Cabotegravir Plus Rilpivirine in Real-World Evidence: A Systematic Literature Review of Outcomes Following Virological Failure, Including Resistance and Subsequent Treatment Options

P074

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Key Takeaways

- **This systematic literature review found that, across 20 non-overlapping cohorts including 16,688 people with HIV-1 and suppressed viral load at long-acting cabotegravir plus rilpivirine initiation, virologic failure was low, ranging from 0% to 3% across publications**
- **Virologic failure with resistance was uncommon, with rates of ≤1% across publications**
- **Post–virologic failure regimen selection was more varied in real-world practice than in phase 3 trials, with greater use of integrase inhibitor–based regimens (42% vs 21%) and lower use of protease inhibitor–based regimens (55% vs 75%), suggesting that multiple treatment approaches may be considered following virologic failure. Most (76%) individuals switched to single-tablet regimens**

Plain Language Summary

- Long-acting cabotegravir plus rilpivirine is an HIV treatment, given 6 or 12 times a year as injections, for people with an undetectable level of virus in the blood (suppressed)
- This review looked at data from routine clinic visits around the world to study what happens if treatment does not work and virus levels rise above a certain threshold (virologic failure)
- Researchers found 20 studies in medical databases and conferences, collecting results on 16,688 people who were suppressed across North America, Europe, and Asia
- Virologic failure was low, occurring in less than 3% of people
- Virologic failure with drug resistance (mutations that make the treatment less effective) was uncommon, occurring in less than 1% of people treated with long-acting cabotegravir plus rilpivirine
- After virologic failure, the medications people switched to differed from what was typically used in clinical trials. More people moved to a newer class of HIV drugs called integrase inhibitors (42% vs 21% in clinical trials), while fewer switched to protease inhibitors—the drug class most commonly used in clinical trials (55% vs 75%). Most people (76%) switched to a single pill taken once daily

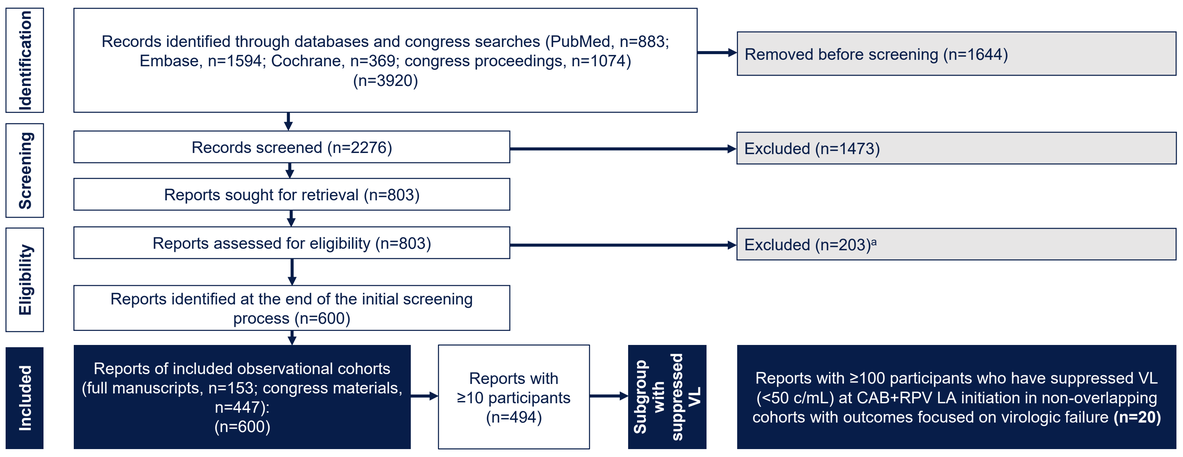
Introduction

- Cabotegravir (CAB) plus rilpivirine (RPV) is the first and only complete long-acting (LA) injectable regimen approved for people with HIV-1 who have suppressed viral load (VL)[1-4]
- CAB+RPV LA has demonstrated high rates of virologic suppression; however, virologic failure can occur and may be accompanied by resistance-associated mutations (RAMs) to integrase inhibitors (INIs) and/or non-nucleoside reverse transcriptase inhibitors (NNRTIs)[5,6]
- In phase 3 clinical trials, protease inhibitor (PI)–based regimens were commonly used after CAB+RPV LA virologic failure,[7-9] whereas available real-world evidence (RWE) suggests greater variation in subsequent treatment approaches, including use of second-generation INIs[10,11]
- Synthesizing real-world outcomes can complement clinical trial data by further characterizing virologic failure, resistance, subsequent treatment regimens, and re-suppression with CAB+RPV LA, helping to inform clinical decision-making
- Here, we present a systematic literature review (SLR) of these outcomes among people with suppressed VL at CAB+RPV LA initiation across diverse real-world settings

Methods

- An SLR of RWE was conducted following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines
- Literature searches were conducted in Embase®, PubMed®, and Cochrane Library databases, supplemented by manual searches of major international HIV congresses to capture both journal articles and congress proceedings from January 2020 to March 2026 (Figure 1)
- Eligible RWE studies were those conducted in routine clinical practice or non-interventional settings that reported virologic failure and related outcomes from non-overlapping cohorts among ≥100 people who had suppressed VL (<50 c/mL) at CAB+RPV LA initiation
- Publications, defined here as peer-reviewed manuscripts and congress materials, were assessed for overlapping cohorts to avoid double-counting
- Virologic failure (individually defined by publication) and related resistance outcomes, as well as antiretroviral therapy regimen after virologic failure, were synthesized and presented descriptively
  - Virologic failure definitions are included in Table 1

Figure 1. SLR PRISMA Flowchart



[a]Reasons for exclusion: intervention, n=50; study design, n=33; publication type, n=55; outcomes, n=36; lack of sufficient information for individuals using CAB+RPV LA, n=20; presentation was withdrawn or presumed to have been withdrawn from congress, n=4; full text was not available or encore included instead, n=2; abstract or final presentation with incomplete data, n=1; unclear if the study included individuals receiving CAB+RPV LA, n=1; individual in the study died from other complications soon after starting CAB+RPV LA, n=1.

Results

Overview of Included RWE

- A total of 494 publications were identified, representing 364 studies, 133 cohorts, and 45,596 people with HIV-1 using CAB+RPV LA
- Of these, 20 non-overlapping cohorts reported virologic failure outcomes for 16,688 people with HIV-1 who had suppressed VL at CAB+RPV LA initiation and are included in this analysis[12-31]
  - Across publications, virologic failure definitions varied based on VL thresholds and single versus confirmatory testing, reflecting diverse clinical practices and study designs[15,19-24,26-31]
- The included cohorts represented routine clinical practice, comprising 4 cohorts from the United States,[15,19,25,29] 3 from France,[12,23,28] 6 from Italy,[13,16-18,26,30] 1 each from Germany,[31] Spain,[21] Taiwan,[22] Poland,[14] and the United Kingdom,[27] and 2 multi-country European cohorts[20,24]

Virologic Failure and Resistance-Related Outcomes

- Virologic failure was reported among 187 individuals, with rates ranging from 0% to 3% across these publications[12-31]; 4 publications, including 778 people, reported no virologic failures (Table 1)[16,18,22,24]
- Among the 11 publications (10,664 people) reporting resistance outcomes after virologic failure, rates of virologic failure with resistance were ≤1% across publications[13,15,17,20,21,23,25,26,28,30,31]
- INI RAMs were reported in 47 individuals, with rates of ≤1% across publications (Table 1)[13,15,17,20,21,23,25,26,28,30,31]

Table 1. Virologic Failure After CAB+RPV LA Treatment and Resistance-Associated Mutations

Publication	People with suppressed VL at CAB+RPV LA initiation, n/N (%)	Follow-up time	Virologic failure definition	Virologic failure, n/N (%)	Virologic failure with RAMs, n/N (%)	Virologic failure with INI RAMs, n/N (%)[a]	Historic INI/NNRTI RAMs in people with virologic failure, yes/no/NR, n/N (%), details
Psomas et al, 2023[12]	142/142 (100)	NR	NR	1/142 (1)	NR	NR	NR
Canavesi et al, 2024[13]	758/758 (100)	NR	NR	14/758 (2)	8/758 (1)	7/758 (1)[b]	Yes, 2/14 (14) NNRTI: 2
Dawiec et al, 2024[14]	170/188 (90)	1.278 patient-years[c]	NR	2/170 (1)	NR	NR	NR
Sax et al, 2025[15]	1198/1198 (100)	Median (IQR): 12 (5-19) months	2 consecutive VLs >200 c/mL or 1 VL >200 c/mL with D/C within 4 months	15/1198 (1)	3/1198 (<1)	1/1198 (<1)	NR[d]
Moschese et al, 2025[16]	322/322 (100)	Median (IQR): 70 (24-96) weeks	NR	0/322 (0)	NA	NA	NA
Muccini et al, 2025[17]	549/549 (100)	24 months	NR	6/549 (1)	3/549 (1)	3/549 (1)	No, 0/6 (0)
Sangaletti et al, 2025[18]	100/100 (100)	48 weeks	NR	0/100 (0)	NA	NA	NA
Blick et al, 2025[19]	233/308 (76)	24 months[c]	2 consecutive VLs ≥200 c/mL or CAB+RPV LA D/C within 3 months of 1 VL ≥200 c/mL	2/233 (1)	NR	NR	NR
Pozniak et al, 2025[20]	956/956 (100)	Median (IQR): 10.2 (7.1-16.6) months	2 VLs ≥200 c/mL or 1 VL ≥200 c/mL and CAB+RPV LA D/C	5/956 (1)	3/956 (<1)	2/956 (<1)	NR
Buzón-Martín et al, 2025[21]	3146/3203 (98)	Median (IQR): 13.8 (8.8-19.1) months[c]	2 consecutive VLs ≥200 c/mL or 1 VL >500 c/mL resulting in CAB+RPV LA D/C	20/3146 (1)	12/3146 (<1)	10/3146 (<1)[e]	Yes, 1/20 (5) NNRTI: 1
Cheng et al, 2025[22]	229/229 (100)	13 months	2 consecutive VLs >200 c/mL, with an interval of ≥1 month between tests	0/229 (0)	NA	NA	NA
Deschanvres et al, 2025[23]	2196/2196 (100)	Median (IQR): 13 (7-19) months	2 consecutive VLs >50 c/mL or 1 VL >200 c/mL	42/2196 (2)	13/2196 (1)	12/2196 (1)	Yes, 2/42 (5) INI: 1 NNRTI: 1
Peters et al, 2025[24]	127/142 (89)	Median (IQR): 323 (204-466) days[c]	2 consecutive VLs ≥200 c/mL or 1 VL ≥200 c/mL resulting in CAB+RPV LA D/C within 1 month	0/127 (0)	NA	NA	NA
Faggiano et al, 2025[25]	392/438 (89)	Median (IQR): 612 (355-848) days[c,f]	NR	4/392 (1)	3/392 (1)	2/392 (1)	Yes, 1/4 (25) NNRTI: 1
Mazzitelli et al, 2025[26]	483/483 (100)	Median (IQR): 22 (13-26) months	2 consecutive VLs >200 c/mL or 1 VL >200 c/mL leading to treatment withdrawal	7/483 (1)	5/483 (1)	4/483 (1)	Yes, 2/7 (29) NNRTI: 2
Orkin et al, 2025[27]	114/114 (100)	12 months	2 consecutive VLs >200 c/mL	1/114 (1)	NR	NR	NR
Hessamfar et al, 2026[28]	444/464 (96)	Median (IQR) 21.1 (12.2-29.6) months[c]	1 VL >1000 c/mL or 2 consecutive VLs >50 c/mL	13/444 (3)	3/444 (1)	3/444 (1)	Yes, 3/13 (23) NNRTI: 1 INI: 3
Hsu et al, 2026[29]	4587/5264 (87)	Median (IQR): 14 (7-23) months[g]	2 consecutive VLs ≥200 c/mL or CAB+RPV LA D/C after a VL ≥200 c/mL	43/4196 (1)[h]	NR	NR	NR
Lagi et al, 2026[30]	191/191 (100)	Median (IQR): 1.0 (0.5-1.5) years	2 consecutive VLs >50 c/mL or 1 VL >1000 c/mL	5/191 (3)	1/191 (1)	1/191 (1)	Yes, 1/5 (20) NNRTI: 1
Wyen et al, 2026[31]	351/351 (100)	24 months	2 consecutive VLs ≥200 c/mL or D/C for any reason after 1 VL ≥200 c/mL	7/351 (2)	4/351 (1)	3/351 (1)	No, 0/7 (0)

D/C, discontinuation; IQR, interquartile range; NA, not applicable; NR, not reported; NNRTI, non-nucleoside reverse transcriptase inhibitor; VL, viral load. [a]Includes individuals who had INI RAMs only or INI and NNRTI RAMs. [b]One individual had polymorphisms that were classified as NNRTI RAMs. [c]Follow-up time shown in the overall population. [d]Baseline resistance only reported for 3/15 individuals who experienced virologic failure; none of those 3 individuals had baseline NNRTI or INI RAMs. [e]One individual had a PI mutation that was classified as an INI RAM. [f]Reflects time on CAB+RPV LA. [g]Time on CAB+RPV LA until first censoring event among complete initiators with VL <50 c/mL at initiation. [h]Denominator reflects complete initiators.

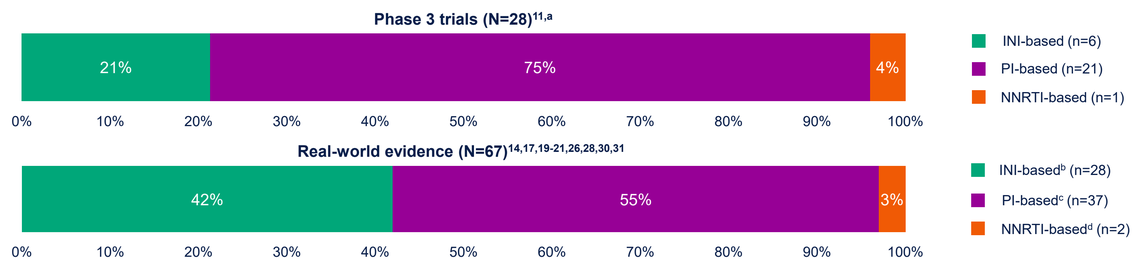
- Among 67 individuals with available post–virologic failure regimen data, most (76%, 51/67) switched to a single-tablet regimen[14,17,19-21,26,28,30,31]
- Post–virologic failure regimens were PI-based in 37/67 (55%),[14,17,20,21,26,28,30,31] INI-based in 42% (28/67),[14,17,19,20,21,26,28,30,31] and NNRTI-based in 2/67 (3%) individuals[20,28]; the INI-based group included 6/67 individuals (9%) who continued CAB+RPV LA[17,28,31] (Table 2)
- Compared with phase 3 trials, post–virologic failure regimen selection was more varied, with greater use of INI-based regimens (42% vs 21%) and lower use of PI-based regimens (55% vs 75%; Figure 2)
  - The most commonly reported regimens in RWE publications were DRV/c/FTC/TAF (31/67 [46%]),[14,17,20,21,26,30,31] BIC/FTC/TAF (13/67 [19%]),[17,19,21,28,31] and CAB+RPV LA (6/67 [9%])[17,28,31]
- Most publications reported high rates of virologic re-suppression after regimen switch; among 48 individuals across 7 publications, rates ranged from 60% to 100% with some variation likely reflecting differences in follow-up available at the respective data cut offs[14,15,20,21,28,30,31]

Table 2. Post–Virologic Failure Regimen and Suppression

Publication	People with suppressed VL at CAB+RPV LA initiation, n/N (%)	Post–virologic failure regimen, n/N (%)	Re-suppression post–virologic failure, n/N (%)
Dawiec et al, 2024[14]	170/188 (90)	DRV/c/FTC/TAF: 1/2 (50) DTG + TDF/FTC: 1/2 (50)	2/2 (100)
Sax et al, 2025[15]	1198/1198 (100)	NR	6/8 (75)
Muccini et al, 2025[17]	549/549 (100)	DRV/c/FTC/TAF: 3/6 (50) BIC/FTC/TAF: 2/6 (33) CAB+RPV LA: 1/6 (17)	NR
Blick et al, 2025[19,a]	233/308 (76)	DTG/3TC: 1/2 (50) BIC/FTC/TAF: 1/2 (50)	NR
Pozniak et al, 2025[20]	956/956 (100)	DRV/c/FTC/TAF: 2/5 (40) DRV/r + ABC/3TC followed by BIC/FTC/TAF then DTG/3TC: 1/5 (20) DRV/c/FTC/TAF followed by DOR/3TC/TDF: 1/5 (20) DRV/r/FTC/TDF: 1/5 (20)	4/4 (100)[b]
Buzón-Martín et al, 2025[21]	3146/3203 (98)	DRV/c/FTC/TAF: 13/20 (65) BIC/FTC/TAF: 5/20 (25) DRV/c/ABC/3TC: 1/20 (5) DTG/3TC + DOR: 1/20 (5)	12/20 (60)
Mazzitelli et al, 2025[25]	483/483 (100)	DRV/c/FTC/TAF: 6/7 (86) DTG + DOR: 1/7 (14)	NR
Hessamfar et al, 2026[28]	444/464 (96)	CAB+RPV LA: 4/13 (31) BIC/FTC/TAF: 3/13 (23) DTG + DOR: 1/13 (8) DOR/TDF/3TC: 1/13 (8) DRV/r/FTC/TDF: 4/13 (31)[c]	11/12 (92)[b]
Lagi et al, 2026[30]	191/191 (100)	DTG/3TC: 2/5 (40) DTG/RPV: 1/5 (20) DRV/c/FTC/TAF: 2/5 (40)	1/1 (100)[b]
Wyen et al, 2026[31]	351/351 (100)	DRV/c/FTC/TAF: 4/7 (57) BIC/FTC/TAF: 2/7 (29) CAB+RPV LA: 1/7 (14)	1/1 (100)[b]

ABC, abacavir; BIC, bictegravir; c, cobicistat; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; FTC, emtricitabine; NA, not applicable; NR, not reported; r, ritonavir; TAF, tenofovir alafenamide; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate; VL, viral load. [a]Post–virologic failure regimen data from Dandachi et al. *Open Forum Infect Dis*. 2025;12:ofaf220. [b]Data on re-suppression not available for all individuals for which post–virologic failure regimen was reported. [c]Due to rounding, percentages may equal greater than 100.

Figure 2. Post–Virologic Failure Regimen Utilization in Phase 3 Trials and Real-World Evidence Studies



BIC, bictegravir; c, cobicistat; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; FTC, emtricitabine; NNRTI, non-nucleoside reverse transcriptase inhibitor; r, ritonavir; TAF, tenofovir alafenamide; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate. [a]Phase 3/3b trial data shown are pooled from ATLAS, ATLAS-2M, CARES, CARISEL, FLAIR, FLAIR open-label extension, and SOLAR.[11] [b]INI-based regimens were BIC/FTC/TAF (13 people), CAB+RPV LA (6 people), DTG/3TC (4 people), DTG + DOR (2 people), DTG/RPV (1 person), DTG/3TC + DOR (1 person), and DTG + TDF/FTC (1 person). [c]PI-based regimens were DRV/c/FTC/TAF (31 people), DRV/r/FTC/TDF (5 people), and DRV/c/ABC/3TC (1 person). NNRTI-based regimen was DOR/TDF/3TC (2 people).

Outcomes in Publications Reporting CAB+RPV LA Use in ≥100 People With Suppressed VL (<50 c/mL) at Initiation in Line With the Licensed Indication

- Across 11 publications including 7975 people who initiated CAB+RPV LA within the licensed indications,[1,3,4,12,16-20,22,25,27,29,31] virologic failure rates ranged from 0% to 2%[12,16-20,22,25,27,29,31]
- Resistance outcomes were reported across 4 publications including 2248 people, and rates of virologic failure with resistance were ≤1% across publications[17,20,25,31]
- 4 publications reported post–virologic failure regimens for 20 individuals[17,19,20,31]
- DRV/c/FTC/TAF was the most commonly reported (9/20, 45%),[17,20,31] followed by BIC/FTC/TAF (5/20, 25%)[17,19,31]
  - All individuals with available with re-suppression outcomes (5 people across 2 publications) had re-suppressed VLs[20,31]

Conclusions

- This SLR identified 494 publications representing 45,596 people with HIV-1 using CAB+RPV LA, including 20 non-overlapping cohorts reporting virologic failure and related outcomes in 16,688 people with suppressed VL at CAB+RPV LA initiation
- Virologic failure and virologic failure with resistance were uncommon across diverse real-world settings, consistent with clinical trial evidence
- Following virologic failure, real-world regimen selection was more varied than in clinical trials, with greater use of INI-based regimens and lower use of PI-based regimens compared with phase 3 clinical trials; most individuals received a single-tablet regimen
- These findings show that, when virologic failure occurs with CAB+RPV LA, multiple subsequent treatment options can support effective management and restoration of virologic suppression

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References: 1. Cabenuva [prescribing information]. ViiV Healthcare; 2025. **2.** Hsu et al. *J Int AIDS Soc*. 2025;28:e70068. **3.** Vocabria [summary of product characteristics]. ViiV Healthcare; 2025. **4.** Rekambys [summary of product characteristics]. ViiV Healthcare; 2025. **5.** Cutrell et al. *AIDS*. 2021;35:1333-1342. **6.** Orkin et al. *Clin Infect Dis*. 2023;77:1423-1431. **7.** Jonsson-Oldenbüttel et al. *J Acquir Immune Defic Syndr*. 2024;96:472-480. **8.** Overton et al. *Clin Infect Dis*. 2023;76:1646-1654. **9.** Ramgopal et al. *Lancet HIV*. 2023;10:e566-e577. **10.** Ring et al. *HIV Med*. 2025;26:1267-1288. **11.** Elias et al. HIV Glasgow 2025; Glasgow, Scotland. Poster P062. **12.** Psomas et al. EACS 2023; Warsaw, Poland. Poster eP.A.016. **13.** Canavesi et al. HIV Glasgow 2024; Glasgow, Scotland. Poster P074. **14.** Dawiec et al. HIV Glasgow 2024; Glasgow, Scotland. Poster P097. **15.** Sax et al. CROI 2025; San Francisco, CA. Poster 675. **16.** Moschese et al. ICAR 2025; Padova, Italy. Oral SC31. **17.** Muccini et al. ICAR 2025; Padova, Italy. Oral OC35. **18.** Sangaletti et al. ICAR 2025; Padova, Italy. Poster P105. **19.** Blick et al. IAS 2025; Kigali, Rwanda. Poster EP0178. **20.** Pozniak et al. IAS 2025; Kigali, Rwanda. Poster EP0171. **21.** Buzón-Martín et al. *J Antimicrob Chemother* 2025;80:3438-3451. **22.** Cheng et al. EACS 2025; Paris, France. Poster eP096. **23.** Deschanvres et al. EACS 2025; Paris, France. Poster eP124. **24.** Peters et al. EACS 2025; Paris, France. Poster eP.LB007. **25.** Faggiano et al. *HIV Med*. 2025;27:217-225. **26.** Mazzitelli et al. *J Antimicrob Chemother*. 2025;80:2732-2741. **27.** Orkin et al. *Clin Infect Dis*. 2025;80:1103-1113. **28.** Hessamfar et al. CROI 2026; Denver, CO. Poster 526. **29.** Hsu et al. CROI 2026; Denver, CO. Poster 527. **30.** Lagi et al. *J Med Virol*. 2026;98:e70779. **31.** Wyen et al. *AIDS*. 2026;40:733-743.

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