Eur J Clin Pharmacol (2008) 64:357–365
DOI 10.1007/s00228-007-0412-3

PHARMACOGENETICS

High prevalence of the *CYP2B6* 516G→T(**6*) variant and effect on the population pharmacokinetics of efavirenz in HIV/AIDS outpatients in Zimbabwe

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Received: 30 August 2007 / Accepted: 6 November 2007 / Published online: 5 December 2007

Abstract
Objective The study sought to investigate the relationship between efavirenz exposure and the *CYP2B6* 516G→T(**6*) genotype in HIV/AIDS outpatients, using pharmacokinetic modelling and simulation.
Methods Blood samples where obtained from 74 outpatients treated with a combination regimen including 600 mg efavirenz daily for a duration of at least 3 weeks at clinics in Harare, Zimbabwe. The subjects were genotyped for the major *CYP2B6* variant, *CYP2B6*6*, associated with reduced enzyme activity, using a PCR-RFLP method. Efavirenz plasma concentrations were determined by HPLC-UV. Population pharmacokinetic modelling and simulation of the data were performed in NONMEM VI.
Results A high allele frequency of the *CYP2B6*6* allele of 49% was observed. Efavirenz plasma concentrations were above 4 mg/L in 50% of the patients. Genotype and sex were identified as predictive covariates of efavirenz disposition. Pharmacokinetic parameter estimates indicate that a dose reduction to 400 mg efavirenz per day is possible in patients homozygous for the *CYP2B6*6* genotype without compromising therapeutic efficacy.
Conclusion The *CYP2B6*6* allele occurs at a high frequency in people of African origin and is associated with high efavirenz concentrations. Simulations indicate that an a priori 35% dose reduction in homozygous *CYP2B6*6* patients would maintain drug exposure within the therapeutic range in this group of patients. Our preliminary results suggest the conduct of a prospective clinical dose optimization study to evaluate the utility of genotype-driven dose adjustment in this population.

Keywords Efavirenz · HIV/AIDS patients · CYP2B6 polymorphism · Pharmacokinetic modelling · NONMEM

Christopher Nyakutira and Daniel Röshammar made equal contributions to this work.

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Introduction

The use of highly active antiretroviral therapy (HAART) has been scaled up in sub-Saharan Africa during recent years and is currently recommended by WHO as a first-line treatment [1]. The HAART most countries use consists of two nucleoside analogue reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor (NNRTI). There are mainly three FDA-approved NNRTIs that are widely available: efavirenz, nevirapine, and

delavirdine [2]. Nevirapine is the most commonly used because of its effectiveness and low cost. The more expensive efavirenz, however, is finding increasing use in patients who develop severe adverse reactions to nevirapine [3–5] and in patients who are undergoing HIV/AIDS and TB co-treatment [6]. The latter practice is based on the likely drug-drug interaction between nevirapine (mainly metabolized by CYP3A4) and rifampicin (major inducer of CYP3A4) compared to between efavirenz (mainly metabolized by CYP2B6) and rifampicin. The treatment of HIV/AIDS-TB co-infections is a challenge in sub-Saharan Africa where over 60% of TB patients are also HIV-positive [7].

Efavirenz pharmacokinetics is associated with a long steady-state half-life of 40–55 h, suitable for once-a-day dosing [8]. Efavirenz was shown to induce its own metabolism [9]. This auto-inducible process was observed to give a three-fold increase in oral clearance after multiple administrations [10]. In vitro, efavirenz is primarily metabolized to 8-hydroxyefavirenz by CYP2B6, with secondary contribution from CYP3A [11]. High plasma concentrations of efavirenz have been significantly associated with the *CYP2B6* 516G→T (**6*) allele single nucleotide polymorphism (SNP), which results in a Gln-to-His amino acid change [12]. The median estimated efavirenz plasma half-lives associated with GG, GT, or TT genotypes were 23, 27, and 48 h, respectively [13]. Increased plasma concentrations and the TT genotype have also been shown to correlate with increased neuropsychological toxicity [14].

The efficacy of efavirenz has been demonstrated in several clinical trials in Caucasians [15–17] and in African patients [18–21]. Efavirenz mid-dosing interval plasma concentrations below 1 mg/L have been associated with treatment failure and may select for viral drug resistance, while concentrations exceeding 4 mg/L increase the risk of adverse neuropsychiatric effects [22]. Due to the large between-subject variability [coefficient of variation (CV) 118%] in drug concentrations, in combination with a narrow therapeutic margin, therapeutic drug monitoring (TDM) has been suggested to be clinically useful during efavirenz treatment [22]. An alternative and less costly conceptual strategy to TDM has been proposed. The target concentration approach aims to explain between-subject variability in concentrations with patient-specific factors such as creatinine clearance, age, weight and/or pharmacogenetics and to let the individually predicted pharmacokinetic parameter estimates guide dosing in order to achieve optimum drug exposure and the target effect [23]. While TDM is an empirical approach, offering no explanation why a patient is having deviating drug concentrations, target concentration intervention uses pharmacokinetic models and knowledge about the concentration-response relationship.

The aim of this study was to investigate clinical correlations of efavirenz plasma concentrations with the *CYP2B6*6* genotype in HIV/AIDS outpatients and to include *CYP2B6* genetic polymorphism as a covariate in explaining the between-subject variability, using population pharmacokinetic modelling. Findings from this study would make a case as to whether individualization of efavirenz drug therapy could be based on the patient's genotype rather than the current "one dose fits all" approach.

Materials and methods

HIV/AIDS outpatients

Seventy-four black African HIV-positive patients (26 men and 48 women, age 39±7 years, body weight 60±11 kg) assigned to receive efavirenz (600 mg, once a day) in combination with two nucleoside analogue inhibitors (73 patients were on a combination of stavudine and lamivudine and one patient on a combination of zidovudine and lamivudine) were recruited at the Wilkins and Beatrice Infectious Disease Clinics in Harare, Zimbabwe. Informed consent was obtained from all participants prior to study enrolment. The study was approved by the ethics committees at the Medical Research Council of Zimbabwe and at the Joint Parirenyatwa Hospital and College of Health Science Research, Harare.

Sampling

Samples were collected from patients who had been prescribed efavirenz for at least 3 weeks. Single blood samples were collected in EDTA, BD Vacutainer tubes (Plymouth, UK) at 11–16 h after dose administration. To support that sampling was done at steady state, 12 patients were sampled twice at a 4-week interval. After centrifugation (5 min) at 5,000 rpm, plasma was decanted and heated for 60 min at 60°C to inactivate the HIV virus. The plasma was frozen at −80°C until analyzed for drug concentrations.

Efavirenz analysis

A reversed-phase high-performance liquid chromatography (HPLC) assay was used for the determination of efavirenz steady-state concentrations. The method was validated over the range of 0.47–15 μg/mL. Sample clean-up was performed by protein precipitation of 250 μl plasma using 500 μl acetonitrile followed by centrifugation for 10 min at 20,000 *g*. A 240-μl supernatant aliquot was then diluted by adding 160 μl water, and 100 μl of the mixture was injected onto a ZORBAX C18 150 × 4.6 mm, 5-μm column set up in a HP1100 HPLC Agilent System with UV detection (247 nm).

The mobile phase was a mixture of solutions A and B in a 65:35 proportion. Both solutions A and B consisted of glacial acetic acid, acetonitrile and 25 mM ammonia acetate buffer in proportions 1:900:100 and 1:100:900, respectively. A flow rate of 1 ml/min resulted in an efavirenz retention time of 5.2 min. An external standardization method was used with drug concentration interpolated on a calibration curve (0.47–15 μg/ml) constructed from the spiked plasma standards. Analysis of chromatograms was carried out on an Agilent HP1100 HPLC System, and data acquisition and processing were performed with Chemstation Software (Agilent Technologies, Santa Clara, CA, USA). The lower limit of quantification was 0.47 μg/mL. The inter-day precision was < 8.3 CV% and the recovery ranged from 95 to 103% for low (0.75 μg/mL), intermediate (7.50 μg/mL), and high (11.25 μg/mL) efavirenz concentrations spiked into blank human plasma.

To demonstrate the stability of the samples after inactivation at 60°C, two sets of efavirenz-spiked plasma solutions at three concentration levels (0.75, 7.5, and 11.25 μg/ml) were compared; one set at room temperature (25°C) and the other set in a water bath at 60°C, the temperature used for deactivating the samples, for 1 h. There was no significant difference between the two sets.

Stability studies (freeze-thaw, autosampler, and long-term) were carried out at three concentration levels (0.75, 7.5, and 11.25 μg/ml). The stability was assessed by calculating the percent difference between the nominal concentration and the mean obtained concentration at each concentration level of the spiked samples. The maximum percent differences were found to be 4, 2.67, and 4% for freeze-thaw, autosampler, and long-term stabilities, respectively. These results are indicative of good sample stability under the various conditions used during the study.

Potentially co-administered drugs—stavudine, lamivudine, rifampicin, isoniazid, sulfamethoxazole and trimethoprim—did not chromatographically interfere with efavirenz.

*CYP2B6*6* genotyping

Patients were genotyped for *CYP2B6* 516G→T polymorphism using a PCR-RFLP method according to Rotger et al. [14]. Of the 74 HIV/AIDS patients, 71 were genotyped for the *CYP2B6*6* polymorphism. Due to a sample processing error, there was no blood available for genotyping the remaining three patients.

Pharmacokinetic modelling

Pharmacokinetic data were evaluated using population mixed effects non-linear regression modelling in NONMEM VI level 1.1 [24]. Population estimates, between-subject variability and residual errors were quantitated using the first-order conditional estimation method with interaction (FOCE-I) for all models tested during model development.

The observed concentration in the *i*th subject at any measurement *j* was modelled as a function of the vector of pharmacokinetic model parameters ϕ_i and the set of study design variables x_{ij} for this subject. The random residual error between the observed and the predicted concentration was accounted for by a slope-intercept model in terms of $\varepsilon_{\text{prop}}$ (mean 0, variance σ^2_{prop}) and ε_{add} (mean 0, variance σ^2_{add}) as expressed in Eq. (1).

$$y_{ij} = f_{ij}(\phi_i, x_{ij}) \times (1 + \varepsilon_{\text{prop},ij}) + \varepsilon_{\text{add},ij} \quad (1)$$

The vector of subject-specific model parameters was described as a function of typical population model parameters θ and of known subject-specific covariates z_i such as genotype and sex. The log-normally distributed random deviation between the typical parameter values in the population and the individual parameter estimates was expressed by the vector η_i (mean 0, variance ω^2) as can be seen in Eq. (2).

$$\phi_i = g(\theta, z_i) \times \exp(\eta_i) \quad (2)$$

During model development, single and multi-compartment pharmacokinetic structural models were tried. In order to quantitate the impact of *CYP2B6*6* genetic polymorphism on the metabolism of efavirenz, genotype was tested as a categorical covariate on efavirenz oral clearance. Other mechanistically plausible covariates (sex, body weight and age), showing any trend when plotted against the empirical Bayesian parameter estimates obtained from the base model, were included in a stepwise additive forward manner. Suggested covariates were retained in the full model if they were found to be important also after backward deletion using a stricter statistical significance criterion ($P<0.01$). For a covariate to be considered clinically relevant, it has to reduce some of the unexplained between-subject variability in the pharmacokinetic parameter. Missing genotype data records were handled by creating a missing genotype category. Clearance values in these individuals were modelled as the weighted average clearance for the GG, GT, and TT genotypes. Missing sampling times were replaced by the median sampling time (12 h). To evaluate the impact of the imputed data, the final model was rerun with the missing data excluded.

In NONMEM, maximum likelihood parameter estimates are obtained after nonlinear regression by the minimization of an objective function value (OFV) approximately equal to -2 × log-likelihood of the data. Discrimination between nested models was achieved by using the log-likelihood ratio where the difference in the OFV between the full and the reduced model is asymptotically chi-square distributed. Differences were evaluated at the $P<0.05$ and the $P<0.01$ significance levels corresponding to a reduction of 3.84 and 6.63 OFV

points, respectively, for one degree of freedom. Diagnostic goodness-of-fit plots and evaluation of parameter precision, including a comparison of estimates derived from a nonparametric bootstrap (n=200) in PsN 2.2.3 [25], were also guiding model selection. S-plus version 7.0 (Insightful, Seattle, WA, USA) was used to generate goodness-of-fit plots and other graphs. The extent of shrinkage, associated with poor individual parameter estimates, was calculated for clearance using the following equation:

$$\text{Shrinkage} = 1 - \frac{\text{SD}_{\eta\text{CL}}}{\omega_{\text{CL}}} \quad (3)$$

Where $\text{SD}_{\eta\text{CL}}$ is the standard deviation of the individual estimates of η for CL and ω_{CL} is the standard deviation of the estimated population variance. If the two values are similar, the extent of shrinkage would be low, which is desirable [26].

Dose individualization

Finally, the developed model was used to evaluate the potential for a priori dose adjustment of efavirenz in poor metabolizers. Simulations of concentration time profiles in virtual subjects (n=2,000, 50% males) were undertaken to investigate whether a dose reduction from 600 to 500, 400 or 300 mg efavirenz once daily in intermediate and/or poor metabolizers would meet a predefined clinically relevant criterion. In this case it was considered acceptable if at least 95% of patients had concentrations exceeding 1 mg/L at the mid-dose interval and if the proportion of patients reaching concentrations greater than 4 mg/L was minimized.

Results

Out of 71 genotyped patients, 30% (12 females), 44% (31 females), and 27% (19 females) were classified as extensive (GG), intermediate (GT), and poor (TT) metabolizers of efavirenz, respectively. A total of 86 concentrations from 74 patients were included in the study database. Concentrations with recorded sampling times (n=64) were available from 58 of these patients. None of the HIV/AIDS outpatients studied had efavirenz plasma concentrations below 1 mg/L, predicted to be a therapeutically effective level, but approximately 50% of the patients exhibited plasma concentrations exceeding the upper safety limit of 4 mg/L. Observed plasma concentrations grouped by sex and genotype are shown in Fig. 1. With a mean concentration ratio for the patients with two sampling occasions of 1.00 (96%CI 0.87, 1.14), efavirenz plasma concentrations appeared stable.

A modified one-compartment pharmacokinetic model with first-order absorption was fitted to the observed concentration-time data. As a best-guess model, clearance was parameterized with genotype as a predictive categorical covariate. This gave a significant decrease in the OFV (13 points), and the unexplained between-subject variability was reduced from 87 to 79%. Further, explorative plots gave evidence of a relationship between the individually

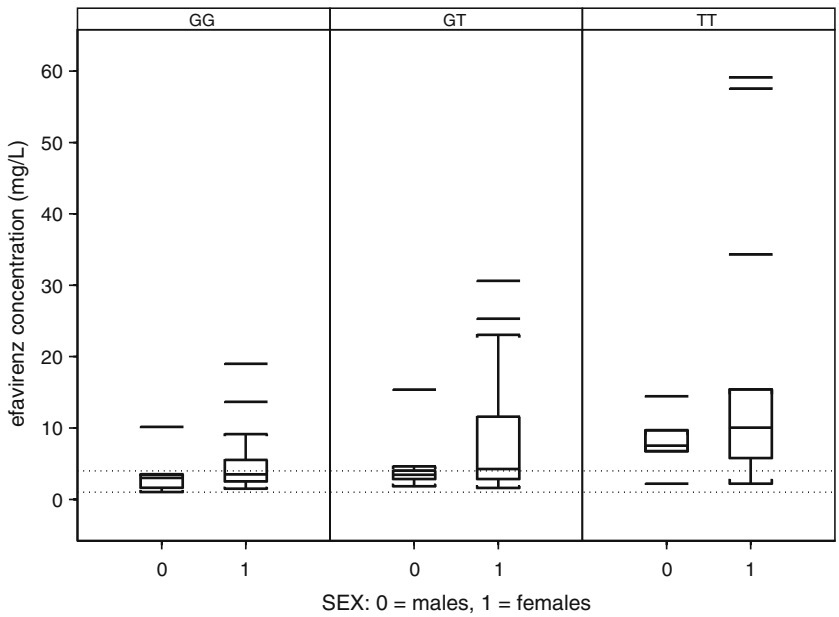

Fig. 1 Box and whiskers plot showing the observed efavirenz plasma concentrations at steady state in 71 HIV/AIDS patients of Zimbabwean origin. *GG* Extensive metabolizer, *GT* intermediate metabolizer, *TT* poor metabolizer. The *dotted horizontal lines* show the optimum concentration interval (1–4 mg/L). A total of 30% (12 females), 44% (22 females), and 27% (11 females) were classified as GG, GT, and TT genotype, respectively

Table 1 Efavirenz pharmacokinetic parameter estimates of the final model

Parameter	Mean (RSE%)	Bootstrap mean (SE)[a]
CL/F_{GG} (L/h)	9.4 (17)	9.2 (1.6)
CL/F_{GT} (L/h)	7.2 (16)	7.2 (1.2)
CL/F_{TT} (L/h)	4.0 (19)	4.0 (0.8)
CL/F_{sex}	0.70 (17)	0.72 (0.11)
V_d/F (L)	150 (98)	131 (105)
Ka (h^{-1})	0.18 (42)	0.18 (0.18)
ω_{CL} (%)	76 (19)	72 (11)
σ_{prop} (CV%)	0.12 (18)	0.11 (0.02)
σ_{add} (SD: mg/L)	0 FIX[b]	

CL/F Oral clearance, *GG* extensive metabolizer, *GT* intermediate metabolizer, *TT* poor metabolizer, CL/F_{sex} fraction expressing oral clearance in females relative to oral clearance in males, V_d/F volume of distribution, *Ka* absorption rate constant, ω_{CL} between-subject variability for clearance, σ_{prop} proportional residual error, σ_{add} additive residual error, *SE* standard error, *RSE* relative standard error (SE/mean × 100%), *CV%* coefficient of variation, *SD* standard deviation

[a] Estimates from a nonparametric bootstrap (n=200) of the final model

[b] FIX: the additive part of the residual error was set to zero in the final model because it turned out to be insignificant

predicted clearance values and sex. Inclusion of sex gave a significantly lower OFV (7 points), and the between-subject variability was reduced from 79% to 76%. Oral clearance was estimated at 9.4 (95%CI 6.2, 12.6) L/h for extensive-metabolizing men. The ratio of efavirenz clearance for intermediate- and poor-metabolizing men relative to extensive metabolizers was 0.77 (95%CI 0.46, 1.1) and 0.42 (95%CI 0.21, 0.63), respectively. Females were estimated to have a metabolizing capacity of 70% (95% CI 0.47, 0.94) compared to that in males. The magnitude of the shrinkage for clearance was 5.1%. Pharmacokinetic parameter estimates are presented in Table 1. Basic goodness-of-fit plots for the final model are shown in Fig. 2. An overall diagnostic plot, displaying the differences between the typical concentration-time profiles in the specific subpopulations, is given in Fig. 3.

Simulations of potential dose adjustments demonstrated that a reduction in the efavirenz dose from 600 to 400 mg once a day would give reduced but acceptable efavirenz exposure in poor metabolizers. In poor-metabolizing females, the dose could be further reduced to 300 mg once a day. A priori dose adjustments were not found to be achievable for intermediate-metabolizing men, but a daily dose of 500 mg would give acceptable exposure in intermediate-metabolizing females (Table 2).

Discussion

In this study, efavirenz plasma concentrations and the prevalence of the *CYP2B6*6* variant were investigated in HIV/AIDS outpatients in Zimbabwe. The results showed a prevalence of the *CYP2B6*6* allele variant of 49% and a predicted frequency of extensive metabolizers (GG) of 30%,

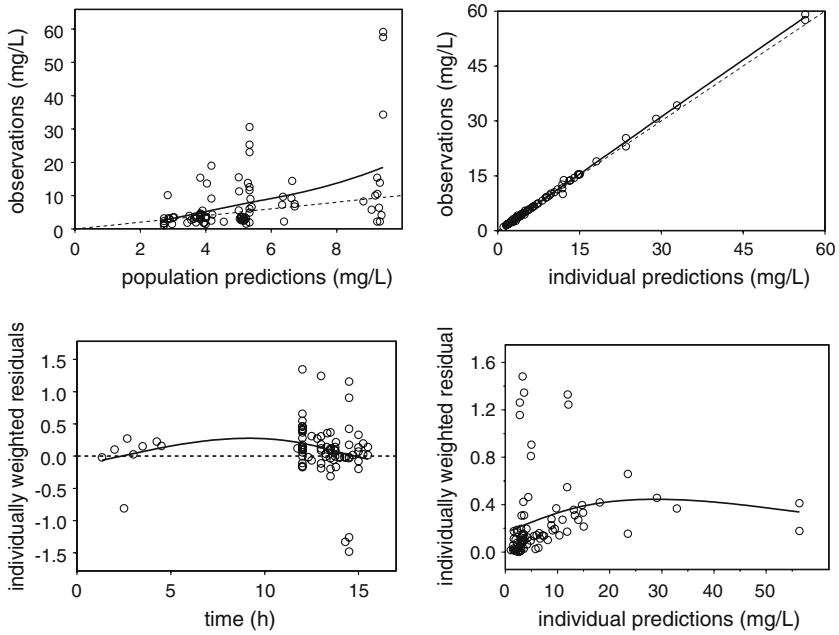

Fig. 2 Basic goodness of fit of the final efavirenz model. The predictions should match the observations. The residuals should be distributed evenly around the reference line over time and should not give a pronounced slope over the predicted concentration range. *Upper left panel* The observations are plotted versus the population predictions. *Upper right panel* The observations are plotted against the individual predictions. *Lower left panel* The individually weighted residuals are plotted versus time after dose. *Lower right panel* The absolute values of the individually weighted residuals are seen versus the individual predictions. The *dashed lines* are the lines of identity or the zero reference lines. The *solid line* is a smooth nonparametric regression line

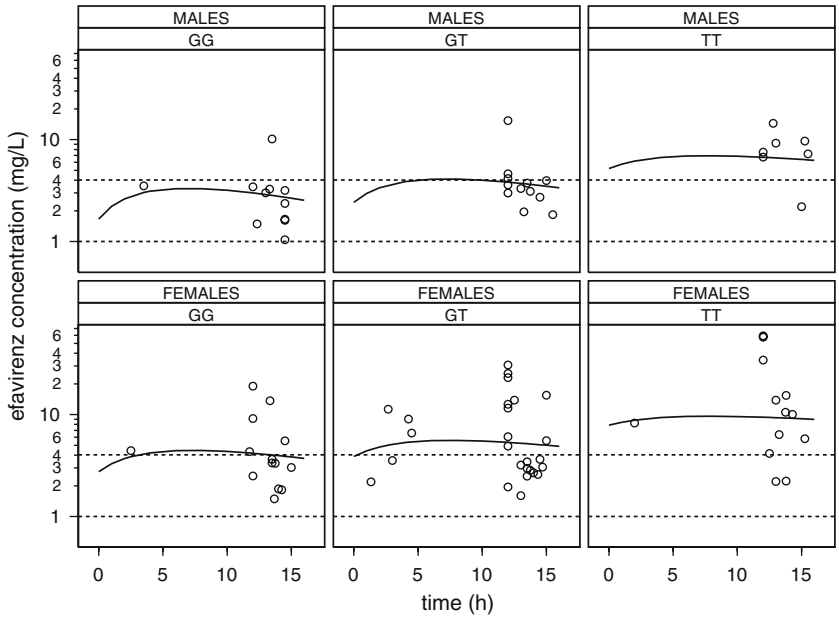

Fig. 3 Overall goodness-of-fit plot of the final model. Observed and predicted efavirenz steady-state concentrations are sorted by sex and genotype. *Open circles* are the observed concentrations. The *solid lines* are the model predictions in a typical individual. The *dashed horizontal lines* show the optimum concentration interval (1–4 mg/L). Note that concentrations without recorded sampling times are imputed at 12 h

intermediate metabolizers (GT) of 44%, and poor metabolizers (TT) of 27%. There was an association between high efavirenz clinical concentrations and the poor metabolizer genotype. In addition, women were shown to have higher efavirenz plasma concentrations compared to men irrespective of genotype. Pharmacokinetic modelling of the data demonstrated the predictive value of including both sex and genotype data as covariates in the model to explain the between-subject variability of efavirenz exposure.

The high frequency of approximately 50% of the *CYP2B6*6* mutation in the outpatients is in agreement with population genotype data showing that the low-activity *CY2B6*6* variant is more prevalent in people of African origin compared to Caucasians and Asians [10, 12, 27, 28]. Our finding that women have high plasma concentrations is also in agreement with previous reports that females appear to be more susceptible to efavirenz adverse drug reactions [29]. Furthermore, females have also been seen to have a higher discontinuation rate of efavirenz therapy [30]. The reason for the metabolic difference between men and women is however still not known. A recent study has shown that women of Hispanic origin have increased CYP2B6 metabolic capacity compared to women and men of African and Caucasian origin [31]. This difference was

Table 2 Simulated treatment outcomes[a] after adjusted dosing strategies in poor, intermediate and extensive efavirenz metabolizers

Genotype	Dose (mg)	All patients		Males		Females	
		% Patients Css > 4 mg/L	% Patients Css < 1 mg/L	% Patients Css > 4 mg/L	% Patients Css < 1 mg/L	% Patients Css > 4 mg/L	% Patients Css < 1 mg/L
Poor metabolizers	600	77	0.8	72	1	85	0.5
	500	69	1.2	62	1.8	79	0.9
	400	59	2.2	51	3.6	68	1.3
	300	45	5.5	37	7.1	54	2.8
	200					34	8.2
Intermediate metabolizers	600	50	4.4	42	5.3	60	2.4
	500	42	6.5	32	8.7	51	3.6
	400	31	10.3			39	6.1
Extensive metabolizers	600	37	7.6	27	10.6	46	4.3
	500	29	11.3	21	15.4	38	7.0

Css Efavirenz steady-state plasma concentration at the mid-dose interval
[a] Percentage of 2,000 virtual patients (50% males)

attributed to some SNPs in the regulatory regions of *CYP2B6* resulting in Hispanic women having more CYP2B6 mRNA, protein, and enzyme activity compared to males and females of African and Caucasian origin. So, in addition to the need to genotype for other SNPs associated with CYP2B6 reduced activity [32], there is need to genotype for SNPs in the regulatory region that might explain gender differences in *CYP2B6* expression and activity.

Several reports have described the impact of race on efavirenz metabolism. Ethnic differences in plasma drug exposure has been observed [33]. Burger et al. identified race as a predictive factor with consistently higher efavirenz plasma concentrations in non-Caucasian patients [27], and lower clearance values were predicted in Asian and black relative to Caucasian subjects [10]. The relationship between *CYP2B6*6* genotype and efavirenz pharmacokinetics has been described in several studies [12, 13]. However, genetic polymorphism has, to our knowledge, never been included as a covariate in a pharmacokinetic model explaining the between-subject variability in efavirenz exposure.

In this study, which is the first report describing the population pharmacokinetics of efavirenz in an African population, as many as 50% of the patients were exposed to efavirenz plasma concentrations associated with risk for adverse reactions but none had suboptimum exposure. The data therefore clearly demand a redress of the clinical dosing of efavirenz in HIV/AIDS patients in Zimbabwe. To explain the between-subject variability in efavirenz disposition and to evaluate the impact of seemingly important covariates, we carried out population pharmacokinetic modelling of the data. After inclusion of *CYP2B6* genotype and sex, the typical extensive metabolizer was identified to have a two-fold faster oral clearance than the typical poor metabolizer and the typical female patient only 70% of the metabolic capacity compared to the typical male patient.

Due to the large between-subject variability, the effects may be smaller or even greater in the individual patient, as is evident from Fig. 3. Still, the remaining unexplained between-subject variability (76%) is considerable in comparison with the effects of sex and genotype on efavirenz pharmacokinetics. Some of this variability can potentially be reduced by considering any interference of co-medication and drug-drug interactions involving the expression and/or activities of CYP2B6 and CYP3A4, enzymes involved in the metabolism of efavirenz [37]. Unfortunately the use of concomitant medication was not recorded in the present study, but participants in this study were also taking anti-TB drugs, including rifampicin, which is known to be an inducer of CYP3A4 to a major extent and CYP2B6 to a lesser extent.

Post-dose times were based on trust that the participants were all taking their medication at the stipulated time, which could be another source of unexplained variability. Other potential factors affecting efavirenz pharmacokinetics include plasma-protein binding and other pharmacogenetic polymorphisms.

Model parameter estimates expressing oral clearance values were in general well estimated. The estimate in extensive-metabolizing men was in agreement with what has been previously observed in other populations [10, 33–35]. On the contrary, the absorption rate constant and the volume of distribution (V/F) were estimated with a higher level of uncertainty. This may arise from the fact that sparse sampling at steady state was employed. Essentially only one sample was collected from each patient, and few samples were taken during the early concentration-time profile. However, a sensitivity analysis performed with various fixed values of the absorption rate constant and the volume of distribution resulted only in marginal changes in the estimation of clearance and did not alter the OFV. The volume of distribution and absorption rate constant were similar to estimates reported in previous population pharmacokinetic analyses [10, 33–35]. Sparse or uninformative data may also cause the empirical Bayes estimates to shrink towards the mean [26], which can lead to falsely included covariates or failure to identify true covariates. In the present analysis we did not observe any substantial shrinkage for the clearance parameter.

Simulation of clinical trials is a powerful predictive tool and has been shown to be useful for optimum dose selection, optimization of study design and for hypothesis-generating purposes [36]. In the present analysis, we sought to simulate possible dose adjustments by genotype and sex. Simulations assessed that a reduction in the dose in poor metabolizers would maximize the percentage of patients reaching target plasma concentrations without compromising the therapeutic efficacy of efavirenz therapy. An a priori dosing regimen of 400 mg once a day would be a suitable initial dose adjustment in these patients. Based on feedback observations, further dose individualization is possible in each individual if required. Since the upper bound of the 95% CI describing sex differences is close to 1, no specific dose adjustments are proposed for females although simulations suggested that dose reductions to 500 and 300 mg are feasible for intermediate- and poor-metabolizing females, respectively.

In conclusion, modelling and simulation are important tools in pharmacogenetically guided optimization of pharmacotherapy. Understanding the effect of *CYP2B6* pharmacogenetic variability on the population pharmacokinetics of efavirenz can assist in adopting a priori individualized efavirenz dosage in routine clinical care. The possibility of individualizing efavirenz dosage in poor metabolizers should ultimately be confirmed in combination with pharmacodynamic variables in directed prospective clinical trials.

Acknowledgements We are grateful to the Wilkins and Beatrice Infectious Disease Clinics for assistance with sample collection. We are grateful to AstraZeneca, Mölndal, DMPK Development Section and Dr. Xueqing Li for hosting Christopher Nyakutira for a 3-month bioanalytical training. Emmanuel Chigutsa is a recipient of a master's fellowship from the International, Clinical and Operational Health Services Research Training Award (ICOHRTA) for AIDS and TB. Tafadzwa Mhlanga's assistance with the *CYP2B6*6* genotyping work is also acknowledged.

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