

Population pharmacokinetic analysis of elvitegravir and cobicistat in HIV-1 infected individuals



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Objectives

To develop a population pharmacokinetic model for elvitegravir (EVG) and cobicistat (COBI) and identify individual factors and co-medications influencing their disposition, taking into consideration the interaction between both compounds.

Methods

- ♦ HIV-positive individuals treated with a fixed-dose combination containing EVG/COBI/tenofovir disoproxil fumarate/emtricitabine 150/150/300/200 mg in a single tablet, once daily
- ♦ NONMEM 7.3 and the FOCE-I method
- ♦ EVG and COBI interaction models tested:
 - AUC_{COBI} linear
 - AUC_{COBI} power
 - AUC_{COBI} exponential
 - C_{COBI} linear
 - C_{COBI} exponential
 - C_{COBI} maximum-effect

Results

- ♦ 186 EVG and 167 COBI plasma concentrations obtained from 144 individuals from the SHCS with Therapeutic Drug Monitoring data
- ♦ Structural models:
 - $BSV CL/F_{EVG}$ estimated at 38.8% (RSE 15.2%)
 - $BSV CL/F_{COBI}$ estimated at 40.7% (RSE 11.1%)
- ♦ Interaction model selected: **power function** for cobicistat exposure effect on EVG clearance ($\Delta AIC/\Delta BIC = -63.5/-59.6$)

Final population pharmacokinetic models

	Estimate (RSE)
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Elvitegravir

CL/F_{EVG} (L/h)	7.6 (4.4%)
V/F_{EVG} (L)	61.0 (16.7%)
k_{a_EVG} (h ⁻¹)	0.17 (16.4%)
θ_{ATV_EVG}	-0.35 (25.7%)
θ_{AUC_COBI}	1.12 (14.9%)
$BSV CL/F_{EVG}$ (%)	16.6 (31.2%)
Add.residual error (ng/mL)	148 (28.0%)
Prop. residual error (%)	39.8 (10.9%)

Cobicistat

CL/F_{COBI} (L/h)	16.0 (11.3%)
V/F_{COBI} (L)	88.3 (15.2%)
k_{a_COBI} (h ⁻¹)	0.76 (40.6%)
θ_{ATV_COBI}	-0.47 (38.4%)
θ_{DRVr}	-0.27 (30.1%)
$BSV CL/F_{COBI}$ (%)	41.9 (12.1%)
Add. residual error (ng/mL)	2.5 FIX
Prop. residual error (%)	69.6 (12.0%)

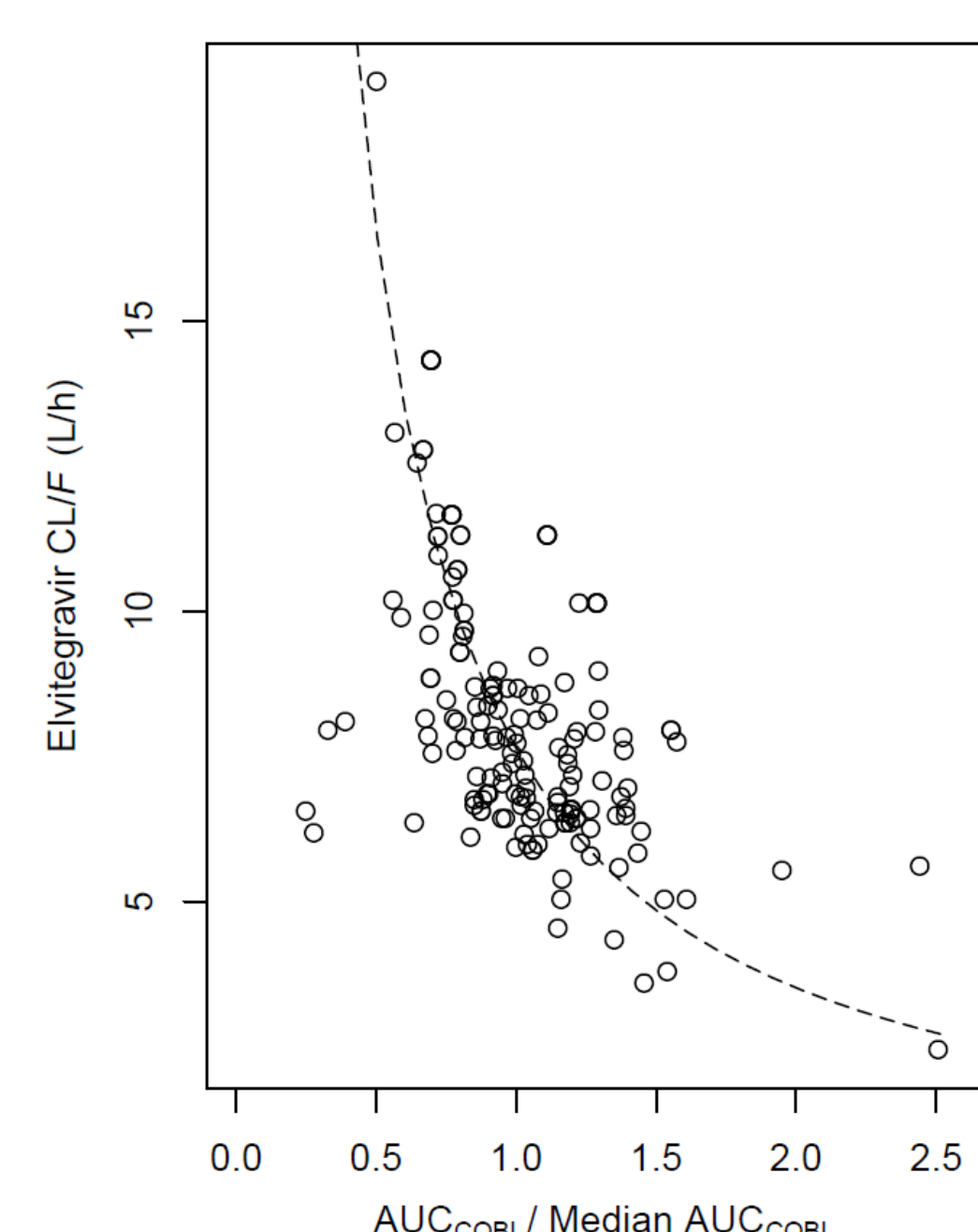


Figure 1. Interaction model. Open circles represent individual EVG apparent clearance vs AUC_{COBI} centred on the median value, obtained from COBI pharmacokinetic model. The dashed line corresponds to the population median prediction

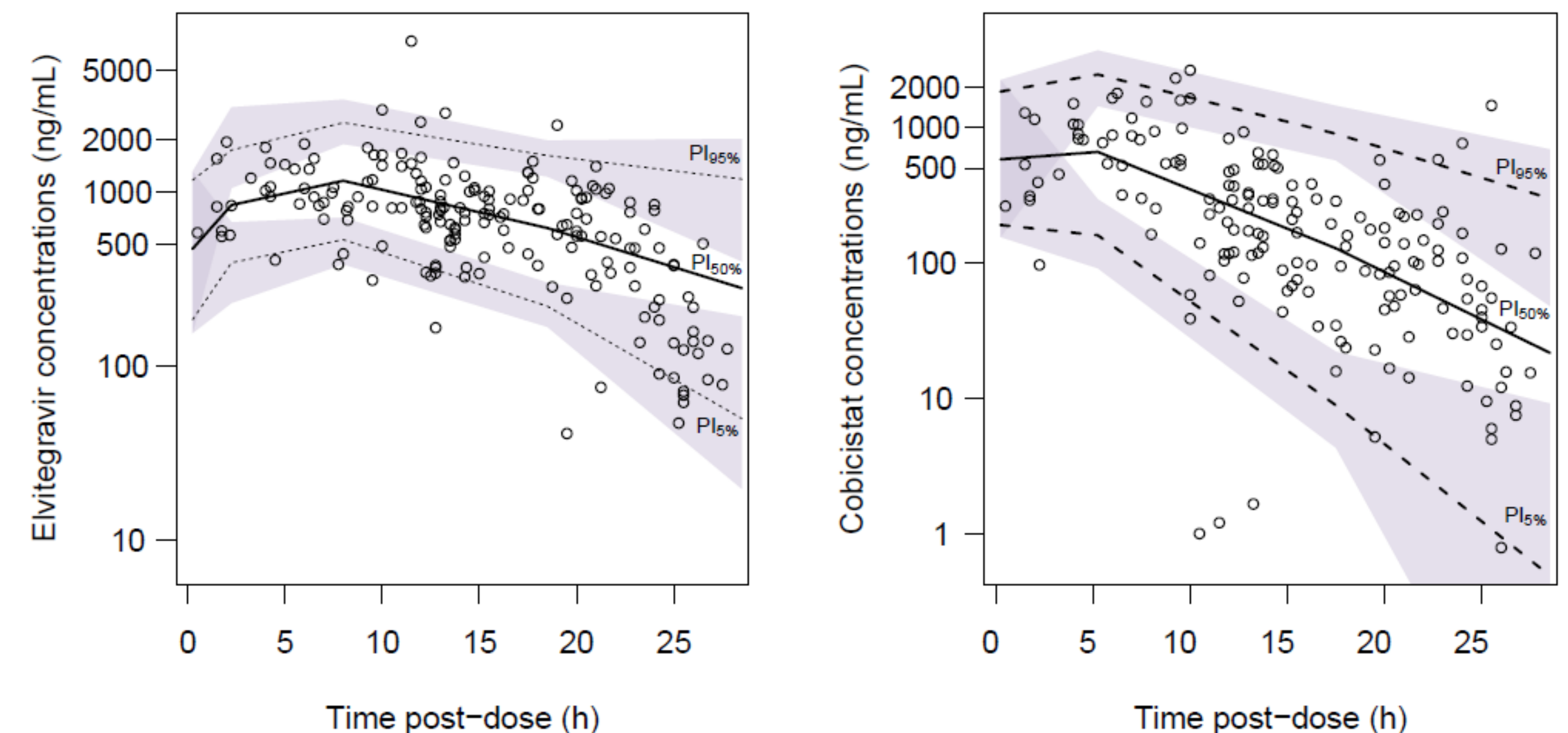


Figure 2. pcVPC of EVG and COBI final model. Open circles represent elvitegravir and cobicistat plasma concentrations. Continuous line represent the population median prediction from the final model and dashed lines represent the $PI_{90\%}$

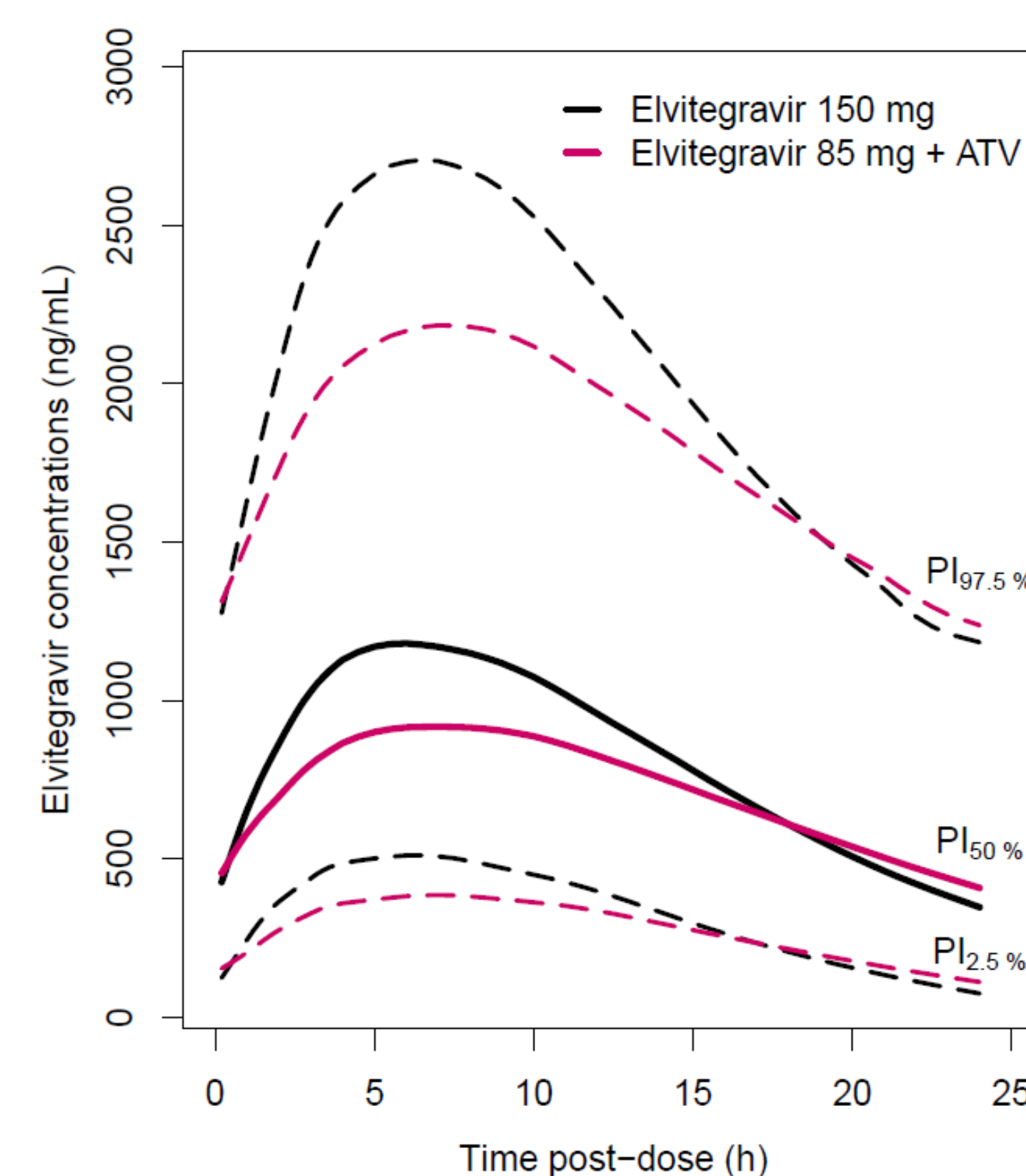


Figure 3. EVG simulated plasma concentrations at the dosage regimen of 150 mg and 85 mg using median AUC_{COBI} and ATV co-administration as covariates on EVG clearance

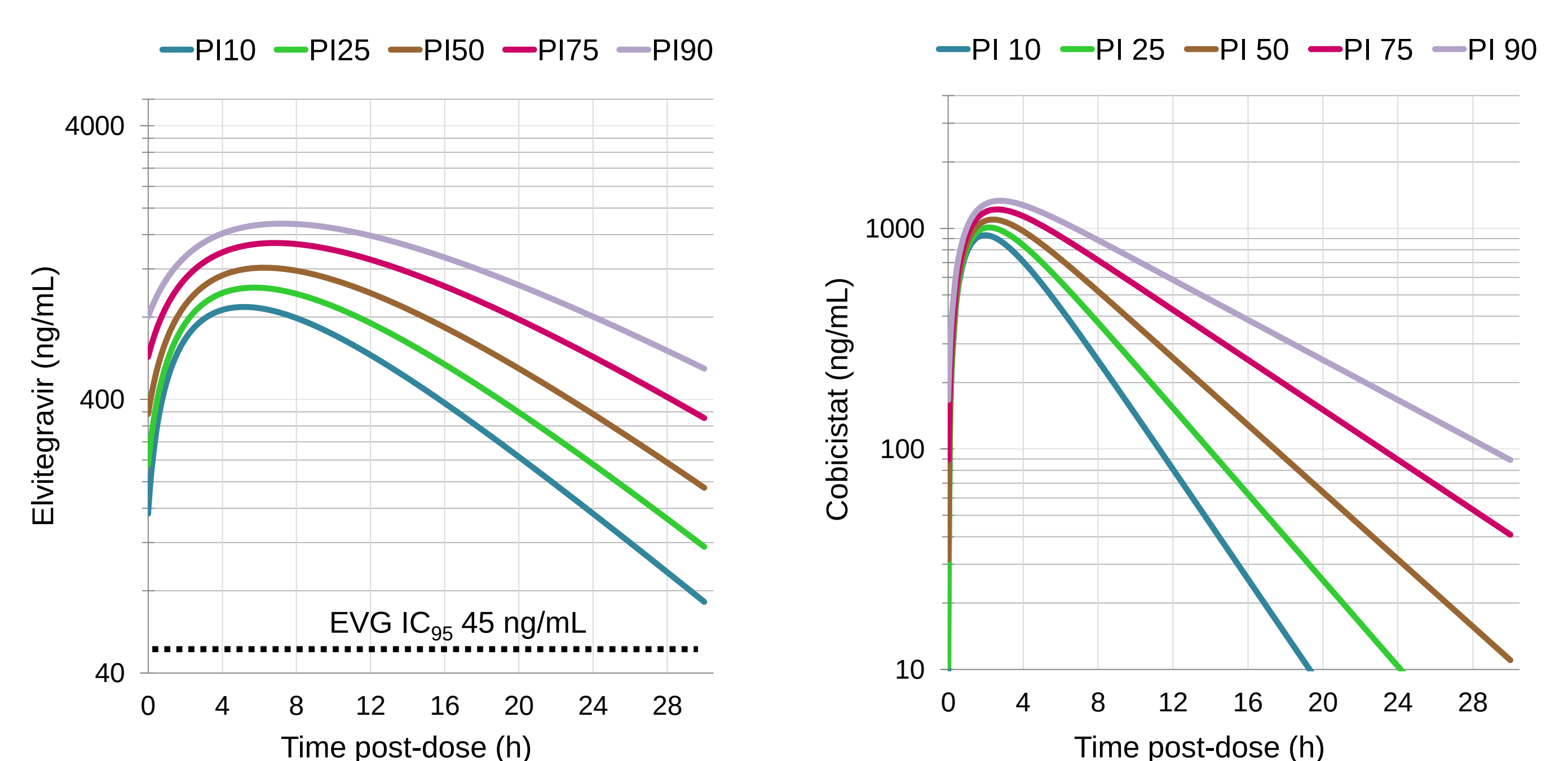


Figure 4. Percentile curves derived from EVG 150 mg and COBI 150 mg population pharmacokinetic models

Conclusions

- ♦ EVG and COBI pharmacokinetic variability appears to be mainly explained by drug-drug interactions that may be encountered in routine clinical practice
- ♦ Co-administration of non-boosted atazanavir decreased CL/F_{EVG} by 35%, likely due to UGT1A1 inhibition
- ♦ Co-administration of non-boosted atazanavir and ritonavir-boosted darunavir decreased CL/F_{COBI} by 49%, and 28%, respectively
- ♦ The integrated exposure of COBI influences CL/F_{EVG} , in line with mechanism-based cytochrome inhibition. A 2 fold increase in AUC_{COBI} induced a 46% reduction of CL/F_{EVG}
- ♦ These models might serve to derive percentile reference curves or implemented in a Bayesian tool for dosage adjustment.

Final EVG and COBI model:

$$CL/F_{EVG} \text{ (L/h)} = 7.6 \times (1 - 0.35 \times ATV) \times (AUC_{COBI}/\text{median } AUC_{COBI})^{-1.12}$$

$$CL/F_{COBI} \text{ (L/h)} = 16 \times (1 - 0.47 \times ATV) \times (1 - 0.27 \times DRVr)$$

ATV: atazanavir; AUC_{COBI} : cobicistat area under the curve; median AUC_{COBI} : 9.8 mg·h/L; DRVr: darunavir