CABOTEGRAVIR AND RILPIVIRINE PK FOLLOWING LONG-ACTING HIV TREATMENT DISCONTINUATION

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Introduction

- Long-acting (LA) regimens of the integrase inhibitor cabotegravir (CAB) + the non-nucleoside RT inhibitor rilpivirine (RPV) given monthly or every 2 months are in development for maintenance of HIV suppression.
- Both products exhibit absorption-rate limited pharmacokinetics (PK) following intramuscular (IM) administration, with mean apparent half-life (t1/2) estimates of 5.6-11.5 weeks (CAB) and 28 weeks (RPV).
- Following LA treatment discontinuation, CAB and RPV may remain measurable in plasma for a year or longer.
- PK data from HIV-infected subjects in the long-term follow-up (LTFU) of Phase 2b/3 studies (LATTE-2/ATLAS) are presented.

Methods

- Subjects who received CAB LA + RPV LA every 4 (Q4W, n=33) or every 8 (Q8W, n=5) weeks and withdrew for any reason were switched to alternative antiretroviral therapy (ART) and entered LTFU (1 year).[1,2]
- PK sampling occurred at 1, 3, 6, 9 and 12 months after final CAB LA + RPV LA IM injections.
- Plasma CAB and RPV concentrations were determined by validated LC-MS/MS assays (LLOQ 0.025 µg/mL and 1 ng/mL, respectively).
- RPV concentrations in subjects receiving oral RPV as part of their alternative regimen in LTFU were excluded from the results.
- Individual CAB and RPV LTFU concentrations are shown in comparison to respective LLOQ and in vitro protein adjusted IC90 (PA-IC90) values.
- Where possible, terminal slopes during LTFU were determined to approximate absorption rate constants and estimate associated half-lives.

Results

Figure 1. Number of Injection Visits Before Subjects Entered LTFU

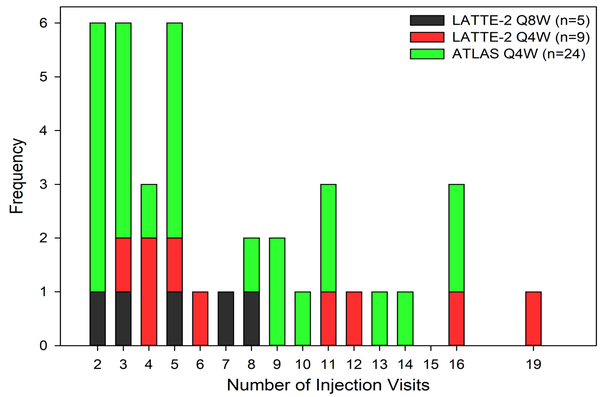


Table 1. Subject Demography and LTFU Alternative ART

Parameter		LATTE-2 (P2b) (n=14)	ATLAS (P3) (n=24)	Overall (n=38)
Study Regimen	Q4W	9	24	33
	Q8W	5	NA	5
Sex	Female	1	8	9
	Male	13	16	29
Age (years) (median, range)		34.5 (21 - 48)	38 (21 - 51)	37.5 (21 - 51)
Baseline Weight (kg) (median, range)		72.3 (52.7 - 95.0)	71.6 (41.2 - 120)	72.3 (41.2 - 120)
Baseline BMI (kg/m^2) (median, range)		24.2 (19.4 - 29.3)	23.3 (15.3 - 37.9)	23.7 (15.3 - 37.9)
LTFU ART[a]	Rilpivirine (oral)	1	6	7
	Dolutegravir	7	5	12
	Elvitegravir[b]	2	3	5
	Raltegravir	0	3	3
	Efavirenz	0	4	4
	Darunavir[b]	4	1	5
	Lopinavir[b]	0	3	3
	Atazanavir[b]	0	2	2
	Unspecified	2	0	2

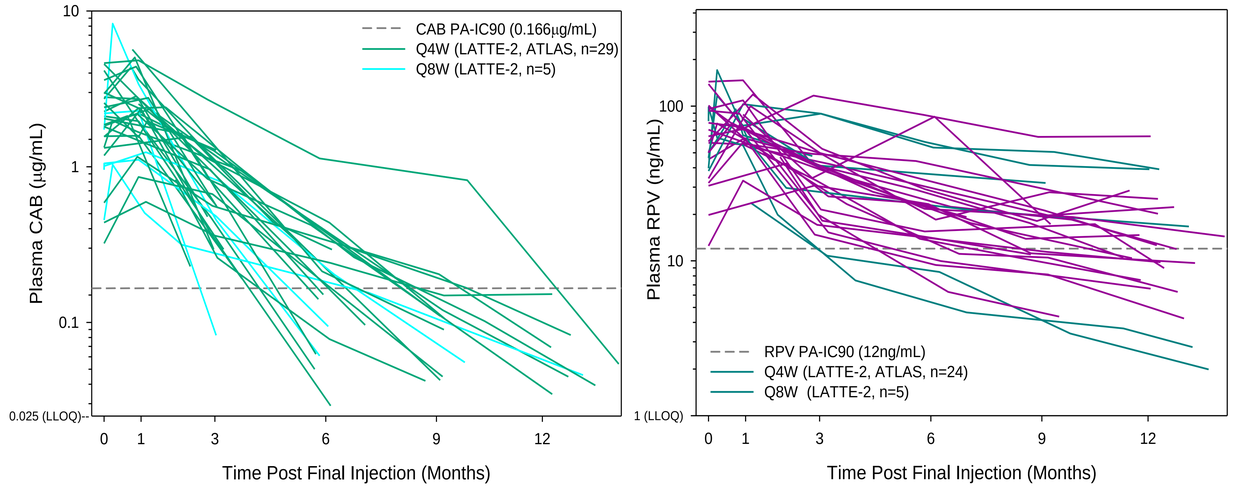
[a]Some individuals used multiple different ART regimens throughout the LTFU.
[b]Co-administered with boosting agents ritonavir or cobicistat except for 1 on atazanavir.

Table 2. Median (5th, 95th Percentile) Parameter Estimates of Individual LTFU Concentration-Time Data (Figure 2)

Parameter	CAB (n=34)	RPV (n=27)
Slope (hr^{-1})	0.00064 (0.00028, 0.00183)	0.00014 (0.00008, 0.0003)
Half-life (weeks)[a]	6.4 (2.3, 14.7)[a]	29.6 (15.2, 56.7)[a]

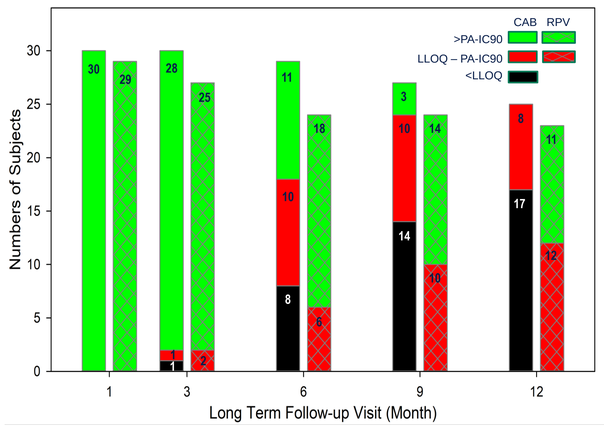
[a]Apparent terminal phase half-life should be interpreted with caution as data were insufficient (<2 half-life lengths) for accurate estimation in some profiles.

Figure 2. Individual Concentration-Time Profiles Following Discontinuation of Long-Acting Treatment in LATTE-2 and ATLAS (CAB left, RPV right)



LLOQ, lower limit of quantification; PA-IC90, protein adjusted IC90.

Figure 3. Range of CAB (left) and RPV (right) Concentrations by LTFU Visit Following Discontinuation of Q4W and Q8W Regimens



Discussion

- CAB and RPV PK observed during the one-year LTFU phase of P2b/3 studies is consistent with the respective absorption-rate limited half-life of each product.
- CAB and RPV have low drug interaction potential as perpetrators and pose no PK-related limitations to alternative ART selection after discontinuation of injections.
- Use of UGT1A1 and/or CYP3A enzyme inhibitors or inducers could, respectively, decrease or increase the CAB and/or RPV systemic clearance, while ongoing absorption of residual drug from the injection sites remains unaffected.
- Adverse events were uncommonly reported, and no patients met CVF criteria during LTFU on alternative ART, which included integrase inhibitor–, NNRTI-, and protease inhibitor–based regimens.

Conclusions

Alternative ART selection after discontinuing CAB LA + RPV LA is unrestricted with respect to drug interactions and may include CYP3A and/or UGT1A1 inducers or inhibitors without efficacy or safety concerns.

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References: 1. Margolis D, et al. *Lancet.* 2017;390:1499-1510. **2.** Swindells S, et al. CROI 2019; Seattle, WA. Abstract 1475.