

Background and Objectives

Ritonavir-boosted darunavir (DRV/r) with efavirenz (EFV) is an alternative nucleoside-sparing regimen for HIV treatment.

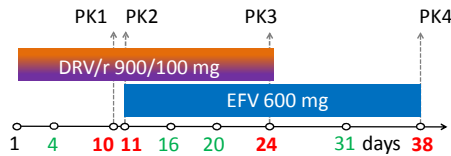
The metabolic pathways involved in the pharmacokinetics of these drugs are intertwined and complex drug-drug interactions are expected.

We aim to develop a population model to characterize these interactions and help to make predictions about possible dosing regimens.

Methods

Twelve healthy Asian volunteers were included in the study and blood samples collected across 38 days [1].

Timeline of DRV/r and EFV dosing, trough only and intensive PK sampling are in Fig. 1.



An integrated POP-PK model described the interaction of DRV and RTV, while a separate model was designed for EFV, whose effect on DRV and RTV was modelled as dichotomous.

Allometric scaling (Fat Free Mass or total weight) adjusted for body size [2].

BLQ data modelled with an additive error equal to BLQ/2. In case of series of BLQ values only the last (in absorption) or the first (in elimination) were retained.

Some of the samples were processed with Paque-Ficoll solution, a correction factor (Tube) for their concentration was estimated.

Results

For all three drugs the structural model was a 2-compartment disposition with transit absorption [3].

Fat Free Mass was best for scaling of CL/F, total weight for Q/F and volumes.

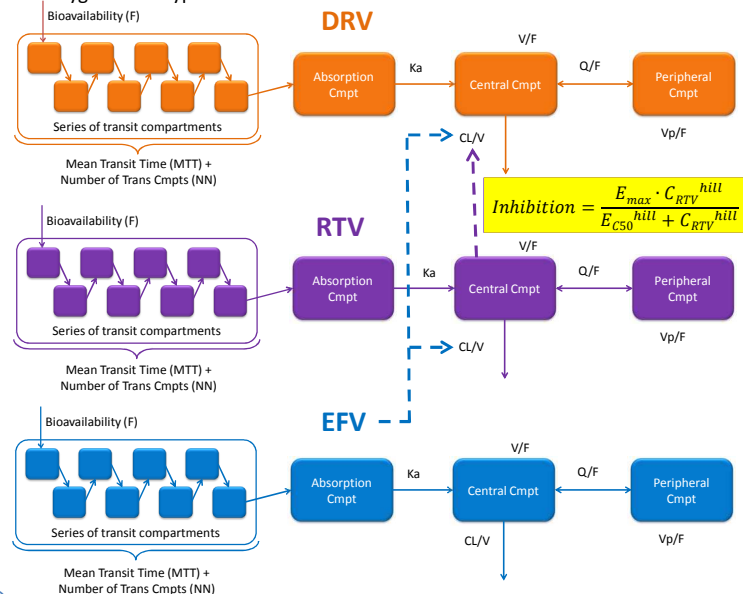
The BOV CL, MTT and bioavailability of DRV and RTV were strongly correlated.

The dynamic effect of RTV concentration on DRV CL was modelled with a sigmoidal function, providing DRV CL values of ~6 L/h for the range of observed RTV concentrations.

The extrapolated typical value of DRV CL in absence of RTV (a scenario not observed in this dataset) was fixed to the value of ~33 L/h, reported by Sekar et al. [4], and the model estimated a low value of RTV EC50.

EFV co-administration was found to increase the CL of DRV and RTV by more than 15%.

CL of EFV decreased by about 30% for each CYP2B6 *6 allele, with respect to homozygous wild type.



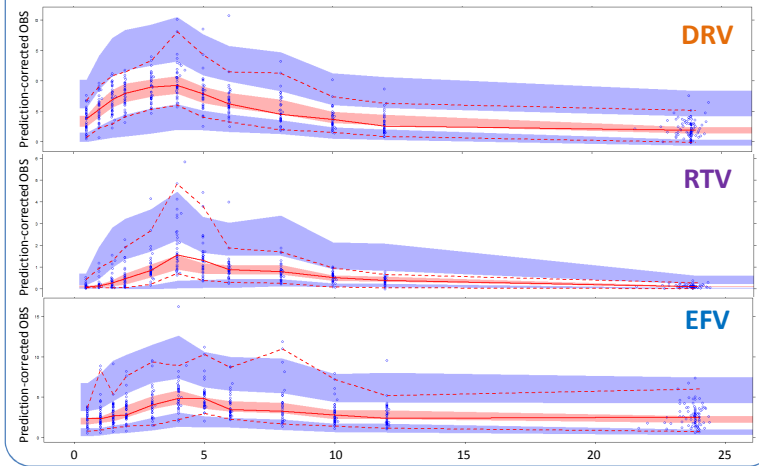
Parameter Typical Value BSV BOV

Darunavir			
CL/F [L/h]	33 FIX	20.4%	31.6%
V/F [L]	34.8		
Ka [h ⁻¹]	0.477		
MTT [h]	0.430		142.2%
F	1 FIX		25.5%
NN: 2 FIX	Q/F [L/h]: 8.37	V ₂ /F [L]: 112	
Tube: +9.9%	Add [ug/L]: 0.558	Prop [%]: 14.3%	BLQ [ug/L]: 0.11 FIX

Ritonavir			
CL/F [L/h]	6.31	12.0%	11.2%
V/F [L]	25.9		
Ka [h ⁻¹]	0.962		53.2%
MTT [h]	1.95		85.5%
F	1 FIX		40.8%
NN: 9.81	Q/F [L/h]: 2.08	V ₂ /F [L]: 92.0	
Tube: +26.0%	Add [ug/L]: 0.00139	Prop [%]: 26.5%	BLQ [ug/L]: 0.036 FIX

Combined DRV/r			
Correlations	BOV CL: 100%	BOV BIO: 61.8%	BOV MTT: 80.5%
EFV on CL: +26.7%	Emax: 0.825	EC50: 0.032 ug/L	Hill: 5 FIX

Efavirenz			
CL/F [L/h]	4.92	18.8%	36.5%
V/F [L]	71.7		
Ka [h ⁻¹]	0.852		59.9%
MTT [h]	1.63		48%
F	1 FIX		35.9%
NN: 8.24	Q/F [L/h]: 22.5	V ₂ /F [L]: 377	2B6 *6 on CL: -32%
Tube: +11.2%	Add [ug/L]: 0.178	Prop [%]: 21.2%	BLQ [ug/L]: 0.0315



Conclusions

The low value of RTV EC50 indicates the potency of RTV as an inhibitor, already strongly active at low concentrations.

This suggests that a reduction in RTV dose could preserve its inhibitory effect on DRV CL, as long as the concentration is kept above the (low) active concentration. A RTV dose reduction in DRV/r has been previously advocated by Hill et al. [5].

EFV auto induction was not evident, maybe masked by the inhibition by RTV. The further integration of EFV in the combined model could help separate the expected RTV inhibition effect on EFV CL and the EFV auto-induction effect.

References

- [1] G. H. Soon, et al., "Pharmacokinetics of darunavir at 900 milligrams and ritonavir at 100 milligrams once daily when coadministered with efavirenz at 600 milligrams once daily in healthy volunteers," *Antimicrobial agents and chemotherapy*, vol. 54, no. 7, pp. 2775-80, Jul. 2010.
- [2] B. J. Anderson and N. H. G. Holford, "Mechanism-based concepts of size and maturity in pharmacokinetics," *Annual review of pharmacology and toxicology*, vol. 48, pp. 303-32, Jan. 2008.
- [3] R. M. Savic, et al., "Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies," *Journal of pharmacokinetics and pharmacodynamics*, vol. 34, no. 5, pp. 711-26, Oct. 2007.
- [4] V. Sekar, et al., "Absolute bioavailability of TMC114, administered in the absence and presence of low-dose ritonavir," in *Program and abstracts of 7th International Workshop on Pharmacology of HIV Therapy*, 2006, p. Abstract 86.
- [5] A. Hill, et al., "How much ritonavir is needed to boost protease inhibitors? Systematic review of 17 dose-ranging pharmacokinetic trials," *AIDS (London, England)*, vol. 23, no. 17, pp. 2237-45, Nov. 2009.