P088

Virological failure rate and emergent resistance in real-world studies evaluating long-acting cabotegravir and rilpivirine in people with baseline viral suppression

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BACKGROUND

- Long-acting (LA) cabotegravir and rilpivirine (CAB+RPV) is the first complete LA regimen recommended for the maintenance of virologic suppression in people with HIV-1. Switching to LA CAB+RPV administered monthly or 2-monthly was non-inferior to daily oral antiretroviral therapy (ART) in the Phase 3/3b FLAIR, ATLAS, SOLAR and CARES studies.
- Virological failure (VF) (two consecutive measurements of HIV-1 RNA ≥200 c/mL) rate in Phase 3/3b studies evaluating LA CAB+RPV for treatment of HIV-1 ranged from 0-1.8% through 3 years of follow-up [ATLAS, FLAIR, SOLAR, ATLAS-2M, CUSTOMIZE, CARISEL, CARES].
- Little is known about VF and emergent resistance among LA CAB+RPV users in the real world.

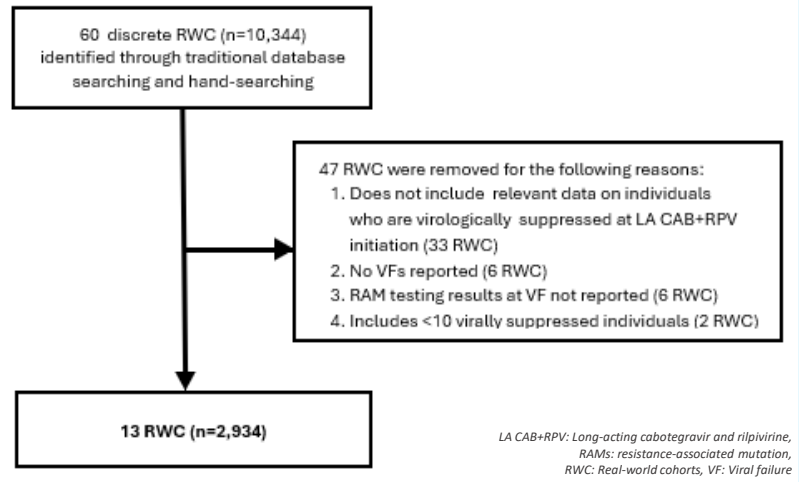
METHODS

- We present results from a systematic literature review (SLR) using Pubmed, Embase, Cochrane and 23 HIV-related conferences through March 2024 to identify all real-world cohorts (RWC) evaluating LA CAB+RPV.
- Data was extracted from studies that included individuals who were virally suppressed at initiation, identified VFs and reported on resistance-associated mutation (RAM) testing results at VF. All studies that met these criteria were included regardless of treatment duration, follow-up period, and VF definition used. Cohorts including less than 10 virally suppressed individuals were excluded (Figure 1).
- Data on cases of VF and RAMs at VF were summarised descriptively, as VF definitions and follow-up times varied across studies. Major RAMs were identified as defined by the Stanford Algorithm.

RESULTS

- 13 RWC provided information about resistance following VF (Table 1).
- While the definitions of VF varied, many included 1 or 2 consecutive measurements of HIV RNA > or ≥200 copies/mL [1-6, 8, 10, 13]. Many did not explicitly define VF criteria [7, 9, 11-12].

Figure 1. Number of real-world cohorts and people living with HIV (n) included in the systematic literature review



LA CAB+RPV: Long-acting cabotegravir and rilpivirine, RAMs: resistance-associated mutation, RWC: Real-world cohorts, VF: Viral failure

Table 1. Resistance at VF data available on people who experienced VF in real-world cohorts*

Real world cohorts	Study country/ countries	Follow-up time	LA CAB+ RPV Dosing	VF definition	N	VF, n (%)	Genotype available at initiation for those with VF**, n/N [Mutations]	Genotype Available at VF, n/N	VF with No RAMs, n (%)	VF with INI RAMs, n (n/N%, n/VF%) [RAMs] @	VF with NNRTI RAMs, n (n/N%, n/VF%) [RAMs] @	VF with NNRTI & INI RAMs, n (n/N%, n/VF%)
Deschanvres et al., 2023 (Dat'AIDS cohort) (1)	France	196 Days (median)	Q2M	2 VL >50 c/mL or 1 VL >200 c/mL	1134	14 (1.2%)	14/14 [Not available]	6/14	2 (0.2%)	3 (0.3%, 21.4%) [**Q148H/R/K**; **Q148R; Q148R**, **R263K**, **N155H**]	3 (0.3%, 21.4%) [**E138K**; **E138K**; **Y181C**, **E138K**]	2 (0.2%, 14.2%)
Jongen et al., 2023 (ATHENA cohort)$ (2)	Netherlands	0.8 Years (median)	Q2M	VL >200 c/mL	588	5 (0.9%)	5/5 [1/5: **179D**; 4/5: None]£	5/5	3 (0.5%)	2 (0.3%, 40%) [**155H**; **138K, 148R**]	2 (0.3%, 40%) [**101E, 138K, 230L**; **101E, 138K**]	2 (0.3%, 40%)
Maguire et al. 2024 (3)	USA	255 Days (median)	Q1M and Q2M	2x VL ≥200 c/mL	374	4 (1.1%)	4/4 [1/4: **K103E**, **K103Q**, **V179I**, **M50I**; 3/4: None]	3/4	1 (0.3%) ‡	2 (0.5%, 50%) [**Q148R**; **N155H, R263K**] ‡	2 (0.5%, 50%) [**Y188L; K101E**] ‡	2 (0.5%, 50%) ‡
Borch et al. 2022 (CARLOS) (4)	Germany	6 Months	Q2M	2x VL ≥200 c/mL or 1x VL ≥200 c/mL + discontinuation	200	2 (1%) #	0/2 [Not available]	2/2	0 (0%)	1 (0.5%, 50%) [L74I, T97A, **E138K**, **Q148R**, **N155H**]	2 (1%, 100%) [**Y181C**; **K101E**, **Y181C, G190A**]	1 (0.5%, 50%)
Sinclair et al., 2023 (BEYOND) (5)	USA	6 Months	Q1M and Q2M	2x VL ≥200 c/mL or 1x VL ≥200 c/mL + discontinuation within 3 months	150	2 (1.3%)	1/2 [None] (1 not available)	1/2 (same individual with genotype at initiation)	0 (0%) ‡	1 (0.7%, 50%) [**E138KA**, **G140SAC**, **Q148HRK**]‡	1 (0.7%, 50%) [**L100I**, **K103NS**] ‡	1 (0.7%, 50%) ‡
Pozniak et al., 2023 (COMBINE-2 C2C) (6)	Switzerland, Germany, France, Spain, Netherlands	5.2 Months (median)	Q2M	2x VL>200 c/mL or 1 VL≥200 c/mL + discontinuation	89	1 (1.1%)	0/1 [Not available]	1/1	0 (0%)	0 (0%, 0%)	1 (1.1%, 100%) [**E138A**]	0 (0%, 0%)
Liegeon et al., 2024 (7)	USA	8 Months (median)	Q1M and Q2M	NR	78	1 (1.3%)	1/1 [None]	1/1	0 (0%)	1 (1.3%, 100%) [**E138A**, **G140S**, **Q148S**]	1 (1.3%, 100%) [**K101E**, **N348I**]	1 (1.3%, 100%)
Shankaran et al., 2024 (8)	USA	NR	NR	2x VL >200 c/mL	75	3 (4%)	2/3 [M184V; **K103N**] (1 not available)	3/3	0 (0%)	3 (4%, 100%) [**G140S, L74L/M**, **T97T/A, Q148H**, **E138K**, I178L, Q207E; **L74I**, **T97T/A**, **S147S/G**, **N155H**; **G140G/S**, **Q148Q/R**]	1 (1.3%, 33.3%) [**K101P**]	1 (1.3%, 33.3%)
Nguyen et al., 2024 (9)	USA	9 Months (median)	Q1M and Q2M	NR (Detectable: >200 c/mL)	73	3 (4.1%)	3/3 [1/3: **K103N**, **E138Q**; 2/3: None]	3/3	0 (0%)	1 (1.4%, 33.3%) [**E138E/K**, **Q148Q/K**]	3 (4.1%, 100%) [**K103N**, **E138Q**; **K103K/R**, **E138G/R**; **M230M/L**]	1 (1.4%, 33.3%)
Rubenstein et al., 2023 (10)	France	15 Months (median)	Q2M	2x VL ≥200 c/mL	72	1 (1.4%)	0/1 [Not available]	1/1	1 (1.4%)	0 (0%, 0%)	0 (0%, 0%)	0 (0%, 0%)
Pérez et al., 2023 (11)	USA	24 Weeks	Q1M and Q2M	NR	62	1 (1.6%)	0/1 [Not available]	1/1	0 (0%)	0 (0%, 0%)	1 (1.6%, 100%) [**M230L**, **V179E**]	0 (0%, 0%)
Masich et al., 2023 (12)	USA	12 Months	NR	NR (Viral rebound: >200 c/mL)	24	1 (4.2%)	1/1 [R211K, L214F, G333E, E35D, L63Q, I64V, V77I, **M50T**]	1/1	1 (4.2%)	0 (0%, 0%)	0 (0%, 0%)	0 (0%, 0%)
Collins et al. 2022 (13)	USA	3 Months	Q1M	VL ≥200 c/mL	15	1 (6.7%)	0/1 [Not available] &	1/1	0 (0%)	0 (0%, 0%)	1 (6.7%, 100%) [**K103N**, **L100I**]	0 (0%, 0%)

Abbreviations: INI: Integrase Inhibitor, LA CAB+RPV: long-acting cabotegravir and rilpivirine, NR: Not reported, NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor, Q1M: monthly, Q2M: 2-monthly, RAMs: resistance-associated mutations, VL: Viral load, VF: Viral failure

*We included studies where relationship between drug class and RAMs was specified. Bolded mutations represent major RAMs according to Stanford Algorithm; **Genotype at initiation includes BL and/or historical genotype; @ Each individual's RAMs are separated by a semi-colon (;); $Information on the ATHENA cohort was also extracted from van Welzen et al., 2024 (14); £Baseline resistance testing for 5/5 VFs only available for reverse transcriptase RAMs; ‡genotype at VF missing for 1 VF; #1/2 VFs with off-label use (prior VF with NNRTIs) discovered post-hoc; &study excluded individuals with baseline RAMs

LIMITATIONS

Limitations include data availability, heterogeneity in cohort size, definitions of VF, duration of follow-up and lack of resistance data at baseline.

CONCLUSIONS

Calculating an accurate VF rate using real-world evidence is difficult due to heterogeneity of VF definition, follow-up time, and study design. Real-world data on treatment emergent resistance in the context of LA CAB+RPV is scant so far; however, existing findings suggest it is infrequent. Further research which evaluates emergent resistance whilst on LA CAB+RPV in real-world settings is needed. Consensus on definitions of VF in the context of LA CAB+RPV would aid interpretation.

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