P077

EFFECTIVENESS OF LONG-ACTING ART WITH CABOTEGRAVIR/RILPIVIRINE IN THE ICONA COHORT

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Background

Phase 3 RCT (FLAIR, ATLAS, ATLAS-2M, SOLAR studies) showed efficacy of cabotegravir + rilpivirine (CAB+RPV) Long Acting (LA) in mantaining HIV-1 suppression and demonstrated non-inferiority to oral therapy. Real-life data are limited but critical for understanding the use and the outcomes of CAB+RPV in broader groups

Aim

Evaluate the effectiveness in real-world of CAB+RPV as risk of treatment discontinuation, toxicity and virological failure

Materials & Methods

Study population

HBsAg negative people with HIV (PWH) enrolled in the Icona Cohort who started CAB+RPV LA as maintenance therapy with HIV-RNA< 50 cp/ml at start and with at least 1 follow-up visit

Endpoints

- Incidence and time to treatment discontinuation for any causes (TD)
- Incidence and time to treatment discontinuation for toxicity/adverse events (AEs)
- Incidence and time to virological failure (VF)
- Emergence of resistance-associated mutations (RAMs) at VF

Definitions

Virological failure: 2 consecutive HIV-RNA > 50 cp/ml or 1 HIV-RNA >1000 cp/mL followed by ART-change;
Baseline: the first CAB-RPV injection.

Statistical analysis

- Cumulative probability of the endpoints was estimated by means of standard survival analysis: Kaplan-Meier (KM) curves
- Incidence rate was estimated as number of events over patient-year follow-up (PYFU) on CAB+RPV
- Adjusted Cox regression models stratified by center have been used to investigate the role different demographical and clinical factors as predictors of TD and TD for toxicity/AEs

Results

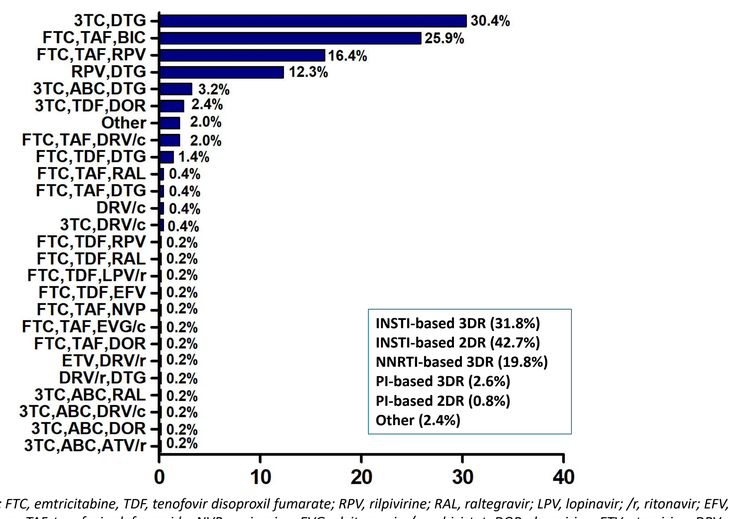
- A total of 506 PWH started CAB+RPV LA, with a median follow-up of 8.7 months (IQR, 4.8-10.8).
- Demographical and clinical characteristics at CAB+RPV LA initiation are reported in Table 1
- The majority came from an INSTI-based regimen (74.5%), particularly the 2DR 3TC+DTG (30.4%) and RPV+DTG (16.4%) [Figure 1]

Table1. Main characteristics of PWH switching to CAB+RPV LA

Female sex, n(%)	57 (11.3%)
Italian nationality, n (%)	452 (88.7%)
Mode of HIV transmission, n(%)	
Heterosex	129 (25.5%)
IDU	9 (1.8%)
MSM	344 (68%)
Other/unknown	24 (4.7%)
BMI, median (IQR)	24.4 (22.7-26.8)
BMI > 30, n(%)	39 (7.7%)
CD4 at BL, median (IQR)	766 [590-959]
CD4 at nadir, median (IQR)	387 (243-532)
CD4< 200 at nadir, n(%)	98 (19.4%)
Age, median (IQR)	46 [37-54]
Age > 50 years	165 (32.6%)
Years of viral suppression, median (IQR)	7.0 (3.7-9.6)
ART exposure, years, median (IQR)	7.3 (4.4-10.2)
Previous AIDS event, n (%)	42 (8.3%)
HBcAb positive, n (%)	79 (19.8%)
HCV-Ab positive, n(%)	35 (7.2%)
ART line, median (IQR)	4 [3-5]
GRT RT pre CAB/RPV, n (%)	415 (82.0%)
RPV fully susceptible, n(%)	405 (97.6%)
GRT INSTI pre CAB/RPV, n (%)	231 (45.7%)
CAB fully susceptible, n (%)	231 (100%)
Oral lead-In, n (%)	78 (15.0%)
HIV subtype, n(%)	
A1	7 (1.4%)
B	280 (55.3%)
Others	71 (14.0%)
Missing	148 (29.2%)

Notes: IQR, interquartile range; IDU, intravenous drug users; MSM, men who have sex with men; BMI, body mass index; BL, baseline; GRT, genotype resistance test; RT, retrotrascriptase; CAB, cabotegravir; RPV, rilpivirine; INSTI, integrase inhibitors.

Figure 1. ART regimen before CAB+RPV initiation



Notes: FTC, emtricitabine, TDF, tenofovir disoproxil fumarate; RPV, rilpivirine; RAL, raltegravir; LPV, lopinavir; /r, ritonavir; EFV, efavirenz, TAF, tenofovir alafenamide; NVP, nevirapine; EVG, elvitegravir; /c, cobicistat; DOR, doravirine; ETV, etravirine; DRV, darunavir; DTG, dolutegravir; 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; BIC, bictegravir; 3DR, 3-drug regimens; 2DR, 2-drug regimens; INSTI, integrase inhibitors; NNRTI, non-nucleoside retrotrascriptase inhibitors; PI, protease inhibitors

Treatment discontinuation

- 47 treatment discontinuations for any causes
- Incidence rate of TD: 13.1 x 100 PYFU (95%CI 9.8-17.4%)
- 1-year cum. probability of TD: 13.3% (95%CI 9.7-18.1%) [Figure1]
- Injection site reactions were the most frequent cause of discontinuation (n=17) followed by choice of the PWH (n=11) [Table 2]
- 51% of PWH switched to an oral 2DR after CAB+RPV TD [Figure 2]
- Heterosexuals and Injecting Drug Users (IDU) had higher risk of TD [Table 3]

Figure 1. Probability of TD by KM curve

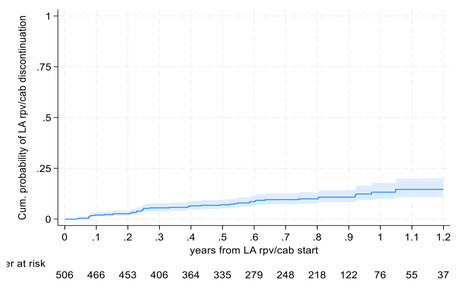


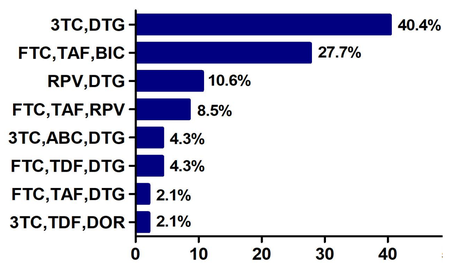
Table 2. Causes of TD of CAB+RPV

	N (% over PWH included)
Toxicity/adverse events	33 (6.5%)
Arthro-myalgia	1 (0.2%)
Clinical contraindications	2 (0.4%)
Constitutional symptoms	1 (0.2%)
Gastro-intestinal intolerance	3 (0.6%)
Allergic reactions	2 (0.4%)
Reactions injection site	17 (3.4%)
Neuropsychiatric adverse events	2 (0.,4%)
Hepatic toxicity	2 (0.4%)
Pancreatic toxicity	1 (0.2%)
Metabolism issues	1 (0.2%)
Skin reactions	1 (0.2%)
PWH's choice	11 (2.2%)
Other	2 (0.4%)
Pregnancy	1 (0.2%)
Drug-drug interactions	1 (0.2%)
Virological Failure	1 (0.2%)

Table 3. HR and aHR of TD by Cox regression models

	Unadjusted			Adjusted		
	HR	95%CI	p	aHR	95%CI	P
Female (vs. male) [1]	0.78	(0.27-2.25)	0.649	0.34	(0.10-1.12)	0.075
Age. per 10 years older [2]	1.00	(0.76-1.31)	0.997	0.93	(0.70-1.23)	0.605
Mode HIV transmission [3]						
Heterosexual (vs MSM)	2.26	(1.10-4.68)	0.027	3.60	(1.53-8.47)	0.003
IDU (vs MSM	4.21	(0.95-18.63)	0.058	4.80	(1.07-21.55)	0.041
Other/Unknown (vs MSM	0.43	(0.06-3.23)	0.408	0.47	(0.06-3.59)	0.465
Italian (vs non Italian born) [4]	1.17	(0.41-3.32)	0.771	0.95	(0.33-2.75)	0.92
BMI ≥25 (vs <25 kg/m²) [4]	0.93	(0.50-1.73)	0.823	0.82	(0.43-1.57)	0.553
Oral Lead-In (vs no oral Lead-In) [4]	2.35	(0.88-6.27)	0.088	2.11	(0.75-5.90)	0.156
HCV-Ab pos (vs HCV-Ab neg) [4]	1.02	(0.31-3.35)	0.978	0.87	(0.24-3.09)	0.826
Previous AIDS event (vs. no AIDS) [4]	1.45	(0.59-3.53)	0.418	1.55	(0.60-4.01)	0.362
Prev. NNRTI use (vs no NNRTI use) [4]	0.87	(0.47-1.63)	0.668	0.92	(0.48-1.75)	0.79

Figure 2. ART started after TD of CAB+RPV



***Adjusted for**: [1] age and mode of HIV transmission; [2] sex and mode of HIV transmission; [3] age and sex; [4] age, sex, mode of HIV transmission;*
Notes: HR, Hazard Ratio; aHR, adjusted Hazard Ratio; CI, confidence interval.

Treatment discontinuation for toxicity/AEs

- 33 TD for toxicty/AEs, with an Incidence Rate of 9.2 x 100 PYFU (95%CI 6.5-12.9)
- 1-year cum. probability of TD for toxicity/AEs: 10.1% (95%CI 6.7-14.3%)
- Heterosexual had a higher risk of TD for toxicity/AEs, conversely females presented a lower risk [Table 4]

Table 4. HR and aHR of TD for toxicity/AEs by Cox regression

	Unadjusted			Adjusted		
	HR	95%CI	p	aHR	95%CI	p
Female (vs. male)[1]	0.53	(0.12-2.29)	0.395	0.18	(0.04-0.88)	0.035
Age, per 10 years older[2]	1.16	(0.84-1.61)	0.358	1.07	(0.75-1.51)	0.719
Mode HIV transmission[3]						
Heterosexual (vs. MSM)	3.08	(1.28-7.38)	0.012	5.61	(2.03-15.52)	0.001
IDU (vs. MSM)	3.36	(0.42-26.66)	0.252	3.54	(0.44-28.87)	0.237
Other/Unknown (vs. MSM)	0.59	(0.07-4.60)	0.611	0.62	(0.08-4.84)	0.646
Italian (vs non-Italian born)[4]	1.07	(0.32-3.61)	0.909	0.73	(0.21-2.54)	0.626
BMI ≥25 (vs <25 kg/m²)[4]	0.72	(0.34-1.54)	0.398	0.56	(0.26-1.24)	0.152
Oral lead-in (vs no oral lead-in)[4]	3.63	(1.11-11.87)	0.033	3.46	(0.97-12.26)	0.055
HCV-Ab pos (vs HCV-Ab neg)[4]	0.49	(0.07-3.70)	0.493	0.43	(0.05-3.50)	0.427
Previous AIDS event (vs no AIDS)[4]	0.56	(0.13-2.42)	0.435	0.43	(0.09-1.99)	0.277
Previous NNRTI use (vs no NNRTI use)[4]	1.12	(0.53-2.35)	0.766	1.10	(0.51-2.40)	0.802

***Adjusted for**: [1] age and mode of HIV transmission; [2] sex and mode of HIV transmission; [3] age and sex; [4] age, sex, mode of HIV transmission;*

Virological failure

- 2 VF, Incidence rate of VF 0.59 x 100 PYFU (95%CI 0.15%-2.37%)
- 1-year cumulative probability of VF 0.57% (95% CI 0.14-2.38%)
- Details of the VF showed in Table 5

Table 5. Details of the VF

ID	HIV subtype	RAM NNRTI or INSTI	Nadir CD4	HIV-RNA at zenith, log10 cps/ml	BMI, kg/m²	ART pre CAB/RPV	N° inj.	VL at VF, cps/ml	RAM at VF	ART post CAB/RPV	VL<50 post-VF
1	B/F1	NNRTI: None INSTI: None	899	5.24	29.7	FTC/TAF/BIC	2	55, 69	NA	Continued CAB/RPV	YES
2	B	NNRTI: None INSTI: not tested	24	6.14	24.9	FTC/TAF/BIC	5	636, 66500	NNRTI: K101E INSTI: E138A / E157Q	FTC,TAF,BIC, then DRV/c/TAF/FTC	NO

Conclusions

- Large series of Italian real-world data, including data on individuals over 50 years of age (constituting one-third of the population studied) but with underrepresentation of females and non-Italian PWH
- Two virological failures reported, with one of these cases showing the emergence of new resistance-associated mutations
- 13% of CAB+RPV discontinuation at 1-year
  - 10% attributable to toxicity or AEs, primarily localized injection site reactions
  - Higher among males and PWH whose modes of HIV transmission included heterosexual intercourse or injection drug use
  - Rate higher than that observed in phase 3 trials, but within the range of estimated of first real-life studies
- Longer follow-up is needed to confirm the virological efficacy in long-term

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