

Simultaneous population pharmacokinetic modeling of darunavir and cobicistat in a cohort of HIV patients

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Background

- **Darunavir** (DRV) is a widely used protease inhibitor in *de novo* and pretreated HIV patients, combined with a background regimen (often two nucleoside reverse transcriptase inhibitors).
- It is coadministered with a pharmacoenhancer, either ritonavir (RTV) or **cobicistat** (COB) to increase DRV plasma exposure.
- DRV is characterized by a **large PK variability**, but the sources of that variability have yet to be fully elucidated. Additionally, fewer PK studies are available for the more recently commercialized COB-boosted DRV.
- **Our objectives** were:
 - ❖ to explore the PK of DRV and COB in a representative cohort of HIV patients and to model the effect of covariates, including single nucleotide polymorphisms (SNPs), drug-drug interactions (DDIs) and clinical chemistry parameters.
 - ❖ to evaluate the feasibility and safety of reduced doses or short cycle therapy (planned treatment interruptions).

Methods and results

- For all 127 participants, sparse blood samples for drug quantification were drawn at random post-intake times (1 sample per visit, total of 249 data points). DRV, RTV and COB were quantified in plasma using a validated UPLC-DAD assay [1].
- Participants were genotyped for CYP3A4*22, CYP3A5*3, and ABCB1 1199G>A and 3435C>T. Clinical chemistry data, DDIs and demographic parameters were recorded.
- The nonlinear mixed effects modeling software **NONMEM** was used. DRV and COB PK were first modeled separately: both were adequately described by a one-compartment model with first-order absorption (**Table 1** and **Table 2**). However, shrinkage and RSEs were high.

Table 1. DRV final model parameters

Parameter	Value	ω	Shrinkage (%)	RSE (%)
CL/F (l.h ⁻¹)	9.6	0.26	39.1	4.4
θ _{AAG} *	-0.302			73.1
V/F (l)	140	0.52	56.3	40.1
k _a (h ⁻¹)	0.38	0.31	87.4	53.4
ε				
Multiplicative	0.43		12.8	6.3

* CL/F = θ_{CL} × (1 + θ_{AAG} × (AAG - 0.77)) × EXP(η_{CL})

Table 2. COB final model parameters

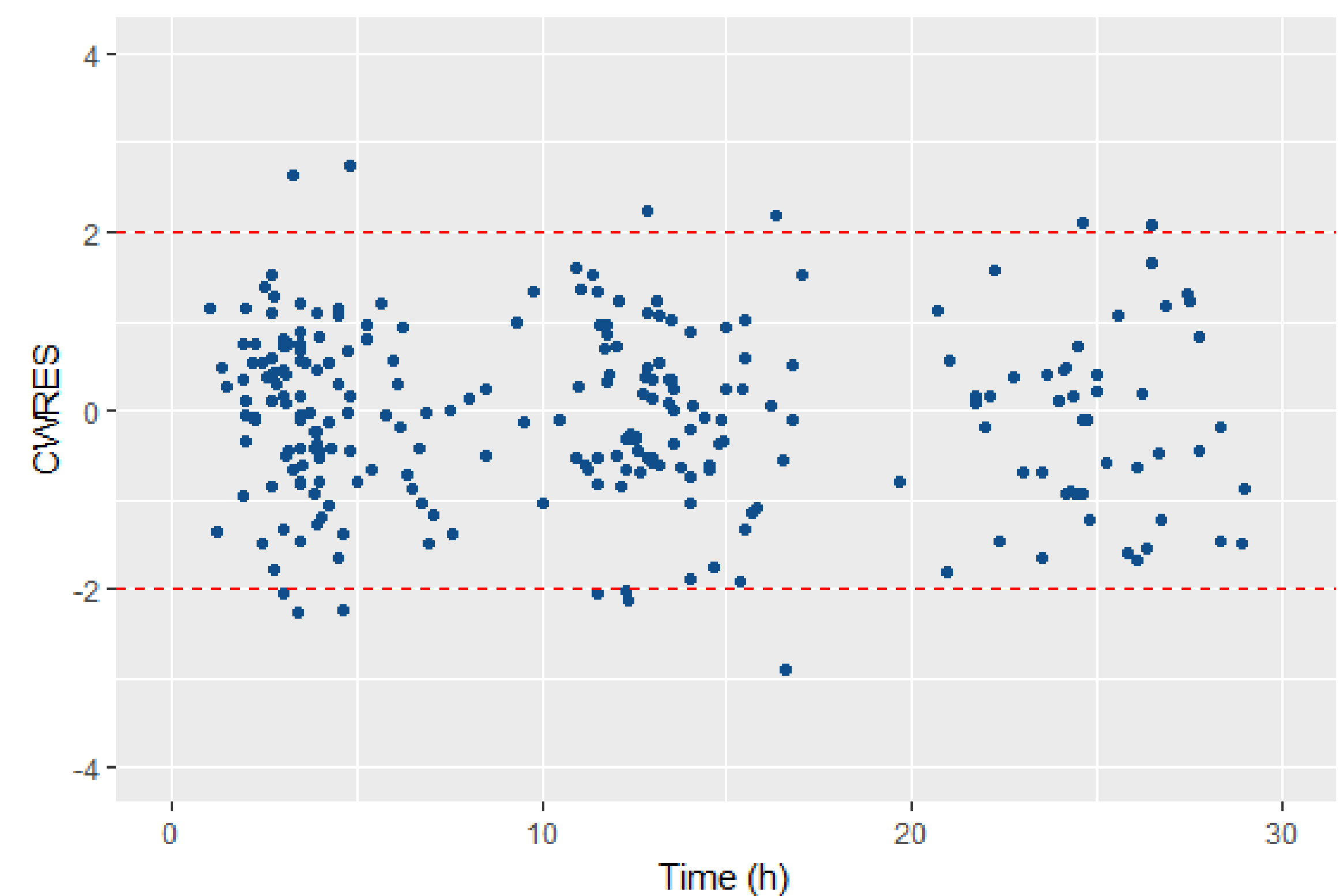
Parameter	Value	ω	Shrinkage (%)	RSE (%)
CL/F (l.h ⁻¹)	8.7	0.34	34.4	5.5
V/F (l)	97	0.40	60.5	27.9
k _a (h ⁻¹)	0.86	0.44	86.1	20.0
ε				
Multiplicative	0.47		22.0	7.8
Additive	0.08		22.0	>100

- While COB concentrations were found to inhibit DRV CL in a linear fashion (r=0.47, p-value<0.05), inclusion of this relationship in a joint DRV/COB model did not improve the fit.
(All further data presented for DRV only)

Methods and results (cont.)

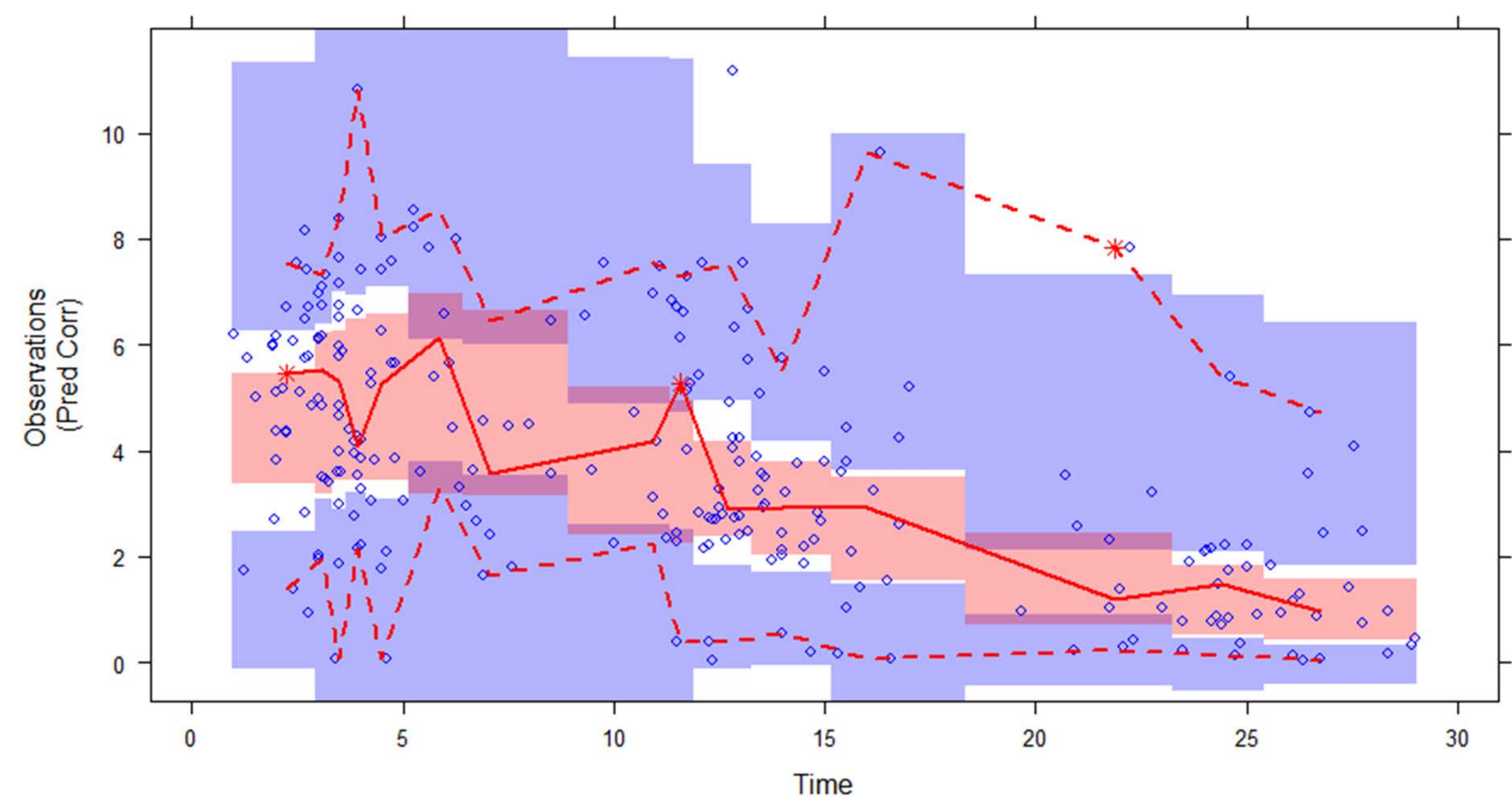
- **Covariates** were then added in a stepwise manner. Higher levels of α-1 acid glycoprotein (AAG) were found to correlate with lower DRV CL, in accordance with previous studies [2,3]. None of the other clinical or genetic covariates were retained in the final model.
- No relationship was apparent between PK parameters and HIV viral load (pharmacodynamic biomarker).
- **Goodness of fit** was assessed using plots of predicted versus observed concentrations, plots of weighted residuals (**Figure 1**), as well as bias, imprecision and shrinkage on parameter estimates (**Tables 1 and 2**). Model adequacy was considered suboptimal.

Figure 1. Conditional weighted residuals versus time



- The prediction-corrected **Visual Predictive Check** is displayed below in **Figure 2**.

Figure 2. Prediction-corrected Visual Predictive Check



- Nonparametric bootstrapping was used to evaluate the DRV model stability and generate confidence intervals (CIs). Large CIs were calculated, especially for parameter eta's.

Conclusions

A population PK model was developed for DRV and COB. However, with such sparse data, accurate estimation of individual PK parameters proved difficult (as evidenced by high shrinkage), limiting the applicability of this model (including its predictive power and ability to detect covariate relationships). The next step will be to enrich our model with dense PK data collected in a subset of participants, expand our panel of SNPs and perform extensive and rigorous internal and external validation of the model. We will also simulate the effect of alternative dose regimens on PK and treatment outcomes.

References

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- [2] P. Vis et al, Development and application of a population PK model of TMC114 in healthy volunteers and HIV-1-infected patients after administration of TMC114 in combination with low-dose ritonavir, PAGE 2006.
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