Dosage Optimization of Efavirenz Based on a Population Pharmacokinetic–Pharmacogenetic Model of HIV-infected Patients in Thailand

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ABSTRACT

Purpose: Efavirenz exhibits high interindividual variability in plasma concentrations, leading to unpredictable efficacy and toxicity. Polymorphism of *CYP2B6* 516G > T has been found to predominantly contribute to efavirenz variability. However, dosage recommendations incorporating *CYP2B6* 516G > T polymorphism have not been investigated in the Thai population. This study aimed to develop a population model of the pharmacokinetic properties of efavirenz, and to investigate the impact of patients' characteristics and *CYP2B6* 516G > T polymorphism on the pharmacokinetic properties of efavirenz. Model-based simulations were performed to provide genotype-based dosage optimization in a Thai population.

Methods: Plasma efavirenz concentrations measured at 12 h post-dose in 360 Thai HIV-infected patients with and without tuberculosis were analyzed by the nonlinear mixed-effects modeling approach. A 1-compartment model with first-order absorption and elimination was used for describing the pharmacokinetic properties of efavirenz.

Findings: The allele frequency of *CYP2B6* 516G > T was 34.17%. The efavirenz oral clearance were 11.9, 8.0, and 2.8 L/h in patients weighing 57 kg and having the *CYP2B6* 516 GG, 516 GT, and 516 TT genotypes, respectively. The use of rifampicin increased efavirenz oral clearance by 28%. The results from the simulations suggest that efavirenz dosages of 400, 300, and 100 mg once daily in Thai HIV mono-infected patients, and 800, 600, and 200 mg once daily in HIV/tuberculosis co-infected patients carrying *CYP2B6* 516 GG, 516 GT, and 516 TT, respectively.

Implication: The results from this study provide a rationale for efavirenz dose adjustment based on *CYP2B6* 516G > T polymorphism in Thai HIV-infected patients, which could help to improve treatment outcomes in this population. ClinicalTrials.gov identifier: NCT01138267. (*Clin Ther*. 2020;42:1234–1245) © 2020 Elsevier Inc.

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INTRODUCTION

Efavirenz is the first-line non-nucleoside reverse-transcriptase inhibitor, used with 2 nucleoside reverse-transcriptase inhibitors, recommended for the first-line treatment of HIV-infected, treatment-naïve patients, according to the Thailand National Guidelines on HIV/AIDS Treatment and Prevention 2017.[1] The proposed target range of efavirenz concentration is 1−4 mg/L.[2] Subtherapeutic efavirenz concentrations may lead to treatment failure, whereas supratherapeutic concentrations may increase the risk for toxicities, including neurologic adverse effects.[2,3] The recommended dose of efavirenz is 600 mg once daily in HIV mono-infected patients and 800 mg once daily in HIV/tuberculosis (TB) co-infected patients who receive rifampicin as co-medication.[1] The pharmacokinetic properties of efavirenz are subject to substantial interindividual variability (IIV)[2]; thus, using a fixed dose of efavirenz 600 mg once daily may result in efavirenz concentrations that fall outside of the target concentration range. Previous studies have shown that genetic and nongenetic factors could explain the high variability in pharmacokinetic properties of efavirenz.[4−13] Therefore, it is a challenge to identify the factors that explain the IIV in the pharmacokinetic properties of efavirenz. This information is crucial for dose optimization to achieve the target concentration of efavirenz.

Cytochrome (CYP) 2B6 is the major enzyme involved in efavirenz metabolism. Genetic variations in the *CYP2B6* gene, particularly *CYP2B6* 516G > T, have been shown to have a large impact on the pharmacokinetic properties of efavirenz.[7−10,12−14] Previous studies have shown that variations in *CYP2B6* 516G > T polymorphism significantly increase efavirenz concentrations and CNS-related adverse effects, resulting in >2-fold of efavirenz discontinuation.[15−23] Therefore, dose adjustment according to *CYP2B6* 516G > T is worth considering when efavirenz is prescribed.

There is evidence that a reduced dose of efavirenz to 400 mg once daily is noninferior to the standard dose (600 mg).[22,24,25] Nonetheless, several studies have suggested that efavirenz dose adjustment based on patients' characteristics and genetic polymorphism of *CYP2B6*, especially *CYP2B6* 516G > T, should be leveraged to individualize efavirenz dosage regimens.[13,19,26−28] Even though the impact of *CYP2B6* polymorphisms on efavirenz concentrations has been confirmed in Thai HIV-infected patients,[16−18,29] dose recommendations according to patients' characteristics and genetic polymorphism of *CYP2B6* have not been investigated in this population. Therefore, this study aimed to develop a population model of the pharmacokinetic properties of efavirenz, and to investigate the impact of patients' characteristics and *CYP2B6* 516G > T on the pharmacokinetic properties of efavirenz. Additionally, model-based simulations were performed to determine the optimal dose of efavirenz in Thai HIV-infected patients.

MATERIALS AND METHODS

Study population and blood collection

This cross-sectional analytical study was performed at the HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT), Thai Red Cross AIDS Research Centre (Bangkok, Thailand), from May 2009 to December 2010 (ClinicalTrials.gov identifier: NCT01138267). A total of 229 Thai HIV-infected patients who were aged ≥18 years, nonpregnant, and had been receiving efavirenz for at least 2 weeks were enrolled in this study. Blood samples for the determination of efavirenz concentration and *CYP2B6* 516G > T genotyping analysis were collected at 12 h post-dose. The time and amount of last dose administration and time of blood collection were recorded. This study was approved by the institutional review board of the Faculty of Medicine, Chulalongkorn University (Bangkok, Thailand) and the Ethics Committee of Pharmacy, Faculty of Pharmacy, Chiang Mai University (Chiang Mai, Thailand). Written informed consent was obtained from all patients. Additionally, data from 131 patients enrolled in a previous clinical study of the impact of *CYP2B6* polymorphisms and plasma efavirenz concentrations were included in the analysis.[17] All patients in that study were HIV/TB co-infected and receiving a once-daily antiretroviral regimen of tenofovir (300 mg), lamivudine (300 mg), and efavirenz (600 mg) at bedtime. Rifampicin 450 and 600 mg/d was given in patients with body weights of ≤50 kg and >50 kg, respectively. Blood samples were collected at 12 h after efavirenz dosing for at least 12 weeks.

Determination of Efavirenz Concentration

The plasma efavirenz concentrations were measured using a validated HPLC assay at the HIV-NAT pharmacokinetics laboratory. The method of analysis has been developed at the Department of Clinical Pharmacology, the University Medical Centre Nijmegen (Nijmegen, The Netherlands). The HIV-NAT laboratory participates in an international quality-control and quality-assessment program. The sample peak heights were processed by ChromQuest software version 4.1 (Thermo Fisher Scientific, Waltham, Massachusetts). The lower limit of quantification (LLOQ) of efavirenz was 0.2 mg/L. The intraday and interday precisions were <10%. The accuracy was between 95% and 105%.

Genotyping analysis

Genomic DNA was extracted from the stored EDTA cell pellets using a QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Genotype of the single-nucleotide polymorphism *CYP2B6* 516G > T was determined by polymerase chain reaction−restriction fragment length polymorphism using primer and restriction enzyme as previously described.[30]

Population pharmacokinetic analysis

The population pharmacokinetics model was developed using the nonlinear mixed-effects model by NONMEM software version 7.3 (Icon Development Solutions, Ellicott City, MD) with Pirana version 2.9.6, Perl-speaks-NONMEM version 4.7.0, and R version 3.4.2 (R Development Core Team; www.r-project.org). The first-order conditional estimation method with interaction was used for parameter estimation throughout the modeling. One-compartment model with first-order absorption and elimination was used for characterizing the pharmacokinetic properties of efavirenz. The IIV of efavirenz pharmacokinetic parameters was described by the exponential model assuming a log-normal distribution. Residual unexplained variability was described by the additive error model. Structural model selection was guided by the objective function value (OFV), successful convergence, goodness-of-fit plots, and precision of parameter estimates.

Covariates that potentially affected the population pharmacokinetic parameters of efavirenz, including body weight, age, sex, *CYP2B6* 516G > T polymorphism, and rifampicin use, were investigated by the stepwise approach with forward selection, followed by backward deletion. Continuous covariates, including body weight and age, were tested by the linear, exponential, and power models. Categorical covariates including *CYP2B6* 516G > T polymorphism, sex, and rifampicin use were tested by the additive, exponential, and fractional models. The polymorphisms of *CYP2B6* 516G > T were categorized into 3 groups: homozygous wild type (GG), heterozygous variant (GT), and homozygous variant (TT). During forward selection, a decrease in OFV of at least 3.84 (χ^2 distribution; $P \leq 0.05$, $df = 1$) was used as a cutoff criterion for including the covariate into the model. An increase in the OFV of at least 6.63 (χ^2 distribution; $P \leq 0.01$, $df = 1$) was used as a cutoff criterion for retaining covariates in the model during backward deletion.

Model evaluation

The bootstrapping approach and prediction-corrected visual predictive check (pcVPC) were used for assessing the reliability of the final parameter estimates and predictive performance of the final model.[31,32] For the bootstrap analysis, 1000 resampling datasets were generated by sampling with replacement from the original data. The medians and 95% CIs (the values at the 2.5th and 97.5th percentiles) obtained from the bootstrap analysis were compared with the corresponding values of the final model obtained from NONMEM. For the pcVPC, 1000 simulated concentrations were generated from the final model using the original data as a template. The 95% CIs of the medians and 5th and 95th percentiles of the simulated concentrations were plotted against the medians, 5th and 95th percentiles of the observed data.

Simulations for dose optimization

To explore the impact of significant covariates on efavirenz exposure and investigate the optimal dose of efavirenz in the Thai population, the final model was used for generating the simulated concentrations of efavirenz at 14 h post-dose (C_{14}) of *in silico* patients receiving the standard efavirenz dosage (600 mg once daily in HIV mono-infected patients, and 800 mg once daily in HIV/TB co-infected patients receiving rifampicin) and the low-dose

efavirenz regimens (500, 400, 300, 200, or 100 mg once daily) by Monte Carlo simulations. For each dosage regimen, 1000 efavirenz C_{14} values were simulated for each category of covariate: the genotype of *CYP2B6* 516G > T (GG, GT, and TT genotypes), rifampicin use, and body weight. Efavirenz C_{14} was chosen based on the median sampling time of the study suggesting the target range of efavirenz of 1–4 mg/L.[2] The percentage of patients in each dosage group having a simulated efavirenz C_{14} within the target range was calculated by dividing the number of simulated patients having the simulated efavirenz C_{14} within the target range by the total number of simulated patients.

RESULTS

Demographic characteristics

A total of 360 efavirenz concentrations from 360 Thai HIV-infected patients were included in the analysis. Patients' characteristics are summarized in Table I. One (0.3%), 351 (97.5%), and 8 (2.2%) patients received efavirenz 800, 600, and 400 mg once daily, respectively. The frequency of the T allele at 516G > T of the *CYP2B6* gene among these patients was 34.17%. Seven observed efavirenz concentrations were lower than LLOQ and were set to a value of LLOQ/2. Among all patients, 8 patients (2.2%) had an efavirenz concentration below 1 mg/L, and 102 patients (28.3%) had an efavirenz concentration above 4 mg/L. The median efavirenz concentrations among the groups carrying the *CYP2B6* 516 GG, 516 GT, and 516 TT genotypes were 2.02, 3.185, and 8.4 mg/L, respectively.

Table I. Summary of patient characteristics (N = 360).

Characteristic	Value
Age, mean (SD) [range], y	39.0 (7.8) [19–66]
Body weight, mean (SD) [range], kg	58.1 (10.7) [32.2–105]
Sex, no. (%)	
Male	232 (64.4)
Female	128 (35.6)
Co-medications, no. (%)	
TDF + 3 TC	203 (56.4)
RIF	102 (28.3)
AZT + 3 TC	73 (20.3)
TDF + FTC	23 (6.4)
Other NRTIs + 3 TC	23 (6.4)
CYP2B6 516G > T polymorphism, no. (%)	
GT	184 (51.11)
GG	145 (40.28)
TT	31 (8.61)

3 TC = lamivudine; AZT = zidovudine; FTC = emtricitabine; NRTIs = nucleoside reverse-transcriptase inhibitors; RIF = rifampicin; TDF = tenofovir.

Population pharmacokinetics analysis

During structural model building, as all of the data were sparse and were clustered at 12 h post-dose, the IIV of the apparent volume of distribution (V/F) and absorption rate constant (K_a) could not be precisely estimated. Therefore, V/F was estimated without its IIV, and K_a was fixed to a literature-based value of 0.3 h^{-1}.[4] Among all of the covariates investigated in this study, body weight, age, *CYP2B6* 516G > T polymorphism, and rifampicin use were found to significantly influence apparent oral clearance of EFV (CL/F) during forward selection. However, age failed to reach a significant level when backward deletion was performed. Thus, the covariates that significantly affected CL/F and were included in the final model were body weight, *CYP2B6* 516G > T polymorphism, and rifampicin use. The inclusion of these significant covariates in the final model resulted in a substantial drop in the IIV of CL/F from the base model (71.7% in the base model vs 52.9% in the final model). The estimated parameters of the final model are shown in Table II. The CL/F of efavirenz was calculated using the following equation:

$$\begin{aligned} CL/F(L/h) = {} & \theta_1 \times (1 + \theta_2 \times CYP2B6\ 516GT) \\ & \times (1 + \theta_3 \times CYP2B6\ 516TT) \times (1 + \theta_4 \times \text{rifampicin}) \\ & \times \{1 + [\theta_5 \times (\text{body weight} - 57)]\} \end{aligned} \quad \text{(Equation 1)}$$

where *CYP2B6* 516 GT and TT were assigned a value of 1 or 0 according to the presence or absence of the corresponding polymorphism, and rifampicin was 1 if rifampicin was used concurrently.

Based on the final model, the estimated CL/F of efavirenz was 11.9 L/h among patients weighing 57 kg, carrying the *CYP2B6* 516 GG genotype, and

Table II. The final parameter estimates from NONMEM and bootstrapping analyses.

Parameter	NONMEM Estimate (95% CI*)	Bootstrap Median (95% CI†)
θ_1	11.89 (10.65–13.11)	11.83 (10.70–13.19)
θ_2	–0.33 (–0.41 to –0.24)	–0.33 (–0.41 to –0.24)
θ_3	–0.77 (–0.82 to –0.71)	–0.77 (–0.81 to –0.70)
θ_4	0.28 (0.11–0.45)	0.28 (0.13–0.47)
θ_5	0.014 (0.01–0.02)	0.014 (0.01–0.02)
V/F (L)	237.67 (77.34–398.00)	237.14 (149.36–575.59)
$IIV_{CL/F}$, %CV	53 (47–58)	52 (46–58)
RUV, mg/L	0.17 (0.04–0.29)	0.16 (0.06–0.31)

CL/F (L/h) = $\theta_1 \cdot (1 + \theta_2$ *CYP2B6* 516 GT) $\cdot (1 + \theta_3$ x *CYP2B6* 516 TT) $\cdot (1 + \theta_4$ x RIF) $\cdot \{1 + [\theta_5 \cdot$ (body weight − 57)]}. CL/F = apparent oral clearance; $IIV_{CL/F}$ = interindividual variability of CL/F; RUV = residual unexplained variability; V/F = apparent volume of distribution.

* Calculated as the final parameter estimate ±1.96 · SE.

† The 2.5th and 97.5th percentiles of the bootstrap parameter estimates.

not using rifampicin. The efavirenz CL/F rates were 33% and 77% lower among patients carrying the *CYP2B6* 516 TT and GT genotypes, respectively, compared to the rate in the group carrying the GG genotype. The concurrent use of rifampicin increased CL/F by 28%. Moreover, it was found that every 10-kg increment of body weight increased CL/F by 14%. The goodness-of-fit plots of the final model are shown in Fig. 1.

Model validation

From 1000 bootstrap runs, 999 runs minimized successfully with successful covariance. The results from the bootstrap analysis are shown in Table II. The medians (95% CIs) of the parameter estimates obtained from the bootstrapping were comparable to the values obtained from NONMEM. These results confirmed the reliability of the parameter estimates of the final model from NONMEM.

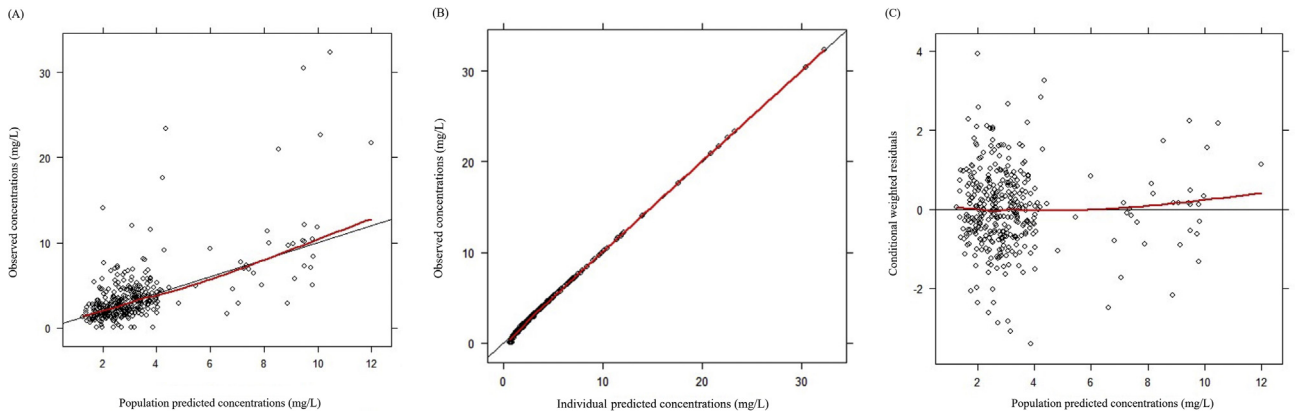

Fig. 1. Goodness-of-fit plots of the final model. A and B: Observed efavirenz (efavirenz) concentrations versus population predicted concentrations (A) and individual predicted concentrations (B). C, Conditional weighted residuals versus population predicted concentrations.

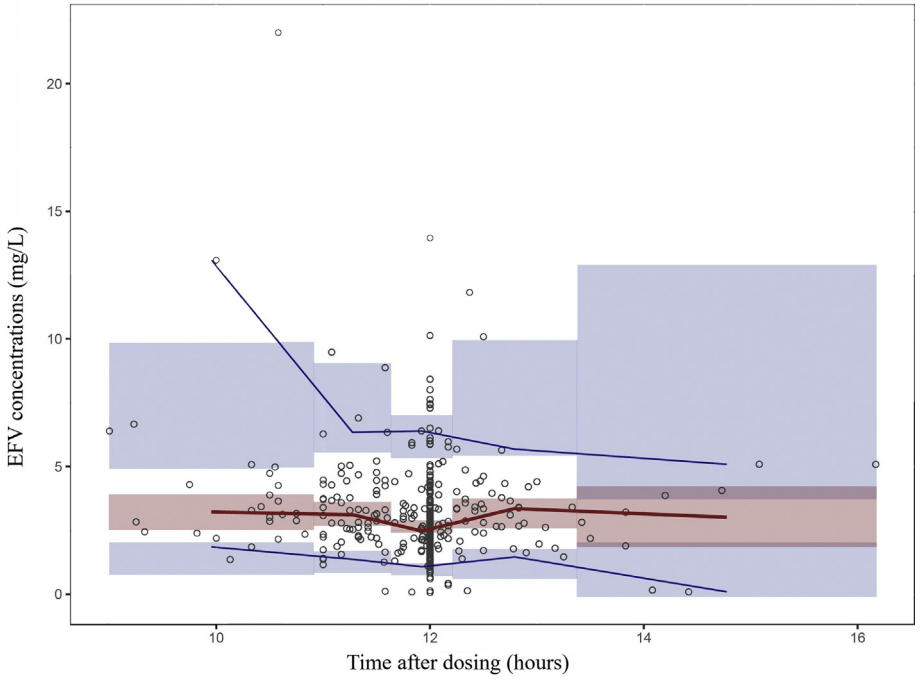

Fig. 2. Plot of prediction-corrected visual predictive check (pcVPC), showing the predicted concentrations versus observed efavirenz (efavirenz) concentrations (circles). Red line is 50th percentile, blue lines are 5th and 95th percentiles, of the observed concentrations. Shaded areas are 95% CIs of the corresponding model-predicted percentiles.

The pcVPC plot obtained from 1000 simulations is shown in Fig. 2. The medians, 5th and 95th percentiles of the observed data consistently overlaid within 95% CIs of the medians and corresponding percentiles of the simulated data. The results from pcVPC indicated that the final model provided a good description of the observed data and sufficient predictability of the final model. Therefore, the final model was adequate for use in determining the optimal dose of efavirenz by simulation.

Simulation for dose optimization

The simulation results showed that the use of a standard fixed dosage of efavirenz of 600 mg once daily in HIV mono-infected patients and 800 mg once daily in HIV/TB co-infected patients receiving rifampicin as co-medication provided a lower percentage of patients having efavirenz C_{14} within the target range of 1–4 mg/L, especially in those with the TT genotype (Tables III and IV). The suggested optimal dosages of efavirenz for Thai HIV mono-infected patients carrying the *CYP2B6* 516 GG, GT, and TT genotypes are 400, 300, and 100 mg once daily, respectively. With these suggested dosages, >70% of patients had efavirenz C_{14} within the target range. In Thai HIV/TB co-infected patients receiving rifampicin and carrying the *CYP2B6* 516 GG, GT, and TT genotypes, the suggested optimal dosages of efavirenz are 800, 600, and 200 mg once daily, respectively. With these suggested dosages, >70% of patients could achieve the target concentration of efavirenz, and ~65% of patients weighing >60 kg and carrying the GG genotype would achieve the target concentration.

DISCUSSION

The efavirenz-based regimen is considered the preferred first-line antiviral therapy in Thailand.[1] Even though the efficacy of the efavirenz-based regimen is clearly established, considerable variability

Table III. Percentages of *in silico* HIV mono-infected patients (n = 8400) having simulated efavirenz concentrations within target range, by efavirenz once-daily dosage.

CYP2B6 516G > T Genotype/Body Weight	Patients With Simulated Concentrations Within the Target Range, %						
	800 mg	600 mg	500 mg	400 mg	300 mg	200 mg	100 mg
GG genotype							
32.2–39.9 kg	44.5	62	72	78*	72	59	22
40.0–59.9 kg	41.7	61	70	75*	71	54	24
60.0–79.9 kg	62.6	73	76	72*	64	41	16
80.0–105 kg	61.5	72	75	74*	65	44	15
GT genotype							
32.2–39.9 kg	20.7	35	49	65	73*	76	40
40.0–59.9 kg	19.7	36	51	64	76*	73	41
60.0–79.9 kg	36.8	56	67	76	78*	64	30
80.0–105 kg	36.0	55	65	76	77*	62	25
TT genotype							
32.2–39.9 kg	0.3	2	3	7	19	40	76*
40.0–59.9 kg	0.3	2	3	6	20	39	79*
60.0–79.9 kg	0.8	5	7	17	31	59	76*
80.0–105 kg	1.2	3	7	15	32	59	75*

* Suggested efavirenz dose for different genotype.

in efavirenz concentrations has been observed, mainly resulting in high plasma concentrations of efavirenz when the standard dosage of efavirenz is given.[2] Efavirenz concentrations higher than target range of 1–4 mg/L have been found to be associated with CNS adverse events, hepatotoxicity, and efavirenz discontinuation among patients receiving the efavirenz standard dose.[2,22,33] Therefore, identifying factors that could explain the high IIV in the pharmacokinetic properties of efavirenz is important for dose optimization. Although efavirenz dosage adjustment according to *CYP2B6* polymorphisms and patient characteristics is encouraged to help to optimize patient treatment,[13] dosage-adjustment guidance in the Thai population has never been suggested. This study is the first to develop a population model of the pharmacokinetic properties of efavirenz in Thai HIV-infected patients and to investigate the impact of *CYP2B6* 516G > T and other patients' characteristics on the pharmacokinetic properties of efavirenz. The developed model was further used for efavirenz dose optimization in the Thai population.

The estimated mean of the population CL/F from this study was 11.9 L/h among patients weighing 57 kg, carrying *CYP2B6* 516 GG genotype, and not using rifampicin, which was similar to the value reported in a Chinese population (9.7 L/h).[13] However, the estimated CL/F in this study was slightly lower than the value reported in white patients of 12.2 L/h.[10] Even though the estimated CL/F among the population was not weight normalized, this result confirmed the differences in efavirenz CL/F among ethnicities and provides a rationale for dose optimization in the Thai population.

Overall, the allele frequency of *CYP2B6* 516G > T was 34.17%, which is consistent with previous reports in the Thai population.[16,18] The reported frequency from this study was higher than in a white population (22.8%) and differed from that in other Asian populations, that is, Chinese (43%), Japanese (18%), and Koreans (47%).[13,26,34–38] The results from our study show that the variability in efavirenz CL/F depends largely on the *CYP2B6* 516G > T polymorphism, which is very much expected and consistent with those in previous reports.[7–10,12,13]

Table IV. Percentages of *in silico* HIV/tuberculosis co-infected patients (n = 8400) having simulated efavirenz concentrations within target range, by efavirenz once-daily dosage.

CYP2B6 516G > T Genotype/Body Weight	Patients With Simulated Concentrations Within the Target Range, %						
	800 mg	600 mg	500 mg	400 mg	300 mg	200 mg	100 mg
GG genotype							
32.2–39.9 kg	72.8*	68	62	52	34	18	7
40.0–59.9 kg	71.1*	66	59	50	34	20	5
60.0–79.9 kg	65.6*	56	50	41	23	15	6
80.0–105 kg	64.7*	57	49	39	26	11	6
GT genotype							
32.2–39.9 kg	68.4	77*	77	70	57	35	13
40.0–59.9 kg	67.1	75*	72	68	55	37	12
60.0–79.9 kg	73.0	72*	65	58	44	26	9
80.0–105 kg	73.0	73*	69	58	42	25	9
TT genotype							
32.2–39.9 kg	7.1	19	33	46	66	79*	54
40.0–59.9 kg	9.9	21	32	47	70	78*	57
60.0–79.9 kg	18.6	36	47	64	73	74*	40
80.0–105 kg	18.3	33	47	60	76	75*	45

* Suggested efavirenz dose for different genotype.

The inclusion of *CYP2B6* 516G > T polymorphism in the model resulted in a decrease in the IIV in CL/F from 71.7% to 56.2%. Patients carrying the GT and TT genotypes had 33% and 77% lower efavirenz CL/F compared to patients carrying the GG genotype. The impact of *CYP2B6* 516G > T polymorphism on efavirenz CL/F reported in this study is in line with that in previous studies.[10,13,19] The reduced CL/F in patients with homozygous or heterozygous *CYP2B6* 516G > T genotype could result in an increased efavirenz exposure, leading to a higher risk for neurologic adverse effects and efavirenz discontinuation.[22,23]

Similar to findings from several studies, body weight was one of the significant covariates influencing efavirenz CL/F. A lower body weight was found to be associated with a lower CL/F of efavirenz.[9,12,13] In the present study, the CL/F of efavirenz was increased by 1.4 L/h with each 10 kg above 57 kg. These results are consistent with a previous report in Thai HIV/TB co-infected patients demonstrating that a higher body weight was associated with a lower efavirenz concentration at 12 h post-dose.[39]

Although rifampicin is known as a strong CYP2B6 inducer, the impact of rifampicin on pharmacokinetic properties of efavirenz was inconclusive. While the pharmacokinetics study of efavirenz showed a significantly higher efavirenz CL/F in patients receiving co-administration with rifampicin compared to that in patients who did not use rifampicin (0.269 vs 0.167 L/h/kg),[40] the results of previous population pharmacokinetics studies did not find a significant impact of rifampicin on the pharmacokinetic properties of efavirenz.[12,13] These conflicting results could have been due to the small number of patients using rifampicin in some studies. In this study, a significant number of patients (28%) received rifampicin as co-medication; thus, the impact of rifampicin on the pharmacokinetic properties of efavirenz could be confirmed. The results from this study indicated that the use of rifampicin as co-medication increased the CL/F of efavirenz by 25%,

which is consistent with the results reported in a previous interaction study by Lopez-Cortes et al.[41]

Regarding the suggested target concentration of efavirenz at 1−4 mg/L, the simulation results of this study highlight the possibility of efavirenz dosage reduction in the Thai population. Moreover, efavirenz dosage optimization based on the *CYP2B6* 516G > T polymorphism is advisable. A dosage reduction of efavirenz to 400, 300, and 100 mg once daily is recommended in Thai HIV mono-infected patients carrying the *CYP2B6* 516 GG, GT, and TT genotypes, respectively. In Thai HIV/TB co-infected patients receiving rifampicin as a co-medication and having the *CYP2B6* 516 GG, GT, and TT genotypes, the recommended efavirenz dosages are 800, 600, and 200 mg once daily, respectively. When the guideline-recommended dosages of 600 and 800 mg once daily are used in Thai HIV mono-infected and HIV/TB co-infected patients, a relatively low percentage of patients having efavirenz concentrations within the target range (<5% and <18%) and a high percentage of patients with supratherapeutic concentrations (>95% and >81%) (data not shown) were observed among patients carrying the TT genotype. Thus, in the homozygous variant group, a reduced dosage of efavirenz should be strongly considered.

The ENCORE1 (Efficacy of 400 mg Efavirenz Versus Standard 600 mg Dose in HIV-infected, Antiretroviral-naive Adults) study[24,25] clearly demonstrated the efficacy and tolerability of efavirenz 400 mg once daily, and efavirenz 400 mg once daily is currently included in the World Health Organization's guideline for alternative first-line regimens. Our study supports that the use of efavirenz 400 mg once daily provides sufficient efavirenz exposure. However, this dosage regimen should not be considered in patients concurrently receiving rifampicin, particularly those carrying the *CYP2B6* 516 GG and GT genotypes. As ~90% of our patients carry the *CYP2B6* 516 GG and GT genotypes, it is expected that the use of efavirenz 400 mg once daily among patients concurrently receiving rifampicin could lead to subtherapeutic concentrations of efavirenz and may cause treatment failure. Additionally, supratherapeutic concentrations of efavirenz should be aware when 400 mg of efavirenz was given in Thai HIV mono-infected patients carrying the TT genotype.

Some study limitations should be acknowledged. First, as all of the data were measured at 12 h post-dose, the IIVs in V/F and K_a could not be precisely estimated. Therefore, V/F was estimated without its IIV, and K_a was fixed to a previous literature-based value. In order to be able to estimate the IIVs of K_a and V/F, more samples around the absorption phase are required. Second, only the impact of the *CYP2B6* 516G > T polymorphism was investigated in this study. Efavirenz is primarily metabolized by CYP2B6; however, CYP 2A6, 1A2, 3A4/3A5, and UDP-glucuronosyltransferase 2B7 are involved to a lesser extent. There is evidence that genetic polymorphisms of these minor isozymes may influence the pharmacokinetic properties of efavirenz, but to a lesser extent than *CYP2B6* polymorphisms.[9,42,43] Thus, a study investigating the influence of these polymorphisms on the pharmacokinetic properties of efavirenz and their role on efavirenz dose adjustment is needed. Third, due to the variable impact of *CYP2B6* 516G > T polymorphism on the pharmacokinetic properties of efavirenz among ethnicities, the results from this study may not be applicable to patients of other ethnicities. Lastly, the dose suggestions from simulations were targeted at obtaining a concentration within the optimal range; however, clinical outcomes including efficacy and adverse events were not assessed in this study. A further study should be conducted to investigate clinical outcomes when genotype-based dose individualization is implemented.

CONCLUSIONS

This study provides evidence that *CYP2B6* 516G > T polymorphism accounts for a major part of IIVs in the pharmacokinetic properties of efavirenz. Moreover, rifampicin use and body weight were significant covariates that influenced the CL/F of efavirenz. The results from this study provide evidence to support the clinical application of efavirenz dose individualization based on *CYP2B6* 516G > T polymorphism. Efavirenz dose adjustment according to *CYP2B6* 516G > T polymorphism in Thai HIV mono-infected and HIV/TB co-infected patients receiving rifampicin as co-medication is proposed for maintaining efavirenz exposure within the target concentration. Dose adjustment could lead to a higher probability of successful viral suppression

and a lower prevalence of efavirenz concentration–related neurologic adverse effects.

AUTHOR CONTRIBUTIONS

P.C.: literature search, data analysis, figures and table generation, manuscript preparation. A.A.: design the study, data collection, manuscript preparation. W.M.: data collection, manuscript preparation. S.U.: data collection, EFV concentration analysis. S.T.: genotyping analysis. V.S.: genotyping analysis, manuscript preparation. B.P.: design the study, data analysis, figures generations, manuscript preparation.

DISCLOSURES

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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