Pharmacokinetics of Efavirenz and Treatment of HIV-1 Among Pregnant Women With and Without Tuberculosis Coinfection

Kelly E. Dooley,1 Paolo Denti,2 Neil Martinson,1,4 Silvia Cohn,1 Fildah Mashabela,4 Jennifer Hoffmann,1 David W. Haas,2 Jennifer Hull,5 Regina Msandiwa,4 Sandra Castel,3 Lubbe Wiesner,3 Richard E. Chaisson,1 and Helen McIlleron,3 for the TSHEPISO Study Team

1Johns Hopkins University School of Medicine, Baltimore, Maryland; 2Vanderbilt University, Nashville, Tennessee; 3Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, 4Perinatal HIV Research Unit, University of the Witwatersrand, and 5Department of Obstetrics, Chris Hani Baragwanath Hospital and University of the Witwatersrand, Soweto, South Africa

Background. Pregnancy and tuberculosis treatment or prophylaxis can affect efavirenz pharmacokinetics, maternal human immunodeficiency virus type 1 (HIV-1) treatment outcomes, and mother-to-child transmission (MTCT) risk.

Methods. We evaluated a prospective cohort of pregnant, HIV-infected women with and without tuberculosis in Soweto, South Africa. Pharmacokinetic sampling was performed at gestation week 37 and during the postpartum period. Efavirenz trough concentrations (\(C_{\text{min}}\)) were predicted using population pharmacokinetic models. HIV-viral load was measured at delivery for mothers and at 6 weeks of age for infants.

Results. Ninety-seven women participated; 44 had tuberculosis. Median efavirenz \(C_{\text{min}}\) during pregnancy was 1.35 µg/mL (interquartile range [IQR], 0.90–2.07 µg/mL; 27% had an efavirenz \(C_{\text{min}}\) of < 1 µg/mL), compared with a median postpartum value of 2.00 µg/mL (IQR, 1.40–3.59 µg/mL; 13% had an efavirenz \(C_{\text{min}}\) of < 1 µg/mL). A total of 72% of pregnant women with extensive CYP2B6 genotypes had an efavirenz \(C_{\text{min}}\) of <1 µg/mL. Rifampin did not reduce the efavirenz \(C_{\text{min}}\). Isoniazid (for prophylaxis or treatment), though, reduced the rate of efavirenz clearance. At delivery, median durations of ART were 13 weeks (IQR, 9–18 weeks) and 21 weeks (IQR, 13–64 weeks) for women with and those without tuberculosis, respectively; 55% and 83%, respectively, had a viral load of <20 copies/mL (\(P = .021\)). There was 1 case of MTCT.

Conclusions. Pregnancy increased the risk of low efavirenz concentrations, but MTCT was rare. A detectable HIV-viral load at delivery was more common among pregnant women with tuberculosis, in whom ART was generally initiated later.

Keywords. pregnancy; efavirenz; population pharmacokinetics; HIV/tuberculosis co-infection; rifampin; isoniazid preventive therapy; pharmacogenetics.

Human immunodeficiency virus (HIV) and tuberculosis are leading infectious causes of death among women of reproductive age [1–5]. In South Africa, 40% of maternal deaths are caused by HIV or HIV-related disease [6]. Pregnancy increases the risk of tuberculosis [7], and in pregnant women with HIV infection, the risk for active tuberculosis disease is high, ranging from 0.7% to 7.9% in high-burden countries [8–12].

Treatment of HIV infection in pregnant women regardless of CD4+ T-cell count is recommended by the World Health Organization [13]. Combination antiretroviral treatment (ART) is safe and effective during pregnancy and is associated with reduced infant mortality and mother-to-child transmission (MTCT) of HIV [14]. First-line treatment for much of Africa includes tenofovir, entecritabine or lamivudine, and efavirenz.
This combination is increasingly used for pregnant women, although there are limited data describing EFV pharmacokinetics (PK), virologic outcomes, and MTCT in this population [16, 17].

Rifampin, an essential first-line tuberculosis drug, is a promiscuous inducer of drug metabolizing enzymes, including cytochrome P450 (CYP) [18]. Initial drug interaction studies suggested that rifampin coadministration reduced EFV concentrations [19]. However, HIV treatment outcomes do not appear to be influenced by rifampin-containing tuberculosis treatment, and current guidelines suggest using EFV with rifampin-containing tuberculosis treatment without dose adjustment [20–23]. The effect of rifampin on EFV exposures varies by CYP2B6 metabolizer status. Further, isoniazid influences EFV concentrations via inhibition of CYP2A6 [24, 25]. The effect of pregnancy and isoniazid and/or rifampin (used for prophylaxis against or treatment of tuberculosis) on EFV PK, virologic suppression, and MTCT have never been studied.

METHODS

Study Population

TSHEPISO is a prospective cohort study evaluating the effects of tuberculosis on maternal and infant outcomes in pregnant women with HIV infection. HIV-infected pregnant women with active tuberculosis (cases) or matched controls were recruited from antenatal clinics and obstetrics wards at Chris Hani Baragwanath Hospital (Soweto, South Africa) between January 2011 and January 2013. Eligible participants were ≥18 years old and pregnant (gestational age, ≥13 weeks). Cases had confirmed or probable tuberculosis, while controls had no evidence of tuberculosis. In the parent study, 2 controls were enrolled for each case, matched on gestational age (within 2 weeks), maternal age (within 5 years), date of enrollment (within 8 weeks), and site of planned delivery but not on ART use or regimen. Antiretroviral and tuberculosis treatment regimens were determined by participants’ primary care physicians, according to national treatment guidelines. As per national guidelines, EFV is given at a dose of 600 mg once daily at bedtime; the isoniazid dose is 5 mg/kg (maximum, 300 mg), while the rifampin dose is 10 mg/kg (maximum, 600 mg). Patients receiving EFV-based ART for ≥10 days by gestation week 36 could participate in the EFV PK substudy. This study was approved by the institutional review boards of Johns Hopkins Medicine, the University of the Witwatersrand, and the University of Cape Town. Participants provided written informed consent.

Study Protocol

Women enrolled in the EFV PK substudy underwent PK sampling at gestation week 37 or delivery, if it preceded the scheduled PK visit. Sampling was performed again 6 weeks after delivery. Blood samples for PK analysis were collected at arrival in the clinic in the morning and then 2, 4, and 6–8 hours later. Samples were generally collected between 10 and 24 hours after the previous EFV dose. For patients presenting in labor, PK samples were collected at 3-hour intervals from presentation until delivery (maximum of 4 samples). Timing of the last 3 doses of EFV was recorded. A cord blood PK sample was collected. A PK sample was collected from the infant 1 week after delivery. HIV-viral load was measured at delivery, for mothers, and at 6 weeks of age, for infants. CYP2B6 and NAT2 genotyping was performed on maternal whole-blood specimens.

Drug Concentration Analysis

EFV plasma concentrations were determined by liquid chromatography–tandem mass spectrometry in the Division of Clinical Pharmacology, University of Cape Town (Supplementary Materials). The method was linear over the range of 0.02 to 20 µg/mL. The lower limit of quantification was 0.02 µg/mL. The interassay coefficient of variation (CV) and residual error (RE) were 5.72%–8.01% and −0.09% to 3.18%, respectively, and the intraassay CV and RE were 1.13% to 8.53% and −6.10% to 11.96%, respectively.

CYP2B6 and NAT2 Metabolizer Status

Genomic DNA was extracted from whole blood. Genotyping of known functional polymorphisms CYP2B6 516G→T (rs3745274, CYP2B6*6) 983T→C (rs28399499, CYP2B6*18), and 15582C→T (rs4803419, CYP2B6*15) was performed using MassARRAY iPLEX Gold (Sequenom, Inc). Composite CYP2B6 genotypes were assigned as follows: extensive metabolizer (no variant allele at 516 or 983), intermediate metabolizer (single variant allele at position 516 or 983), slow metabolizer (2 variant alleles (ie, 516 TT, 983 CC, or 516 GT plus 983 TC), or very slow metabolizer (2 variants alleles at position 983) [26]. None were homozygous for 15582 TT. Genotyping of known functional polymorphisms NAT2 191G→A (rs1801279, *14), 341 T→C (rs1801280, *5), 590G→A (rs1799930, *6), and 857G→A (rs1799931, *7) was performed using TaqMan assays and the ABI Prism 7900 HT Sequence Detection System. The NAT2 genotypes were assigned as rapid (no variant allele), intermediate (1 variant allele), or slow (heterozygous for 2 different polymorphisms or homozygous for 1 polymorphism). Intermediate and rapid metabolizers were grouped together.

PK and Statistical Analyses

Sample Size

The sample size was based on determining the effect of rifampin on EFV concentrations. Using pilot study and published data [27], we estimated that 100 participants contributing 4–8 samples each (during the intrapartum and postpartum periods) would be sufficient to detect a 35% difference in oral clearance (CL/F) at a significance level of 0.05 with a power of 85%.
Population Pharmacokinetic Analyses

A population PK model of steady-state EFV was developed using nonlinear mixed effects modeling with NONMEM software [28], version 7.2. Perl Speaks NONMEM [29], Xpose, and Pirana were used for model diagnostics and to facilitate modeling [30,31]. For the structural model, besides the standard 1- and 2-compartment models with first-order elimination and first-order absorption (possibly with inclusion of a delay), a semiphysiological model with hepatic extraction, as presented by Gordi et al [32], also was tested. This latter model was implemented, justified by the disposition of EFV, with the intention to capture hepatic clearance and first-pass extraction with 1 parameter (hepatic intrinsic clearance [CLint]) and allow for effects on this parameter, such as CYP2B6 genotype, to affect systemic clearance and bioavailability. This model required the following assumptions: EFV protein binding of 99.5% [33]; a fixed plasma liver flow of 50 L/h for a typical individual weighing 70 kg [34]; and a fixed liver volume of 1 L, as assumed by Gordi et al [32]. Inclusion of between-subject and between-occasion random effects was tested on PK parameters, using a log-normal distribution, and the error model was assumed with an additive and proportional component. Inclusion of allometric scaling to adjust clearance and volume parameters (and liver flow and volume for the semiphysiological model) was tested at an early model development stage, as suggested in the article by Anderson and Holford [35]. Other significant covariate effects were then evaluated in the model, including age, pregnancy, CYP2B6 genotype, and effect of concomitant tuberculosis treatment or prophylaxis (accounting for NAT2 acetylator genotype). Model development was guided by the NONMEM objective function value (OFV; assumed to be χ² distributed), goodness-of-fit plots, visual predictive checks (VPCs) [36], clinical significance, and biological plausibility. The population PK model was used to generate individual post-hoc Bayesian estimates of PK parameters, including model-predicted individual trough concentrations (Cmin or C24).

RESULTS

Participants

There were 97 HIV-infected pregnant women receiving EFV, 44 with tuberculosis and HIV infection and 53 with HIV infection alone, plus their infants. Demographic and laboratory characteristics are presented in Table 1.

Population Pharmacokinetics of EFV During Pregnancy and After Delivery

For the 97 participants, there were 176 PK visits (81 during pregnancy or the intrapartum period and 95 during the postpartum period); 73% of patients participated in both PK visits. Seventeen patient visits were excluded from the population PK models (and estimates of Cmin) because drug concentrations in all samples were below the limit of quantification. Three additional patient visits were excluded because time–concentration profiles were inconsistent with recorded doses. The analyses included 87 patients and 468 samples.

The model that provided the best fit for the data was the semiphysiological hepatic extraction model with first-order absorption (Figure 1). Parameter estimates and their precision are presented in Table 2; VPC is shown in Supplementary Figure 1. The semimechanistic hepatic model provided a better fit than a traditional 1-compartment model, without needing the estimation of extra parameters. This mechanistic model captures the effect of changes in liver metabolic activity (CLint) both on hepatic clearance (CLH) and first-pass hepatic extraction (EH). For ease of interpretation, for each value of CLint, the corresponding typical values of systemic apparent clearance (CL/F), and the hepatic contribution to bioavailability (EH) are reported in Supplementary Table 1. Formulas are as follows: EH = [CLint · fu] / [QH + (CLint · fu)], CLH = EH · QH, and |CLH/FH| = |CLH/(1 – EH)|.

To capture variability in bioavailability from other factors, such as reduced absorption or enteric metabolism, a random effect involving prehepatic bioavailability was included. The inclusion of allometric scaling to account for the effects of weight on CL and volume improved the fit and explained part of the between-subject variability (ΔOFV = −22 points). Trying to include and estimate an effect of pregnancy on volume did

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 44)</th>
<th>Controls (n = 53)</th>
<th>All (n = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, y</td>
<td>28 (25–31)</td>
<td>29 (25–31)</td>
<td>28 (25–31)</td>
</tr>
<tr>
<td>Gestational age at enrollment, wk</td>
<td>29 (26–34)</td>
<td>31 (26–34)</td>
<td>30 (26–34)</td>
</tr>
<tr>
<td>CD4+ T-cell count at enrollment, cells/mm³</td>
<td>288 (144–427)</td>
<td>330 (260–414)</td>
<td>311 (217–415)</td>
</tr>
<tr>
<td>HIV RNA load at enrollment, copies/mL</td>
<td>&lt;20</td>
<td>12 (28)</td>
<td>30 (58)</td>
</tr>
<tr>
<td>CYP2B6 metabolizer status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive</td>
<td>10 (23)</td>
<td>11 (21)</td>
<td>21 (22)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>28 (64)</td>
<td>26 (49)</td>
<td>54 (56)</td>
</tr>
<tr>
<td>Slow</td>
<td>5 (11)</td>
<td>14 (26)</td>
<td>19 (19)</td>
</tr>
<tr>
<td>Very Slow</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>NAT2 metabolizer status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid</td>
<td>24 (55)</td>
<td>31 (60)</td>
<td>55 (57)</td>
</tr>
<tr>
<td>Slow</td>
<td>20 (45)</td>
<td>21 (40)</td>
<td>42 (43)</td>
</tr>
<tr>
<td>Genotypic age at delivery, wk</td>
<td>38 (36–40)</td>
<td>39 (38–40)</td>
<td>39 (37–40)</td>
</tr>
<tr>
<td>Duration of EFV use at delivery, wk</td>
<td>13 (9–18)</td>
<td>21 (13–64)</td>
<td>16 (11–24)</td>
</tr>
</tbody>
</table>

Data are median (interquartile range) or no. (%) of subjects.
not provide any improvement in model fit. The main determinant of CLint was CYP2B6 genotype; CLint varied significantly depending on whether the participant had an extensive, intermediate, slow, or very slow CYP2B6 metabolizer status (ΔOFV = −52). The effect of CYP2B6 genotype and isoniazid coadministration on EFV exposure is shown in Figure 2. For one of the subjects, CYP2B6 metabolizer status was not available, so the value was imputed using a mixture model, which allows a multimodal distribution of the individual parameter across the population, taking into account the relative frequency of each genotype in the study population and that subject’s EFV concentrations, as in the report by Keizer et al [37].

After including these covariates in the model, pregnancy increased CLint by 20% (ΔOFV = −11). This was in addition to effects of allometric scaling. Treatment with isoniazid (either with rifampicin for treatment or alone for prophylaxis) among patients with a slow NAT2 acetylator status reduced the EFV CLint by 20%; including this improved model fit modestly (ΔOFV = −5).

### Effect of Pregnancy on Concentrations of EFV

The median model-estimated EFV Cmin during pregnancy or the intrapartum period was 1.35 µg/mL (interquartile range [IQR], 0.90–2.07 µg/mL), compared with 2.00 µg/mL (IQR, 1.40–3.59 µg/mL) during the postpartum period (Tables 3 and 4). The proportion of women with a Cmin of < 1 µg/mL was 27% during pregnancy and the intrapartum period and 13% during the

### Table 2. Final Population Pharmacokinetic Model Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical Value (90% CI)</th>
<th>Variability, % CV (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLint, L/h</td>
<td>3710 (3080–4330)</td>
<td>Between subject: 33.0 (18.2–41.3)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2200 (1970–2440)</td>
<td></td>
</tr>
<tr>
<td>Slow</td>
<td>957 (736–1310)</td>
<td></td>
</tr>
<tr>
<td>Very slow</td>
<td>312 (246–568)</td>
<td></td>
</tr>
<tr>
<td>Vd, L</td>
<td>354 (284–433)</td>
<td></td>
</tr>
<tr>
<td>Prehepatic relative bioavailability</td>
<td>1′</td>
<td>Between occasion: 32.7 (%)</td>
</tr>
<tr>
<td>ka, 1/h</td>
<td>0.471 (0.286–1.14)</td>
<td></td>
</tr>
<tr>
<td>Proportional error, %</td>
<td>9.31 (7.26–10.9)</td>
<td></td>
</tr>
<tr>
<td>Additive error, mg/L</td>
<td>0.0846 (0–128)</td>
<td></td>
</tr>
<tr>
<td>Pregnancy on CLint, %</td>
<td>19.0 (9.62–29.1)</td>
<td></td>
</tr>
<tr>
<td>Isoniazid and slow NAT2 on CLint, %</td>
<td>−20.8 (−32.5 to −6.62)</td>
<td></td>
</tr>
<tr>
<td>VH, L</td>
<td>1′</td>
<td></td>
</tr>
<tr>
<td>QH, L/h</td>
<td>50′</td>
<td></td>
</tr>
<tr>
<td>Fu, %</td>
<td>0.5′</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CLint, clearance intrinsic (for the separate categories of CYP2B6 genotype); fu, unbound fraction of efavirenz in plasma; ka, first-order absorption rate constant; QH, plasma liver flow; Vd, volume of distribution; VH, volume of the liver compartment.

- 90% confidence intervals (CIs) were obtained with a 200-sample nonparametric bootstrap.
- Random effects have been modeled with a log-normal distribution, and the values of variability are reported as approximate percentage CV.
- Scaled with allometric scaling based on weight. The typical value is reported for a 70-kg woman.
- Fixed.

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**Figure 1.** Structural model. Efavirenz is absorbed from the absorption compartment into the liver with a first-order process (k_a). During the first-pass through the liver, a fraction E_H of the amount is extracted, while the rest reaches the systemic circulation. The drug then recirculates in the system with a flow equivalent to liver plasma flow (Q_H), and at each pass the liver extracts a further fraction E_H.

**Figure 2.** Efavirenz exposure, by CYP2B6 genotype and isoniazid inhibition. The box plot summarizes the percentiles in each CYP2B6 category (extensive [EXT], intermediate [INT], slow [SLW], and very slow [VSL]), separating visits in which a patient with slow NAT2 acetylator status was receiving isoniazid (suffix "-I") from those in which they were not. Dots represent individual visits, with hollow dots indicating visits during which isoniazid was co-administered with efavirenz. The area under the concentration–time curve (AUC_{0–24}) was calculated using the formula for linear kinetics, re-adapted using the parameters from the hepatic extraction model, as follows: AUC_{0–24} = \left[\frac{BIO \cdot DOSE}{fu \cdot CLint}\right] \cdot \left(1 - e^{-\frac{Q_H}{V_H}}\right) \cdot \left(1 - \frac{Q_H}{V_H}\right).
postpartum period; 72% of women with extensive CYP2B6 metabolizer status had a $C_{\text{min}}$ of < 1 µg/mL during pregnancy.

**Effects of Tuberculosis Treatment or Prophylaxis on Concentrations of EFV**

During pregnancy and the intrapartum period, the median estimated EFV $C_{\text{min}}$ for women receiving EFV-based ART and concurrent rifampin- and isoniazid-containing tuberculosis treatment was 1.33 µg/mL (IQR, 0.83–2.22 µg/mL), compared with 1.57 µg/mL (IQR, 1.56–1.83 µg/mL) for isoniazid alone for tuberculosis prophylaxis and 1.28 µg/mL (IQR, 1.04–1.92 µg/mL) when no tuberculosis drugs were given (Tables 3 and 4). Among pregnant/intrapartum women, 36% had an EFV $C_{\text{min}}$ of < 1 µg/mL while receiving rifampin and isoniazid, compared with 20% among women receiving only isoniazid and 23% receiving no antituberculosis drugs. Among slow CYP2B6 metabolizers, use of isoniazid (with or without rifampin) was associated with higher EFV $C_{\text{min}}$ values, especially among individuals with slow NAT2 genotypes.

**Cord Blood and Neonatal Concentrations of EFV Among Infants Born to Women Receiving EFV-Based ART**

The median EFV concentration in cord blood (n = 50) was 1.30 µg/mL (IQR, 0.75–2.33 µg/mL) and was below the limit of quantification in 5 of 50 samples (10%). Cord and maternal prepartum concentrations were highly correlated ($r = 0.95$). EFV concentrations in plasma specimens from 7-day-old infants were below the limit of quantification (0.02 µg/mL) for 44 of 67 (66%). The presence of quantifiable EFV in infant plasma correlated with higher cord blood concentrations ($r = 0.75$).

**Virologic Suppression Among Pregnant Women Receiving EFV as Part of ART**

At delivery, the median duration of EFV ART was 13 weeks (IQR, 9–18 weeks) for cases and 21 weeks (IQR, 13–64 weeks) for controls. Among 57 women with viral load measured at the time of delivery, 55% of cases (12/22) and 83% of controls (29/35) had an HIV-1 load of <20 copies/mL ($P = .021$). Viral resistance testing was not routinely performed at delivery, but...
among 5 women who had testing for clinical reasons, there were no M184V, K65R, or K103N and thymidine analog mutations.

Prevention of MTCT Among Women Receiving EFV-Based ART at Delivery

Ninety-one of 93 live-born infants of 95 women receiving EFV-based ART at delivery underwent polymerase chain reaction analysis for HIV-1 at 6 weeks. There was 1 case of MTCT. All infants received nevirapine daily for at least the first 6 weeks of life. In the case of MTCT, the mother enrolled as a case in the study at gestation week 37. At that time, she had received EFV-based ART for 8 weeks; her viral load was 185 copies/mL, and her CD4+ T-cell count was 148 cells/mm³. At delivery, during gestation week 39, she had received EFV-based ART for 67 days and tuberculosis treatment for 51 days. The infant was breastfed exclusively and received nevirapine prophylaxis after birth. At 22 days, the infant tested negative for HIV DNA by PCR and had a CD4+ T-cell percentage of 32%. At the same visit, the infant’s mother had an HIV-1 load of 218 672 copies/mL and reported breast-feeding.

DISCUSSION

Our study is the first to evaluate the combined effects of pregnancy and antituberculosis drugs on EFV PK and is the largest PK study among pregnant women with HIV infection receiving EFV-based ART. Pregnancy increased EFV clearance, and women were at increased risk of low EFV \( C_{\text{min}} \) (ie, < 1 \( \mu g/mL \)) during pregnancy, compared with the postpartum period. Women with extensive CYP2B6 metabolizer status appeared to be at particularly high risk; the majority had a \( C_{\text{min}} \) of < 1 \( \mu g/mL \) during pregnancy. Rifampin had little effect on median EFV concentrations but increased variability. Use of isoniazid (either as part of combination therapy for tuberculosis or alone for prophylaxis) increased EFV exposures. This effect was most apparent in patients with slow NAT2 metabolizer genotypes, a marker of high isoniazid concentrations. The proportion of women with an undetectable HIV-1 load at delivery was lower among women with tuberculosis, compared with those without tuberculosis; of note, ART was started later in these women. MTCT was rare, and the 1 case that did occur was likely related to breast-feeding, coupled with poor maternal treatment adherence.

Pregnancy-induced physiological changes can affect the PK of many drugs, including antiretrovirals [38, 39]. Until recently, there were no data describing the PK of EFV during pregnancy, likely because of concerns about teratogenicity. In one study, intensive PK sampling was performed during pregnancy and the postpartum period for 25 women receiving EFV-based ART [16]. While overall exposures (measured by calculating the area under the concentration–time curve from 0 to 24 hours) and maximum concentrations were not significantly different during pregnancy, \( C_{\text{min}} \) values were modestly reduced; however, the proportion of women with a target \( C_{\text{min}} \) of > 1 \( \mu g/mL \) was 88% during pregnancy and 92% for the same women during the postpartum period. Results of PK studies of EFV in pregnancy may be expected to differ across settings, though, because of geographic differences in metabolizer genotype mix. Since weight affects oral clearance of EFV, it is possible that modest increases in CL/F are related to higher weights during pregnancy. In our study, we used allometric scaling to adjust CL by body weight and detected a further increase in CL beyond the effect of weight alone during pregnancy. While pregnancy may not alter EFV PK significantly enough to warrant dose adjustment broadly in pregnant women, patients with extensive CYP2B6 metabolizer status who already have rapid clearance of EFV may be at particular risk of low EFV concentrations. In the recent ENCORE-1 study involving nonpregnant adults, doses of 400 mg and 600 mg of EFV had similar efficacy over 48 weeks of treatment [40]. The target \( C_{\text{min}} \) for EFV, though, remains unclear, both in general and during pregnancy. Pregnant women with extensive CYP2B6 metabolizer status merit special attention if a dose of 400 mg is to be considered.
Cotreatment of tuberculosis and HIV infection is complicated by drug-drug interactions; while most attention has been focused on rifampin, patients treated for tuberculosis also receive isoniazid, a CYP2A6 inhibitor. EFV is metabolized by CYP2B6 and CYP2A6. Drug interaction studies in healthy volunteers evaluating the effects of rifampin on EFV PK showed reductions in EFV concentrations, and based on modeling work [19, 41], the Food and Drug Administration recommended that the dose of EFV be increased among patients receiving rifampin who weigh >50 kg [42]. However, the need for a dose increase is hotly debated [20–22, 43, 44]. EFV is largely metabolized by CYP2B6, and concentrations are highly variable, with variability largely explained by CYP2B6 metabolizer genotype. CYP2A6 is a minor metabolic pathway for EFV but plays a major role in biotransformation of EFV among individuals with a slow CYP2B6 metabolizer genotype. Isoniazid is always given with rifampin for tuberculosis treatment and inhibits CYP2A6. Drug interaction studies involving just rifampin may produce significantly different results than studies involving full tuberculosis treatment, particularly among patients with slow CYP2B6 metabolizer genotype [25]. Although the numbers were small, patients with a slow EFV metabolizer genotype who were receiving tuberculosis treatment in our study had a median EFV Cmin during pregnancy of 6.54 µg/mL, which was much higher than that for patients who were not receiving tuberculosis treatment (3.86 µg/mL). If EFV-related side effects are concentration dependent, this may be of particular concern in populations where M. tuberculosis and HIV coinfection is common and 516T or 983C single-nucleotide polymorphisms are prevalent. In addition, while median EFV concentrations are similar among patients who are and those who are not receiving tuberculosis treatment, the variability is higher with antituberculosis treatment, and more patients have a Cmin of <1 µg/mL. Our participants overall had good virologic responses to EFV-based ART, whether or not they were receiving tuberculosis treatment, and vertical transmission was rare. However, it is possible that individuals with an extensive CYP2B6 metabolizer status represent a subpopulation at particularly high risk of treatment failure when EFV is given with rifampin-containing tuberculosis treatment. In our study, although the number of observations is limited, 77% of 13 patients receiving tuberculosis treatment with this genotype had a Cmin of <1 µg/mL at their PK visit, compared with only 47% of 19 participants who were not receiving tuberculosis treatment at the time of their PK visit. A rapid CYP2B6 genotyping test to identify subgroups of patients at particular risk for low EFV concentrations (ie, pregnant women, children, and individuals for whom tuberculosis treatment has been coadministered) would be useful.

For patients with HIV and M. tuberculosis coinfection, the current standard of care is to initiate tuberculosis treatment and then ART 2–8 weeks later [45, 46]. The optimal timing for initiation of ART for pregnant women with HIV infection and tuberculosis is less clear. In our study, women with tuberculosis started ART about 2 months later than women without tuberculosis and were much more likely to have a detectable viral load at delivery than women without tuberculosis. The risks and benefits of earlier initiation of ART in this population should be examined on a population level, taking into account the potential impact on the health of the mother and her child.

Median EFV concentrations in cord blood were >1 µg/mL and were highly correlated with maternal concentrations. The target concentration required to prevent transmission is unknown. Since all infants born to participants in this study received nevirapine daily for at least 6 weeks after birth, we cannot determine the contribution of EFV-based ART to the prevention of transmission. EFV concentrations were below the limits of quantification in the majority of infants at 7 days of life, indicating that even if therapeutic concentrations are achieved at birth, they are short-lived.

This study had limitations. It was conducted at a single site; however, genetic diversity was evident in the patient population, as evidenced by the variability in CYP2B6 genotypes. We used a sparse PK sampling strategy beginning several hours after the evening dose of EFV. Although this sampling scheme limited our ability to evaluate pregnancy-associated differences in absorption, we could readily estimate other PK parameters of interest, such as CL/F and Cmin. Despite including multiple covariate effects, the model still detected between-subject variability of 30% in Clint, and between-observation variability of 30% in bioavailability. This likely reflects genuine physiological factors that influence variability in EFV PK and other factors, such as imprecision in the reported dosing, skipping of some doses, and intake of food, and other varying conditions that were not controlled for in this observational study. For all assumptions in the population PK model, such as fixed hepatic volume and plasma flow, sensitivity analyses were performed that showed these assumptions did not significantly alter model results.

In conclusion, pregnancy increased EFV clearance, and the proportion of women with EFV Cmin < 1 µg/mL was higher in pregnancy than after delivery; women with extensive CYP2B6 metabolizer status may be at particularly high risk of low EFV Cmin. Treatment for tuberculosis that includes isoniazid and rifampin does not reduce overall EFV concentrations, but population PK analyses suggest that EFV exposures are increased among patients with a slow NAT2 genotype who are receiving isoniazid. Women with tuberculosis and HIV infection were more likely to have a detectable HIV-1 load at delivery than women with HIV infection alone, likely because HIV treatment was started later in pregnancy in coinfected patients. EFV concentrations in the majority of infants at 7 days of life were below the limits of quantification, so a prolonged protective effect of EFV in these infants is unlikely.
Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org). Supplementary materials consist of data provided by the authors that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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