	**0.29 (0.15–0.58) [<.001]**	**0.38 (0.20–0.75) [.005]**	**0.32 (0.18–0.58) [<.001]**	…[e]	0.79 (0.33–1.88) [.595]	…[e]
Nadir CD4 cell count, cells/μL	0.98 (0.61–1.56) [.925]	…[e]	…[e]	…[e]	0.92 (0.54–1.52) [.737]	…[e]	…[e]	…[e]
Nadir CD4 cell count >350 cells/μL	Ref	…[e]	…[e]	…[e]	Ref	Ref	Ref	Ref
Nadir CD4 cell count 200–350 cells/μL	0.98 (0.52–1.86) [.966]	…[e]	…[e]	…[e]	1.63 (0.76–3.48) [.209]	2.52 (0.95–6.70) [.063]	2.42 (0.89–6.58) [.081]	2.19 (0.85–5.66) [.105]
Nadir CD4 < 200 cells/μL	1.49 (0.82–2.70) [.183]	…[e]	…[e]	…[e]	1.89 (0.89–4.04) [.098]	1.64 (0.62–4.34) [.317]	1.81 (0.67–4.92) [.244]	1.49 (1.08–4.40) [.392]
Preexisting minor RPV mutation: yes/no	1.09 (0.38–3.12) [.864]	…[e]	…[e]	…[e]	1.35 (0.46–3.92) [.585]	…[e]	…[e]	…[e]
Ctrough, log10 ng/mL								…[e]
CAB	1.64 (0.56–4.77) [.358]	1.27 (0.34–4.73) [.719]	1.56 (0.40–6.02) [.515]	…[e]	1.97 (0.56–6.92) [.290]	0.99 (0.21–4.68) [.998]	1.06 (0.22–5.16) [.941]	…[e]
RVP	1.72 (0.74–4.01) [.207]	1.73 (0.68–4.1) [.249]	1.71 (0.61–4.73) [.301]	…[e]	2.00 (0.74–5.45) [.167]	2.53 (0.78–8.20) [.130]	2.48 (0.70–8.60) [.160]	…[e]
Week 4 Ctrough, log10 ng/mL								
CAB	1.47 (0.52–4.17) [.468]	…[e]	…[e]	…[e]	2.69 (0.70–10.20) [.145]	…[e]	…[e]	…[e]
RVP	1.40 (0.56–3.49) [.464]	…[e]	…[e]	…[e]	1.70 (0.56–5.20) [.346]	…[e]	…[e]	…[e]
Week 12 Ctrough, log10 ng/mL								
CAB	0.80 (0.27–2.43) [.705]	…[e]	…[e]	1.12 (0.26–4.79) [.876]	0.87 (0.24–3.14) [.839]	…[e]	…[e]	0.68 (0.13–3.48) [.644]
RVP	1.31 (0.57–3.01) [0.518]	…[e]	…[e]	1.12 (0.42–2.95) [.817]	1.00 (0.38–2.65) [.986]	…[e]	…[e]	1.12 (0.37–3.33) [.836]
CAB Ctrough								
<Q1 (<1714 ng/mL)	1.06 (0.60–1.88) [.826]	…[e]	…[e]	…[e]	1.09 (0.55–2.14) [.800]	…[e]	…[e]	…[e]
<Q1 (<1120 ng/mL)[g]	0.89 (0.35–2.30) [.825]	…[e]	…[e]	…[e]	0.94 (0.32–2.70) [.916]	…[e]	…[e]	…[e]

Table 4. Continued

	Any Plasma HIV-1 RNA ≥20 copies/mL HR (95% CI) [*P* Value]							
	All Participants (171 Patients, 534 Samples)[a]				Participants Switching to CAB + RPV With HIV-1 RNA <20 copies/mL (147 Patients, 486 Samples)			
	Un-adjusted	Adjusted[b]	Adjusted[b]	Adjusted	Un-adjusted	Adjusted[b]	Adjusted[b]	Adjusted
4xPAIC90 (<664 ng/mL)[g]	0.69 (0.09–5.26) [.729]	…[e]	…[e]	…[e]	0.83 (0.11–6.36) [.864]	…[e]	…[e]	…[e]
RPV Ctrough < Q1 (559 ng/mL)	0.75 (0.40–1.40) [.374]	…[e]	…[e]	…[e]	0.68 (0.32–1.45) [.330]	…[e]	…[e]	…[e]

Bolded values represent statistically significant predictors ($P < .05$).

Abbreviations: CAB, cabotegravir; CI, confidence interval; Ctrough, trough concentrations; HIV-1, human immunodeficiency virus type 1; HR, hazard ratio; PAIC90, in vitro protein-adjusted inhibitory concentration required for 90% viral inhibition; Q1 Ctrough, 25th percentile; RPV, rilpivirine.

[a]The 2 patients with virological failure were excluded.

[b]Mixed effects Cox regression models.

[c]Models conducted using data from 121/171 and 103/147 participants with complete records. In total, 49 and 43 patients were excluded due to missing HIV-1 viral load at diagnosis, respectively, and 1 participant due to missing the CAB/RPV measurement at detectable viremia episode. Another participant was lost in model at week 12 (120/171) due to missing the CAB/RPV measurement at week 12.

[d]At least 1 HIV-1 viral load ≥20 copies/mL.

[e]Covariate eliminated from the selected model.

[f]HIV-1 viral load <20 copies/mL (all participants models) and target not detected (participants switching to CAB + RPV with HIV-1 RNA <20 copies/mL).

[g]Trough plasma concentrations thresholds reported in the literature [7, 8, 26–28].

with detectable viremia tended to have lower CAB and RPV concentrations compared to those who maintained viral suppression, the inclusion of PK covariates in multivariable models did not enhance accuracy in predicting non-sustained viral suppression.

Consistent with previous research on oral ART regimens [17, 34–36], our study found that non-sustained viral suppression was associated with high pre-ART VL and low CD4 cell counts, indicating more advanced HIV infection at ART initiation. This suggests a larger proviral reservoir, linked to persistent plasma viremia [37–39], and implies that, as with individuals receiving oral ART, non-suppressible viremia with CAB + RPV LA may originate from virus production by long-lived infected cells established before therapy initiation [40].

Our findings have clinical implications. The identified predictors of non-sustained suppression can help clinicians select appropriate candidates for CAB + RPV LA. Patients with a history of higher VLs or detectable viremia may require closer monitoring to ensure successful outcomes.

The study has limitations, including sample size and therapy duration constraints, which hinder the assessment of long-term implications of non-sustained suppression on drug resistance and virological failure. Additionally, the study population was predominantly non-black and male, which may restrict the applicability of the findings to more diverse populations. The predominance of intermittent low-level viremia in cases of non-sustained viral suppression also limits generalizability. Moreover, a significant percentage of patients lacked documented resistance information for RPV before initiating treatment, which could have influenced the lack of virological suppression. The relatively small number of obese patients in our study also limits our ability to generalize the findings and fully assess the impact of BMI on treatment outcomes. Finally, the observed intra- and inter-patient variability in plasma concentrations of CAB and RPV complicates the interpretation of our results, highlighting the need for greater standardization in therapy administration.

In conclusion, non-sustained viral suppression during CAB + RPV LA therapy was associated with pre-existing factors established before ART initiation, likely linked to the size of the HIV reservoir. No substantial evidence was found to suggest pharmacokinetic contributions to non-suppressible viremia. This study underscores the importance of assessing patient virological history and the degree of viral suppression prior to transitioning to CAB + RPV to optimize treatment outcomes and does not support therapeutic drug monitoring.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. F. G.: conceptualization (lead), methodology (lead), writing—original draft (lead), funding acquisition, project administration, supervision; M. F. G.: resources, project administration (supporting), data curation (supporting), writing—review and editing (equal); C. L.: methodology (supporting), data curation (supporting); writing—review and editing (equal); M. L. E.: plasma drug concentrations measurements, writing—review and editing (equal); E. B. C.: plasma drug concentrations measurements, writing—review and editing (equal); J. G. A.: data curation (supporting); writing—review and editing (equal); D. E.: data curation (supporting); writing—review and editing (equal); L. L.: data curation (supporting); writing—review and editing (equal); M. B.: data curation (supporting); writing—review and editing (equal); S. P.: methodology (supporting), data curation (supporting); writing—review and editing (equal); M. M.: conceptualization (lead), methodology (lead), writing—original draft (lead), funding acquisition, project administration, supervision.

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