Virological Failure to CAB+RPV LAI in Real Life: Resistance and Outcomes in a Large Italian Cohort

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BACKGROUND

Although virological failure (VF) with long-acting injectable (LAI) regimen with cabotegravir (CAB) and rilpivirine (RPV) is rare, it is frequently accompanied by integrase inhibitor (INI) and NNRTI resistance, potentially compromising future ART options.

Objective: We aimed to characterize real-life CAB+RPV LAI failures, resistance and post-failure outcomes in Italy.

METHODS

We conducted a retrospective observational cohort study including adult people with HIV (PWH) followed in 22 Italian clinical centers who started CAB+RPV LAI between March 2022 and February 2025.

VF was defined as 2 consecutive viremia ≥50 copies/mL, or one >50 copies/mL followed by therapy change, or as failure to achieve viral suppression (viremia ≤50 copies/mL).

For individuals with a genotypic resistance test (GRT) after VF to CAB+RPV LAI, resistance and post-failure outcomes were evaluated. Last date of follow-up was February 1, 2026.

RESULTS

Among 2177 PWH who started CAB+RPV LAI, 45 (2.1%) experienced VF (median [IQR] time of VF: 6.6 [3.6-10.6] months).

For 43/45 individuals a GRT at VF was available. At CAB+RPV start, their ART duration was 11.9 (7.5-17.4) years, and their BMI was 25.2 (23.4-28.9) Kg/m^2 (Table 1). Thirty-nine individuals were virologically suppressed since a median of 47.7 (6.0-118.5) months, 2 had low-level viremia (79 and 146 copies/mL), while 2 had very high viremia levels (1180000 and 154000 copies/mL). No individuals presented >1 of the known risk factors for VF (subtype A6, BMI ≥30 Kg/m^2, pre-existing RPV resistance).

At VF, 32/43 (74.4%) individuals harbored NNRTI and/or INI resistance, with viremia levels higher than those without resistance; 43.9% of them showed intermediate/high levels of bictegravir/dolutegravir cross resistance (Table2).

After VF, almost all individuals (42, 99.7%) changed therapy, while one had discontinued therapy voluntarily. Among those who changed therapy, 92.9% of them achieved virological suppression after a median (IQR) follow-up time of 2.0 (1.1-4.5) months, with a similar rate between groups with and without resistance.

In a large real-life Italian cohort, the **rate of virological failure** with CAB+RPV LAI was **low (2.1%)**, but with a high rate of NNRTI and/or INI resistance (74.4%). Despite this, **more than half of the individuals** (56.1%) **was still eligible for second-generation INIs, and most individuals (92.9%)** achieved **virological control** in a **very short time** after therapy change.

Table 1. Patients' characteristics, overall and according to the presence/absence of NNRTI/INI resistance at failure

Characteristics	Overall (N=43)	NNRTI/INI resistance (N=32)	No NNRTI/INI resistance (N=11)	P-value[f]
Age at CAB+RPV start, median years (IQR)	51 (45-57)	52 (45-58)	47 (45-52)	0.231
Male, n (%)	35 (81.4)	26 (81.3)	9 (81.8)	1.000
Mode of transmission, n (%):				
Hetero	14 (32.6)	7 (21.9)	5 (45.5)	
MSM	22 (51.1)	16 (50.0)	6 (54.5)	0.158
Other/Unknown[a]	7 (16.3)	7 (21.9)	0 (0.0)	
HBV coinfection, n (%)	4 (9.3)	3 (9.4)	1 (9.1)	1.000
HCV coinfection, n (%)	3 (7.0)	2 (6.3)	1 (9.1)	1.000
Subtype, n (%):				
B	35 (81.4)	25 (78.1)	10 (90.9)	
Non-B[b]	8 (18.6)	7 (21.9)	1 (9.1)	0.656
Years of ART, median (IQR)	11.9 (7.5-17.4)	10.3 (6.8-18.7)	14.4 (10.7-15.4)	0.646
Previous NNRTI failure, n (%)	5 (11.6)	5 (15.6)	0 (0.0)	0.300
Previous INI failure, n (%)	3 (7.0)	3 (9.4)	0 (0.0)	0.558
Viremia at CAB+RPV start, copies/mL, n (%):				
≤50 (target detected)	22 (51.2)	16 (50.0)	6 (54.5)	1.000
≤50 (target not detected)	17 (39.5)	12 (37.4)	5 (45.5)	0.728
Low level viremia (51-199 copies/mL), n (%)[c]	2 (4.6)	2 (6.3)	0 (0.0)	1.000
>200 copies/mL , n (%)[d]	2 (4.6)	2 (6.3)	0 (0.0)	1.000
Time under virological suppression (≤50 copies/mL) before CAB+RPV start (months), median (IQR)[e]	47.7 (6.0-118.5)	62.9 (6.0-121.1)	19.0 (6.1-79.6)	0.452
BMI at CAB+RPV start (Kg/m^2), median (IQR)	25.2 (23.4-28.9)	24.9 (23.3-28.4)	28.2 (25.0-30.7)	0.179
BMI ≥30 Kg/m^2 at CAB+RPV start, n (%)	8 (18.6)	4 (12.5)	4 (36.4)	0.172
Oral lead-in, n (%)	7 (16.3)	5 (15.6)	2 (18.2)	1.000
Administration according to schedule (+/7 days), n (%)	41 (95.3)	30 (93.8)	11 (100.0)	1.000

[a]Other: Injection drug use (N=2), sexual (N=2), vertical (N=1), unknown (N=2). [b]Non-B: A1 (N=2), A6 (N=1), D (N=1), G (N=1); CRF02_AG (N=1), CRF08_BC (N=1), CRF20_BG (N=1). [c]79 and 146 copie/mL [d]1180000 and 154000 copies/mL; [e]Estimated on 39 partecipants that were virological suppresed at CAB+RPV start. [f]Two-sided P-values were calculated by Mann-Whitney test or Fisher's exact test.

Table 2. Viremia levels and resistance at CAB+RPV failure and virological outcomes after therapy change

Characteristics	Overall (N=43)	VF with resistance (N=32)	VF without resistance (N=11)	P-value[l]
Duration of CAB+RPV at VF (months), median (IQR)	7.0 (3.5-10.7)	6.6 (4.1-10.8)	4.9 (3.0-10.6)	0.531
Viremia at CAB+RPV at VF (copies/mL), median (IQR)	1077 (238.0-6373.5)	3540 (295-11181)	226 (95-522)	0.018
Presence of NNRTI mutations at VF, n (%)	28 (72.5)[a]	28 (90.3)[e]	0 (0.0)[g]	<0.001
Presence of INI mutations at VF, n (%)	26 (63.4)[b]	26 (81.3)	0 (0.0)[h]	<0.001
Presence of NNRTI & INI mutations, n (%)	22 (57.9)[c]	22 (71.0)[f]	0 (0.0)[i]	0.001
Intermediate/high level resistance to RPV according to the GRT at VF[d], n (%)	16 (40.0)[a]	16 (51.6)[e]	0 (0.0)[g]	0.006
Intermediate/high level resistance to BIC/DTG according to the GRT at VF[d], n (%)	18 (43.9)[b]	18 (53.3)	0 (0.0)[h]	0.002
Intermediate/high level resistance to DRV according to the GRT at VF[d], n (%)	0 (0.0)[a]	0 (0.0)[e]	0 (0.0)[g]	1.000
Change therapy after CAB+RPV failure, n (%)	42 (97.7)	31 (96.9)	11 (100)	1.000
Change to an INI-based regimen, n (%)	11 (26.2)	8 (25.8)	3 (27.3)	1.000
Change to a PI-based regimen, n (%)	31 (73.8)	23 (74.2)	8 (72.7)	1.000
Virological suppression after therapy change, n (%)	39 (92.9)	29 (93.5)	10 (90.9)	1.000
Time of virological suppression after therapy change (months), median (IQR)	2.0 (1.1-4.5)	2.3 (1.3-4.6)	1.1 (1.0-2.8)	0.257

[a]GRT obtained successfully for PR/RT: N=40; [b]GRT obtained successfully for IN: N=41; [c]GRT obtained successfully for both RT&IN: N=38; [d]Drug resistance level estimated by HIVdb algorithm (v9.10.1; https://hivdb.stanford.edu/); [e]GRT obtained successfully for PR/RT: N=31; [f]GRT obtained successfully for both RT&IN: N=31; [g]GRT obtained successfully for PR/RT: N=9; [h]GRT obtained successfully for IN: N=9; [i]GRT obtained successfully for both RT&IN: N=7; [l]P-values were calculated by Mann-Whitney test or Fisher's exact test.

CONCLUSIONS

In this large real-life Italian cohort, the rate of VF with CAB+RPV LAI was low (2.1%), and none of the participants presented more than one of the known risk factors for VF. NNRTI and/or INI resistance was detected in 74.4% of cases and higher viremia levels in PWH with drug resistance.

Despite this, more than half of the participants (56.1%) was still eligible for second-generation INIs. Morevoer, post-failure outcomes were generally successful, with a suppression rate of 92.9% regardless of the presence of resistance.

These findings support the importance of prompt management of PWH who failed CAB+RPV LAI to restore their virological control.

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