MODELING TAIL-PHASE PK FROM EARLY PREGNANCY TO POSTPARTUM AND FETAL EXPOSURE TO LONG-ACTING CAB-RPV

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INTRODUCTION

- Long-acting injectable cabotegravir and rilpivirine combination has (LA-CAB/RPV) been approved as a complete regimen for the treatment of HIV-1 infection in adults who are virologically suppressed.
- After an optional 1-month daily oral lead-in (30/25 mg), LA-CAB/RPV dosing starts with 600mg LA-CAB and 900 mg LA-RPV injections at separate gluteal sites at the same visit, continued with 400/600 mg every 28 (±7) days.
- Individuals who become pregnant may discontinue LA-CAB/RPV due to lack of definitive data on safety and efficacy during gestation.

AIM

- The aim of this study was to describe the time course of CAB and RPV plasma levels and fetal exposure following LA-CAB/RPV discontinuation early in pregnancy.

METHODS

- Adult and pregnancy physiologically based pharmacokinetic (PBPK) models were previously qualified for repeated dose LA-CAB/RPV, including tail-phase PK using available clinical data[1,2.3].
- Standard LA-CAB/RPV, without oral lead-in, was initiated and continued to steady state in a virtual population of 100 non-pregnant women.
- Discontinuation was simulated at steady state after only one injection during first trimester (T1) of pregnancy (n = 100).
- Continuous simulation from pre-pregnancy to postpartum period, including a 9-month gestation, was enabled by transfer of residual drug in muscle depot to the next stage.
- Tail-phase PK of LA-CAB and LA-RPV was simulated until 6 months postpartum. Maternal and fetal exposure measures were computed from time-concentration data for pregnancy (weeks 15-40) and postpartum.

When LA-CAB/RPV is discontinued in early T1, predicted maternal plasma levels remain detectable until 6 months postpartum: CAB, 125 (115-139) ng/ml and RPV, 7.84 (7.30-8.49) ng/ml.

RESULTS

- A total of 8 scenarios were simulated (n = 100 each) in virtual cohorts of non-pregnant, pregnant and postpartum women.
- Median (interquartile range) age was 26.5 years (22.2-30.8) for all cohorts. Also, median (interquartile range) body weight for the pregnant and postpartum cohort was 64.1 kg (54.8-73.8) and 59.9 kg (51.5-68.5), respectively.
- PK tail was driven by residual drug in muscle depot which stabilised at steady state (Figure 1). CAB: 1546 mg pre-pregnancy, 925 mg end of T1 and 208 mg end of T3. RPV: 2309, 1383, and 312 mg, respectively.

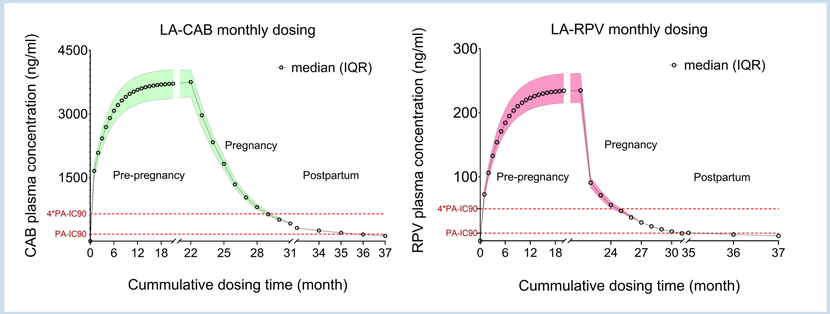


Figure 1: Predicted tail-phase PK of LA-CAB/RPV until 6 months postpartum.

- Maternal plasma levels were predicted to be above the respective 4*PA-IC90 for both drugs in 100% of the cohort at gestation week 8, compared with 0% at delivery (Table 1).

Gestation week 8	CAB	RPV
% Above 4*PA-IC90	**100**	**100**
At delivery (40 weeks)	**CAB**	**RPV**
% Above 4*PA-IC90	0	0
% Above PA-IC90	100	38
5 Months postpartum		
% Above PA-IC90	33	7
6 Months postpartum		
% Above PA-IC90	4	2

Table 1: Predicted proportion of women with plasma concentration above MEC.

*Abbreviations: CAB – cabotegravir; RPV – rilpivirine; GW – gestation week; MEC – minimum effective concentration; PA-IC90 – protein binding-adjusted IC90 (166 ng/ml for cabotegravir and 12 ng/ml for rilpivirine).

- Predicted cord-maternal blood ratio was greater than 1 for cabotegravir, but less than 1 for rilpivirine close to delivery (Table 2).
- Whilst predicted 1st quartile cord plasma levels were above 4*PA-IC90 for cabotegravir, predicted 3rd quartile cord plasma levels were below PA-IC90 for rilpivirine (Table 2).

Table 2: Predicted fetal exposure during the tail-phase PK of LA-CAB/RPV in pregnancy.

Gestation age	CAB	RPV
	Cord plasma concentration (ng/ml)	
Week 15	132 (123-140)	0.80 (0.75-0.86)
Week 27	1432 (1342-1564)	13.7 (13.0-14.8)
Week 38	837 (786-914)	11.0 (10.4-11.8)
Week 40	764 (717-834)	10.2 (9.7-11.0)
	Cord-maternal blood ratio	
Week 15	0.07	0.02
Week 27	1.69	0.57
Week 38	1.84	0.85
Week 40	1.85	0.88

Concentration data presented as median (interquartile range). CAB – cabotegravir, RPV – rilpivirine.

CONCLUSION

- The PK tails of LA-CAB/RPV extend to several months postpartum, with predicted levels above PA-IC90 in 100/38% at delivery, and 4/2% 6 months postpartum.
- Ongoing breastfed infant exposure is likely, though not investigated in this study.
- Strategies to minimise the unknown risk associated with LA-CAB/RPV use during pregnancy need to be reviewed in the light of ongoing long-term exposure after discontinuation.

REFERENCE

- [1]Spreen et al (2014). doi:10.1097/QAI.0000000000000365; [2]Patel et al (2023). doi : 10.1111/hiv.13439; [3]Atoyebi et al. (2024). doi: 10.1111/bcp.16006.

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