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Population PK and CYP3A Inhibition Capacity of Ritonavir in Pregnancy: A Model-Based Meta-Analysis

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BACKGROUND

- Ritonavir (RTV), a strong CYP3A inhibitor, is widely used as a pharmacokinetic (PK) enhancer with HIV-1 protease inhibitors to increase systemic drug exposure, and more recently with nirmatrelvir for the treatment of COVID-19.
- Pregnancy-related changes in RTV disposition and boosting capacity have not been systematically assessed, yet such data may inform RTV dosing in pregnancy for future emerging infectious diseases.
- The objective of this study was to perform a model-based meta-analysis for the population PK (popPK) of RTV using historical data from 11 separate arms of IMPAACT P1026s, a phase IV study that evaluated the PK of selected antiretroviral (ARV) drugs in pregnant and postpartum women with HIV.

METHODS

- IMPAACT P1026s study was a multicenter, nonrandomized, open-label, parallel-group, prospective study of antiretroviral PK in pregnant and postpartum women living with HIV.
- Pregnant women who were at least 20 weeks gestational age and not receiving tuberculosis treatment were enrolled.
- RTV was used as a PK booster for lopinavir, darunavir, or atazanavir (with or without tenofovir-DF).
- Intensive PK samples were collected pre-dose and at multiple time points post-dose (1-24 hours) in the 2nd and 3rd trimesters of pregnancy and 2-12 weeks postpartum.
- RTV plasma concentrations were determined using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantitation of 0.5 ng/mL.
- A popPK model was developed using non-linear mixed effects modeling (NONMEM v. 7.5).
- Covariates tested included: age, weight, gestational age, gestational stage, pregnancy status, ethnicity, albumin, total daily dose, and concomitant ARV therapy.
- Fixed allometric and estimated allometric scaling were assessed. Both had similar significant improvements in model fit; however, fixed scaling had improved model stability and was carried forward.
- A 1000 sample bootstrap assessment of the final model was performed using Wings for NONMEM (version 7.5).
- A simulation with 1000 virtual pregnant and postpartum subjects using the final popPK model was performed to assess the effects of pregnancy on ritonavir exposure.

Table 1. Participant Demographics

	Overall	Second Trimester	Third Trimester	Postpartum
	(N=279)	(N=89)	(N=249)	(N=215)
Age Median [Min, Max]	29 [15,44]	29 [15,44]	29 [15,44]	29 [18,44]
Weight Median [Min, Max]	66.4 [41.0, 138]	64.2 [43.0, 124]	68.3 [46.3, 138]	62.6 [41.0, 136]
Gestational Age/ Weeks Postpartum Median [Min, Max]	32.0 [20.0, 38.0]	24 [20,27]	33 [26,38]	6 [2,12]
Ethnicity	Hispanic or Latino (N=144) Not Hispanic or Latino (N=132) Unknown (N=3)			

Ritonavir (RTV) exposures were lower in pregnancy than postpartum which is predicted to lead to a 1.8-fold reduction in RTV-mediated CYP3A inhibition during pregnancy

RESULTS

- A total of 279 participants contributed to 3798 RTV plasma concentrations (565 2nd trimester, 1632 3rd trimester, and 1601 postpartum). Participant demographics are shown in **Table 1**.
- Observed RTV concentrations versus time after dose during pregnancy and postpartum are shown in **Figure 1**.
- RTV disposition was best described with a one-compartment structural model.
- Pregnancy was an independent predictor of both apparent clearance (CL/F) and apparent volume of distribution (Vd/F). No other covariates significantly impacted RTV disposition.
- Fixed allometric scaling significantly improved the model. Final model parameter estimates are shown in **Table 2**.
- The following equations describe the final popPK model. Model diagnostic plots are shown in **Figure 2**.

$$\text{CL/F (L/h)} = 12.0 \times 1.84 \text{ (if Pregnant)} \times (\text{WT}/66.4)^{0.75}$$
$$\text{V/F (L)} = 21.1 \times 2.27 \text{ (if Pregnant)} \times (\text{WT}/66.4)$$

- Monte Carlo simulations of 1000 virtual subjects receiving a 100 mg daily RTV dose predicted a median $AUC_{0\text{-}24,\ ss}$ of 3.85 and 7.09 µg*hr/mL during pregnancy and postpartum, respectively. Simulated ritonavir AUC is shown in **Figure 3**.
- Based on established *in vivo* concentration-effect relationships of CYP3A inhibition by RTV[1], at a RTV dose of 100 mg daily, CYP3A metabolic clearance is expected to be reduced to 13% of baseline in non-pregnant adults compared to 24% of baseline during pregnancy.

Table 2. Final Model Parameter Estimates

	Final parameter estimates	Bootstrap[a] estimates Median (95% CI)
Θ_1 (V/F; L)	21.1	21.1 (12.9 - 25.7)
Θ_2 (CL/F; L/h)	12.0	12.0 (12.9 - 25.7)
Θ_3 (KA; h^{-1})	0.109	0.109 (0.093 - 0.12)
Θ_4 (Pregnancy on CL)	1.84	1.84 (1.67 - 1.951)
Θ_5 (Pregnancy on V)	2.27	2.27 (1.64 - 3.25)
Variability (η)		
Between-subject (V)	128%	129% (118% - 147%)
Between-subject (CL)	49.9%	49.6% (45.7% - 53.41%)
Correlation		
Interaction Between CL/F and V/F	0.441	0.439 (0.296 - 0.559)
Error (ε)		
Proportional	45%	45.5% (43% - 48%)
Additive (ng/mL)	36.4	31.05 (43.47 - 47.32)

CI, confidence interval; CL/F, apparent clearance; V/F, apparent volume of distribution; KA, first-order absorption rate constant.
[a]Bootstrap successfully converged 91.49% of the time.

Figure 3. Simulated Ritonavir AUC During Pregnancy and Postpartum

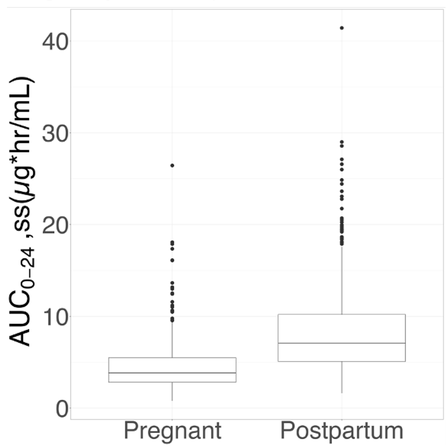


Figure 1. Ritonavir Concentrations vs. Time

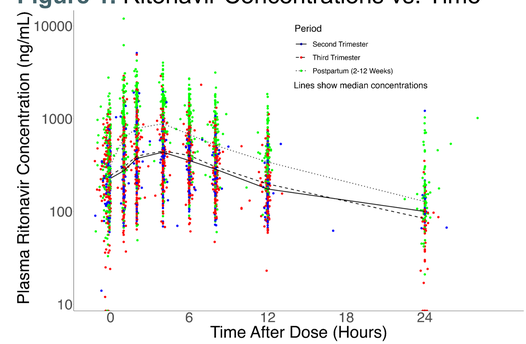
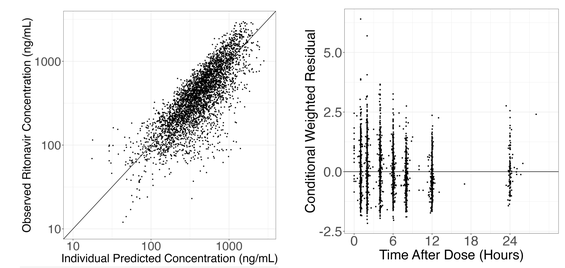


Figure 2. Model Diagnostic Plots



CONCLUSIONS

- RTV PK was best described by a one compartment model with first-order elimination and pregnancy significantly increased RTV CL/F and V/F.
- Pregnant women with HIV have an increased apparent clearance (84% increase) and apparent volume of distribution (127% increase) compared to postpartum.
- Decreased RTV exposures during pregnancy are predicted to lead to a 1.8-fold reduction in RTV-mediated CYP3A inhibition.
- Dosing requirements of RTV and/or boosted CYP3A substrates may be altered during pregnancy.

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1. Eichbaum C, Cortese M, Blank A, Burhenne J, Mikus G. Concentration effect relationship of CYP3A inhibition by ritonavir in humans. Eur J Clin Pharmacol. 2013 Oct;69(10):1795-800

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