

Pharmacogenetics-Based Population Pharmacokinetic Analysis for Dosing Optimization of Ritonavir-Boosted Atazanavir in Thai adult HIV-Infected Patients



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BACKGROUND

- Pharmacokinetics (PK) of Ritonavir-Boosted Atazanavir (ATV/RTV) exhibit high interindividual variability that is influenced by patient characteristics and genetic factors. Single nucleotide polymorphisms (SNPs) of metabolizing enzymes, protein transporters and gene regulation were found to be associated with PK of ATV/RTV.
- Thai patients have a lower oral clearance of ATV (CL/F_{ATV}) compared to other ethnicities, leading to higher drug exposure.¹ Although non-genetic and genetic factors including *CYP3A5* and *NR1I2* polymorphisms had significant effect on CL/F_{ATV} in Caucasian, this information in Thai patients is limited.
- The aims of this study were to characterize the population PK of ATV and RTV and identify potential factors influencing their disposition, taking into account the inhibition effect of RTV on ATV. In addition, the optimal dosage regimens of ATV/RTV for Thai HIV-infected patient were investigated.

METHODS

- A total of 544 Thai adult HIV-infected patients with 1464 concentrations were obtained from two clinical studies.²⁻³ Among all patients, 27 patients had intensive PK data (0, 1, 2, 4, 6, 8, 10, 12 and 24 h after dosing) and 517 patients had plasma trough concentrations.
- Genetic polymorphisms of *CYP3A5* 6986A>G, *ABCB1* 3435C>T, *ABCB1* 2677G>T, *SLCO1B1* 521T>C and *NR1I2* 63396C>T were genotyped using Taqman allelic discrimination assay.
- A population PK model was developed using the nonlinear mixed-effect modelling software (NONMEM®). The model of ATV and RTV was developed separately and then were incorporated to describe an interaction between drugs using sequential approach.
- The covariates including genetic factors and non-genetic factors (age, sex, body weight, liver function test and using of tenofovir disoproxil fumarate) were evaluated using a stepwise forward selection ($\alpha=0.05$) and backward elimination ($\alpha=0.01$). An effect of RTV concentrations on CL/F_{ATV} was investigated. Model evaluation was performed using bootstrap method.
- Monte Carlo simulations were conducted based on the final model to compare percentages of achieving the therapeutic range of ATV (C_{trough} 0.15-0.85 mg/L) under different dosing regimens and various covariates.

RESULTS

Table 1. Patient characteristics (n=544)

Characteristics	Data
Male / Female, n (%)	274 (50.37) / 270 (49.67)
Age (y), mean (SD)	41.88 (7.52)
Body weight (kg), mean (SD)	60.75 (11.54)
ALT (mg/dL), median (Q ₁ , Q ₃)	32 (22, 53.5)
ATV/RTV 300/100 mg, n (%)	275 (50.55)
ATV/RTV 200/100 mg, n (%)	269 (49.45)
Use of Tenofovir, n (%)	384 (70.59)
Genetic polymorphisms	Genotype (%)
• <i>CYP3A5</i> 6986A>G	AA 12.77 AG 43.33 GG 43.91
• <i>ABCB1</i> 3435C>T	CC 27.08 CT 50.87 TT 22.05
• <i>ABCB1</i> 2677G>T	GG 27.85 GT 42.75 TT 29.40
• <i>SLCO1B1</i> 521T>C	TT 79.69 TC 16.44 CC 3.87
• <i>NR1I2</i> 63396C>T	CC 15.86 CT 46.23 TT 37.91

- The PK of ATV and RTV were best described by a one-compartment model with first-order absorption and elimination. The E_{max} model best described the inhibition effect of RTV concentrations on CL/F_{ATV} .
- The CL/F_{ATV} in the absence RTV was 7.39 L/h. Patients with *CYP3A5* 6986 GG had a 7.3% lower CL/F_{ATV} than those with AA or AG genotype. The CL/F_{ATV} decreased by 10.5% for females compared with males.
- The CL/F_{RTV} (IIV), V/F_{RTV} and ka_{RTV} were 8.46 L/h (30.3%), 58.3 L and 1.23 h⁻¹, respectively. The CL/F_{RTV} was influenced by body weight using allometric scaling and *CYP3A5* 6986A>G.
- The simulation results showed that the median (Q₁, Q₃) predicted ATV C_{trough} was 0.437 (0.243, 0.738) mg/L for the low dose of ATV/RTV (200/100 mg, once daily) and 0.643 (0.345, 1.086) mg/L for the standard dose of ATV/RTV (300/100 mg, once daily).
- More patients in the low dose group achieved the target ATV C_{trough} (67.98%), while 36.21% of patients in the standard dose group had ATV concentrations above the target (ATV $C_{trough}>0.85$ mg/L).

Table 2 Population pharmacokinetic parameter estimates of atazanavir

Parameters	Final model		Bootstrap results (n=500 samples)	
	Estimate	95% CI*	Median	95% CI**
CL/F_{ATV} (L/h)	7.39	6.08, 8.70	7.46	6.48, 9.36
V/F_{ATV} (L)	76	59.67, 92.33	76.62	65.21, 100.95
ka (h ⁻¹)	1.64	0.95, 2.33	1.68	1.12, 3.23
Effect of female on CL/F_{ATV}	-0.105	-0.15, -0.06	-0.11	-0.16, -0.06
Effect of <i>CYP3A5</i> 6986 GG on CL/F_{ATV}	-0.073	-0.13, -0.02	-0.07	-0.12, -0.02
I_{max}	0.667	0.097, 1.431	0.72	0.232, 2.599
IC_{50}	0.561	0.013, 1.135	0.53	0.248, 3.456
IIV of CL/F (%CV)	27.98	24.55, 31.04	27.61	23.95, 30.75
RUV, proportional (%CV)	45.61	41.89, 49.04	45.68	42.54, 49.53

*95%CI was estimated value $\pm$ (1.96 x SE)
**95%CI was defined as 2.5 th and 97.5 th percentiles of the bootstrap parameter estimates
 I_{max} is the maximum inhibitory effect of RTV on CL/F_{ATV} , and IC_{50} is RTV concentration producing 50% of I_{max} .

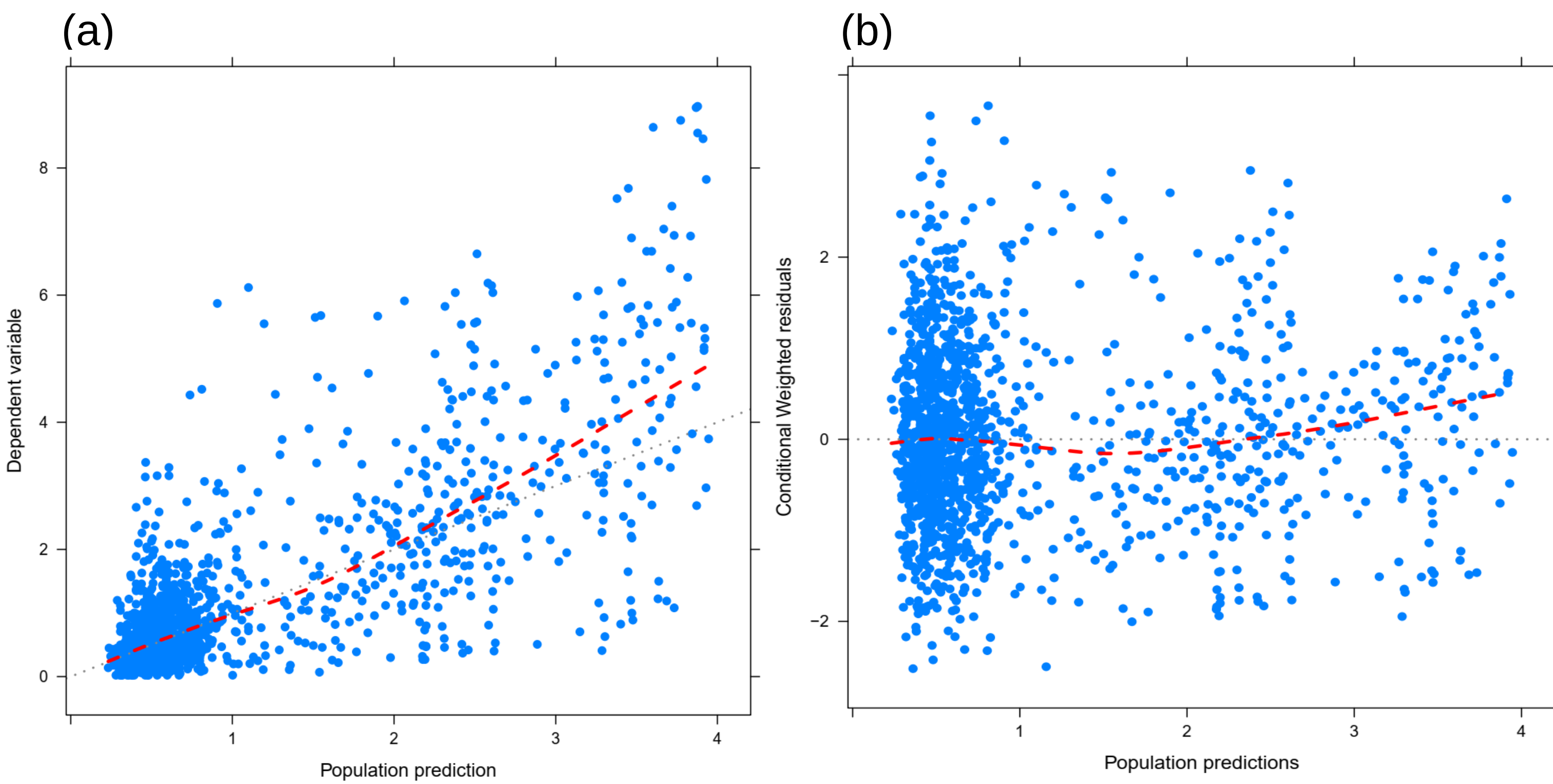


Figure 1. The goodness of fit plot of the final model

- (a) observed concentration versus population prediction
- (b) conditional weighted residual error (CWRES) versus population prediction

Table 3 The percentages (%) of achieving the target C_{trough} of ATV in different ATV dosing regimen, stratified by sex and *CYP3A5* 6986 genotype

		$C_{trough} < 0.15$ mg/L		$C_{trough} 0.15-0.85$ mg/L		$C_{trough} > 0.85$ mg/L	
Sex	<i>CYP3A5</i>	ATV/RTV 200/100 mg	ATV/RTV 300/100 mg	ATV/RTV 200/100 mg	ATV/RTV 300/100 mg	ATV/RTV 200/100 mg	ATV/RTV 300/100 mg
Female	6986A>G	10.97	8.18	69.83	56.65	19.20	35.17
	AA/AG						
Male	GG	9.05	2.92	62.74	51.77	28.21	45.30
	AA/AG	18.35	10.36	67.93	60.89	13.71	28.75
	GG	11.20	7.48	71.31	56.96	17.43	35.55

CONCLUSIONS

- A pharmacogenetics-based population PK model has been developed to describe PK of ATV/RTV in Thai adult HIV-infected patients.
- Patients with *CYP3A5* 6986 GG had a decrease in CL/F_{ATV} and CL/F_{RTV} .
- Female had a decrease in CL/F_{ATV} .
- A low dose of ATV/RTV (200/100 mg, once daily) was sufficient to achieve the target concentrations of ATV in Thai patients.

ACKNOWLEDEMENTS

- We thank all patients participating in the LASA study and intensive PK study, the LASA study team and the HIV-NAT staff.
- This study was supported by Chiang Mai University and the Royal Golden Jubilee PhD Program, The Thailand Research Fund (grant number PHD/0114/2558).

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