



Population Pharmacokinetic Model of Darunavir and Ritonavir in Pregnant and Postpartum Women with Human Immunodeficiency Virus Infection



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BACKGROUND

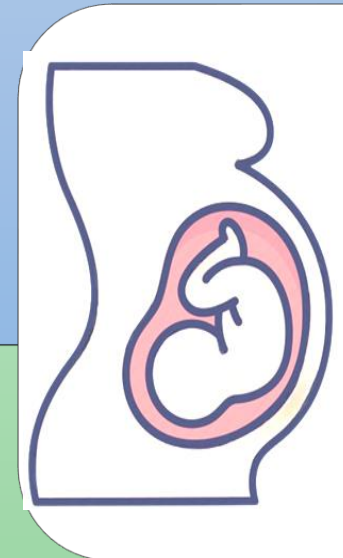
Anatomical & physiological changes during pregnancy can affect the medication pharmacokinetic (PK) profile

Absorption

- ↓ GI motility
- ↑ gastric pH

Metabolism

- ↑ hepatic blood flow
- CYPs activity alterations



Changes during pregnancy

Distribution

- ↑ total body water/fat
- ↑ unbound level

Elimination

- ↑ renal blood flow & GFR
- Transporter function alterations

↓ antiviral exposure in **human immunodeficiency virus (HIV) infection**:
↑ risk of virologic failure, prenatal transmission, &/or drug resistance.

Darunavir (DRV - protease inhibitor) + Ritonavir (RTV - PK booster):
high genetic barrier to resistance

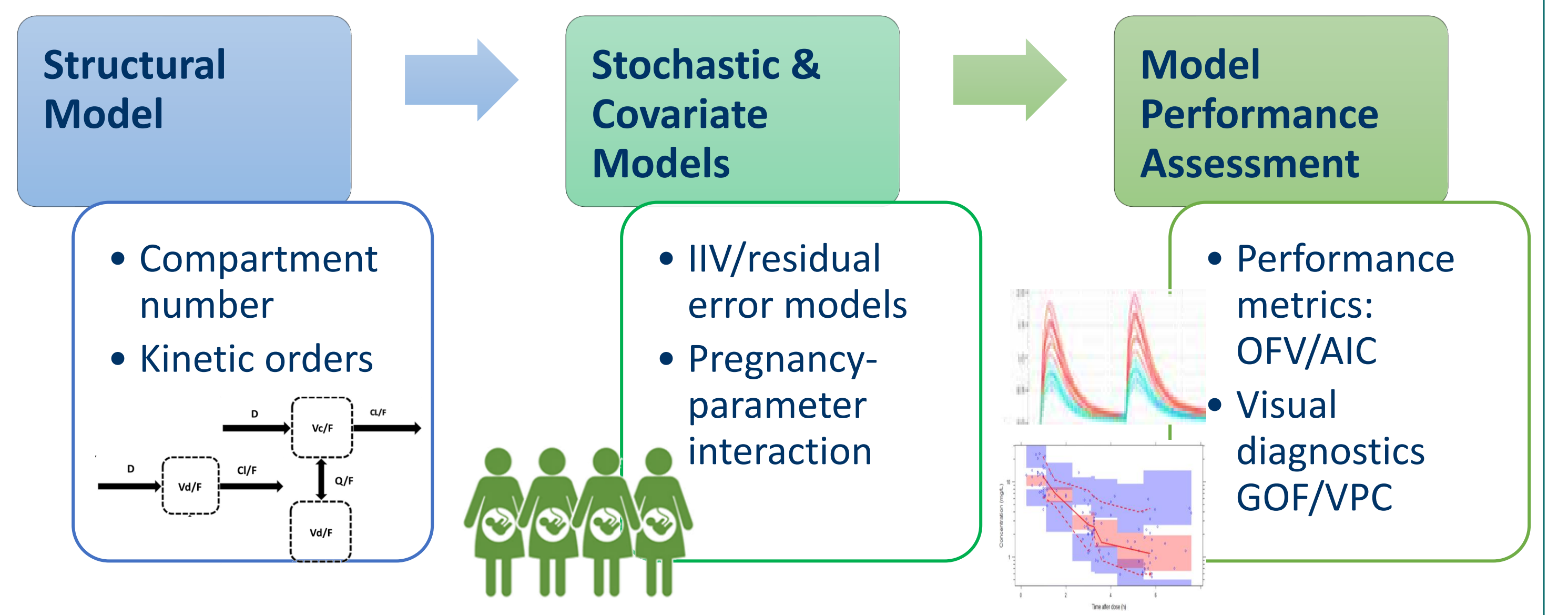
- Highly bound to protein
- Primarily metabolized by cytochrome P450 (CYP) 3A & potential substrate of p-glycoprotein (Pgp) transporter
- EC90 wild-type HIV: 200 ng/mL; EC50 resistant strain: 550 ng/mL.

STUDY OBJECTIVES AND METHOD

Objective: Develop a model to predict the PK profile & influence of pregnant status on the exposure to DRV in HIV-infected women treated with DRV/RTV.

Method

- **Simulated PK data:** systematic review of clinical PK studies:
 - Adult pregnant women treated with DRV/RTV
 - Reporting the number of patients & mean (SD) or individual-level concentration data at each time point.
- **Nonlinear mixed-effects modeling:** NONMEM version 7.5.1. & PsN - Perl-speaks-NONMEM, version 5.5.0.



RESULTS

Characteristics of eligible studies

Seven studies provided PK data of DRV/RTV in pregnant women, including 2nd & 3rd trimesters, & post-partum. The mean ratio of Ctrough values between the pregnant & postpartum periods was [0.43 - 0.64].

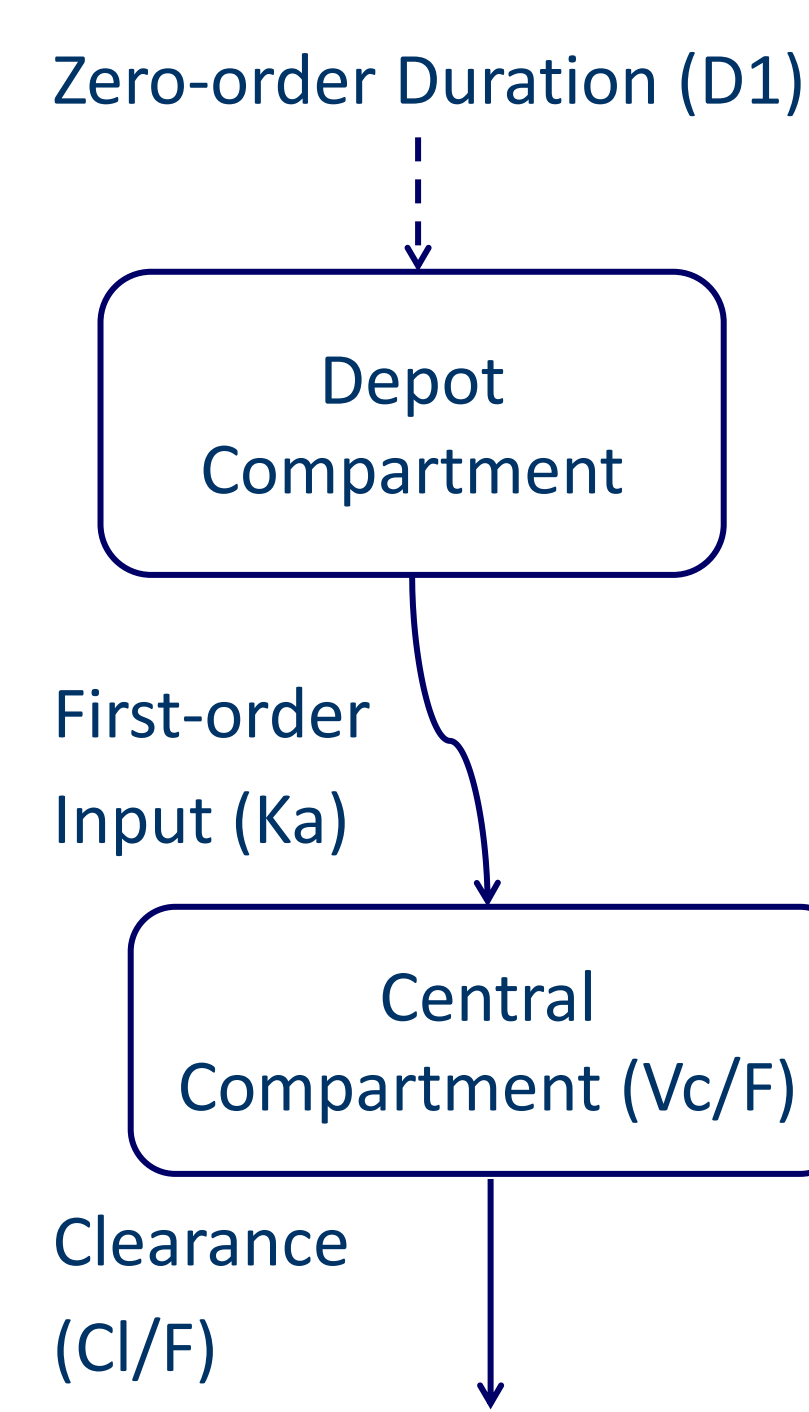
Table 1 - Study characteristics

Author, years	Number of patients			Dosage regimen (mg)	Mean age (year)
	Trimester 2	Trimester 3	Post-partum		
Eke 2020	9	24	-	DRV800/ RTV100 BID	26.9
Crauwels 2016	16	14	15	DRV800/ RTV100 QD	24.0
Colbers 2015	-	16	8	DRV800/ RTV100 QD	33.0
	-	5	5	DRV600/ RTV100 BID	31.0
Stek 2015	15	30	23	DRV800/ RTV100 QD	27.6
	13	34	27	DRV600/ RTV100 BID	27.0
Zorrilla 2014	11	11	11	DRV600/ RTV100 BID	24.0
Ivanovic 2010	-	-	1	DRV800/ RTV100 QD	40.0
Pinnetti 2010	1	1	1	DRV600/ RTV100 BID	22.0

Simulated individual PK data based on: (1) observed mean (SD) concentrations per time in each study (n=50 each study arm) or (2) mean/median values only (n=1).

Population PK model of DRV

Model structure



GOF & VPC plots

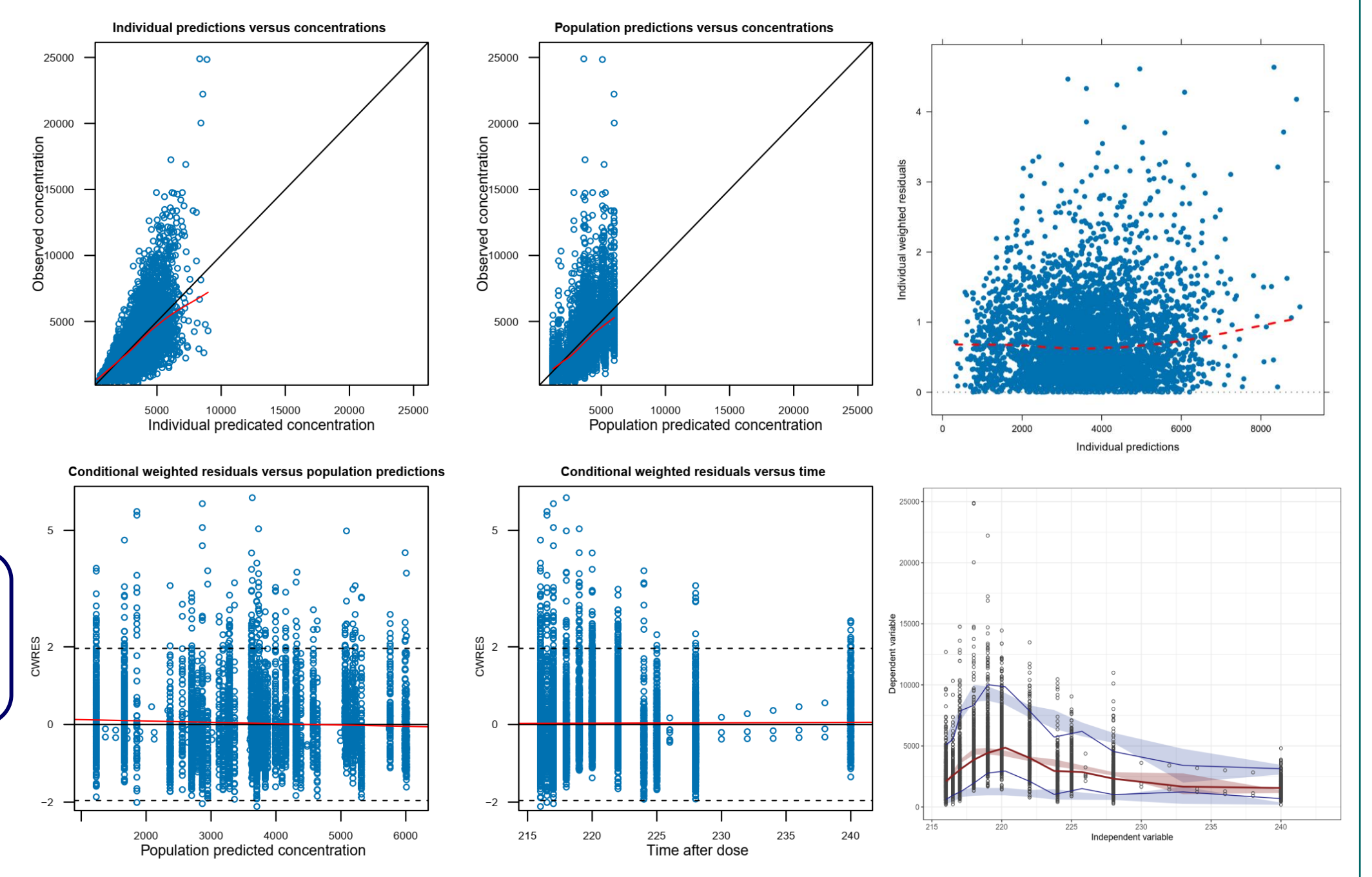


Table 2 - Numerical values

Model parameters	Estimate (RSE%)	Covariates	Estimate [95% CI] (RSE%)
D1 (h)	0.6 (8%)	Cl/F ~ Pregnancy	1.38 [1.33 - 1.43] (2%)
Ka (1/h)	1.1 (6%)		
Cl/F (L/h)	12.3 (2%)		
Vc/F (L)	212 (5%)	Vc/F ~ Pregnancy	1.42 [1.27 - 1.58] (6%)
IIV Cl/F	0.02 (13%)		
IIV Vc/F	0.2 (15%)		
Proportional Residual Error	0.4 (2%)		

CONCLUSIONS

- This is our effort to optimize dosing selection during pregnancy by developing a model of drug exposure based on simulated data.
- DRV clearance & distribution may increase during the 2nd & 3rd trimesters.
- Validated model in pregnancy using individual data should be used to confirm the PK profile & optimize dosage regimens for pregnant patients in clinical practice.

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