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ORIGINAL RESEARCH ARTICLE

A Mechanism-Based Population Pharmacokinetic Analysis Assessing the Feasibility of Efavirenz Dose Reduction to 400 mg in Pregnant Women

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Abstract

Background Reducing the dose of efavirenz can improve safety, reduce costs, and increase access for patients with HIV infection. According to the World Health Organization, a similar dosing strategy for all patient populations is desirable for universal roll-out; however, it remains unknown whether the 400 mg daily dose is adequate during pregnancy.

Methods We developed a mechanistic population pharmacokinetic model using pooled data from women included in seven studies (1968 samples, 774 collected during pregnancy). Total and free efavirenz exposure (AUC_{24} and C_{12}) were predicted for 400 (reduced) and 600 mg (standard) doses in both pregnant and non-pregnant women.

Results Using a 400 mg dose, the median efavirenz total AUC_{24} and C_{12} during the third trimester of pregnancy were 91 and 87% of values among non-pregnant women, respectively. Furthermore, the median free efavirenz C_{12} and AUC_{24} were predicted to increase during pregnancy by 11 and 15%, respectively.

Conclusions It was predicted that reduced-dose efavirenz provides adequate exposure during pregnancy. These findings warrant prospective confirmation.

Key Points

Reduced-dose efavirenz (400 mg) is non-inferior to standard-dose efavirenz (600 mg) for HIV treatment and may be less toxic. Pregnancy impacts efavirenz pharmacokinetics, however the question remains as to whether efavirenz exposure at the reduced dose is adequate for pregnant women?

Pregnancy is associated with a minimal decrease in total efavirenz exposure, but predicted free (pharmacologically active) exposure is not decreased.

Reduced-dose efavirenz likely provides adequate efavirenz exposure during pregnancy.

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1 Introduction

In the past 20 years, the development of effective and safe interventions for the prevention of mother-to-child transmission (PMTCT) of HIV-1 has been one of the great successes in global and public health [1]. World Health Organization (WHO) antiretroviral treatment guidelines currently recommend lifelong treatment for all pregnant and breastfeeding women living with HIV [2]. In parts of the world where HIV is most prevalent, the antiretroviral drug efavirenz is a key component of antiretroviral treatment and PMTCT of HIV due to its excellent antiviral potency, long-term efficacy, once-daily dosing, generic availability, and substantial data demonstrating its efficacy and safety during pregnancy [3].

To date, the standard efavirenz 600 mg dose has been approved by regulatory authorities such as the US FDA, and recommended by major HIV treatment guidelines [4, 5]; however, there has been global interest in reducing the standard efavirenz dose, in part to avoid drug toxicities but largely to reduce cost [6]. A 33% dose reduction may translate into 3-year cost savings of up to US$336 million [7], which could be critical in the efforts to advance universal access to antiretroviral therapy for HIV-infected individuals. The ENCORE1 study was performed to assess the efficacy of a reduced-dose of efavirenz (400 mg once daily) versus standard of care (600 mg once daily). In this study, conducted in non-pregnant, treatment-naive adults, reduced-dose efavirenz was non-inferior to the standard dose in terms of virologic response [8].

Lower efavirenz doses will inevitably lead to lower efavirenz exposures. Efavirenz mid-dose interval (MDI) concentrations lower than 0.7–1 mg/L have been associated with virological failure [9, 10]. Although the reductions in exposure seen with efavirenz 400 mg once daily versus 600 mg were not clinically important in non-pregnant adults, the pharmacokinetics of antiretroviral drugs may be altered, leading to a higher risk of subtherapeutic exposures in that population [11]. In turn, this may lead to treatment failure, emergence of drug-resistance, and mother-to-child transmission of HIV [11]. Thus, it is essential to get drug dosing right in pregnant women. For example, efavirenz is highly albumin bound (>99%) and primarily metabolized by the hepatic cytochrome P450 (CYP) 2B6 enzyme [4]. Consequently, pregnancy-induced alterations in plasma albumin concentrations or hepatic enzyme activities could change the pharmacokinetics [12]. In fact, several studies have investigated the impact of pregnancy on the pharmacokinetics of efavirenz 600 mg once daily. Although most studies found reduced efavirenz exposure during pregnancy compared with postpartum for the 600 mg regimen, the reductions were modest and unlikely to be clinically relevant [13–15]; however, to date no studies have been conducted to assess the adequacy of drug exposures with a 400 mg dose in pregnancy.

The WHO strives to recommend a limited formulary of preferred treatment options that is applicable across all patient populations, and this knowledge gap regarding low-dose efavirenz pharmacokinetics during pregnancy is an important barrier towards universal roll-out of reduced-dose efavirenz [6]. As it is pivotal to bridge this knowledge gap, we performed a mechanistic pharmacokinetic analysis of efavirenz in pregnant and non-pregnant women to assess the adequacy of efavirenz exposure when reducing the efavirenz dose.

2 Methods

2.1 Pharmacokinetic Data

Data from six studies (studies 2–7; Table 1) that included HIV-positive subjects taking efavirenz were pooled [13, 14, 16–19]. Only data from women were retained for further analysis. Data from non-pregnant women were added first to evaluate the general structural and stochastic aspects of the model, and data from pregnant women were then added to incorporate the pregnancy-related covariate effects into the model. At each step, the structural model was re-evaluated and the effect of pregnancy was implemented and investigated. Data from study 1 were used for external model evaluation.

In total, 1968 plasma samples from 258 women were available. Of these women, 116 were only sampled when the patient was not pregnant. For the remaining 142 women, samples were available when the patient was pregnant and not pregnant (postpartum). Overall, 774 samples were taken during pregnancy (Table 1). In these samples, total plasma concentrations were determined. Women using potentially interacting concomitant medicines (e.g. rifampicin or isoniazid) were excluded [14]. All except five of the patients included received the standard efavirenz 600 mg once-daily dose. Patient characteristics for each study are summarized in Table 1.

2.2 Mechanistic Information Used for Pharmacokinetic Modeling

Based on a review of published efavirenz pharmacokinetic data and relevant pregnancy-related changes in physiology, we took into account the following considerations and made the following decisions prior to the modeling process. This was prespecified in an analysis plan that was circulated to all coauthors involved.

Table 1 Patient and study characteristics summarized by study [reference]

	Study 1 [50]	Study 2 [18]	Study 3 [17]	Study 4 [19]	Study 5 [13]	Study 6 [16]	Study 7 [14]
Number of patients	14	1091	25	172	25	27	97
Number of patients included	11	129	7	14	25	26	46
Number of samples							
Pregnant	110	NA	NA	NA	224	317	123
Not pregnant	109	541	77	23	199	199	46
Median gestational age at sampling times, years (range)	34 (32–36)	NA	NA	NA	34 (29–38)	29 (21–37)	37 (33–39)
Sampling design (hours postdose)	Rich crossover: 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 12, 24	Sparse: mid-dose	Rich: 0 (predose), 1, 2, 3, 4, 6, 8, 10, 12, 16, 24	Sparse: mid-dose	Rich crossover: 0 (predose), 1, 2, 4, 6, 8, 12, 24	Rich crossover: 0 (predose), 1, 2, 4, 6, 8, 12, 24	Sparse crossover: mid-dose
Lower limit of quantification (mg/L)	0.05	0.05	0.05	0.01	0.03	0.03	0.02
Median weight (range)							
Second trimester	NA	NA	NA	NA	78 (69–89) [n = 3]	83 (54–129) [n = 14]	NA
Third trimester	69 (45–124) [n = 11]	NA	NA	NA	69 (40–130) [n = 25]	80 (55–128) [n = 25]	72 (52–112) [n = 33]
Not pregnant	76 (50–132) [n = 11]	60 (40–100)	53 (46–64)	60 (49–71)	63 (37–125) [n = 25]	74 (47–126) [n = 26]	67 (42–105) [n = 39]
CYP2B6 phenotype	Not determined	Not determined	Not determined	Not determined	Not determined	Not determined	1 not determined
Poor metabolizer							10
Intermediate metabolizer							25
Extensive metabolizer							26
Efavirenz dose, mg	600	600	600	600 (300 mg, n = 1; 400 mg, n = 1)	600 (800 mg, n = 3)	600	600
Population	100% Black	Mixed international (Thailand, South Africa, South America, Western Countries)	100% Black	100% Caucasian	84% Thai, 16% Caucasian	56% Hispanic, 4% unknown, 40% non-Hispanic	100% Black

NA not available, *CYP* cytochrome P450

To account for the relationship between hepatic systemic and first-pass metabolism, we implemented a well-stirred liver model (Eqs. 1, 2) [20].

$$CL_{hep}/F = Q_{hep,plasma} \times E_h \quad (1)$$

$$E_h = \frac{CL_{int,hep} \cdot f_u}{Q_{hep,plasma} + CL_{int,hep} \cdot f_u} \quad (2)$$

Apparent hepatic clearance (CL_{hep}/F; F = bioavailability) is expressed as a function of hepatic plasma flow ($Q_{hep,plasma}$) and hepatic extraction ratio (E_h). E_h is defined as a function of apparent intrinsic hepatic clearance ($CL_{int,hep}/F$), and fraction unbound (f_u). With regard to $CL_{int,hep}/F$ (i.e. enzyme pool), CYP2B6 genetic polymorphisms have a clinically relevant impact on the extent of efavirenz biotransformation [21]; therefore, we assumed three subpopulations (metabolic phenotypes): poor metabolizers (PMs), intermediate metabolizers (IMs), and extensive metabolizers (EMs). If data on an individual CYP2B6 genotype (CYP2B6 516G → T and 983T → C) were available, the women were assigned to a subpopulation based on a classification proposed previously: EMs (no variant allele at 516 or 983), IMs (single variant allele at position 516 or 983), slow metabolizer (two variant alleles, i.e. 516 TT, 983 CC, or 516 GT plus 983 TC), or very slow metabolizer (two variant alleles at position 983). Further details can be found in the study by Dooley et al. [14]. Additionally, pregnancy can induce enzymatic pathways, but the available evidence was not sufficiently convincing to *a priori* assume pregnancy-related induction of CYP2B6 [22].

Since efavirenz is highly albumin-bound (> 99%), changes in albumin plasma concentrations can result in relatively large differences in f_u and, consequently, CL_{hep}/F [23]. This has been previously observed for other drugs [24]. Another known factor affecting CL_{hep}/F during pregnancy is an increased $Q_{hep,plasma}$, which is related to a decrease in hematocrit (Ht) during pregnancy [22]. Additionally, cardiac output is higher during pregnancy, potentially translating into an increased hepatic blood flow (Q_{hep}). However, based on the current body of literature, we could not describe the magnitude or relevance of changes in Q_{hep} during pregnancy and therefore this was not included and fixed to the literature values (109 L/h) for non-pregnant women [22, 25]. A pregnancy-induced increase in $Q_{hep,plasma}$ (Eq. 3) and decrease in f_u (Eq. 4) were included a priori using the following relations:

$$Q_{hep,plasma} = (1 - Ht) \cdot Q_{hep}, \quad (3)$$

$$f_u = \frac{k_D}{(k_D + [P])}. \quad (4)$$

Efavirenz protein (albumin)-binding dissociation constant (k_D) was fixed to the in vitro literature value, 2.05 μM [23]. For efavirenz, the range of free concentrations encountered in vivo is much lower than the k_D [26], implying linear binding and an f_u independent of the free efavirenz concentration [27]. Polynomial relations describing the relationship between gestational age (GA) and albumin concentrations (P) (Eq. 5), as well as Ht (Eq. 6), were used to predict pregnancy-induced changes in f_u and $Q_{hep,plasma}$, respectively, on a population level [22, 26].

$$[P(\mu M)] = \frac{(45.8 - 0.1775 \cdot GA - 0.0033 \cdot GA^2)}{0.07} \quad (5)$$

$$[Ht(v/v\ \%)] = 39.1 - 0.0544 \cdot GA - 0.0021 \cdot GA^2 \quad (6)$$

2.3 Population Pharmacokinetic Analysis

Data were analyzed using NONMEM® 7.3.0 (ICON Development Solutions, Hanover, MD, USA). The first-order conditional estimation method was used with eta–epsilon interaction. We used Pirana 2.9.1 (http://www.pirana-software.com) as an interface for NONMEM to structure and document model development [28]; R v3.2.2 (with Rstudio interface v1.0.136) for data preparation, and graphical visualization and evaluation; and PsN 4.6.0 for automation of a diverse range of processes related to model development [29].

Several population pharmacokinetic models have been developed for efavirenz but most were purely empirical and not based on data from pregnant women. A model previously developed by Dooley et al. [14] was both semi-mechanistic and based on data from pregnant women, hence this model was suitable as a starting point for further development. We tested one- to three-compartmental distribution. Models tested to describe absorption included zero- and first-order processes and implementation of transit compartments to describe a gradual onset of absorption. The transit rate constant (k_{tr}) for the transit compartments was estimated and the mean absorption time (MAT) was calculated based on Eq. 7:

$$k_{tr} = (n + 1)/MAT \quad (7)$$

where n equals the number of transit compartments [30]. Because no data were available that allowed estimation of absolute bioavailability, the typical value of bioavailability was fixed to 1. For the estimation of model parameters, we assumed log-normal distributions for the interindividual variability (IIV) and interoccasion variability (IOV) according to Eq. 8:

$$\theta_i = \theta \cdot e^{(\eta_i)} \quad (8)$$

where θ_i is the individual parameter value, θ is the typical population value, and η_i is the random effect drawn from a normal distribution with mean 0 and variance ω^2.

Correlations between random effects were evaluated and included when identifiable and substantial (> 30%). Each occasion was defined as a pharmacokinetic assessment visit, ranging from 1 to 6 assessments per individual. Different residual error models with additive, proportional, and combined error structures were tested.

To account for body-weight-induced changes in pharmacokinetics a priori, all flow parameters and volumes were scaled to a total non-pregnant body weight of 70 kg according to allometric theory. The allometric exponents were fixed to 3/4 for flow parameters and 1 for volumes of distribution [31, 32].

2.4 Structured Covariate Analysis

Pregnancy was tested as a covariate (dichotomous) on all estimated model parameters (CL_{int}/F, V_c/F, Q, V_p/F, MAT, and F) using a forward inclusion and backward elimination approach. The covariate selection was based on scientific and physiological plausibility and on maximum likelihood statistics (quantified by the objective function value [OFV]), with a 5% significance level (dOFV > -3.84) applied for likelihood ratio testing of nested models. Backward elimination was based on a 1% significance level (dOFV > -6.64). The Akaike information criterion was used for comparison of non-nested models.

2.5 Handling of Missing Covariates and Data Below the Lower Limit of Quantification

Only one study included data for participant height. Consequently, we did not explore and test the relation between model parameters and body size descriptors other than weight (e.g. fat-free mass). Data on the CYP2B6 genotype in our population were limited (18%). In case of a missing CYP2B6 genotype, a mixture model was implemented to account for the multimodal distribution of CL_{int}/F as a result CYP2B6-related phenotypes: PMs, IMs, and EMs. Subjects with missing genotype data were assigned to the mixture (subpopulation) with the highest individual probability [33, 34]. The number of plasma concentrations below the lower limit of quantification (LLOQ) for each individual study was very low (< 1%) and hence these data were ignored.

2.6 Model Evaluation and Qualification

We evaluated precision in parameter estimates and standard goodness-of-fit plots. For the final model, parameter uncertainty was obtained from the default covariance step in NONMEM, as well as the sampling importance resampling (SIR) procedure [35]. To further evaluate and qualify the model for simulation, we used prediction corrected visual predictive checks (pcVPC) [36]. In the case of a model including a mixture, prediction correction cannot be performed in a standard way since there can only be one population prediction for each subpopulation to which the subject can be assigned. To account for this, we employed a strategy previously proposed for nevirapine [36]. Additionally, we conducted an external model evaluation to further qualify the developed model. External model performance was visually evaluated based on pcVPC, and statistically based on the observations normalized prediction distribution errors (NPDE), under the null hypothesis that the model developed based on studies 2–7 adequately describes the data from study 1, i.e. the NPDE follow an $N(0,1)$ distribution. This hypothesis was tested based on three statistics as proposed by Brendel et al.: (1) Student's t test for the mean; (2) Fisher's test for variance; and (3) Shapiro–Wilks test for the distribution [37, 38].

2.7 Simulation

The final model was used to simulate efavirenz concentrations for women during the third trimester of pregnancy, as well as non-pregnant women. The third trimester of pregnancy was chosen since the risks of mother-to-child transmission are highest during late pregnancy and labor [39]. In addition, absolute differences in pharmacokinetics are expected to be highest during the third trimester. Simulations (500×/phenotype) were performed for efavirenz 400 and 600 mg once daily, assuming linear pharmacokinetics over this dosing range [4]. Bodyweights used for simulation were randomly drawn from a log-normal distribution with geometric mean ± geometric standard deviation (SD) of 62 ± 1.3 kg, based on the distribution found in our data. GA during the third trimester of pregnancy was drawn from a normal distribution with a mean ± SD of 34 ± 2.3 weeks, based on the distribution found in our data. Secondary steady-state pharmacokinetic parameters of total concentrations at steady state (AUC_{24} and C_{12}) were derived, and the C_{12} were then compared with the suggested mid-dose target concentrations for efavirenz pharmacotherapy, i.e. 1 and 0.7 mg/L [9, 10].

Additionally, we explored the predicted free efavirenz plasma AUC_{24} and C_{12} as these parameters are a better proxy for the pharmacologically active concentration at the site of action and are not biased by pregnancy-induced changes in drug-protein binding [40]. This was carried out using the predicted (concentration-independent) f_u based on GA and the model predicted individual total efavirenz plasma concentration (C_{tot}), using Eq. 9:

$$C_{free} = f_u \times C_{tot}. \quad (9)$$

To evaluate the free efavirenz C_{12}, the therapeutic target of 0.7 mg/L was multiplied by the predicted f_u in the non-

pregnant population, providing a free efavirenz target plasma concentration of 0.002 mg/L.

3 Results

In addition to the well-stirred liver model, a two-compartment disposition model with first-order elimination and absorption through three absorption transit compartments best described the data (Fig. 1). IIV was included for CL_{int}/F (ΔOFV −52) and MAT (ΔOFV −51). The associated correlation was minor (6%) and was not included. IOV was included for F (ΔOFV −63). The inclusion of IOV for other pharmacokinetic parameters led to over-parameterization and model instability. The residual error structure was proportional. We explored separate error models (also for different studies), but the changes were minor and neither resulted in changes in parameter estimates nor improved residual versus prediction goodness-of-fit plots; hence this strategy was abandoned. Overall, no indication of bias was observed.

Initially, the mixture population frequencies were estimated. This led to model instability, and stochastic simulation and estimation showed that the population frequencies of the mixture could not be numerically identified. Therefore, population frequencies were fixed to 14, 36 and 50% for the PMs, IMs and EMs, respectively, based on the available data on race or region (Table 1) combined with reported prevalence of the CYP2B6 genotypes in these races/regions in several studies (c.516G > T) [ΔOFV −309; $p < 0.001$] [41–43]. Efavirenz has properties related to auto-induction, but this could not be identified because almost all data available contained information at steady-state only [4]. Final population estimates are shown in Table 2.

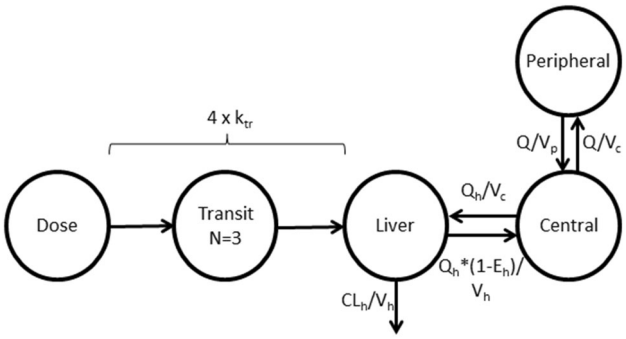

Fig. 1 Final structural model. Efavirenz is absorbed through three transit compartments into the liver compartment, based on four identical first-order rate constants. For the first pass through the liver, a fraction of the efavirenz amount is extracted and cleared, and the fraction of the amount remaining reaches the systemic circulation and becomes available for redistribution into the peripheral compartment. Efavirenz recirculates from the central compartment to the liver with a flow equivalent to liver plasma flow, and at each pass the liver extracts a further fraction. k_{tr} first-order rate constant, E_h fraction of efavirenz extracted, Q_h liver plasma flow, N number of transit compartments, CL_h hepatic clearance, Q intercompartmental clearance, V_h, V_c and V_p volume of ditribution of the liver, central and peripheral compartments, respectively

Based on the fixed mechanistic relations that we incorporated a priori, the pregnancy-related decrease in albumin concentration over GA led to an increase in the fraction of unbound efavirenz. This relationship is graphically presented in electronic supplementary material (ESM) 2. In turn, this led to an increased apparent hepatic efavirenz clearance over GA. The a priori implementation of this relationship was accompanied by a ΔOFV of −53. With univariate testing of pregnancy on the pharmacokinetic parameters, associations were found for V_c (ΔOFV −22; $p < 0.001$), F (ΔOFV −15; $p < 0.001$), and MAT (ΔOFV −35; $p < 0.001$). Forward inclusion and stepwise elimination led to the inclusion of parameter–pregnancy relationships for MAT and F (total ΔOFV −49; $p < 0.001$). Further details can be found in ESM 2.

Standard goodness-of-fit plots of the final model indicated no bias in the structural model, or unaccounted heterogeneity in the data (Fig. 2). A pcVPC stratified for pregnancy based on 500 samples is shown in Fig. 3. The pcVPC indicated that the model has internal predictive value in terms of both structural and stochastic model components. The pcVPC stratified for pregnancy based on 500 samples for the external model evaluation indicated that the model developed based on the data from studies 2–7 adequately described the data from study 1. This was further supported by the evaluation of the observations NPDE based on 2500 samples, as the null hypothesis (an $N(0,1)$ distribution) could not be rejected based on the three statistics specified in the Methods section, using a 10% significance level ($p > 0.1$; pcVPC and NPDE diagnostic plots are shown in ESM 1). This indicated that besides internal predictive performance, the developed model has adequate external predictive performance, and, altogether, qualified the model for further use in the simulation phase of this study. An a posteriori power evaluation using Monte Carlo Mapped Power (available in PsN), based on the number of paired (pregnant versus non-pregnant) observations available in our dataset, indicated > 80% power to detect pregnancy covariate effects (≥ 20%) for all structural model parameters, except those associated with the peripheral compartment (data not shown) [44].

The simulated total efavirenz steady-state pharmacokinetic parameters (AUC_{24} and C_{12}) following oral administration of efavirenz 600 and 400 mg once daily are shown in Table 3, stratified for pregnancy as well as metabolizer status. During the third trimester of pregnancy, the median AUC_{24} and C_{12} across all phenotypes were 91 and 87%, respectively, when compared with non-pregnant women.

Table 2 Final parameter estimates

Parameter	Parameter estimate	RSE (%)	RSE (%) from SIR
MAT (h)	2.12	7	7
MAT (h) in pregnant women	1.67	2	4
CL_{int}/F (L/h)[a]			
Poor	1380	6	7
Intermediate	3340	8	6
Extensive	4580	6	5
V_c/F (L)[a]	133	7	6
V_p/F (L)[a]	390	5	6
Q/F (L/h)[a]	35	7	7
F (%) relative to non-pregnant women	116	5	4
IIV CL_{int}/F (%)	32	7	14
IIV MAT (%)	44	8	15
IOV F (%)	24	4	12
Proportional residual error (%)	18	1	5

MAT mean absorption time (three transit compartments), CL_{int}/F intrinsic clearance, V_c/F central volume of distribution, V_p/F peripheral volume of distribution, Q/F intercompartmental clearance, F relative bioavailability, *IIV* interindividual variability, *IOV* interoccasion variability, *SIR* sampling importance resampling, *RSE* relative standard error

[a]The data refer to a typical individual of 70 kg

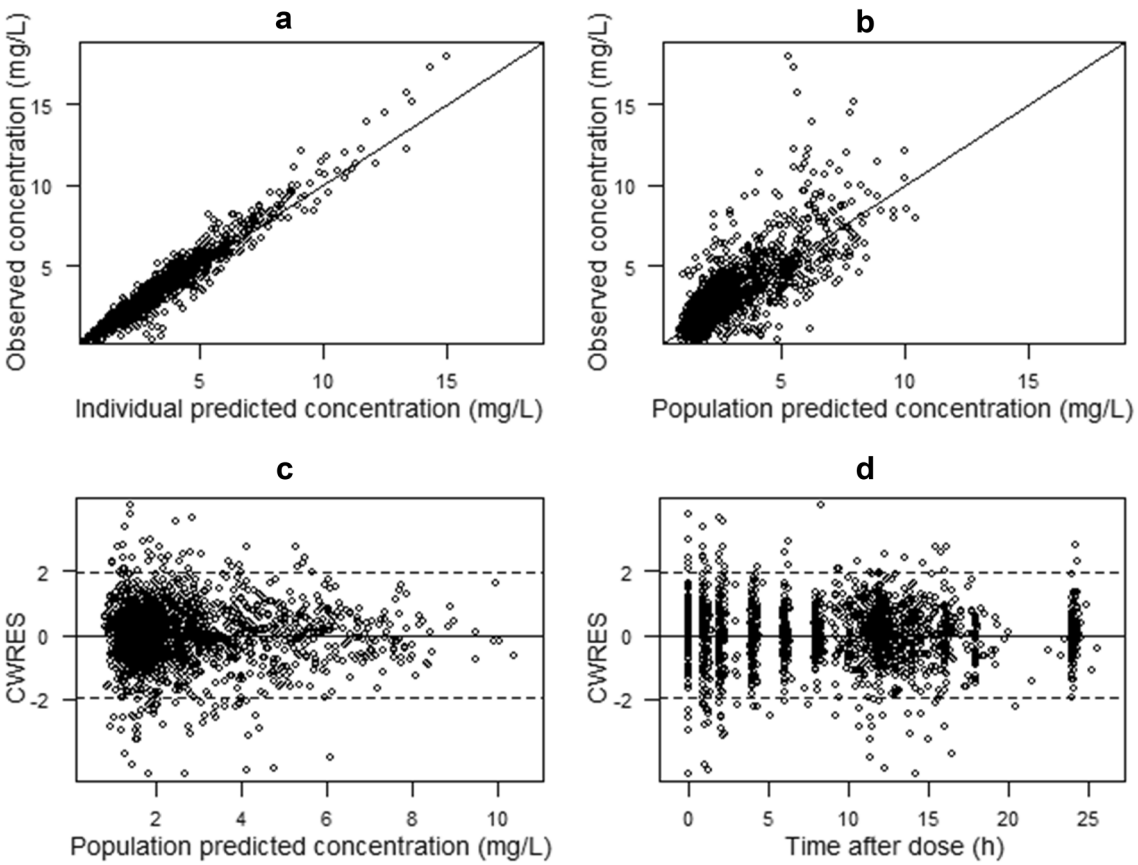

Fig. 2 Standard goodness-of-fit plots for the final model. **a** Observed concentration versus individual-predicted concentration around the line of unity. **b** Observed concentration versus population-predicted concentration around the line of unity. **c** CWRES versus population-predicted concentrations. **d** Conditional weighted residual versus time after dose. The dotted lines represent the 95% limits of the assumed CWRES distribution (i.e. 0 ± 1.96). *CWRES* conditional weighted residual

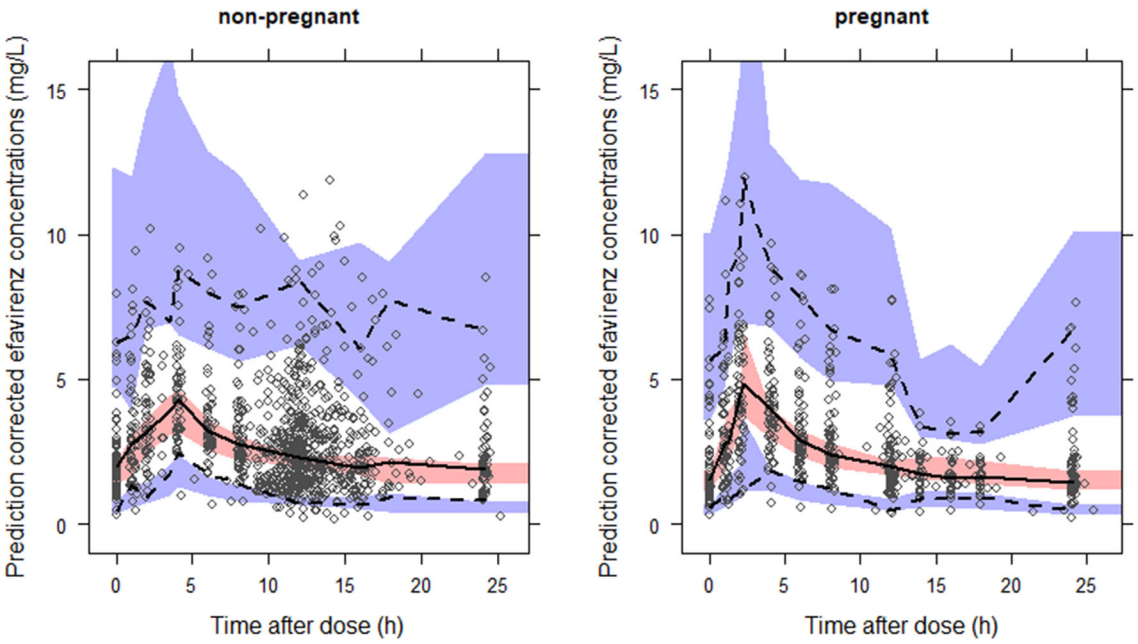

Fig. 3 pcVPC of the final model for efavirenz 600 mg stratified for pregnancy. The observations are indicated by the *open circles*. The median (continuous line) and 5th and 95th percentiles (dashed line) of the observations are shown, as well as the 95% confidence interval around the median (pink-shaded areas) and 5th and 95th percentiles (purple-shaded areas) of the simulated data. *pcVPC* prediction corrected visual predictive checks

Table 3 Median (IQR) *total* efavirenz exposure (AUC_{24} and C_{12}) and the percentage of simulated (C_{12}) below 1 and 0.7 mg/L following administration of efavirenz 400 and 600 mg once daily to pregnant (third trimester) and non-pregnant women, stratified for metabolizer status

Parameter	PM	IM	EM
Non-pregnant			
Efavirenz 600 mg QD			
AUC, mg/h·L	154 (121–194)	63 (50–80)	46 (37–61)
C_{12}, mg/L	6.1 (4.6–7.9)	2.4 (1.8–3.2)	1.7 (1.2–2.3)
$C_{12} < 1$ mg/L	0%	3%	9%
$C_{12} < 0.7$ mg/L	0%	0%	2%
Efavirenz 400 mg QD			
AUC, mg/h·L	103 (81–130)	42 (33–54)	31 (24–41)
C_{12}, mg/L	4.1 (3.1–5.2)	1.6 (1.2–2.1)	1.1 (0.81–1.5)
$C_{12} < 1$ mg/L	0%	15%	41%
$C_{12} < 0.7$ mg/L	0%	4%	14%
Pregnant, third trimester			
Efavirenz 600 mg QD			
AUC, mg/h·L	140 (110–177)	57 (45–73)	42 (33–56)
C_{12}, mg/L	5.4 (4.1–7.0)	2.1 (1.6–2.8)	1.4 (1.0–2.0)
$C_{12} < 1$ mg/L	0%	7%	23%
$C_{12} < 0.7$ mg/L	0%	1%	5%
Efavirenz 400 mg QD			
AUC, mg/h·L	93 (73–118)	38 (30–49)	28 (22–37)
C_{12}, mg/L	3.9 (2.7–4.7)	1.4 (1.1–1.9)	1.0 (0.69–1.4)
$C_{12} < 1$ mg/L	0%	23%	53%
$C_{12} < 0.7$ mg/L	0%	8%	26%

PM poor metabolizer, *IM* intermediate metabolizer, *EM* extensive metabolizer, *QD* once daily, *AUC* area under the concentration–time curve, AUC_{24} area under the concentration-time profile over the dosing interval, C_{12} mid-dose concentration

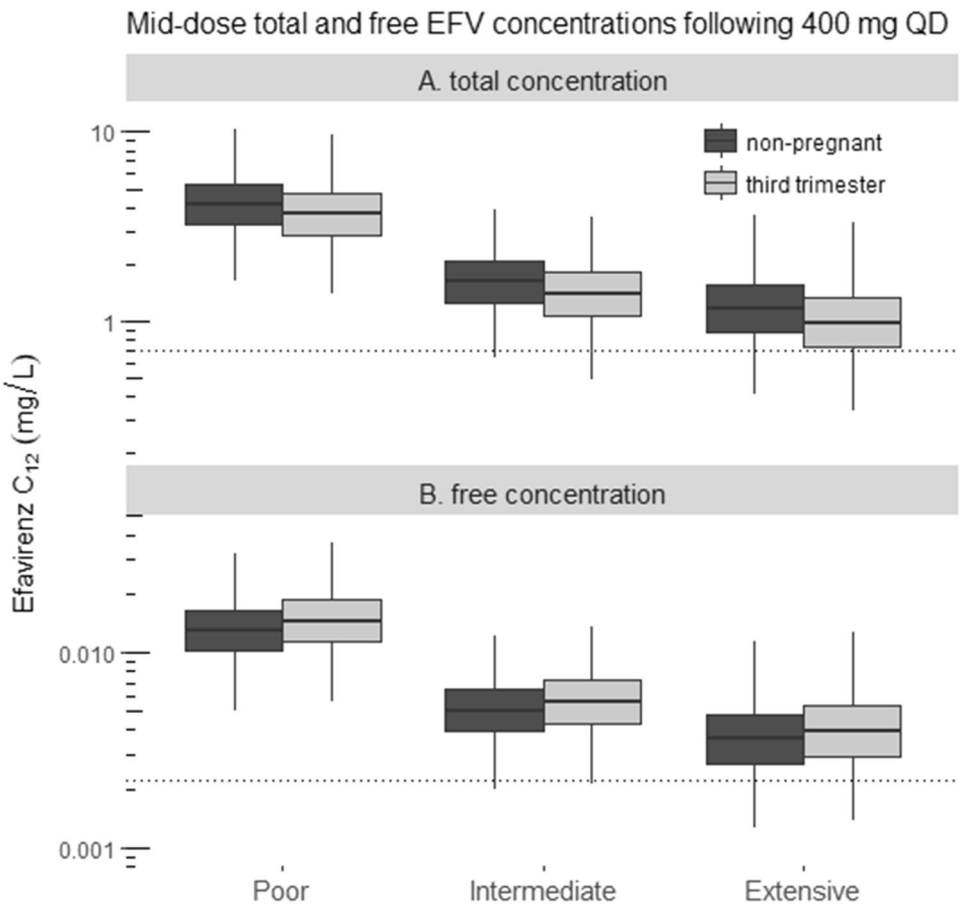

Fig. 4 Simulated **a** total and **b** free concentrations following administration of efavirenz 400 mg once daily during the third trimester of pregnancy and for non-pregnant women, stratified by metabolizer status. The horizontal dotted lines represent the total and free efavirenz plasma target concentrations of **a** 0.7 mg/L and **b** 0.002 mg/L, respectively. *EFV* efavirenz, *QD* once daily. C_{12} mid-dose concentration

The simulated *total* C_{12} during pregnancy compared with non-pregnant women, stratified by phenotype, is plotted in Fig. 4a. More subtherapeutic C_{12} was predicted during the third trimester of pregnancy compared with non-pregnant women for all phenotypes except the PMs. The percentage of *total* C_{12} below 0.7 or 1 mg/L for SMs, IMs, and EMs are reported in Table 3.

However, the simulated *free* C_{12} concentrations, based on the individual predicted f_u, were not lowered by pregnancy. Instead, the median *free* efavirenz C_{12} concentrations are predicted to increase during pregnancy by 11% (Fig. 4b). Overall, the median *free* efavirenz exposure ($AUC_{24,free}$) is predicted to be 15% higher during pregnancy.

4 Discussion

In this study, we found a modest effect of pregnancy on the efavirenz total AUC_{24} and C_{12}—a 9 and 13% reduction during the third trimester of pregnancy compared with non-pregnant women, respectively. Previous pharmacokinetic studies have indicated that pregnancy-related effects on the standard efavirenz 600 mg regimen are limited and of minor clinical relevance [13, 14]. In the current study, for the newly proposed efavirenz 400 mg regimen, an increase in the proportion of women having subtherapeutic *total* drug concentrations was predicted during the third trimester of pregnancy. Efavirenz C_{12} below 0.7 mg/L was predicted for 19% of women with EM status during the third trimester of pregnancy, compared with 9% for non-pregnant women. Although the rate of C_{12} below 0.7 mg/L for efavirenz 400 mg once daily was predicted to be twice as high during the third trimester of pregnancy, the difference was mostly restricted to the EM subpopulation and, in absolute terms, was small (median C_{12} of 1.0 vs. 1.1 mg/L). Even lower protein-binding corrected concentrations for 95% viral inhibition (PBIC95) have been suggested based on in vitro assessments (0.13 mg/L [45]), but translating in vitro to in vivo potency measures is not straightforward for several reasons, including potential interaction between the host, bug and drug, and that combination antiretroviral therapy may alter the potency of an individual antiretroviral agent [46]. Consequently, the pharmacokinetic outcomes in this study were compared against potency data from clinical studies that are also routinely used in therapeutic drug monitoring, which indeed may be conservative [45].

Importantly, because efavirenz is highly albumin-bound (> 99%) and only the free concentrations (at the target site) are related to the pharmacological effects, conclusions solely based on total concentrations may be misleading [40]. Ideally, the free efavirenz concentrations during pregnancy would be measured, but no such data were available for modeling and we relied on model predictions to distinguish between total and free efavirenz concentrations. Fortunately, the predicted free efavirenz exposure was not decreased during pregnancy. This indicates that any decrease in total efavirenz concentrations following 400 mg once daily is unlikely to be clinically relevant since only the free efavirenz concentration is available for the pharmacological effect at the site of action.

As no additional pregnancy-related covariate effects on hepatic clearance were identified, the increase in hepatic clearance during pregnancy can be primarily ascribed to the pregnancy-related increase in f_u. Physiologically, this indicates the absence of a significant and relevant pregnancy-induced efavirenz biotransformation, such as induction of the major efavirenz metabolizing enzyme CYP2B6. Although pregnancy-related induction of CYP2B6 has been suggested based on in vitro assays, to date this has not been confirmed in vivo [47]. Since efavirenz has a low E_h, changes in f_u should not alter free efavirenz concentrations [27]. Consequently, the model-predicted (minor) increase in free efavirenz exposure (C_{12} and AUC_{24}) is most likely related to alterations in efavirenz relative bioavailability and MAT during pregnancy. Reduced small intestine motility in pregnant women could increase the incomplete efavirenz absorption and maintain higher intestinal concentration gradients [12, 48]. Additionally, increased blood flow to the gastrointestinal tract resulting from increased cardiac output during pregnancy may result in an increased absorption rate and decreased MAT [22]. This has been previously observed in a population pharmacokinetic analysis [49].

For a model-based investigation of the efavirenz dose reduction to 400 mg in pregnancy, accurate identification of the pregnancy-related effects on the primary pharmacokinetic parameters was essential. Given that efavirenz pharmacokinetics are highly variable and the effects of pregnancy are relatively small, a large sample size is needed for sufficient power to detect these effects [13]. Smaller studies with less informative design may not have been capable of identifying these effects, but pooling the data from multiple sources allowed us to investigate these effects with higher statistical power. Furthermore, external evaluation of a pharmacokinetic model for efavirenz in pregnancy has not been performed. It should be noted that the dataset used for external evaluation was relatively small (other datasets were retained for sufficient statistical power), limiting the ability to fully evaluate the external predictive performance. Nevertheless, no indications of misspecification were found. This was reassuring given the mechanistic nature of the analysis, the associated assumptions, and the implemented mixture model.

Pooling data also comes at a cost as it may introduce bias related to interstudy differences. For example, a large amount of data were from studies with a crossover design (i.e. intrasubject comparison) [13, 14, 16, 50]. The postpartum assessment served as the control for the non-pregnant situation, and it can be questioned to what extent pregnancy-induced physiological processes have normalized during the early postpartum period. Furthermore, the timing of the postpartum assessment may vary between studies. Fortunately, in the current study, postpartum samples were mostly taken 4–6 weeks after delivery. Previous work indicated that this time span is sufficient for relevant physiological processes to normalize, allowing us to pool these data with other datasets from non-pregnant women [51]. The impact of such interstudy differences was monitored by means of stepwise integration of data from different sources and continued goodness-of-fit evaluation. Because the number of studies included in this analysis was still limited, we did not include interstudy variability [36].

Another strength of this study is its mechanism-based nature. Where purely empirical modeling of total concentrations would have led us to the conclusion that the pregnancy-related effects on efavirenz 400 mg once daily are modest and probably not relevant, our mechanism-based approach allowed us to take inferences one step further. Namely, our analysis suggests that even if exposure in terms of total concentrations may be affected, free concentrations are unlikely to be decreased and free efavirenz exposure following 400 mg once daily is thus sufficient during pregnancy. To reach such a conclusion, it was of paramount importance to ensure that the incorporated mechanistic information was valid and reasonable. To ensure that the inclusion of mechanistic information relied on evidence and quality, we prespecified all mechanistic information to be included in the model. This allowed us to statistically test the mechanistic relations included and prevented us from enforcing effects that were absent in the (clinical) data. For example, the pregnancy-related change in f_u increased hepatic efavirenz clearance. Although seemingly more complex, this is basically a time-varying parameter–covariate relationship between GA and (hepatic) plasma clearance, through predicted albumin levels and f_u.

There were some limitations to this study, including pharmacodynamic data not being available (e.g. viral load) from the vast majority of the studies included, which limited our ability to assess the exposure–response relationship in this particular population. Consequently, we relied on target concentrations for efavirenz established in

previous pharmacokinetic–pharmacodynamic analyses. A long-standing efavirenz target total drug concentration is 1 mg/L [9]. However, in the ENCORE1 study, the lower 400 mg once-daily dose was non-inferior to the standard 600 mg dose despite more observed subtherapeutic exposure, defined as < 1 mg/L [52]. This indicates that this threshold is not fully evidence-based and is most likely conservative. Another limitation is that data on individual CYP2B6 genotypes were only available from one study [14]. Nonetheless, we were able to differentiate between metabolic phenotypes using the mixture model [33]. As mentioned previously, free efavirenz concentrations were not determined. In addition, the individual plasma albumin concentrations were not available and we relied on predicted population albumin concentrations based on GA for the prediction of free efavirenz concentrations. Potentially, pregnancy-induced changes in albumin levels in women included in the current study were substantially different from that assumed from the literature. The albumin affinity may also be different in several populations. These potential confounders limit the ability to better explain variability in CL/*F* and to rely on individual predicted free efavirenz concentrations. However, on a population level, the free efavirenz AUC_{24} and C_{12} provide useful insights and hypothesis for further study.

5 Conclusions

Our model predicts a modest decrease in total efavirenz exposure during the third trimester of pregnancy. For efavirenz 400 mg once daily, this decrease seems of minor clinical relevance. Moreover, the model predicted that free, pharmacologically active efavirenz exposure was not decreased. These findings warrant prospective confirmations by a clinical trial studying the pharmacokinetics (preferably total and free efavirenz concentration), virologic response, and safety. Currently, a prospective pharmacokinetic study with the reduced-dose efavirenz in pregnant women is being conducted (NCT02499874). When the outcomes of this trial are positive and in line with our findings, the proposed dose reduction to efavirenz 400 mg can also be extended to pregnant women.

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Author Contributions SS and RH wrote the manuscript, designed and performed the research, and analyzed the data. ACC, KED, and TRC wrote the manuscript, and designed and performed the research. ADRH, BMB, MM, and DMD designed and performed the research. PD and EC designed and performed the research and analyzed the data. RG and FGMR wrote the manuscript and performed the research.

Compliance with Ethical Standards

Conflict of interest Stein Schalkwijk, Rob ter Heine, Angela C. Colbers, Alwin D.R. Huitema, Paolo Denti, Kelly E. Dooley, Edmund Capparelli, Brookie M. Best, Tim R. Cressey, Rick Greupink, Frans G.M. Russel, Mark Mirochnick, and David M. Burger declare that they have no conflicts of interest.

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