Pharmacometric Characterization of Efavirenz Developmental Pharmacokinetics and Pharmacogenetics in HIV-Infected Children

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The aim of this analysis was to create a pharmacometric model of efavirenz developmental pharmacokinetics and pharmacogenetics in HIV-infected children. The data consisted of 3,172 plasma concentrations from 96 HIV-1-infected children who participated in the Pediatric AIDS Clinical Trials Group 382 (PACTG382) study. Analyses were performed using NONMEM, and the impacts of body weight, age, race, sex, formulation, liver function, and cytochrome P450 2B6 (CYP2B6)-G516T polymorphism were assessed. A one-compartment model using weight-based alometry on oral clearance and apparent volume of distribution adequately described the data. A sigmoid maximum-effect ($E_{\text{max}}$) maturation model demonstrated an increase in oral clearance with age to reach 90% of its mature level by the age of 9 months. The liquid formulation bioavailability relative to the capsule was found to increase with age to reach 90% of its mature value by the age of 8 years. The CYP2B6-G516T polymorphism decreased oral clearance, while the MDR1-C3435T polymorphism demonstrated no effect.

Efavirenz (EFV) is a potent nonnucleoside reverse transcriptase inhibitor (NNRTI) that is indicated, in combination with other antiretroviral agents, for treatment of human immunodeficiency virus type 1 (HIV-1) infection (1). EFV is highly bound to plasma proteins, predominantly albumin (2). It is mainly metabolized by cytochrome P450 enzymes to hydroxylated derivatives that are subsequently glucuronidated and renally excreted (2).

High interindividual variability (IIV) and intraindividual variability in EFV pharmacokinetics (PK) has been observed in both adults and children (3–5). This variability is of particular concern due to the narrow therapeutic index of EFV (6, 7). Studies have shown that elevated EFV concentrations are associated with an increased risk of central nervous system (CNS) toxicity (8) and elevated liver enzymes (9). In addition, differences in EFV concentrations were found between responders and nonresponders (4), and children with higher intraindividual PK variability, presumably arising from more variable medication-taking behavior, have been reported to have a higher likelihood of viral rebound and a shorter time to their first viral rebound (3).

Sources of EFV PK variability have been extensively studied in adults (4, 5, 10–12). Covariates found to account for this variability include the polymorphic nature of cytochrome P450 2B6 (CYP2B6) and other isoforms that are responsible for EFV metabolism (13, 14). In addition, some studies have shown EFV PK to vary across genders and ethnicities (10–12, 15). Little information is available about the correlation between EFV PK parameters and pediatric population covariates and the influence of developmental changes that take place during infancy and childhood on CYP2B6 expression and EFV PK (16). Moreover, some clinical studies have reported a high prevalence of subtherapeutic EFV concentrations among children, suggesting a need to develop alternative dosing guidelines for this important population (17–19).

The aims of the current study were to quantify the interindividual and intraindividual variability of EFV PK in HIV-1-infected children; to identify factors that describe this variability, including growth and maturation; and to develop a population pharmacokinetic model that incorporates these covariates in order to guide EFV dosing in children.

MATERIALS AND METHODS

Patient population and study design. The population pharmacokinetic analysis included EFV plasma concentration data from HIV-1-infected children who participated in the Pediatric AIDS Clinical Trials Group 382 (PACTG382) study (20). This was an open-label phase I/II study that enrolled children who were less than 16 years old and had a plasma HIV-1 RNA level of more than 400 copies per milliliter using the reverse transcription-PCR (Amplicor) Monitor assay. In addition to EFV, the children received nevirapine and at least one nucleoside reverse transcriptase inhibitor. The trial included two cohorts; cohort I enrolled patients who were 3 to 16 years old, and cohort II included patients who were between 2 months and 8 years old at the time of enrollment. The trial was approved by the institutional review boards of all 18 participating sites. Informed written consent was obtained from the parents or guardians of the patients.

EFV was administered orally as one of three formulations, capsule, suspension, or solution. It was initially dosed allometrically to provide exposures comparable to those for adults according to the following formula: dose (mg/day/child) = (weight of child in kg/70 kg)$^{0.7} \times 600$ (mg/day/adult) for the capsule formulation.

For the oral suspension or solution, the standard adult dose of 600 mg was replaced with 720 mg to account for the anticipated reduction in bioavailability.

Doses were rounded to the nearest 25-mg increment. The study used an area under the concentration–time curve (AUC)-controlled design. Blood samples were obtained for quantification of the EFV concentration before a dose and 2, 5, 8, and 12 h after a dose at weeks 2 and 6 and at week...
10 if additional dosage changes were made at week 6. EFV AUCs were also collected at weeks 56 and 112 to monitor for changes in exposure during growth and development. Additional samples after 6 and 24 h were obtained for cohort I patients only. A 24-h steady-state area under the concentration–time curve (AUC_{24}) was computed at weeks 2 and 6 and used to guide EFV dosing. If the AUC for EFV was not within the prespecified target range of 190 to 380 μM·h, the dose was adjusted proportionately up to a 200-mg maximum dosing increase. Participants were monitored for up to 4 years, and clinical evaluations that included EFV trough concentrations and determination of plasma HIV-1 RNA levels were conducted monthly.

Measurement of plasma efavirenz concentrations. Plasma EFV concentrations were determined within 2 weeks at a PACTG Pharmacology Laboratory by a validated high-performance liquid chromatographic method. The total assay variability (a composite of within- and between-day variabilities) of the assay was 1 to 4.5% over the standard–curve range of concentrations. The limit of quantitation was 0.020 mg/liter.

Population pharmacokinetic analysis. All subjects who had at least one EFV plasma concentration were included in the analysis. PK data analysis was performed using the nonlinear mixed-effects modeling methodology as implemented in the NONMEM software (version 7, level 1.2). The first-order conditional estimation with eta-epulsion interaction (FOCEI) was used throughout the model development. Diagnostic graphical analysis was performed using R (version 3.0.0).

Development of the population pharmacokinetic base model. Based on exploratory data analysis and our previous experience with EFV (3, 17), we used a one-compartment model with first-order absorption and elimination (the ADVAN 2 subroutine in NONMEM). The model was parameterized in terms of the absorption rate constant (KA), oral clearance (CL/F), and apparent volume of distribution (V/F). Four residual-error models were explored: the exponential-error model, proportional-error model, additive-error model, and combined proportional–plus additive-error model. Individual CL/F and V/F values were assumed to be log-normally distributed, and their variability was estimated using an exponential-error model as follows: \( CL/F = TVCL \times \exp(ETA) \), where TVCL is the typical population PK parameter estimate under a regression equation (oral CL in this case), CL/F is the individual PK parameter, and ETA is the random variable representing the deviation between CL/F and TVCL, which is assumed to be independent and normally distributed around 0 with a variance that represents the variability of the PK parameter. Since patients were sampled on several occasions over several years, partitioning the variability of the PK parameters into IIV and interoccasion variability (IOV) was tested.

Development of the covariate model. Covariates screened for their possible effects on PK parameters included body weight, body surface area, age, race, sex, formulation, CYP2B6-G516T polymorphism, multi- drug resistance transporter gene (MDR1)-C3435T polymorphism, and liver function tests (bilirubin, aspartate transaminase [AST], and alanine aminotransferase [ALT]). Covariate modeling was done using the forward-inclusion, backward-elimination approach and was guided by evaluation of the empirical Bayesian PK parameter estimates versus covariate plots and likelihood ratio testing (chi-square; \( df = 1, P < 0.01 \)), as well as clinically meaningful changes in the estimates of PK parameters. Mixture modeling, as implemented in NONMEM, was used to identify any significant patterns in patients whose CYP2B6-G516T genotype or MDR1-C3435T genotype was missing (about 25% of the patients).

Body weight was chosen as the primary covariate in the population analysis (21). Both total body weight and fat-free mass (FFM) were used as measures of body size, and the results were compared (22). Fat-free mass was computed from total body weight (WT) and height (HT) using the following equations (23):

\[
\text{FFM}_{\text{male}} = 42.92 \times \text{WT}/[30.93 + (\text{WT}/\text{HT})^2] \\
\text{FFM}_{\text{female}} = 37.99 \times \text{WT}/[35.98 + (\text{WT}/\text{HT})^2].
\]

CL/F and V/F were allometrically scaled to a weight of 70 kg to allow use of the model for prediction of adult pharmacokinetics and to facilitate comparison of the parameter estimates with those obtained in other studies (21). The exponents in the allometric model were fixed to 0.75 and 1 for CL/F and V/F, respectively (24).

The maturation of CL/F in the patients was tested using a sigmoid maximum-effect \( (E_{\text{max}}) \) model to allow a gradual increase in clearance during early-life years and a mature clearance to be achieved at a later age, as follows (24, 25): \( CL/F = TVCL \times [\text{AGE}^{\text{H}}/(\text{AGE}^{\text{H}} + \text{TM}_{\text{50}}^{\text{H}})] \), where TVCL is the population estimate for the oral clearance standardized to a 70-kg person using the allometric model, \( \text{AGE} \) is the postnatal age of the subject in months, \( \text{TM}_{\text{50}} \) is the age in months at which clearance is 50% of the mature value, and \( H \) is the Hill coefficient for the maturation of the oral clearance.

Maturation in the apparent volume of distribution was explored using an exponential asymptotic model (24, 26, 27): \( V/F = TVV \times [1 + B \times \exp\{-k\times(\text{AGE} - \text{TM}_{\text{50}})^{\text{H}}\}] \), where TVV is the population estimate for the apparent volume of distribution standardized to a 70-kg person using the allometric model, \( B \) is a parameter estimating the fractional volume at birth, and \( T_{1/2} \) describes the maturation half-life of the age-related changes in the apparent volume of distribution.

Differences in bioavailability of the EFV solution and suspension formulations were tested relative to the oral capsule as the reference formulation. A change in relative bioavailability with age was assessed using a sigmoid \( E_{\text{max}} \) model: \( F_{\text{solution}} \) and \( F_{\text{suspension}} \) were estimated using the model prediction in each bin in order to account for variation in sampling times and predictive covariates introduced by binning of the observations. The median and 5th and 95th percentiles of the simulated data sets were then plotted against the original observations. Bootstrapping and PC-VPC simulations were performed using Perl Speaks NONMEM (PsN) (version 3.1) (29).

RESULTS

A total of 3,172 plasma concentrations from 96 subjects were analyzed. The baseline characteristics of the subjects are shown in Table 1. A one-compartment disposition model with first-order absorption and elimination adequately described the data. A combined proportional- and additive-error model best accounted for the residual unexplained variability of the observed concentrations. Inclusion of IOV on CL/F in the model resulted in a significant reduction in the objective function value and hence was incorporated into the model. IOV of V/F, on the other hand, was minimal and hence was not added to the model.

The use of fat-free mass as a body size covariate was equivalent to the use of total body weight and did not explain more of the variability in CL/F or V/F; hence, total body weight was incorporated into the model for simplification. CL/F increased with age, reaching 90% of its mature value by the age of 9 months (Fig. 1).
The mature CL/F was estimated to be 11.2 liters/h/70 kg. Children with the CYP2B6-516-T/T genotype were found to have a CL/F 51% lower than that of the other children. No difference in CL/F was observed between CYP2B6-516-G/T and CYP2B6-516-G/G genotypes, and mixture modeling did not suggest the presence of the T/T genotype in children whose genotype information was missing. Box plots showing the relationship between interindividual variability in EFV CL/F and CYP2B6-G516T and MDR1-C3435T genotypes for both the base and final models are shown in Fig. 2.

The model suggested lower bioavailability for the oral liquid formulations than for the capsule formulation, with no difference in bioavailability between the suspension and the solution. The formulations than for the capsule formulation, with no difference in bioavailability between the suspension and the solution. The formulations were proposed as predictors of the effect of body size on PK since adipose tissue has minimal contribution to clearance and the magnitude of variability in CL/F and V/F, respectively, on drug PK. Due to the lack of information on the development or the maturation of EFV PK parameters in children, current dosing guidelines are based solely on body weight (30). This is insufficient (31–33) and contributes to the vulnerability of pediatric patients to drug toxicities, suboptimal therapy, and emergence of resistance (30).

In this study, we present a population PK model that describes the effects of growth and maturation on EFV PK in children. We used the allometric size model to characterize the influence of body size on EFV oral clearance and apparent volume of distribution due to its strong mechanistic and biological basis (34, 35). Since adipose tissue has minimal contribution to clearance and has unique distribution characteristics, different fractions of fat mass were proposed as predictors of the effect of body size on PK parameters (22). In our study, we compared the use of fat-free mass to the total body weight. Adjustment for the fat-free mass has been previously shown to improve the description of the link between size and clearance (36) and glomerular filtration rate (GFR) (37). In the current study, however, the fat-free mass was found to explain the magnitudes of variability in CL/F and V/F similar to those of the total body weight, and consequently, total body weight was used throughout the model development. This observation may be explained by the minimal amount of fat tissue in HIV-infected children in general (30).

The exponents of the allometric size models were fixed at 0.75 and 1 for clearance and volume, respectively. Fixing these parameters allowed us to overcome the strong colinearity between age and weight in pediatrics and enabled the separation of their influences on EFV PK (24). The maturation of CL/F was described using a sigmoid $E_{max}$ model. This model was successfully applied previously to examine the maturation of vancomycin clearance in

TABLE 1 Baseline characteristics of the subjects included in the analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo) [median (range)]</td>
<td>66 (2–202)</td>
</tr>
<tr>
<td>Wt (kg) [median (range)]</td>
<td>18.7 (4.8–96.4)</td>
</tr>
<tr>
<td>BSA$^a$ (m²) [median (range)]</td>
<td>0.75 (0.27–2.07)</td>
</tr>
<tr>
<td>Sex [no. (%)]</td>
<td>Male 39 (41)</td>
</tr>
<tr>
<td>Race [no. (%)]</td>
<td>Non-Hispanic, white 12 (13)</td>
</tr>
<tr>
<td></td>
<td>Non-Hispanic, black 54 (56)</td>
</tr>
<tr>
<td></td>
<td>Hispanic 28 (29)</td>
</tr>
<tr>
<td></td>
<td>Native American 1 (1)</td>
</tr>
<tr>
<td></td>
<td>Other 1 (1)</td>
</tr>
<tr>
<td>CYP2B6-G516T polymorphism [no. (%)]</td>
<td>G/G 34 (36)</td>
</tr>
<tr>
<td></td>
<td>G/T 28 (30)</td>
</tr>
<tr>
<td></td>
<td>T/T 12 (13)</td>
</tr>
<tr>
<td></td>
<td>Missing 22 (23)</td>
</tr>
<tr>
<td>MDR1-C3435T polymorphism [no. (%)]</td>
<td>C/C 31 (33)</td>
</tr>
<tr>
<td></td>
<td>C/T 33 (35)</td>
</tr>
<tr>
<td></td>
<td>T/T 7 (7)</td>
</tr>
<tr>
<td></td>
<td>Missing 25 (26)</td>
</tr>
</tbody>
</table>

$^a$ BSA, body surface area, calculated using the Mosteller formula: BSA (m²) = [height [cm] × weight [kg]/3,600]0.75.
premature neonates (25). Compared with other models that have also been used to describe maturation (26, 27, 38, 39), the sigmoid $E_{\text{max}}$ model has the distinct advantage of reaching an asymptotic mature value in older children or adults and not predicting biologically unreasonable values (22). In our study, the model predicted an increase in $CL/F$ as a function of age to reach 90% of its mature value by the age of 9 months. Interestingly, the estimates of the maturation model parameters $TM_{50,CL}$ and $H_{CL}$ are very similar to their reported estimates in the maturation models of GFR (37) and drugs that are metabolized by phase II metabolism, such as acetaminophen (22) and morphine (40). This finding may indicate some parallel maturation characteristics for drugs irrespective of their elimination routes.

The effect of age on EFV $CL/F$ in children was recently investigated using a population pharmacokinetic analysis (41). The study demonstrated a decrease in $CL/F$ by age in patients 2.8 to 14.7 years old. The maturation of hepatic metabolizing enzymes is considered to be complete by the age of 2 years, and children are considered mature from a PK perspective and primarily differ from adults only in size (42). Therefore, the decline in clearance reported in the study is unlikely to be due to age. This time trend could be explained by the use of a nonphysiologically based linear model to account for the weight effect on clearance. The increase in EFV $CL/F$ with age that is demonstrated in our study is consistent with a recent study that reported an increase in the expression of CYP2B6, the primary catalyst of EFV metabolism, with age (16). In addition, our model predicted an adult oral mature value of 11.2 liters/h/70 kg (90% confidence interval, 9.9 to 12.5) for $CL/F$, which is in close agreement with estimates from population PK studies conducted in adults, which ranged between 9.4 and 10.8 liters/h (5, 11, 12). This further supports the validity of the allometric size model and sigmoid $E_{\text{max}}$ maturation model and their potential in predicting adult PK parameters from pediatric data (24).

In accordance with our previous findings, which reported a 57% reduction in the median $CL/F$ in patients with a CYP2B6-516-T/T genotype (43), the population PK model estimated a 51% decrease in the $CL/F$ in patients with a CYP2B6-516-T/T genotype. Association between CYP2B6-G516T polymorphism and increased EFV exposure has been reported in several studies (13, 14). It has also been linked with an increased risk of EFV-associated CNS toxicities, such as dizziness, insomnia, and depression (14). Lang et al. (44) have reported a 28.6% prevalence of the CYP2B6-516-T/T genotype, but this frequency increases to 50% in African populations (45, 46). Our results provide a PK basis to investigate genotype-specific dosing for EFV, where patients with

![FIG 1 Maturation of oral clearance. The circles represent individual predicted efavirenz oral clearance standardized to a 70-kg subject. The line represents the sigmoid $E_{\text{max}}$ model used to describe the relationship between age and oral clearance.](image-url)
the fact that the maturation of the volume of distribution is usually completed within a few weeks after birth (42). Since our study cohort did not include any neonates, characterization of this physiological process was not feasible. On the other hand, we were able to describe an increase in the relative bioavailability of the oral liquid formulations compared with the capsule with age using an $E_{\text{max}}$ model. The model estimated a mature value of 0.79 for the relative bioavailability, which is consistent with studies in adults that resulted in the 20% dose increase recommended by the manufacturer when oral liquid formulations are used (48). However, the model suggests that at ages 1 and 3 years, the relative bioavailabilities are only 0.42 and 0.61, respectively, and 90% of the mature value is reached at an age of 8 years. Likewise, previous studies have estimated the relative bioavailability of the oral liquid formulations in children to be 0.47 and 0.62 (48, 49). Such low bioavailability may explain the high incidence of subtherapeutic EFV concentrations among children (17–19) and suggests the need to use oral liquid formulations at doses that are 150% of the capsule doses.

In our analysis, we did not find an association between the MDR1-C3435T polymorphism and any of the EFV PK parameters. The MDR-1 gene is the gene that codes for the cellular drug efflux pump P glycoprotein, and its expression enhances elimination and reduces drug exposure (50). This is consistent with the findings of other studies (51, 52). Haas et al. detected no association between the MDR1-C3435T polymorphism and altered efavirenz exposure, but the polymorphism was a predictor of a decreased risk for virologic failure and a lower incidence of resistance emergence (51). Moreover, an in vitro study failed to show that efavirenz is a substrate for P glycoprotein (52).

No effect of sex or race was found in our analysis of EFV CL/F. Some previous studies also showed no correlation between EFV PK and race (53) or sex (5, 12, 13, 53). This could be attributed to the insignificant differences in CYP2B6 expression between males and females (16). Other studies, however, have reported lower

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base model, original data set</th>
<th>Final model</th>
<th>Bootstrap data sets</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{TVCL} (\text{liters/h})$</td>
<td>0.86 (13)</td>
<td>0.84 (12.6)</td>
<td>0.84 (12.6)</td>
</tr>
<tr>
<td>$\text{TM}_{\text{age,CL}} (\text{mo})$</td>
<td>6.5 (6.5)</td>
<td>9.9–12.5</td>
<td>10.0–12.6</td>
</tr>
<tr>
<td>$\text{H}$</td>
<td>NA</td>
<td>3.9–5.3</td>
<td>4.6</td>
</tr>
<tr>
<td>$\text{CYP2B6} \text{T/T GT}$</td>
<td>NA</td>
<td>3.8–8.9</td>
<td>3.2–8.9</td>
</tr>
<tr>
<td>$\text{TVV} (\text{liters})$</td>
<td>0.79 (12.5)</td>
<td>0.79 (12.5)</td>
<td>0.79 (12.5)</td>
</tr>
<tr>
<td>$\text{TVF}$</td>
<td>NA</td>
<td>0.49 (11.5)</td>
<td>0.49 (11.5)</td>
</tr>
<tr>
<td>$\text{IV of CL/F (CV [%])}$</td>
<td>60.5 (10.0)</td>
<td>186.8 (8.7)</td>
<td>186.8 (8.7)</td>
</tr>
<tr>
<td>$\text{IV of V/F (CV [%])}$</td>
<td>70.5</td>
<td>30.0 (13.7)</td>
<td>30.0 (13.7)</td>
</tr>
<tr>
<td>$\text{IOV of CL/F (CV [%])}$</td>
<td>28.4–35.8</td>
<td>28.4–35.8</td>
<td>28.4–35.8</td>
</tr>
<tr>
<td>$\text{IOV of TVC (CV [%])}$</td>
<td>39.9 (32.8)</td>
<td>39.9 (32.8)</td>
<td>39.9 (32.8)</td>
</tr>
</tbody>
</table>

* CI, confidence interval; KA, absorption rate constant; TVCL, population estimate for the oral clearance, which is standardized to a 70-kg person using an allometric model in the final model; CL/F, oral clearance; $\text{TM}_{\text{age,CL}}$, age in months at which CL/F is 50% of the mature CL/F; $H$ is the Hill factor in the maturation sigmoid $E_{\text{max}}$ model for CL/F; $\text{CYP2B6} \text{T/T GT}$ is the ratio of the CL/F for subjects with $\text{CYP2B6}$-516-T/T genotype relative to the other subjects; the exponent of $\text{CYP2B6} \text{T/T GT}$ is 1 if the patient has a $\text{CYP2B6}$-516-T/T genotype or 0 otherwise; $\text{TVV}$, population estimate for the apparent volume of distribution, which is standardized to a 70-kg person in the final model; TVF, bioavailability of oral liquid formulations relative to the capsule formulation at maturity; $\text{TM}_{\text{age}}$, age in months at which relative bioavailability is 50% that of the mature value; IV, interindividual variability; IOV, interoccasion variability; CV, coefficient of variation; RSE, relative standard error; NA, not included in the base model. The residual unexplained variability in efavirenz observed concentrations was described by a proportional error of 25% and an additive standard deviation of 0.25 $\mu$g/ml.
EFV concentrations in males than in females (10, 15) and lower clearance in blacks and Hispanics than in whites (11, 12). The race effect observed in some studies could be attributed to differences in CYP2B6 genotype distributions.

After accounting for the effects of covariates on CL/F, the remaining interindividual and interoccasion variabilities in the EFV CL/F were still high (45.7 and 30.0%, respectively). Similarly high variability has been estimated in other studies, as well (4, 5, 54, 55), and could be attributed to polymorphisms in metabolizing enzymes and to the unique circumstances that hinder adherence in HIV-infected children (30). About 20- to 250-fold interindividual variability is believed to exist in CYP2B6 expression at the levels of mRNA, protein, and catalytic activity (54). In addition, polymorphisms in CYP2A6 and CYP3A4 isoforms have been recently associated with EFV interindividual variability in clearance (13). Such high variability in EFV PK may suggest the need for therapeutic monitoring of drug concentrations in order to optimize its antiviral effect and minimize its toxicity (54).

In conclusion, we have described the first population PK model that accounts for the influence of growth, maturation, and CYP2B6-G516T polymorphism on EFV PK. The model shows good internal predictability performance, and its application to

FIG 3 Diagnostic plots of the final model. Circles represent observations, and diagonal lines on the left panel represent the identity lines.
improve dosing and optimize exposure in pediatrics warrants further investigation.

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The content is solely our responsibility and does not necessarily represent the official views of the NIH.

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