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Long Acting injectables: the Italian experience

OC 10 Effectiveness of long-acting ART with cabotegravir/rilpivirine in the Icona Cohort

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ABSTRACT

Background: Cabotegravir (CAB) + Rilpivirine (RPV) Long Acting (LA) has shown its efficacy and tolerability in Phase 3 studies and has been commercialized since 2022 in Italy for virally suppressed people with HIV-1 (PWH). Real life clinical data on the effectiveness and discontinuation of CAB+RPV LA is scarce.

Methods: All PWH enrolled in the Icona Cohort who started CAB+RPV LA as maintenance therapy with viral load (VL) < 50 cp/ml at start and with at least one follow-up (FU) were included. Baseline of the analysis was the first CAB-RPV injection. Incidence and time to treatment discontinuation (TD) and to virological failure (VF, 2 consecutive VLs > 50 cp/ml or 1 VL>1000 cp/mL followed by ART-change) were estimated using the Kaplan-Meier method. Moreover, Cox regression models, adjusted for age, sex and mode of HIV transmission were employed. Fine-Gray models were fitted to investigate predictors of TD for toxicity.

Results: Overall, 470 virologically suppressed PWH started CAB+RPV LA, with a median FU of 8.1 months (interquartile range, IQR, 4.7-10.5). Main characteristics are presented in Table 1. Notably, 11.1% of subjects were females, 33.2% >50 years and 7.4% had BMI > 30 kg/m2. Oral lead-in was prescribed in 16% of cases.

44 treatment discontinuations were observed, with an incidence rate of 13.9 x 100 person year follow up (PYFU) (95% confidence interval, CI, 10.3-18.7%). One-year estimated cumulative probability of TD was 14.2% (95% CI 10.1-19.7%). Causes of TD were toxicity/adverse events (6.6%), PWH's choice (2.1%), virological failure (0.2%), pregnancy (0.2%), drug-drug interactions (0.2%) (Table 2). Incidence rate of TD for toxicity/adverse events was 9.8 x 100 PYFU (95%CI 6.9-13.9%) and 1-year cumulative probability of TD for toxicity/adverse events was 10.9% (95% CI 7.1-16.4%).

Factors associated to TD overall at multivariable Cox regression models were heterosexual sexual intercourses (aHR 2.76, 95% CI 1.33-5.70) and IDU as risk factor (aHR, 6.65, 95% CI 1.91-23.16) (Table 3). Heterosexual had also a higher risk of discontinuation due to toxicity (aSHR 3.64, 95% CI 1.58-9.37)

Two VFs were observed, with 1-year cumulative probability of VF of 0.63% (95% CI 0.15-2.62%). One VF was in a subject with HIV subtype B/F1, no previous resistance associated mutations (RAM) to NNRTI or INSTI, BMI 29.7 kg/m2, who failed with VL of 55 cp/ml and then 69 cp/ml and resuppressed without ART change. The other was in a subject with subtype B, no previous RAM to NNRTI (INSTI not tested), BMI 24.9 kg/m2, who failed with 636 cp/ml and 66,500 cp/ml; resistance test showed K101K/E, E138E/A and E157Q at failure and ART was changed firstly in FTC/TAF/BIC and then in DRV/c/TAF/FTC.

Conclusions: This analysis shows good short-term effectiveness of CAB-RPV LA, with a low rate of virological failure. A 14% probability of discontinuation overall and 10% for toxicity/adverse events emerged, higher than in phase 3 studies but similar to other real-life data.

Table 1: Main characteristics of PWH switching to CAB+RPV LA

	N=470
Female sex, n(%)	52 (11.1%)
Italian nationality, n(%)	417 (88.7%)
Mode of HIV transmission, n(%)	
Heterosex	118 (25.1%)
IDU	9 (1.9%)
MSM	316 (67.2%)
Other/unknown	27 (5.7%)
BMI, kg/m^2, median (IQR)	24.4 (22.6-26.8)
BMI > 30 kg/m^2, n(%)	35 (7.4%)
CD4+ at CAB/RPV switch, median (IQR)	756 [590-959]
<200 cells/mmc	2 (0.4%)
200-350 cells/mmc	18 (3.8%)
350-500 cells/mmc	47 (10.0%)
>500 cells/mmc	403 (85.7%)
CD4+ at nadir, median (IQR)	389.0 (239-525)
CD4+ < 200 cells/mmc at nadir, n(%)	96 (20.4%)
Age, years, median (IQR)	46 [37-54]
Age>50 years	156 (33.2%)
Years of viral suppression, median (IQR)	7.0 (3.7-9.5)
Years of art, median (IQR)	7.3 (4.4-10.1)
Previous AIDS event, n (%)	40 (8.5%)
Previous ART, n(%)	
DTG/3TC	143 (30.4%)
BIC/TAF/FTC	127 (27.0%)
RPV/TAF/FTC	74 (15.7%)
RPV/DTG	56 (11.9%)
Other	70 (14.9%)
Previous NNRTI failure, n(%)	2 (0.4%)
Previous INSTI failure, n(%)	0 (0.0%)
HBsAg positive, n(%)	0 (0%)
HBcAb positive, n(%)	73 (15.5%)
HCV-ab positive, n(%)	32 (6.8%)
Year of CAB/RPV start, median (IQR)	2023 (2022- 2023)
ART line, median (IQR)	4 (3 – 5)
GRT RT pre CAB/RPV, n (%)	315 (67%)
RPV fully susceptible, n(%)	308 (97.8%)
GRT INSTI pre CAB/RPV, n (%)	178 (38%)
CAB fully susceptible, n (%)	178 (100%)
HIV subtype, n(%)	
A1	4 (0.9%)
B	218 (46.4%)
Others	53 (11.3%)
Missing	195 (41.5%)

Table 2: Causes of treatment discontinuations of CAB/RPV LA

	N	PERCENT OVER PWH INCLUDED
Virological failure	1	0,2%
Other	2	0,4%
Pregnancy	*1*	*0,2%*
Drug-drug interactions	*1*	*0,2%*
PWH's choice	10	2,1%
Toxicity/eas	31	6,6%
Arthro-myalgia	*1*	*0,2%*
Clinical contraindications	*2*	*0,4%*
Constitutional symptoms	*1*	*0,2%*
Gastrointestinal intolerance	*3*	*0,6%*
Allergic reactions	*2*	*0,4%*
Reactions injection site	*16*	*3,4%*
Neuropsychiatric aes	*2*	*0,4%*
Hepatic toxicity	*2*	*0,4%*
Pancreatic toxicity	*1*	*0,2%*
Metabolism issues	*1*	*0,2%*

Notes: PWH, people with HIV-1; CAB, cabotegravir; RPV, rilpivirine; LA, long acting; n, number; IDU, injective drug users; MSM, men who have sex with men; IQR, interquartile range; ART, antiretroviral therapy; DTG, dolutegravir; 3TC, lamivudine; BIC, bictegravir; TAF, tenofovir alafenamide; FTC, emtricitabine; NNRTI, non-nucleoside reverse transcriptase inhibitors; INSTI, integrase inhibitors; GRT, genotype resistance test; RT, retrotranscriptase.

Table 3: Factors associated to treatment discontinuation (overall)

	Unadjusted model				Adjusted model			
	HR	95%CI		p	aHR*	95%CI		p
Female sex (vs. male)	0,79	0,28	2,22	0,661	0,40	0,13	1,25	0,115
Age, per 10 years older	1,08	0,83	1,40	0,585	0,94	0,71	1,26	0,699
Mode HIV transmission								
MSM	1,00				1,00			
Heterosex	1,95	1,04	3,68	**0,038**	2,76	1,33	5,70	**0,006**
IDU	6,22	1,86	20,81	**0,003**	6,65	1,91	23,16	**0,003**
Other/Unknown	0,51	0,07	3,77	0,509	0,57	0,08	4,21	0,580
Years on ART, per 1 more	1,01	0,95	1,08	0,704	0,99	0,92	1,06	0,705
Years VS, per 1 more	1,00	0,93	1,08	0,953	0,99	0,91	1,07	0,75
Italian (vs non-Italian born)	1,04	0,92	1,19	0,506	1,10	0,39	3,14	0,855
BMI ≥25 (vs <25 kg/m^2)	1,02	0,53	1,95	0,961	0,88	0,45	1,71	0,703
Oral Lead In	2,06	1,08	3,94	0,029	1,73	0,89	3,36	0,107
HCVAb pos (vs HCVAb neg)	1,17	0,36	3,79	0,792	0,60	0,14	2,51	0,485
HbcAb pos (vs. HBcAb neg)	0,38	0,11	1,23	0,105	0,38	0,11	1,26	0,114
Previous AIDS event	0,75	0,35	1,62	0,469	1,74	0,71	4,26	0,229
Previous NNRTI use	1,71	0,72	4,04	0,224	0,91	0,49	1,69	0,769
CD4 at nadir, per 100 more	0,94	0,82	1,07	0,347	0,95	0,83	1,10	0,501
CD4 at CAB/RPV switch, per 100 more	0,97	0,88	1,07	0,593	0,98	0,89	1,08	0,724
Previous ART-regimen								
2DR-INSTI	1,00				1,00			
3DR-INSTI	1,30	0,67	2,51	0,431	1,45	0,74	2,81	0,278
3DR-NNRTI	0,97	0,40	2,34	0,948	0,92	0,38	2,23	0,849
other	0,41	0,05	3,08	0,386	0,40	0,05	3,02	0,375

**adjusted for age, sex, mode of HIV transmission; Sex adjusted only for age and mode; mode of HIV transmission adjusted only for sex and age; Age is adjusted only for sex and mode of HIV transmission*

Notes: HR, hazard rate; aHR, adjusted hazard rate; CI, confidence interval; IDU, injective drug users; MSM, men who have sex with men; ART, antiretroviral therapy; VS, viral suppression; VF, virological failure; INSTI, integrase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; CAB, cabotegravir; RPV, rilpivirine; DR, drug regimen.