Impact of Oral Lead-In on PK and Virological Outcomes in People With HIV Transitioning to CAB+RPV LA

680

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BACKGROUND

For people with HIV (PWH) on ART, transitioning to bimonthly long-acting (LA) injectable cabotegravir (CAB) plus rilpivirine (RPV) can be started either directly with injections (SWI) or after an optional one-month oral lead-in (OLI). Recent data suggest lower CAB trough concentrations (Ctrough) with SWI initiation.

Objective: To assess pharmacokinetics (PK) and virological outcomes based on OLI use in a real-world setting.

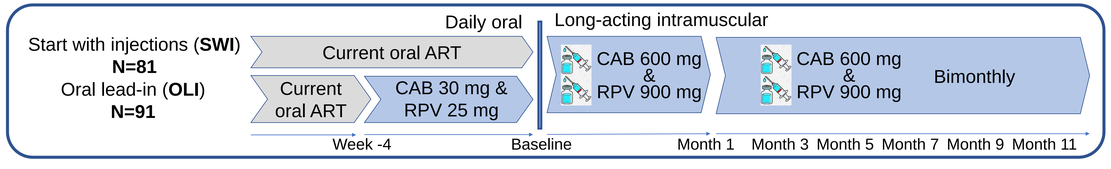
METHODS

- DESIGN: Prospective cohort study
- SAMPLE: PWH on stable ART (HIV-1 viral load [VL]<50 copies/mL prior to enrollment) who switched to bimonthly LA CAB+RPV, were sequentially assigned to SWI (January-April'23) or OLI (May-December'23) groups.
- DATA ANALYSIS: CAB and RPV plasma levels were measured (UHPLC-MS/MS Shimadzu Scientific) before each injection over a 7-month follow-up, with virological monitoring (COBAS® HIV-1 Test, Roche) up to 11 months.
- Virological failure (VF): 2 consecutive VL≥200 copies/mL or one VL≥1000 copies/mL. Non-sustained viral suppression (non-suppression): any VL≥20 copies/mL.
- Linear mixed-effects models adjusted for OLI use, age, sex, BMI and smoking status, including random intercept for between-patients variability, were conducted (R v4.2.3).

RESULTS

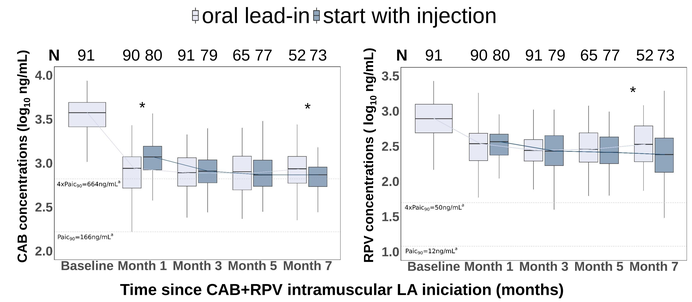
A total of 698 plasma samples from 172 PWH were analyzed. 47.1% initiated LA therapy directly, while 52.9% used OLI. Baseline characteristics were similar between groups (p>.1). Over 11-month follow-up, no significant differences were observed in non-suppression rates between SWI and OLI groups (44.4% vs 40.7%, p=.729) or VF (0.6% vs 1.2%, p=.999). CAB and RPV Ctrough levels, regardless of OLI use, remained well above the PAIC90 threshold from clinical trials. In multivariable models, lower CAB Ctrough was significantly associated with higher BMI (p=.019), male sex (p=.021) and smokers (p=.057), with no influence of OLI use. Lower RPV levels were significantly associated with smoking (p=.011) and younger age (p=.064).

For PWH transitioning to CAB+RPV LA, the use of an oral lead-in did not result in significant differences in pharmacokinetics or virological outcomes, compared to starting directly with injections



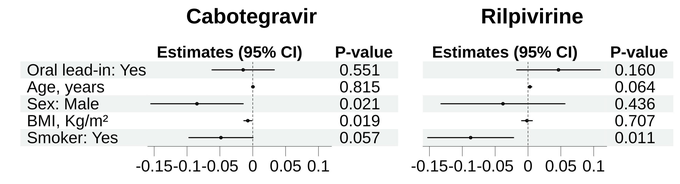
Characteristic, median (IQR)	**All N=172**	**Oral lead-in N=91**	**Start with injections N=81**	**P value**
Age, years	48 (38-56)	47 (38-56)	50 (37-56)	0.514
Sex at birth, Female, n (%)	22 (12.8)	12 (13.2)	10 (12.3)	0.999
Country of origin, Spain, n (%)	133 (77.3)	76 (83.5)	57 (70.4)	0.190
Smoker, n/N (%)	76/167 (45.5)	47/91 (51.6)	29/76 (38.2)	0.112
BMI at baseline, Kg/m2	24.8 (22.6-27.5)	24.8 (22.6-28.0)	24.9 (22.6-27.5)	0.818
BMI ≥30 Kg/m² at baseline, n/N (%)	25/170 (14.7)	15/91 (16.5)	10/79 (12.7)	0.627
HIV-1 subtypes, Non-B, n/N (%)	17/92 (18.5)	13/53 (24.5)	4/39 (10.3)	0.106
Type B	75/92 (81.5)	40/53 (75.5)	35/39 (89.7)	
HIV-1 VL at diagnosis (pre-ART), log_{10} cp/mL	4.78 (4.36-5.22)	4.70 (4.29-5.20)	4.82 (4.48-5.24)	0.437
Nadir CD4 count, cells/µL	270 (147-465)	278 (136-493)	262 (161-430)	0.667
pre-transition ART, INSTI+2 NRTI	36 (20.9)	20 (22.0)	16 (19.8)	0.212
NNRTI+2 NRTI	27 (15.7)	11 (12.1)	16 (19.8)	
PI+2 NRTI	11 (6.4)	7 (7.7)	4 (4.9)	
DTG+LMV	53 (30.8)	27 (29.7)	26 (32.1)	
DTG+RPV	35 (20.3)	17 (18.6)	18 (22.2)	
2-Drug non-INSTI regimen	9 (5.2)	8 (8.8)	1 (1.2)	
Other	1 (0.6)	1 (1.1)	0 (0)	
Time since HIV diagnosis, years	11.5 (4.9-22.9)	11.2 (4.9-22.4)	11.6 (4.9-22.9)	0.999
HIV-1 VL at baseline, <20 copies/mL	147 (85.5)	77 (84.6)	70 (86.4)	0.999
20-49 copies/mL	18 (10.4)	10 (11.0)	8 (9.9)	0.999
50-99 copies/mL	7 (4.1)	4 (4.4)	3 (3.7)	0.999
CD4 cell at baseline, cells/µL	702 (497-940)	700 (552-938)	717 (463-942)	0.275
RPV mutations (low-level resistance), n/N (%)	8/112 (7.4)	3/60 (5.0)	5/48 (10.4)	0.462

Cabotegravir and rilpivirine trough concentrations according to oral lead-in



LA, long-acting; N, number of samples; *p<0.05. [a]Reported thresholds from clinical trials: in vitro protein-adjusted inhibitory concentration required for 90% viral inhibition (PAIC90): 166 ng/mL for CAB, 12 ng/mL for RPV; 4xPAIC90: 664 ng/mL for CAB and 50 ng/mL for RPV

Linear mixed-effects models of baseline predictors of trough plasma concentrations over a 7-month follow-up



CONCLUSIONS

- The use of an oral lead-in did not result in significant differences in pharmacokinetics or virological outcomes for PWH transitioning to CAB+RPV LA over 7 months.
- Patient-specific factors—BMI, sex, and smoking—are more influential determinants of CAB and RPV PK than the use of an OLI phase.
- These findings support flexible and individualized initiation strategies for CAB+RPV LA therapy.

ADDITIONAL KEY INFORMATION

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