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# Population pharmacokinetics and dose optimisation of ritonavir-boosted atazanavir in Thai HIV-infected patients ☆

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ABSTRACT

There is evidence that Thai patients receiving standard doses of ritonavir (RTV)-boosted atazanavir (ATV/r) have high exposure to atazanavir (ATV) leading to a higher risk of toxicity. A lower dose of ATV/r may provide adequate exposure in this population. However, pharmacokinetic data on ATV/r in Thai patients required for dose adjustment are limited. This study aimed to develop a population pharmacokinetic model of ATV/r and to determine the influence of patient characteristics on ATV pharmacokinetics. Monte Carlo simulations were performed to estimate the proportion of patients achieving target ATV trough concentration ($C_{trough}$) with the standard ATV/r dose of 300/100 mg and a low dose of 200/100 mg once daily (OD). A total of 127 Thai HIV-infected patients were included in this study. One random blood sample was collected to determine ATV and RTV concentrations at each clinic visit from 100 patients. Intensive data from 27 patients enrolled in previous studies were also included. Data were analysed using the non-linear mixed-effects modelling approach. A one-compartment model with first-order absorption and elimination and absorption lag time best described the data. The population mean clearance of ATV/r was 4.93 L/h in female patients and was 28.7% higher in male patients. Simulation results showed a higher proportion of patients achieving ATV $C_{trough}$ within the target range with ATV/r 200/100 mg compared with 300/100 mg. The 200/100 mg OD dose of ATV/r provides adequate ATV exposure in Thai HIV-infected patients. Therefore, a lower dose of ATV/r should be considered for Thai and Asian populations.


## 1. Introduction

Atazanavir (ATV) is a potent, well tolerated, once-daily protease inhibitor (PI). According to the 2014 Thai guidelines for antiretroviral therapy for human immunodeficiency virus type 1 (HIV-1)-infected adults and adolescents, ritonavir (RTV)-boosted atazanavir (ATV/r) is recommended among patients who have failed the initial antiretroviral regimen [1].

ATV has favourable pharmacological properties that enable once-daily (OD) dosing as either a 400 mg or 300 mg dose in combination with low-dose RTV (100 mg). In addition, minimal side effects on the lipid profile and a unique resistance profile make ATV an ideal PI for the treatment of HIV infection [2]. Despite its major advantages over other PIs, ATV concentrations show high inter- and intra-individual variability [3], which may have clinical implications with respect to drug efficacy and toxicity [4]. Thus, it is a challenge to identify factors to explain the large inter- and intra-individual variability of ATV. This information is important for dose optimisation to achieve the target concentration of ATV. The proposed target ATV trough concentration ($C_{trough}$) has a lower boundary of 0.15 mg/L, which is the minimum effective concentration for successful viral suppression, and an upper boundary of 0.85 mg/L, a concentration associated with a higher risk of hyperbilirubinaemia [5–8].

There is evidence that Thai patients may require a lower dose of ATV, with sustained virological suppression and decreased toxicity [9–11]. There are clear advantages to lower ATV doses, including reduced toxicity and costs as well as increased availability of this drug in resource-limited settings. However, with highly variable ATV pharmacokinetics, identifying factors influencing its pharmacokinetics is crucial for precisely optimising ATV doses. Therefore, the aim of this study was to develop a population pharmacokinetic model of ATV/r and to identify patient characteristics that impact ATV pharmacokinetics. Model-based simulations were then applied to determine the optimal dose of ATV/r. Simulations of ATV $C_{trough}$

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were performed at a low dose of ATV/r 200/100 mg and at the standard dose of 300/100 mg OD.

## 2. Materials and methods

### 2.1. Patients and drug analysis

This was a cross-sectional study performed at the HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT), Thai Red Cross AIDS Research Centre (Bangkok, Thailand) between May 2011 and June 2014. A total of 100 patients aged ≥18 years receiving branded ATV/r as part of antiviral therapy for ≥3 months were recruited into the study. None of the patients received non-antiretroviral co-medications that interact with ATV/r. At each clinic visit, one random blood sample was collected to determine ATV and RTV concentrations. The median number of blood samples per patient was 2 (range 1–3). The actual time and amount of last dose administration and the time of blood collection were recorded. Among 100 patients, 46 patients received ATV/r 200/100 mg OD and 54 patients received 300/100 mg OD. In addition, 27 patients enrolled in previous pharmacokinetic studies of ATV/r were included in the analysis [10,12]. All of them had nine plasma blood samples collected pre-dose and at 1, 2, 4, 6, 8, 10, 12 and 24 h post-dose.

Among the 27 patients, 22 had plasma blood samples collected on two occasions, at Day 0 while the patients were receiving ATV/r 300/100 mg OD and on Day 15 (2 weeks after switching to ATV/r 200/100 mg OD). The five remaining patients were receiving ATV/r 200 mg OD before blood samples were collected. For all patients with intensive samples, food intake was controlled and ATV/r was taken with food. However, food intake was not strictly controlled for patients with sparse samples, but they were instructed to take ATV/r with food to achieve the target ATV concentration. All of the studies were approved by the Institutional Review Boards of the Faculty of Medicine, Chulalongkorn University (Bangkok, Thailand). All subjects provided written informed consent.

Plasma ATV and RTV concentrations were quantified by a validated high-performance liquid chromatography (HPLC) method with ultraviolet detection [13]. The lower limit of quantification (LLOQ) was 0.045 mg/L for ATV and RTV. The calibration curves were linear over the range of 0.045–30.0 mg/L for both drugs. The intraday and interday precisions were <10% for both drugs. Accuracy ranged between 101 and 103% for ATV and 101 and 104% for RTV%. The HIV-NAT laboratory participates in an international interlaboratory quality control programme for therapeutic drug monitoring (TDM) in HIV infection for external quality control [14].

### 2.2. Population pharmacokinetic analysis

Data were analysed using the non-linear mixed-effects modelling approach in NONMEM 7 (Icon Development Solutions, Ellicott City, MD). First-order conditional estimation with interaction (FOCE-I) was employed throughout the analysis. Drug concentrations below the LLOQ were set to a value of LLOQ/2. One- and two-compartment models with first-order absorption and elimination were fitted to the data. Owing to evidence of delayed absorption of ATV [15–17], zero- and first-order absorption, with and without lag time, and a transit absorption model were investigated. Interindividual variability (IIV) was described by an exponential error model assuming a log-normal distribution, i.e. $CL/F_i = TVCL \times \exp(\eta_i)$, where $CL/F_i$ represents the individual apparent clearance, TVCL represents the typical value of $CL/F$ in the population, and $\eta_i$ is the interindividual random effects assumed to be normally distributed with the mean of zero and variance of $\omega^2$. The proportional error model was used for describing the residual unexplained variability (RUV). The structural model selection was guided by the decrease in the objective function value (OFV), goodness-of-fit plots, the precision of the parameter estimates, and successful convergence. The goodness-of-fit plots were generated using R version 3.1.2 (R Development Core Team; http://www.r-project.org) and Xpose v.4.5.0 [18]. Several patient characteristics that potentially impact the pharmacokinetic parameters of ATV were investigated in the model building process using a stepwise procedure. Evaluated covariates included weight, age, sex, alanine aminotransferase, aspartate aminotransferase and co-medications that were administered to >10% of the study patients, i.e. lamivudine, tenofovir and zidovudine. Continuous covariates that were centred or scaled by its mean value were included into the model as linear, power and exponential functions. Binary covariates were included into the model using a fractional model, e.g. $TVCL = \theta_1 \times (1 + \theta_2 \times X)$, where $\theta_1$ is the typical value of $CL/F$ when $X = 0$, $\theta_2$ is the fractional increase or decrease of the typical value of clearance when $X = 1$, and $X$ is the dichotomous covariate having a value of 0 or 1. During forward inclusion, each covariate was added into the model if its inclusion resulted in a decrease of the OFV of >3.84 ($\chi^2$, $P \leq 0.05$, d.f. = 1). The covariates were retained in the model if their removal from the model resulted in an increase in the OFV of >6.63 ($\chi^2$, $P \leq 0.01$, d.f. = 1) during backward deletion.

The influence of RTV concentrations on the pharmacokinetics of ATV was investigated by various models: (i) a model assuming a direct relationship between observed RTV concentrations and ATV clearance; and (ii) a simultaneous combined ATV and RTV models. For the simultaneous combined ATV and RTV models, separate models were developed for ATV and RTV, and then the combined model was established to incorporate the influence of RTV concentration on ATV $CL/F$. The influence of RTV concentrations on ATV $CL/F$ was assessed using a linear function and a maximum inhibitory effect model with an estimation of the maximum inhibitory effect ($I_{max}$) or fixing the $I_{max}$ to 1.

### 2.3. Model evaluation

The final model was evaluated using a bootstrapping approach and a visual predictive check (VPC). The bootstrap re-sampling was performed to confirm the reliability of the final parameter estimates and their 95% confidence intervals (CIs) [19,20]. One thousand bootstrap replicates of the original data were generated using Wings for NONMEM v.740 (http://wfn.sourceforge.net). The median and 95% CIs of the parameter estimates obtained from the bootstrapping were then compared with the values obtained from the final model. The predictive performance of the final model was evaluated by VPC [21,22]. Five hundred data sets were simulated using the parameter estimates from the final model. The median and 90% prediction intervals (5th and 95th percentiles) were obtained from the simulated data and were superimposed on the observed data.

### 2.4. Simulation of dose reduction

To explore the possibility that lower doses of ATV may be sufficient to achieve target concentration of ATV, Monte Carlo simulations were performed using the parameters from the final model to assess the standard ATV/r dose (300/100 mg OD) and the low-dose ATV/r regimen (200/100 mg OD).

The impact of sex on ATV $C_{trough}$ was assessed. For each dosage regimen, ATV $C_{trough}$ values were simulated in 7000 in silico patients weighing 40–110 kg (at 10 kg increments; 1000 patients/weight range) with an even sex distribution for each weight range. Therefore, a total of 3500 simulations for each sex were performed. An ATV $C_{trough}$ between 0.15 and 0.85 mg/L was defined as the target value. The proportion of patients of each sex achieving the target ATV $C_{trough}$ was calculated by dividing the number of patients with a simulated ATV $C_{trough}$ within the target range by the total number of simulated patients.