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Efficacy, safety and discontinuation of rilpivirine and cabotegravir in HIV-1 virologically suppressed adults: a multicenter observational study in Tuscany (LAHIV study)

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Introduction/Summary

- Cabotegravir (CAB) + rilpivirine (RPV), available in Italy from June 2022, dosed intramuscularly every 2 months is the first long-acting (LA) regimen used to maintain HIV-1 virological suppression.
- We evaluated the efficacy, safety and durability of this regimen.

Study Design

- It is an observational multicenter study in which 10 out of 11 Tuscan Infectious Disease units participated.
- We included all virologically suppressed (HIV-RNA <50 cp/mL) persons living with HIV (PLWH) older than 18 years who initiated CAB+RPV with at least one follow-up visit.
- Discontinuation was defined as a regimen switch or 2 consecutive missed injections. Virological failure (VF) was defined as two consecutive HIV-RNA >50 copies/mL detections or a single HIV-RNA >50 copies/mL followed by ART modification
- Participants were monitored after the first injection until the date of CAB+RPV discontinuation, death, or last visit to the center.
- The study period is from 10/09/2022 to 20/03/2024
- The primary outcomes were "discontinuation due to all causes". The secondary outcome was the assessment of safety.

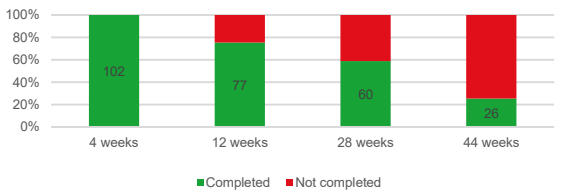
Methods

- Descriptive analysis was employed to illustrate population characteristics.
- Categorical variables were evaluated with X2/Fisher's exact test. Continuous variables with Mann-Whitney test.
- The cumulative risk of discontinuation was assessed using Kaplan–Meier curves.
- The statistical test was considered significant if the p-value was <0.05.

Results

- We enrolled 102 PLWH. We grouped participants based on their duration of follow-up: all completed 4 weeks; 77 remained for 12 weeks; 60 for 28 weeks; and 26 reached 44 weeks. [Figure 1]
- The combined at-risk period for analysis totaled 55,493 days, with a median follow-up of 28 weeks [IQR 11-44]

Figure 1: Percentage of people who completed the follow-up, stratified by weeks of follow-up.



DEMOGRAPHIC

Of the participants, 82 (80.4%) were male, with a median age of 51 years (IQR, 42-57). Participants discontinuing LA showed no clinical/demographic differences from those continuing, except a shorter time from the last detectable HIV-RNA and CAB+RPV introduction and more often lacking the genotype before switching; [Table 1]

Table 1. Clinical/demographic characteristics of adults with HIV-1, ART experienced with HIV-RNA level <50 copies/mL switching to RPV+CAB in 10 out 11 infectious diseases units in Tuscany, Italy.

	On CAB+RPV (n=93)		Discontinued (n=9)		p	TOTAL (n=102)	
Italians, n (%)	79	84.9	9	100	-	88	86.2
Gender, n (%)					-		
• Female	15	16.1	4	44.4		19	18.6
• Male	77	82.8	5	55.6		82	80.4
• Transgender	1	1.1	0	-		1	1
Age at entry, median [IQR]	51	[42-57]	52	[38-56]	0.727	51	[42-57]
Risk of HIV transmission, n (%)					-		
• Heterosexual	25	26.8	4	44.4		29	28.4
• MSM	43	46.2	5	55.6		48	47.1
• Intravenous drug users	10	10.7	0	-		10	9.8
• Other/ Not known	15	16.1	0	-		15	14.7
Years of undetectable viremia, median [IQR]	4.9	[1-9]	0.2	0.2-2.5	0.006	4	[1-9]
AIDS diagnosis, n (%)	12	12.9	1	11.1	0.878	13	12.7
HBc Ab, n (%)	20	24.4	1	11.1	0.369	21	23.1
HIV-RNA Zenit, Log_{10} copies/mL, median [IQR]]	4.8	[4.4-5.4]	5.0	4.9-5.5	0.353	4.9	[4.4-5.4]
Nadir CD4 (cells/mL), median [IQR]	328	[156-453]	237	97-324	0.220	313	[147-435]
Years of HIV, median [IQR]	12	6-19	20	9-23	0.235	12	6-20
CD4+ T cells at baseline/µL, median [IQR]	875	[640-1085]	760	652-836	0.425	857	[640-1080]
CD4/CD8, median [IQR]	1.1	[0.7-1.5]	0.9	0.7-1.3	0.535	1.1	[0.7-1.5]
Type of pre-switch regimen					-		
• NNRTI	38	40.8	5	55.6		43	42.1
• PI	11	11.8	0	-		11	10.8
• INSTI	66	70.9	7	77.7		77	75.4
Number of previous ART regimens, median [IQR]	4	[2-5]	4	3-6	0.322	4	[2-5]
Pre-switch regimen containing rilpivirine, n (%)	34	36.6	5	55.6	0.263	39	28.2
Pre-switch regimen containing dolutegravir, n (%)	42	45.2	7	77.8	0.061	49	48.1
Available genotype before the switch, n (%)	64	68.8	3	33.3	0.008	67	65.7
Reasons for LA introduction					-		
• Simplification	84	90.3	8	88.9		**92**	**90.2**
• Toxicity	1	1	0	-		**1**	**1**
• Other	8	8.7	1	11.1		**9**	**8.8**

ART: antiretroviral treatment; MSM: males who have sex with males; PI: Protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitors; INSTI: integrase strand transfer inhibitor

DISCONTINUATIONS

Overall, we observed 9 discontinuations: 6 from adverse events, 1 by patient choice, 1 from being lost to follow-up, and 1 from VF. The participant who experienced VF had pre-existing high-level mutations for RPV. The genotype at failure showed no mutations for CAB and the patient's virus was suppressed again with TAF/FTC/DRVc. Notably, 4 of the 6 adverse events occurred within the initial 4 weeks and spontaneously regressed after the LA discontinuation. [Table 2]

Table 2. Reasons for RPV/CAB discontinuation of a population of adults with HIV-1, ART experienced with HIV-RNA level <50 copies/mL switching to RPV+CAB in 10 out 11 infectious diseases units in Tuscany, Italy.

Previous regimen	BMI	NNRTI or INSTI mutations on the last genotype	Cause	WEEK	Post-regimen
3TC/DTG	N/A	N/A	High fever and joint pain, Walking impairment	4	3TC/DTG
RPV/DTG	N/A	Not detected	Rash	28	RPV/DTG
3TC/DTG	29.5	98G 106I 108I 181V	Virological Failure	4	T/F/DRVc
RPV/DTG	20.2	N/A	General malaise	4	RPV/DTG
3TC/DTG	25.3	N/A	Depression	4	3TC/DTG
RPV/DTG	22	N/A	Lost-to follow-up	12	//
T/F/RPV	23	Not detected	Panic attacks	12	T/F/RPV
T/F/RPV	23.4	N/A	Excessive clinic visits	28	T/F/RPV
3TC/DTG	21	N/A	Weight gain of 10kg, worsening of depressive symptoms	44	3TC/DTG

nucleoside reverse transcriptase inhibitors; INSTI: integrase strand transfer inhibitor:DTG: Dolutegravi: RPV: Rilpivirine; 3TC: Lamivudine; FTC: emtricitabine; T: TAF: F: Emtricitabine: OLI: oral lead-in: BMI: Body Mass Index: N/A: Not Available

- The discontinuation rate due to all causes was 16.2 x 100 py [95%CI 8.4-31.2]. This rate is higher compared to to RCTs but it could be overstated due to short follow-up times; a 4-week timepoint is the last observation for over 25% of patients.

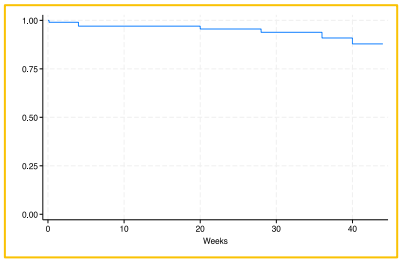


Figure 2. Probability of remaining free from treatment discontinuation for all causes in adults with HIV-1 ART experienced with HIV-RNA level <50 copies/mL switching to RPV+CAB in 10 out 11 infectious diseases units in Tuscany, Italy.

SAFETY

- Apart from the 6 discontinuations due to adverse events (10.8 x 100 py 95%CI 4.8-241), we observed 76 adverse events of grade 1: 63 local reactions and 13 systemic ones. Over time, the frequency of these reactions lessened, as shown in Figure 2. [Figure 3]

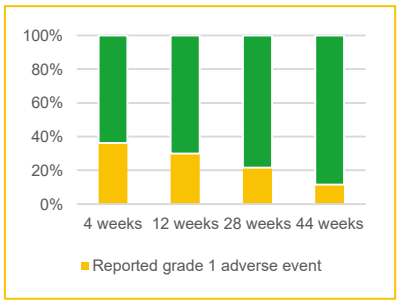


Figure 3. Percentage of adults with HIV-1 ART experienced with HIV-RNA level <50 copies/mL switching to RPV+CAB who reported a mild adverse event during the follow-up weeks in 10 out of 11 infectious diseases units in Tuscany, Italy.

Conclusion

- Our preliminary findings suggest the RPV+CAB effectively sustains virological suppression: the only VF observed was linked to a pre-existing RPV resistance.
- Safety is acceptable; only 5% stopped due to toxicity. However, data could be skewed by the small sample and short follow-up. The decrease in mild local adverse reactions with use may indicate an increasing adaptation of patients to the regimen.