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Developmental Pharmacokinetic Changes of Lamivudine in Infants and Children

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Abstract

Lamivudine is a nucleoside reverse transcriptase inhibitor widely used in infants and children in combination antiretroviral therapy to treat human immunodeficiency virus (HIV) infection. Developmental changes in lamivudine pharmacokinetic disposition were assessed by combining data from 7 studies of lamivudine (Pediatric AIDS Clinical Trials Group 300, 353, 356, 358, 386, 1056, and 1069) representing subjects across the pediatric age continuum. A population pharmacokinetic model was developed to identify factors that influence lamivudine disposition. Age and Thai race were independent predictors of apparent clearance (CL/F), whereas the use of a fixed drug combination formulation (GPO-VIR) was an independent predictor of bioavailability, with CL/F more than doubling from birth to adolescence. Serum creatinine was not associated with CL/F. Monte Carlo simulations were used to compare the lamivudine exposure achieved with World Health Organization (WHO) weight band and Food and Drug Administration (FDA) label dosing recommendations. WHO dosing yielded higher exposure during the first few months of life, but this difference was less pronounced between 6 months and 14 years of age. Overall, both FDA and WHO dosing provided similar AUC values to those previously reported in HIV-infected adults. Lamivudine WHO weight band dosing results in therapeutic exposure in infants and children and may improve drug dosing in resource-limited countries.

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Keywords

Clinical research; infectious diseases; pediatrics; pharmacokinetics and drug metabolism; virology

Lamivudine is a nucleoside reverse transcriptase inhibitor (NRTI) widely used in infants and children for the prevention and treatment of HIV infection. It is currently recommended as an integral part of first-line NRTI backbone in combination antiretroviral therapy in children because of its favorable safety profile and record of clinical success.^{1,2} Lamivudine has been used in combination with zidovudine and/or nevirapine during the first 1 to 6 weeks of life to reduce perinatal transmission of human immunodeficiency virus (HIV).^{3–5} The World Health Organization (WHO) recommends the combination of lamivudine and zidovudine to prevent resistance following administration of single-dose nevirapine for the prevention of mother-to-child HIV transmission.⁶

WHO weight band dosing has been proposed to simplify drug dosing in resource-limited settings. Although the Food and Drug Administration (FDA)–approved lamivudine dose of 4 mg/kg twice daily after 1 month of age requires individual dosing calculations and rounding to ascertain the required dose, weight bands allow for a comparison of weight to a compact table of doses. However, weight bands are limited in that they include a broad size range of children on the same dose, which can lead to children at the lower end of a weight band being overdosed and at a higher risk of drug toxicities, whereas children at the higher end can be underdosed and at a higher risk of selecting viral drug resistance.

Lamivudine has been studied in adults, and multiple population pharmacokinetic (PK) studies exist.^{7–11} However, despite many studies in infants, children, and adolescents,^{12–19} most current PK studies are limited by small numbers of participants and restricted age range. Using population pharmacokinetics, the current study combines data from 7 clinical trials of lamivudine across a wide range of pediatric ages to assess the impact of age, formulation, and other clinical characteristics on lamivudine disposition and investigates the relative lamivudine exposure achieved with WHO weight band and FDA label dosing recommendations.

METHODS

The data set for this analysis consisted of pooled data from 7 Pediatric AIDS Clinical Trials Group (PACTG)/International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) protocols: 300, 353, 356, 358, 386, 1056, and 1069. A brief summary of each clinical study is described below, and patient demographics at first PK visit and dosing regimens are presented in Table I. The human subjects committee at each participating clinical site approved these studies, and written informed consent was obtained from the children's legal guardians. For all studies, medication administration was directly observed around the time of acquiring the PK samples, and fasting was observed except in infants where milk was allowed.

PACTG 300 was a multicenter, randomized, double-blind clinical trial to compare the efficacy of zidovudine and lamivudine dual therapy against didanosine monotherapy in previously untreated HIV-infected children ages 42 days to 15 years. All children enrolled in the dual-therapy arm of the study received 4 mg/kg per dose twice daily (maximum dose of 150 mg/dose) of an innovator (original commercial formulation) lamivudine liquid formulation. Three PK samples were collected at study weeks 0 and 48 in most participants. Samples were obtained at 30 minutes, 1 to 2 hours, and 3 to 4 hours.²

PACTG 356 was a study of HIV-infected infants initiating therapy within the first 2 years of life. Infants were treated with an innovator liquid formulation of lamivudine at 4 mg/kg twice daily in combination with zidovudine and stavudine, abacavir, nevirapine, or nelfinavir. Samples were obtained predose as well as 1 to 3 hours and 4 to 6 hours postdose.²⁰

PACTG 353, 358, and 386 were studies in HIV-exposed term infants receiving postnatal antiretroviral therapy for the first 4 to 6 weeks of life. Infants received an innovator liquid formulation of lamivudine at 2 mg/kg twice daily in combination with zidovudine and stavudine, abacavir, nevirapine, or nelfinavir. The first PK samples were taken in the first to third weeks of life, and the second set of pharmacokinetic samples was taken at 6 weeks of life. Samples were obtained predose as well as 1 to 3 hours and 4 to 6 hours postdose.²⁰

PACTG/IMPAACT 1056 and 1069 were phase I/II studies of HIV-1-infected children in Thailand from 6 months to 13 years of age designed to assess the pharmacokinetics and safety of a novel pediatric fixed-dose combination (FDC) tablet designed by the Thai Government Pharmaceutical Organization (GPO). P1056 assessed a pediatric FDC chewable tablet composed of stavudine/lamivudine/nevirapine (7:30:50 mg), whereas P1069 assessed an FDC tablet composed of zidovudine/lamivudine/nevirapine (30:15:28 mg). Children received combination therapy with either the FDC tablets (GPO-VIR) or an equivalent innovator liquid formulation. The lamivudine component was dosed at 4 mg/kg (maximum dose of 150 mg/dose) twice daily. Following intensive PK sampling with 7 plasma samples obtained over the dosing interval, patients were crossed over to the alternate formulation, and a repeat intensive PK profile was obtained.²¹

Plasma lamivudine concentrations were determined by a validated enzyme immunoassay method at the University of California, San Diego Pediatric Pharmacology Laboratory (PACTG 353, 358, 386, and 356) or high-performance liquid chromatography at St Jude's Children's Research Laboratory (PACTG 300) and at the Faculty of Associated Medical Sciences, Chiang Mai University PHPT-IRD Clinical Pharmacology Laboratory, Thailand (PACTG 1056 and 1069). All laboratories participated in AIDS Clinical Trials Group (ACTG)/National Institute of Allergy and Infectious Diseases (NIAID) clinical pharmacology quality assurance, including proficiency testing, and passed all tests prior to and after all the assays were performed for these studies.

Pharmacokinetic analysis

Pharmacokinetic data were analyzed using the computer program NONMEM (version VI) with a GNU Fortran G77 Compiler. An open 1-compartment model (ADVAN2, TRANS2 subroutine) and first-order conditional estimation method (FOCE with interaction) were used to describe the lamivudine concentration data. Both first-order and zero-order absorption models were explored. A 2-compartment model (ADVAN4, TRANS4 subroutine) and first-order conditional estimation method (FOCE with interaction) were also developed to describe the data. The 2-compartment model used the following parameters: the steady-state volume of distribution of the peripheral plus the central compartment (V_{ss}), intercompartmental clearance (Q), clearance (CL), bioavailability (F), and the absorption rate constant (K_a). Data were log transformed prior to analysis. An exponential-normal distribution error model was used for intersubject variability, and a proportional residual error model was used to describe the residual error not explained by the model or intersubject variability. Subjects were assumed to be at steady state, and samples below the quantifiable limit of detection were assigned a value of 5 ng/mL, which was half the lower limit of quantification of the assay (10 ng/mL).

Pharmacokinetic parameters were scaled by subject size, with clearance (CL) scaled by allometric weight ($WT^{0.75}$) and volume of distribution (V_d) scaled by weight ($WT^{1.0}$), before evaluation of other potential covariates. Potential covariates were added to the model on CL, V_d , or bioavailability (F) one at a time as either a linear or nonlinear function, with covariates that improved the model fitting by a change in the objective function of at least 4.0 ($P < .05$) being retained in the initial covariate screen. All covariates found in this phase were included in the model and removed sequentially with replacement. To be retained in the final model, an increase in objective function of at least 8.0 was required. Age was considered a nonlinear maturation function, a linear function, and a logarithmic covariate on clearance. Separate residual errors were considered for US and Thai data. Empiric Bayesian estimates of individual infant pharmacokinetic parameters were generated from the final model using the POSTHOC subroutine. A 1000-sample bootstrap assessment of the final model was performed using Wings for NONMEM.

The final population PK model was used to assess the WHO weight band lamivudine dosing proposed by the WHO.²² Monte Carlo simulations were performed to generate concentration profiles for 1000 virtual children from 0.05 to 14 years of age with an equivalent number of subjects at each of the following ages: 0.05, 0.1, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 years. The resulting lamivudine concentration profiles for the WHO weight band dosing recommendations (Table II) were compared with the FDA dosing (2 mg/kg <1 month of age and 4 mg/kg >1 month of age with a maximum of 150 mg).

RESULTS

Intensive and sparse pharmacokinetic data were available for 346 infants, children, and adolescents (2356 samples total). A base 1-compartment model was developed with allometric scaling for weight. Zero-order absorption provided no improvement in objective function over first-order absorption in the base model. The 2-compartment base model yielded an extremely small intercompartmental clearance ($Q \sim 10^{-10}$), which was indicative that this model was not a good fit for the data.

In the 1-compartment base model population (Thai, African American, Hispanic), sex, CD4 percent, total bilirubin, serum creatinine, and age were separately evaluated on clearance. Formulation (GPO-VIR FDC tablet) was evaluated on bioavailability. Covariates identified in the univariate screen were population (Thai, African American, Hispanic), age, GPO-VIR FDC tablet formulation, and serum creatinine. Age and Thai population were found to be independent predictors of clearance, whereas GPO-VIR FDC tablet formulation was found to be an independent predictor for bioavailability (change in the objective function of 262.6, 22.2, and 68.4, respectively), and thus these covariates were retained in the final model. Assigning separate residual errors to US and Thai data improved the objective function.

Final model parameters and variance estimates are shown in Table III. Visual predictive plots for the final model are separated by liquid (Figure 1A) and GPO-VIR tablet formulations (Figure 1B). The residual error for the Thai data was significantly less than that for the US data, likely as a result of the absence of the sparse PK visits in the Thai data. Bootstrap evaluation of the final model successfully converged 98.6% of the time, and estimation results are summarized in Table III. The final parameter estimates of the model fall well within the 95% confidence interval and are close in value to the median bootstrap estimates demonstrating that the final model represents the population well.

Age modeled as a nonlinear maturation function for clearance (see Table III, equation for apparent clearance $[CL/F]$) provided the greatest improvement in objective function as

compared with linear age or logarithmic age and was used in the final model. This function estimated lamivudine CL/F at birth to be 32% of the mature level at birth with a half-life for lamivudine clearance gain of 2.2 months and was 90% of the mature level by 6 months (Figure 2).

A higher serum creatinine was observed in the Thai population (Figure 3A), which may account for the significance of this covariate in the univariate screen but not in the multivariate screen (change in objective function of 0.5), which incorporated the Thai population in the model. Although serum creatinine appears to increase with age (Figure 3B), this observation is likely a population effect as the Thai patients represent older children in the study.

Monte Carlo simulations using FDA dosing (2 mg/kg <1 month of age and 4 mg/kg >1 month of age with a maximum of 150 mg) and WHO weight band dosing were conducted on 1000 virtual children from 0.05 to 14 years of age. Median and interquartile range (IQR) of WHO weight band dosing (mg/kg) were as follows: 0.05 years, 7.3 (6.6–8.4); 0.1 years, 6.7 (5.9–7.5); 0.5 years, 5.8 (5.1–6.6); 1 to 2 years, 5.1 (4.8–5.5); 3 to 6 years, 4.4 (4.1–4.8); 7 to 10 years, 4.5 (4.0–5.3); and 11 to 14 years, 3.4 (3.1–3.8). Age was the only covariate used in the analysis. Subjects were assumed to be taking the innovator liquid formulation and be from the US population. In the first month of life, FDA dosing yielded markedly lower median AUC (Figure 4) values than did WHO dosing, but both dosing methods provided similar values in older infants and children. WHO dosing yielded significantly higher median AUC values early in life, then rapidly declined in later infancy to yield a plateau throughout childhood. The FDA dosing yielded an increase in AUC at 1 month of age prior to a decline and plateau due to the change in dose from 2 mg/kg to 4 mg/kg.

DISCUSSION

Lamivudine is an NRTI widely used in infants and children for both prevention and treatment of HIV infection.¹ Lamivudine is a highly soluble and permeable drug with a rapid dissolution rate, freely penetrating tissue beyond the systemic circulation. Lamivudine is eliminated primarily as unchanged drug via the kidneys. Metabolism of lamivudine is a minor route of elimination with 5% to 10% of the parent compound metabolized to the pharmacologically inactive trans-sulfoxide metabolite, which is primarily renally excreted. Thus, its pharmacokinetics are significantly affected in patients with renal insufficiency.¹⁰

The current study combines 7 separate studies to represent a broad spectrum of ages along with allowing for the assessment of race and formulation. Overall, our PK parameters are consistent with previous pediatric studies. Our post hoc data yielded a mean apparent clearance and volume of distribution of 0.72 (95% confidence interval, 0.36–1.13) L/h/kg and 3.54 (2.09–5.57) L/h, respectively. Prior pediatric studies have reported apparent clearance means from 0.39 to 1.03 L/h/kg with apparent volume of distribution means from 2.29 to 4.31 L/kg.^{13,14,17,19,23} Our study used a 1-compartment model similar to prior studies in HIV-infected adults using oral lamivudine.^{7,11} Consistent with our findings, Moore et al⁷ described that although lamivudine disposition appears to be characterized by a 2-compartment model, attempts to develop the model failed to give a meaningful result. Mueller et al¹⁶ used a 2-compartment model to describe lamivudine disposition in children; however, this study used both intravenous and oral dosing. Intravenous dosing is more conducive to the development of a 2-compartment model as absorption does not need to be considered and the PK of the separate compartments can be better characterized. Bouazza et al¹⁹ used a 2-compartment model for oral lamivudine dosing in children but had to fix the absorption constant to a value from the literature and assumed a model in which K_a and the slope of the distribution phase (α) were equal. In a separate study, Bouazza et al²³ used a

study design that incorporated once-daily dosing with sampling out to 24 hours in some patients, thereby allowing for the fitting of a 2-compartment model, but were still unable to estimate the variability of all parameters in the model. Our study is limited by the measurement of lamivudine concentrations in 3 separate laboratories, although all participated in ACTG/NIAID clinical pharmacology quality assurance and passed proficiency testing.

Age, Thai population, and formulation were significant covariates in the final model of the current study. Although the formulation effect in the model was unexpected as lamivudine is a highly soluble and permeable drug with a rapid dissolution rate, this effect has been previously observed by Gitta et al,²⁴ who found dose-normalized lamivudine exposure to be ~55% higher for tablets compared with liquid. The final model had a lower apparent clearance in patients taking FDC tablets containing lamivudine as compared to the liquid formulation. Only Thai population patients were given FDC tablets, but this was evaluated within the same patients by a crossover study design, thus limiting potential confounders and making it likely that this is a real effect. Yuen et al⁹ demonstrated similar mean absolute bioavailability values for lamivudine (86%–88%) after single 100-mg doses of tablet, capsule, and oral solution formulations of the drug in HIV-infected adults. They also found the absorption of the tablet and capsule similar to or exceeding that of the oral solution. The study was well controlled, with patients not allowed to recline or eat until 4 hours after each dose. The enrollment criteria were limited to HIV-infected adults who were asymptomatic with the exception of potential lymphadenopathy and were not on other HIV drugs. The children in the current study were not healthy, were taking other medications, and were not limited in food intake or activity, all of which could affect the bioavailability of the drug. A difference in stability between the liquid and tablet or a food effect could lead to the bioavailability differences observed in the current study.

Although serum creatinine was significant in the univariate analysis, it was not significant in the final analysis. Although serum creatinine appeared to relate to age, this was likely confounded by race as the Thai population had higher values and represented older patients in the study. Prior adult studies have demonstrated an effect of renal function on lamivudine clearance. Heald et al²⁵ demonstrated that impaired renal function has a significant effect on lamivudine disposition, and Moore et al⁷ found that creatinine clearance was a significant covariate in their pharmacokinetic model. The current study was limited as serum creatinine rather than creatinine clearance was determined. Whereas creatinine clearance more accurately reflects renal function, serum creatinine is an insensitive marker of renal function as it is highly secreted. Abnormal values were rare in the study, and thus it was difficult to distinguish between the good and poor secretors.

Age was best modeled as a maturation function. The age effect mainly occurred within the first year of life and was a small effect; thus, clearance was not observed to change with age in children or adolescents. This was consistent with Moodley et al,¹⁵ who showed that infant clearance increases during the first week of life. In contrast, Burger et al¹⁴ found a difference in clearance between children age <7 years and older in a group of 51 HIV-infected children aged 1.7 to 17 years using noncompartmental methods. It was suggested that the age effect might have been partially due to differences in formulation, with younger children using liquid formulation and older children using tablets. This is supported by the current study, which found a significant formulation effect. The crossover study design for Thai patients allowed for the separation of the age and formulation effects with no significant age differences in clearance observed after the first year of life.

In our simulation, WHO dosing resulted in markedly higher AUC values early in life. After dose adjustment to 4 mg/kg, FDA dosing also yielded higher AUC values than in later

childhood. This is consistent with Moodley et al,¹⁵ who found that neonates had lower apparent clearance and higher AUC compared with older infants. They suggested that this might have been primarily a result of the neonates' immature renal function; changes in absorption might also contribute and be related to irregular neonatal gastrointestinal function and feeding times. The WHO and FDA AUC values in older children were similar to those previously observed in HIV-infected adults, with mean adult AUC values ranging 5.5 to 10.2 $\mu\text{g}\cdot\text{h}/\text{mL}$ on twice-daily dosing at either 4 mg/kg or 150 mg.^{8,10,26–29}

The WHO dosing yielded markedly higher AUC values early in life compared with the FDA dosing. This is likely due to the large discrepancy between WHO weight band and FDA dosing in early life, where the WHO dose is 1.5 to 4 times the FDA dose. These doses become closer in value in older infants and children. The WHO weight bands are a simplification of dosing and provide the same dose for a range of subject weights. Smaller subjects will have higher drug levels and be at risk of toxicity, whereas larger subjects will have lower levels and be at risk of underdosing. Because of the low toxicity of lamivudine, the WHO weight band doses were devised favoring higher doses while avoiding underdosing and potential drug resistance.² The use of weight band dosing, with an easy to read chart, rather than per kilogram dosing, which requires a calculation, is a major advantage in implementing pediatric antiretroviral treatment programs in resource-limited countries. Despite higher lamivudine exposures, we recommend the WHO dosing method for infants and children as a means to limit underdosing and the development of drug resistance resulting from errors in dosing due to calculation.

Although the intracellular triphosphate anabolite of lamivudine is the active moiety, we are currently limited to measuring lamivudine plasma concentrations and extrapolating the clinical effects from what is measured. The volume of blood needed to measure intracellular lamivudine triphosphate concentrations with current technology makes serial evaluations impractical in infants and children. Although newer technologies are currently being developed to measure intracellular concentrations, these methodologies, which include use of radiolabeled drug in microdosing quantities, have not yet been evaluated for antiretrovirals in pediatrics.

In conclusion, age affects lamivudine apparent clearance, but this effect is predominantly present early in life. Formulation and race are important covariates to account for in drug dosing. The WHO weight band dosing is designed to help simplify drug dosing in the developing world where there is a high burden of HIV infection. Although WHO dosing yields significantly higher drug levels in the first month of life, this is not expected to be problematic because of the low toxicity associated with lamivudine use. Small differences in renal function do not have a major effect on apparent clearance. As future studies help define sources of lamivudine pharmacokinetic variability and exposure-response relationships, further refinement of lamivudine use will be possible, thereby ensuring optimal drug concentrations and the improvement of viremic control in pediatric HIV worldwide.

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Figure 1.

Visual predictive plots for the lamivudine population pharmacokinetic model. (A) Liquid formulation. (B) GPO-VIR tablet formulation. Data were adjusted to reflect Food and Drug Administration dosing of 2 mg/kg <1 month of age and 4 mg/kg >1 month of age with a maximum of 150 mg. Solid lines represent median concentrations and dashed lines represent 97.5 and 2.5 percentiles from Monte Carlo simulation of the final model with an age and population distribution identical to that of the data set.

Figure 2.

Estimated lamivudine apparent clearance (CL/F) versus age. The post hoc empiric Bayesian-estimated CL/F was derived from the final pharmacokinetic model. The solid line represents the population-based apparent clearance profile, which was derived using the allometrically scaled median weight for each age group (Centers for Disease Control and Prevention 50th percentile weight).

Figure 3. Serum creatinine (mg/dL). (A) Comparison of serum creatinine by population (Thai vs non-Thai) demonstrating median creatinine values to be higher in patients of Thai race ($P < .01$). (B) Comparison of serum creatinine to age shows serum creatinine increasing with age.

Figure 4.

Median drug exposure (area under the curve) from Monte Carlo simulations using the Food and Drug Administration (FDA) label dose (2 mg/kg <1 month of age and 4 mg/kg >1 month of age, maximum of 150 mg) and World Health Organization (WHO) weight band dosing recommendations. Data represent the median and interquartile range of lamivudine AUC ($\mu\text{g}\cdot\text{h/mL}$). Dashed lines indicate typical range of values in adults.

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Subject Characteristics^a

Table 1

Study	Total Subjects	Age, y, at PK Visits, Median (Range)	Weight, kg, at PK Visits, Median (Range)	Dose, mg/kg	Total Samples by Formulation
300	159	2.7 (0.1–14.1)	13.2 (4.5–52.7)	4	614 liquid
353	20	0.02 (0.01–0.11)	3.1 (2.1–4.6)	2	102 liquid
356	58	0.3 (0.1–2.1)	5.9 (2.8–16.2)	4	338 liquid
358	12	0.06 (0.05–0.11)	3.8 (2.9–4.4)	2	55 liquid
386	12	0.02 (0.01–0.12)	2.9 (2.3–4.1)	2	63 liquid
1056	43	8.3 (0.7–12.0)	21.0 (6.4–28.9)	4	301 liquid, 301 tab (GPO-VIR)
1069	42	6.1 (0.5–12.3)	19.1 (5.9–28.6)	4	287 liquid, 294 tab (GPO-VIR)
Overall	346	1.7 (0.1–14.1)	11.6 (2.1–52.7)	2–4	1760 liquid, 595 tab (GPO-VIR)

^aSummary of study and subject demographics. Age and weight are representative of first pharmacokinetic (PK) visit. Total samples refers to the number of lamivudine concentrations collected for each formulation (liquid vs GPO-VIR tablet).

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Table II

World Health Organization Weight Band Lamivudine Dosing Guidelines

Weight, kg	3-5.9	6-9.9	10-13.9	14-19.9	20-24.9	25-34.9
Dose, mg	30	45	60	75	90	150

Table IIIPharmacokinetic Model Parameters^a

	Final Parameter	Standard Error	Bootstrap Estimates (Median and 95% Confidence Interval)
Θ1 (V _d), L	3.64	0.0954	3.63 (3.45–3.82)
Θ2 (CL), L/h	1.40	0.066	1.41 (1.30–1.56)
Θ3 (K _a), 1/h	3.87	0.414	3.56 (2.90–4.53)
Θ4 (GPO-VIR formulation)	1.35	0.0339	1.35 (1.28–1.41)
Θ5 (Mat)	0.325	0.0445	0.33 (0.25–0.42)
Θ6 (Mat)	3.76	1.13	3.70 (1.55–4.96)
Θ7 (Thai race)	1.35	0.068	1.34 (1.22–1.47)
Variability			
Intersubject (V _d)	29.90%	3.36%	30.17% (23.53%–37.28%)
Intersubject (CL)	24.30%	3.06%	24.15% (18.48%–30.64%)
Intersubject interaction (CL-V)	23.90%	3.01%	
Error			
Proportional (US data)	60.30%	2.77%	59.92% (54.41%–65.91%)
Proportional (Thai data)	46.20%	1.05%	46.04% (43.89%–48.27%)

$$CL/F=WT^{0.75} \times \Theta_2 \times \Theta_4^{-\text{GPO-VIR}} \times (\Theta_5 + (1 - \Theta_5) \times (1 - e^{-\text{AGE} \Theta_6})) \times \Theta_7^{\text{THAI}}$$

^aPopulation pharmacokinetic (PK) final parameter and standard error estimates. Bootstrap evaluation of final population PK model. Equation for apparent clearance (clearance/bioavailability) used in the final model.