

Population pharmacokinetic analysis of the drug interaction between ritonavir-boosted atazanavir and rifampicin.

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Background and objectives

Drug-drug interactions (DDIs) may hinder the use rifampicin (RIF) to treat tuberculosis (TB) in patients on protease inhibitors (PIs) as part of their regimen for HIV.

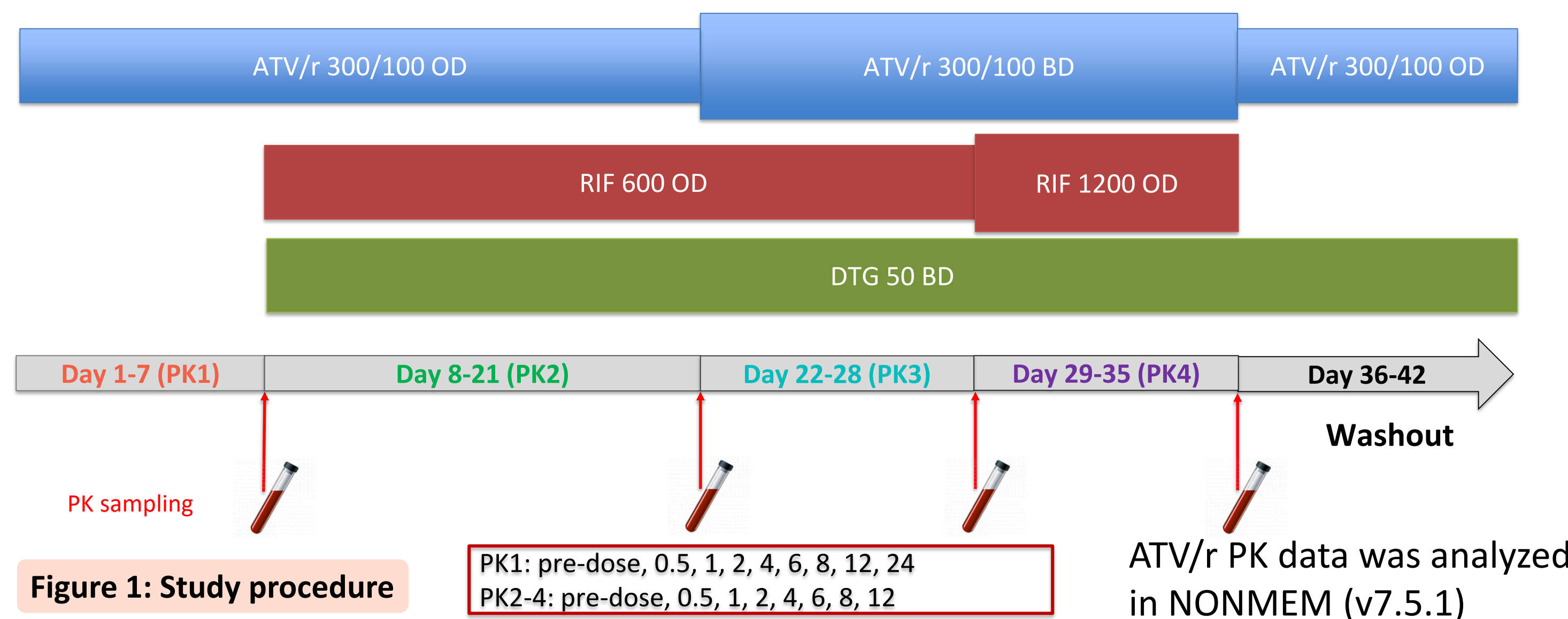
RIF induces metabolizing enzymes like cytochrome P4503A (CYP3A) and transport proteins [1], and its DDIs with older PIs resulted in life-threatening hepatotoxicity [2].

The DERIVE trial demonstrated that RIF could be safely administered with increased dose of ritonavir-boosted atazanavir (ATV/r) [3].

The aim of this analysis was to characterize the pharmacokinetic (PK) interaction between ATV/r and RIF in plasma and peripheral blood mononuclear cells (PBMCs) and simulate treatment target attainment in a more heterogeneous population.

Methods

Data were collected in the DERIVE study (NCT04121195, EDCTP) carried out in Uganda, among participants with HIV and no TB, on >6 months of ATV/r-based ART [3].



Results

Table 1: Participant baseline characteristics

Characteristic	N / Median (IQR)
Sex, M/F (n)	3/23
Age (yr)	44 (26 – 61)
Weight (kg)	67 (50 – 75)
BMI (kg/m ²)	26.1 (19.9 – 31.6)
Background ART (n):	
3TC/AZT	8
3TC/ABC	1
3TC/TDF	17

3TC, lamivudine; AZT, zidovudine; TDF, tenofovir disoproxil fumarate; BMI, body mass index; IQR, interquartile range.

A two-compartment model with first-order absorption (via transit compartments) and elimination adequately fit the ATV PK data as shown by the visual predictive check (VPC) in Figure 2 below. RTV model was similar, and fit was also okay.

PBMC trough concentrations were modeled by an effect compartment linked to the plasma central compartment through a pseudo partition coefficient and equilibration half-life.

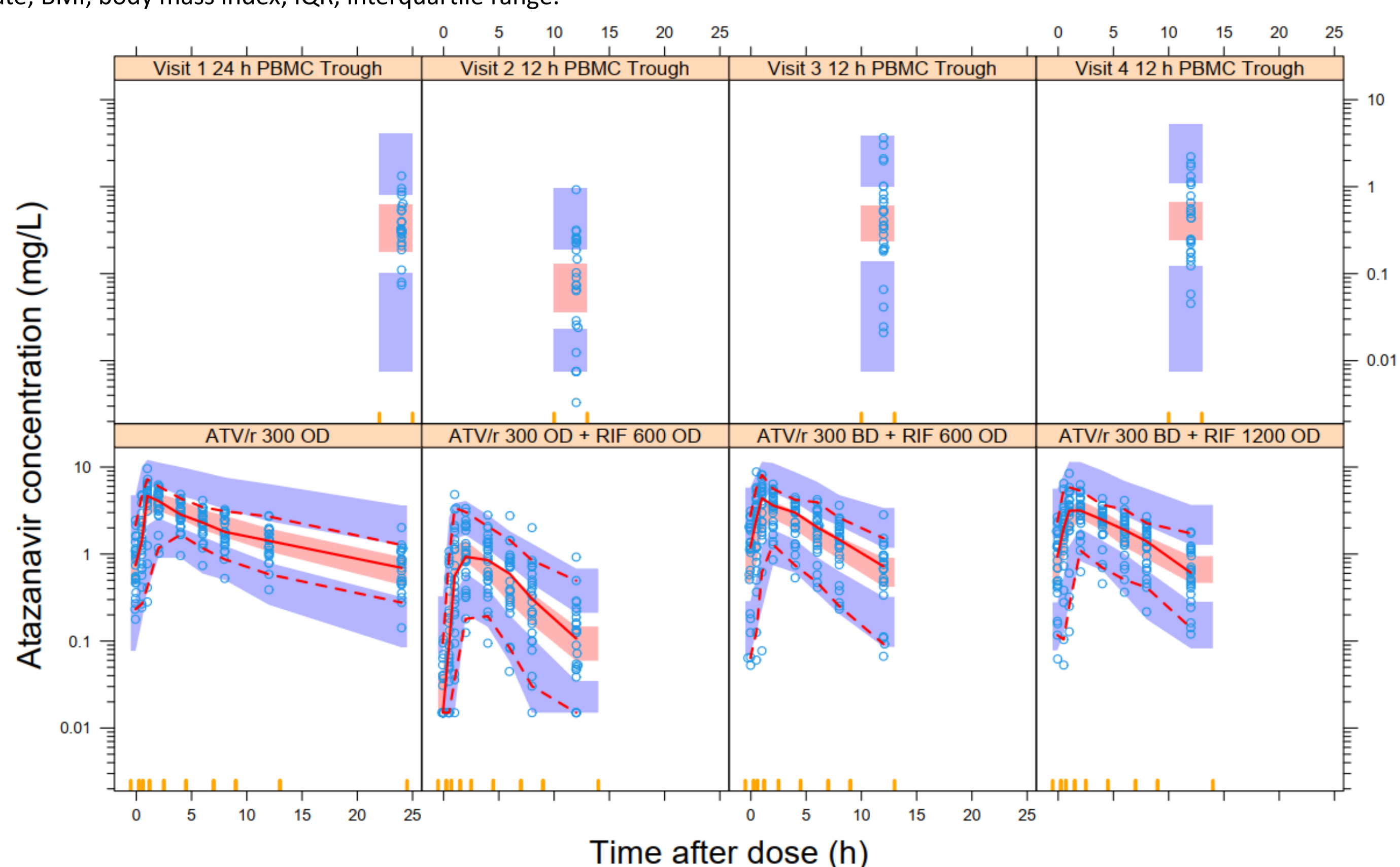


Figure 2. VPC of atazanavir plasma and intracellular concentrations versus time stratified by dosing regimen. The solid and dashed red lines represent the 50th, 5th, and 95th percentiles of the observed data (open blue circles), while the shaded areas represent the model-predicted 95% confidence intervals for the same percentiles.

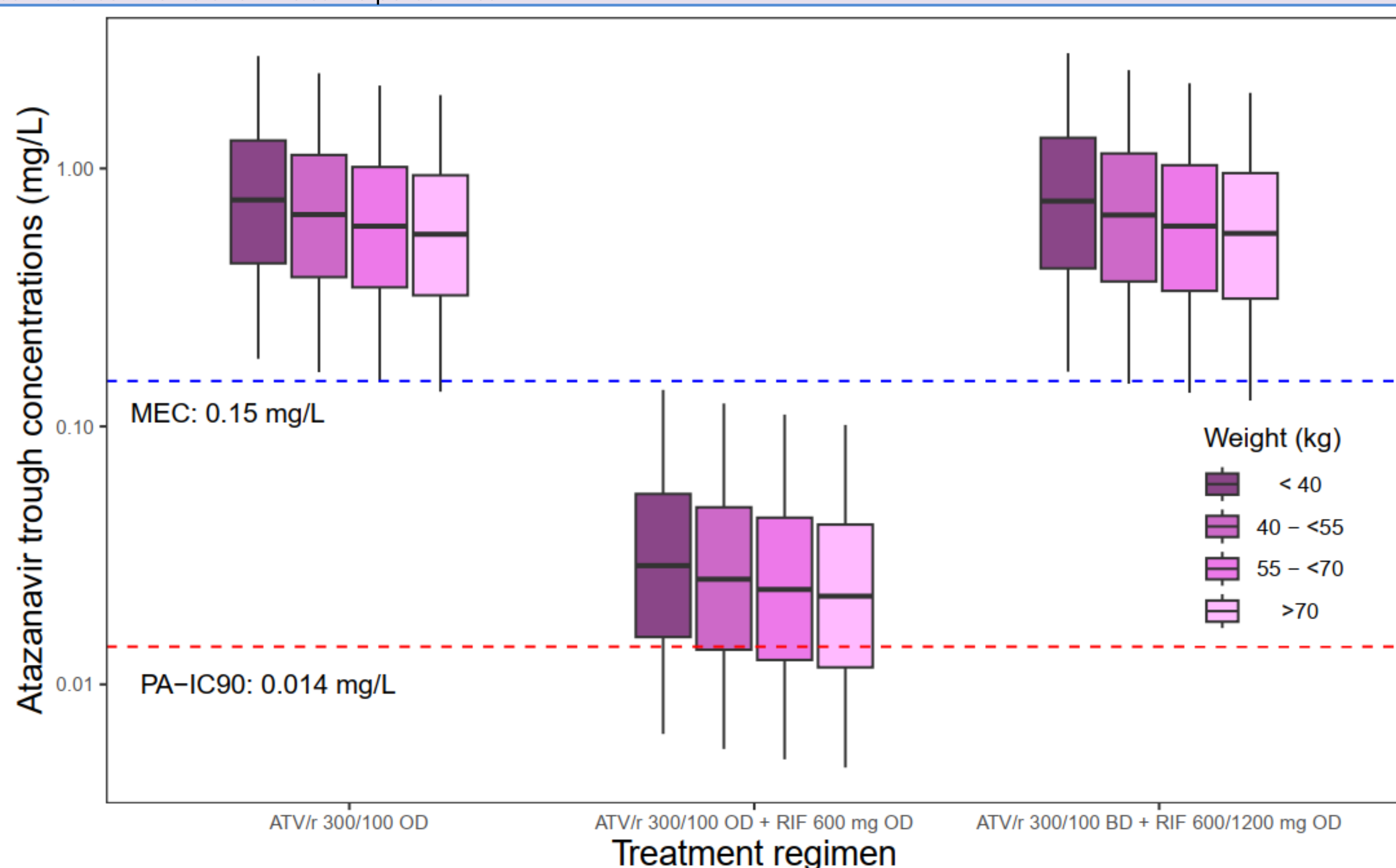


Figure 3. Simulated trough plasma atazanavir concentrations of participants in different dosing scenarios. The dashed lines represent atazanavir target trough concentrations of 0.15 mg/L [4] (blue) and 0.014 mg/L [5] (red), respectively. ATV/r, ritonavir boosted atazanavir; RIF, rifampicin; MEC, minimum effective concentrations; PA-IC90, protein adjusted 90% inhibitory concentration; OD, once daily; BD, twice daily

Results

Table 2. Parameter estimates for ritonavir and atazanavir models

Parameter	Typical parameter estimates (95% CI ^b)	
	Ritonavir	Atazanavir
Clearance, CL (L/h) ^a	9.67 (8.51 – 11.6)	7.55 (6.30 – 9.03)
Fold-increase in CL due to rifampicin (OD ATV/r dose) (-fold)	2.12 (1.95 – 2.31)	3.12 (2.71 – 3.61)
Fold-increase in CL due to rifampicin (BD ATV/r dose) (-fold)	-	2.04 (1.82 – 2.28)
Volume of distribution (central compartment) (L) ^a	55.4 (46.3 – 69.1)	77.3 (68.9 – 87.6)
Inter compartmental clearance (L/h) ^a	1.56 (1.17 – 2.15)	3.51 (2.41 – 4.76)
Volume of distribution (peripheral compartment) (L) ^a	70.1 (39.7 – 125)	48.9 (29.7 – 82.1)
Bioavailability, F (fraction)	1 Fixed	1 Fixed
Change in F due to rifampicin (OD ATV/r dose) (%)	-68.8 (-75.2 to -58.5)	-53.0 (-62.1 to -40.2)
Change in F due to rifampicin (BD ATV/r dose) (%)	-33.3 (-46.6 to -10.9)	-
Absorption rate constant, ka (/L)	1.02 (0.864 – 1.27)	6 Fixed
Change in ka due to rifampicin (%)	-	-71.0 (-78.0 to -56.3)
Mean absorption transit time, MTT (h)	0.483 (0.428 – 0.545)	0.501 (0.435 – 0.575)
Transit compartments, NN (n)	12.3 (6.64 – 17.7)	10 Fixed
Additive error (mg/L) ^c	0.001 Fixed	0.006 Fixed
Proportional error (%)	25.6 (24.1 – 27.8)	18.8 (17.6 – 20.2)
Variability (% CV)^d		
Between subject variability in clearance	16.4 (12.3 – 21.8)	28.0 (19.7 – 36.7)
Between visit variability in clearance	-	19.3 (14.4 – 24.5)
Between occasion variability (BOV) in ka	82.3 (67.3 – 99.1)	101 (80.8 – 125)
BOV in MTT	43.6 (37.7 – 51.6)	60.1 (49.3 – 73.6)
BOV in F	55.5 (48.1 – 63.8)	45.8 (40.7 – 53.6)
Scaling factor on BOV for unobserved dose (-fold change) ^e	-	1.7 (1.30 – 2.17)
Peripheral blood mono-nuclear cell (PBMC)		
Equilibration half-life (h)	1.50 (1.38 – 1.63)	1.13 (0.556 – 1.90)
Maximum pseudo-partition coefficient (.)	1.09 (0.855 – 1.30)	0.533 (0.386 – 0.767)
Proportion error PBMC (%)	51.2 (41.1 – 61.1)	52.0 (42.7 – 63.5)
Additive error PBMC (mg/L) ^c	0.0015 Fixed	0.003 Fixed

All the parameters refer to a typical 67 kg person in the study.

^a Disposition parameters were allometrically scaled by fat-free mass.

^b Parameter uncertainty was determined by sampling importance resampling to obtain the 95% confidence interval (CI).

^c Lower bound of additive error fixed to 20% of lower limit of quantification.

^d Variability was included as between-subject variability, between occasion variability, or between visit variability assuming a lognormal distribution. It is reported here as the percent coefficient of variation (CV) calculated as %CV = $\sqrt{(\omega^2)} \times 100$.

^e Scaling factor for BOV of data from unobserved dosing.

Ritonavir model: Rifampicin doubled ritonavir clearance and reduced its bioavailability by 69%. Doubling the dosing frequency of ATV/r mitigated rifampicin induction effect on bioavailability, reducing it from -69% to -33%.

Atazanavir model: Addition of rifampicin to ATV/r resulted in a 3-fold increase in atazanavir clearance and a 53% reduction in its bioavailability. Doubling the dosing frequency mitigated the induction effects on bioavailability and limited the increase in clearance to only 2-fold. Rifampicin also reduced the atazanavir absorption rate constant by 71%.

Discussion and conclusions

The increase in clearance of PIs when coadministered with rifampicin is an expected effect of its induction of liver CYP3A and other enzymes that metabolize PIs [1]. However, the effect on atazanavir differed with the dosing frequency which may indicate a stronger inhibition effect of the additional dose of ritonavir.

Interestingly, the effect of rifampicin on ritonavir clearance was the same regardless of dosing frequency, indicating differences in its metabolic pathway compared to atazanavir. Ritonavir is also metabolized by CYP2D6 whose induction by RIF may not be to the same extent as CYP3A [6].

The effect of rifampicin on the bioavailability of PIs has been linked to its induction of CYP3A and transporters in the gut [7]. Rifampicin's impact on the absorption rate constant of atazanavir may be attributed to its ability to induce transporters and prolong the drug efflux-reabsorption cycle [8]. This effect could be more pronounced for atazanavir than for ritonavir likely due to atazanavir's greater affinity, as a substrate, for the transporters.

Conclusion: Doubling the dosing frequency of ATV/r restored atazanavir exposure in participants with HIV taking rifampicin. Further studies in patients with TB co-infection are needed to investigate the interaction between the full first-line TB regimen and ATV/r.

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