

Exploring Darunavir/Ritonavir Dosing Regimens for HIV-positive pregnant women using semi-mechanistic pharmacokinetic modeling

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Background

- Darunavir is administered as 800 mg once (QD) or 600 mg twice (BID) daily in combination with low-dose (100 mg) ritonavir (pharmacokinetic booster) as part of combination antiretroviral therapy for the treatment of HIV-positive pregnant women.
- Decreased total darunavir exposure (17%-50%) has been reported during pregnancy, but limited data on unbound darunavir exposure are available. It remains unclear whether standard darunavir/dosing regimens provide adequate exposure throughout pregnancy.
- Important pharmacokinetic aspects to consider: nonlinear darunavir plasma protein binding, CYP3A4/P-glycoprotein-mediated interaction darunavir-ritonavir, and pregnancy-related alterations in expression of CYP3A4 and P-gp.

Objective

Semi-mechanistic modeling to explore total and unbound darunavir exposures following standard darunavir/r dosing, and to explore and propose potential optimized regimens for HIV-positive pregnant women.

Table 1: Data available for pharmacokinetic modeling from two studies with similar design

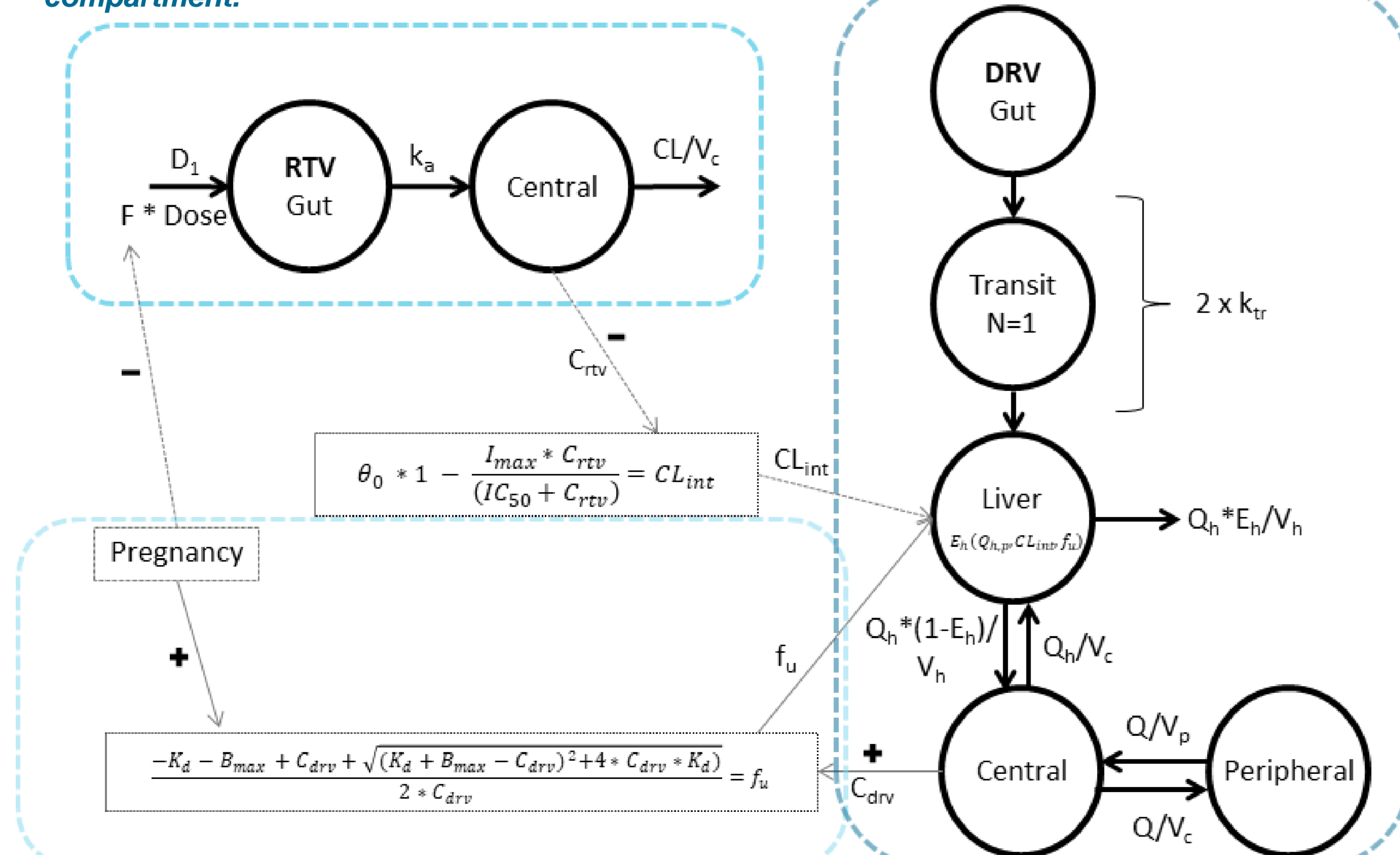
	Study 1 (NCT00825929)		Study 2 (NCT0042289)	
	Total	Unbound	Total	Unbound
Number of women	24	64	24	64
Number of patients included	23	62	23	62
Number of samples ritonavir				
- Pregnant	132	NA	284	NA
- Not pregnant	194	NA	519	NA
Number of samples darunavir				
- Pregnant	132	44	286	NA
- Not pregnant	194	30	524	NA
Median (range) gestational age (weeks)	34 (32 - 37)		33 (20 - 39)	
Sampling design (h postdose)	0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 12 (and 24)		0 (predose), 1, 2, 4, 6, 8, 12 (and 24)	
Lower limit of quantification in mg/L (% BLQ)				
- darunavir	0.1 (1%)	0.09 (1%)		
- ritonavir	0.045 (12%)	0.059 (17%)		
Median (range) weight				
- Second trimester	NA	88 (57 - 200)		
- Third trimester	80 (65 - 117)	83 (56 - 204)		
- Not pregnant	76 (62 - 109)	80 (51 - 194)		
Dosing regimen				
- 600/100 mg BID	5	30		
- 800/100 mg QD	18	32		

NA, not applicable; BLQ, below limit of quantification; QD, once-daily dosing; BID, twice-daily dosing.

Methods

- The darunavir protein (AAG)-binding was evaluated based on nlme analysis of a subset of total with paired unbound darunavir concentrations (pregnant and non-pregnant).
- Separate population pharmacokinetic models were developed for ritonavir and darunavir. For the ritonavir-mediated inhibition of darunavir biotransformation and/or transport we tested several direct response models. A correlation between DRV and RTV clearance was assumed based on their mutual path of biotransformation and elimination.
- Gestational age (GA, weeks) was tested as covariate (linear) on all model parameters using a forward inclusion (dOFV > 3.84) and backward elimination (dOFV > 6.64).
- In a final step, all parameters were estimated in a simultaneous fit.
- The final model was used to simulate $AUC_{0-\tau}$ and C_{trough} following standard and alternative darunavir dosing in typical pregnant (GA=38) and non-pregnant women.
- Also, the probability of therapeutic exposure was assessed. The target was set to 0.55 and 0.03 mg/L, for total and unbound C_{trough} , respectively (the EC_{50} for resistant virus).

Figure 1: Left upper: ritonavir structural PK model. Left lower: darunavir plasma protein binding model. Right: darunavir structural PK model. For the first-pass through the liver a fraction of the darunavir amount is extracted (E_h) and cleared, the fraction of the amount remaining ($1-E_h$) reaches the systemic circulation and becomes available for redistribution into the peripheral compartment.



Results

- The parameter estimates for the darunavir protein binding model are listed in Table 2. These were included and fixed in the darunavir PK model. The external validity was verified based on HV binding data from the registration package (Figure 2).
- The final parameter estimates for the simultaneous darunavir and ritonavir model fit are listed in Table 3 & 4. Parameter uncertainty was evaluated using sampling importance resampling (routine in PsN).

Results (continued)

- Simulated relevant darunavir pharmacokinetic parameters and the probability of therapeutic exposure for pregnant women (GA=38) are provided in Table 5. The simulated typical total and unbound darunavir exposure in pregnant women (GA=38) for several dosing regimens is plotted in Figure 4.

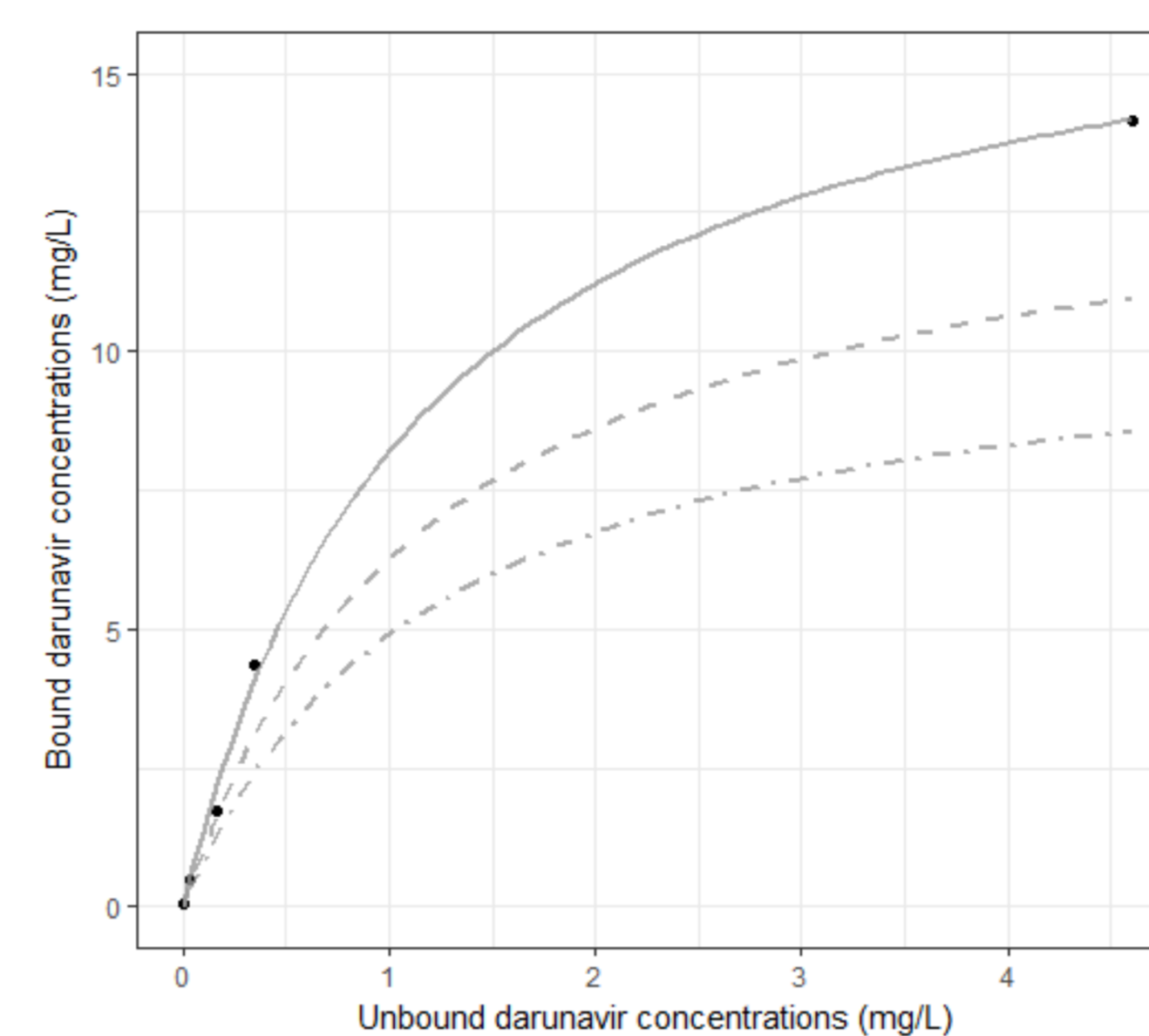


Figure 2: Darunavir protein binding. Summary level HV data compared with the findings for nonpregnant (dashed) and pregnant women (dot-dashed). Using nls the B_{max} and K_d (95% CI) were 18 (16-20) mg/L and 1.16 (0.83-1.7) mg/L, respectively.

Table 2: Darunavir protein binding model

Parameter	Parameter estimates	RSE (%) from SIR
$B_{max, non-pregnant}$ (mg/L)	13.8	(17)
$B_{max, pregnant}$ (mg/L) [§]	10.8	(5)
K_d (mg/L)	1.2	(21)
IIV B_{max} (%)	15	(14)
Prop res error (%)	18	(6)

[§] $\theta_0 = \theta_0 \cdot \theta_1 \cdot \theta_2$

Table 3: Ritonavir PK model

Ritonavir parameters	Parameter estimates	RSE (%) from SIR
CL/F (L/h) [§]	25.1	5
V_d/F (L) [§]	20.6	11
k_a (h ⁻¹)	0.12	4
D_1 (h)	2.1	9
θ_{GA} for $F^{\&}$	-0.012	13
IIV CL/F (%)	37	14
IIV V_d/F (%)	180	13
$\eta_{CL/F} - \eta_{V_d/F}$ (%)	24	21
IOV F (%)	51	13
Prop res error (%)	36	3

[§]The values refer to a typical individual of 70kg.

[&] $\theta = \theta_0 \cdot [1 + \theta_1 \cdot (GA - GA_{mean})]$

Table 4: Darunavir PK model

Darunavir parameters	Parameter estimates	RSE (%) from SIR
MAT (h) ^{&}	4.3	4
CL_{int}/F (L/h) [§]	130	15
V_d/F (L) [§]	8.3	15
Q/F (L/h) [§]	13	9
V_p/F (L) [§]	134	12
$B_{max, non-pregnant}$ (mg/L)	13.8 FIX	-
$B_{max, pregnant}$ (mg/L)	10.8 FIX	-
K_d (mg/L)	1.2 FIX	-
RTV I_{max} (%)	32	28
RTV IC_{50} (mg/L)	0.02 mg/L	16
IIV CL_{int}/F (%)	146	16
IOV CL_{int}/F (%)	48	13
Prop res error (%)	29	2

[§]The values refer to a typical individual of 70kg (FFM 45 kg).

[&] $MAT = (n+1)/k_{tr}$

Figure 3: Visual predictive check darunavir/ritonavir PK stratified for regimen and pregnancy status

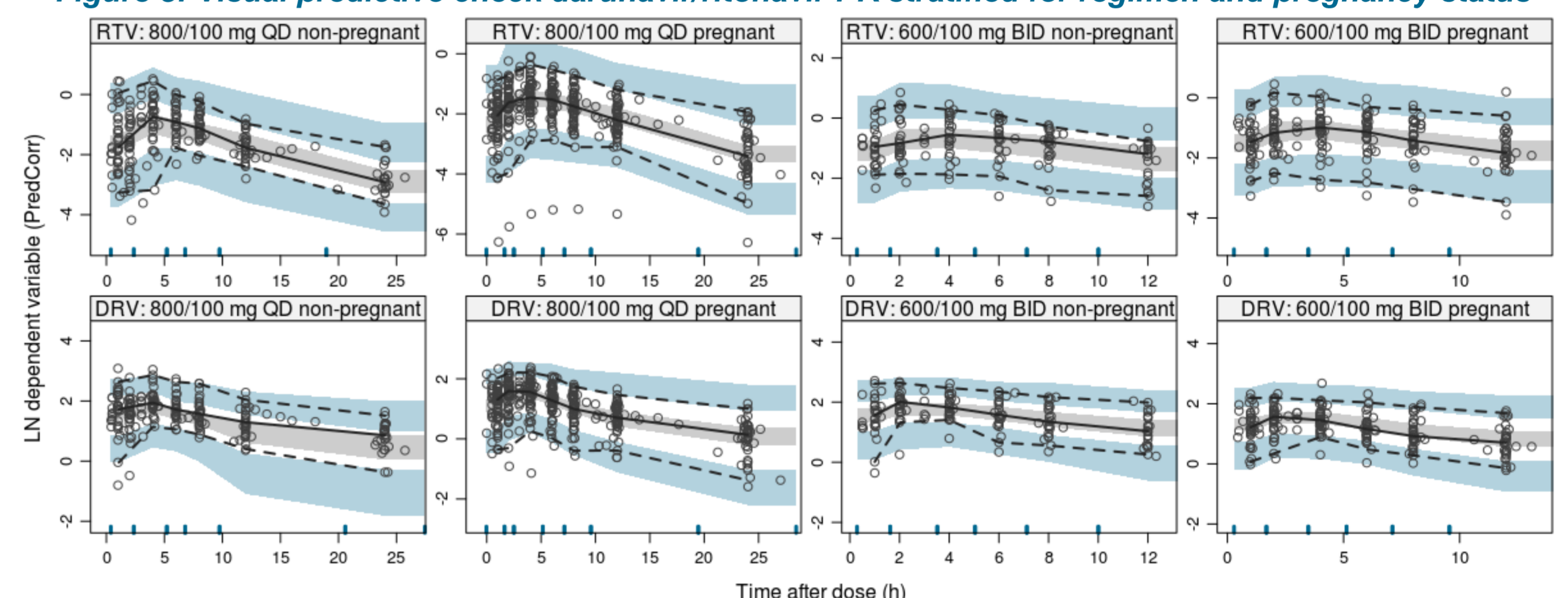


Figure 4: Simulated typical total darunavir exposure in pregnant women (GA=38) for several regimens (100 mg ritonavir dosing).

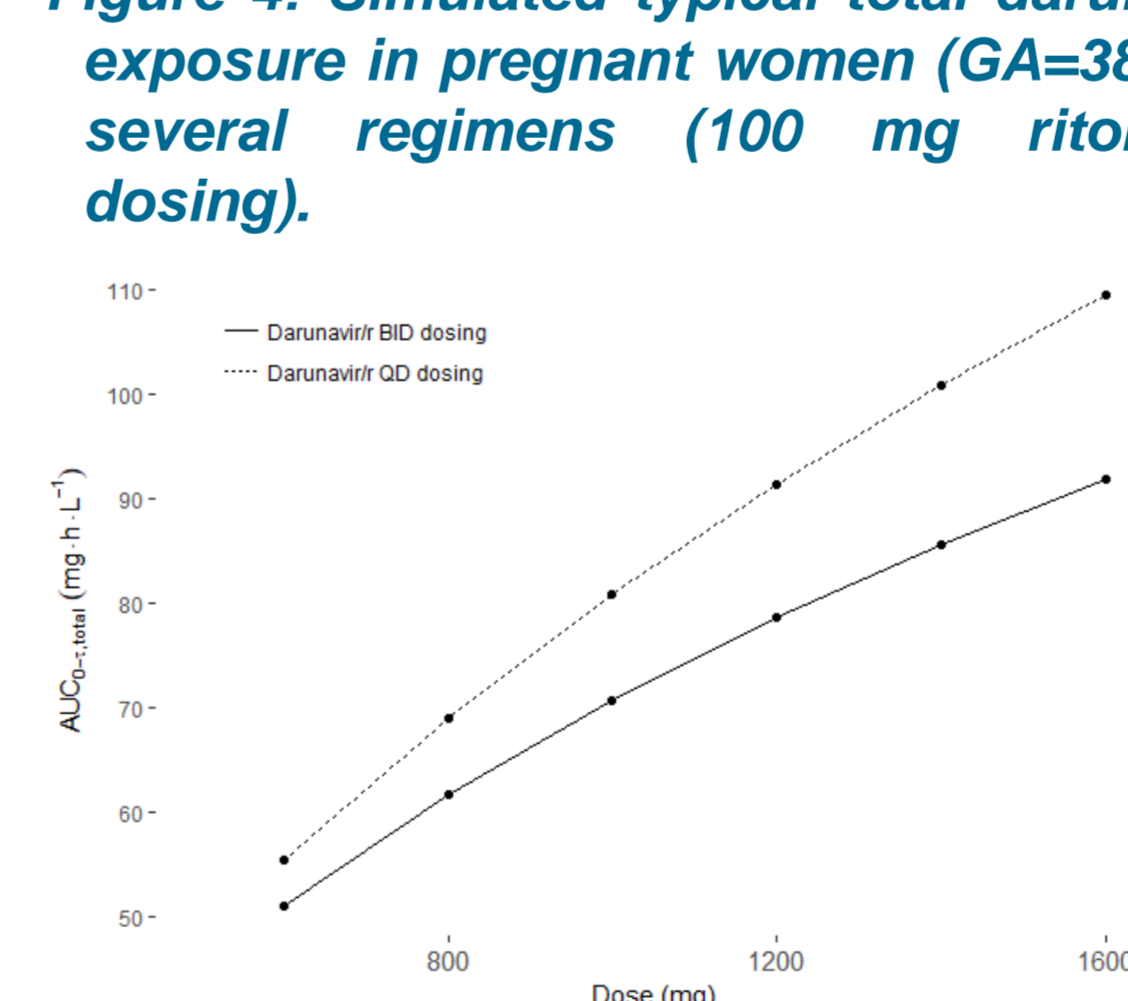


Table 5: Simulated darunavir pharmacokinetic parameters and probability of therapeutic exposure for standard and doubled ritonavir boosting for pregnant women (GA=38).

Regimen	$AUC_{0-24}^{\&}$ (mg*h/L)	$AUC_{0-24}^{\&}$ (mg*h/L)	$C_{trough,t}$ (mg/L)	$C_{trough,u}$ (mg/L)	TA_t (%)	TA_u (%)
800/100 mg QD	65	9.0	1.0	0.11	86.1	95.7
600/100 mg BID	50	7.5	2.7	0.35	99.7	100
800/200 mg QD*	69	9.7	1.4	0.16	90.9	98.8
600/200 mg BID*	51	7.7	2.8	0.36	100	100
1200/100 mg QD*	87	13.6	1.6	0.19	92.4	98.8
800/100 mg BID*	60	10	3.3	0.44	99.9	100

[&]0-24 hours for QD and 0-12 hours for BID, *explored darunavir/r dosing regimens. TA, therapeutic exposure; t, total; u, unbound.

Conclusions and discussion

- Pregnancy reduced ritonavir relative bioavailability and decreased darunavir protein binding. As expected, decreased ritonavir exposure in pregnant women resulted in reduced inhibition of (intrinsic) darunavir clearance. (Table 2, 3 & 4)
- Standard darunavir/ritonavir BID dosing resulted in maximal rates of therapeutic exposure in pregnancy (>99% TA) and was superior to 800/100 mg QD in terms of therapeutic exposure. Darunavir/ritonavir 600/100 mg BID remains the regimen of choice during pregnancy unless (adherence) issues dictate QD dosing. (Table 5)
- The value of alternative dosing regimens for pregnant women seems limited. In a preliminary report of an ongoing study (NCT00042289) it was observed that "Increasing the DRV dose to 800 mg BID during pregnancy failed to significantly increase DRV exposure compared to 600 mg". This could be related to the nonlinearity in protein binding. (Table 5 & Figure 4)

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