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MAJOR ARTICLE

Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics of Efavirenz 400 mg Once Daily During Pregnancy and Post-Partum

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Background. A clinical trial showed that efavirenz 400 mg once daily (EFV400) is as effective as the standard adult dose. World Health Organization recommends EFV400 as an alternative first-line agent, but data are lacking in the third trimester of pregnancy (TT). We investigated the pharmacokinetics, efficacy, and *CYP2B6* pharmacogenetics in HIV-infected women (WLWH) on EFV400 during TT and post-partum (PP).

Methods. An open-label 2-center study (United Kingdom, Uganda) was conducted in WLWH receiving antiretroviral regimens containing efavirenz 600 mg, who had their efavirenz dose reduced to EFV400. Weekly therapeutic drug monitoring (TDM), steady-state pharmacokinetic profiles (TT and PP), safety, virological efficacy, and *CYP2B6* polymorphisms at positions 516 (C > T) and 938 (T > C) were evaluated.

Results. Twenty-five WLWH of African origin were enrolled. All had viral loads <50 copies/mL at baseline, which were maintained throughout the study. No infant was HIV infected. No WLWH were withdrawn due to low EFV400 TDM results. Geometric mean ratios (TT/PP; 90% confidence interval) for EFV400 maximum observed plasma concentration, area under the curve, and plasma concentration measured 24 hours after the observed dose were 0.97 (.85–1.10), 0.87 (.76–.99), and 0.77 (.65–.91), respectively. Five of 25 WLWH were slow metabolizers.

Conclusions. Although EFV400 pharmacokinetic parameters were slightly lower for TT compared with PP values, efavirenz concentrations exceeded cutoff levels established by the study and those measured in antiretroviral-naive patients receiving EFV400 in ENCORE1. All subjects maintained a viral load <50 copies/mL, suggesting that EFV400 can be used in pregnant WLWH.

Keywords. low-dose efavirenz; pharmacokinetics; pregnancy.

The World Health Organization recommends combination antiretroviral therapy (cART) for all pregnant women regardless of $CD4^+$ T-lymphocyte count [1]. This intervention has reduced the annual number of new infections among children by 50% worldwide since 2010 and promoted maternal health and survival [2]. Consequently, cART coverage for pregnant women in low- to middle-income countries has steadily risen, from 47% in 2009 to 77% in 2016 [2].

Although preferred first-line cART regimen is tenofovir disoproxil fumarate (TDF), emtricitabine (FTC) or lamivudine (3TC), and efavirenz 600 mg once daily (OD), the lower dose of efavirenz 400 mg OD is recommended as an alternative to the 600 mg OD dose [1]. Dose reductions achieved after successful dose optimization studies could result in benefits for individuals infected with human immunodeficiency virus (HIV), by allowing access programs to reach more patients for the same public health expenditure, compensate for the finite global drug manufacturing capacity, and address increasing demand [3].

Importantly, the ENCORE1 study (efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults) showed the lack of a significant difference in virological outcome between 400-mg and 600-mg efavirenz, indicating that 400 mg is no less effective than the standard dose. Furthermore, there were significantly fewer efavirenz-associated side effects in the efavirenz 400 mg arm, in particular fewer central nervous system symptoms. Significantly fewer people taking the lower dose discontinued treatment owing to adverse events [4]. Importantly, *CYP2B6* polymorphisms were associated with adverse events but not efficacy [5]. However, the implementation of efavirenz 400 mg has been limited by the lack of information on whether drug exposure is affected by the physiological changes occurring during pregnancy and by rifampicin coadministration in individuals with HIV/tuberculosis coinfection.

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The primary objective of the current study was to describe efavirenz pharmacokinetics in HIV-infected pregnant women receiving efavirenz 400 mg in combination with TDF/FTC and to compare third-trimester (TT) efavirenz exposure with postpartum (PP) exposure. The secondary objective was to describe the pharmacogenetics of *CYP2B6*, which is significantly associated with metabolic clearance of efavirenz [6].

METHODS

Study Population and Design

The study enrolled pregnant women living with HIV (WLWH) from 2 sites: St Stephen's Centre in London, United Kingdom, and the Infectious Diseases Institute, Makerere University, in Kampala, Uganda (ClinicalTrials.gov registration NCT02499874). Each site received country-specific ethical and regulatory approvals. All subjects gave written informed consent before study participation.

The recruited pregnant women were receiving TDF/FTC or 3TC/efavirenz 600 mg, prescribed as part of their routine clinical care. Maternal inclusion criteria were pregnancy, age >18 years, confirmation of HIV infection status, $CD4^+$ T-lymphocyte count >100/μL, and viral load <50 copies/mL. Maternal exclusion criteria were evidence of organ dysfunction, hepatitis B or C infection, and the use of specific medications known to be contraindicated with efavirenz. Subjects were enrolled between gestational weeks 25 and 31. When switched to efavirenz 400 mg, women received Sustiva 200 mg capsules (Bristol-Myers Squibb) in the United Kingdom, and Stocrin 200 mg tablets (Merck, Sharp and Dohme) in Uganda.

Efavirenz therapeutic drug monitoring (TDM) was performed weekly for the study duration from baseline to the PP period. Samples were obtained 10–14 hours after the dose and analyzed for efavirenz in real time using a validated assay, and results were reported to the study team for review. Viral load was tested biweekly and hematology and serum biochemistry at screening, baseline, and full pharmacokinetic visits.

Stopping criteria were met if a viral load >50 copies/mL was detected on 2 consecutive occasions or if efavirenz concentrations were <800 ng/mL on 3 consecutive occasions. The 800-ng/mL study cutoff was derived by the receiver operating characteristic curve analysis performed by Dickinson et al [5] within the pharmacokinetic substudy of the ENCORE1 study. Participants were assessed for adverse events at each study visit. Adverse events were reported according to the Division of AIDS grading scale (December 2004) [7].

Full Pharmacokinetic Assessments

Serial blood samples were collected over 24 hours for measurement of efavirenz concentrations on 2 occasions: during TT (at 31–35 weeks of gestation) and after delivery (at 3–10 weeks PP), as maternal physiological conditions generally normalize to nonpregnant adult conditions within an average of 6 weeks PP.

On sampling days, the predose sample was obtained, and efavirenz 400 mg was administered to participants in the fasting state, along with TDF and FTC or 3TC, under observation by the study clinical staff. Serial blood specimens were collected via intravenous catheter inserted into an arm vein 2, 4, 8, 12, and 24 hours after dosing. At delivery, when possible, 1 maternal plasma and 1 umbilical cord blood sample were obtained after cord clamping.

Efavirenz Concentration Assays and Analysis

Samples for all full profile and London site TDM were analyzed at the Jefferiss Research Trust Laboratories by a validated reversed-phase ultraperformance liquid chromatography method modified from a method published elsewhere [8]. Efavirenz was measured at a wavelength of 246 nm. The lower limit of quantification was 250 ng/mL.

TDM samples collected in Kampala were analyzed at the Infectious Diseases Institute Translational Laboratory using a method described method elsewhere (high-performance liquid chromatography with ultraviolet detection) [9]. The lower limit of quantification was 200 ng/mL. Both laboratories adhere to the International Inter-laboratory Quality Control Program for Measurement of Antiretroviral Drugs in Plasma [10].

The pharmacokinetic parameters calculated for efavirenz were the plasma concentration measured 24 hours after the observed dose (C_{trough}), the maximum observed plasma concentration (C_{max}), and the area under the plasma concentration curve (AUC) from 0 to 24 hours (AUC_{0-24}). All parameters were calculated using noncompartmental modeling techniques (WinNonlin Phoenix, version 7.0; Pharsight). Descriptive statistics, including geometric mean (GM) and 95% confidence intervals (CIs), were calculated for all parameters.

Within-subject changes of drug concentrations (TT vs PP) were assessed by calculating GM ratios (GMRs) and 90% CIs. The CIs were first determined using logarithms of the individual GMR values and then expressed as linear values. The changes in parameters were considered significant when the CI for the GMR did not include the value of 1. Interindividual variability in efavirenz pharmacokinetic parameters was expressed as a percentage coefficient of variation ([standard deviation/mean] × 100).

Pharmacogenetics Assays and Analysis

Pharmacogenetic analysis involved 2 *CYP2B6* polymorphisms (516G > T and 983T > C) known to predict increased steady-state efavirenz exposure [6, 11, 12]. Genomic DNA was extracted from whole blood collected at baseline after specific written consent was obtained for pharmacogenetic studies using the manufacturers protocol (E.Z.N.A Blood DNA Mini Kit; Omega Bio-tek). Extracted DNA was quantified using a NanoDrop spectrophotometer (ThermoFisher Scientific). Genotyping of polymorphisms of primary interest (*CYP2B6* 516G > T [*CYP2B6*6*] and 983T > C [*CYP2B6*18*])

was accomplished using real-time allelic discrimination polymerase chain reaction with a DNA Engine Chromo4 system (Bio-Rad Laboratories). TaqMan Genotyping Master Mix and assays were used to genotype *CYP2B6* polymorphisms 516G > T (rs3745274; assay ID C_7817765_60) and 983T > C (rs28399499; assay ID C_60732328_10); all components were purchased from ThermoFisher Scientific.

Allelic discrimination plots were obtained and genotype identification determined using Opticon Monitor software (version 3.1; Bio-Rad Laboratories). Composite *CYP2B6* genotypes, based on reported associations with steady-state efavirenz pharmacokinetics, were assigned as follows: extensive metabolizer, no variant allele at either position 516 or 983; intermediate metabolizer, a single variant allele at either position 516 or 983, but not both; slow metabolizer, 2 variant alleles (ie, either 516 T/T, 983 C/C, or 516 G/T with 983 T/C).

RESULTS

A total of 39 pregnant WLWH were screened (8 in London and 31 in Kampala). Thirteen women were excluded because of detectable viral load (>50 copies/mL; n = 6), being outside screening gestational age (n = 2), being hepatitis B positive (n = 1), noncompliance with study visits and procedures (n = 2), having a hemoglobin level <10 g/dL (n = 1), or being enrolled in another study at the Infectious Diseases Institute in Kampala (n = 1). Thus, 26 were given efavirenz 400 mg at baseline. One woman was withdrawn from the study because she delivered before the TT intensive pharmacokinetic assessment. Twenty-five women completed the study and were included in the pharmacokinetic analysis. All were of African origin (8 enrolled in London and 17 in Kampala).

Efavirenz Pharmacokinetics

All TDM results for the 25 WLWH who completed the study are illustrated in Figure 1. The number of TDM visits ranged between 18 and 32. Three subjects had efavirenz concentrations below the study cutoff of 800 ng/mL on single occasions, with their remaining samples above this threshold. No subject was excluded from the study for low TDM results. The interval from the efavirenz dose change to the TT full pharmacokinetic assessment ranged from 6 to 43 days, but only 4 women had an interval of <14 days (<10 days in only 2). On the full pharmacokinetic assessment days, efavirenz concentrations measured 12 hours after observed dosing were all above the study established cutoff of 800 ng/mL.

The concentration–time profiles of efavirenz (400 mg OD) during pregnancy and PP are shown in Figure 2. Derived pharmacokinetic parameters and their GMRs (with 90% CI) during PP versus TT are listed in Table 1. Efavirenz C_{max}, AUC_{0-24} and C_{trough} were 3%, 13%, and 23% lower during TT versus PP, respectively. Although only the C_{max} 90% CIs were within the constraints for bioequivalence of 80%–125%, these were maintained for both C_{max} and AUC between the extended CIs of 70%–143% for drugs meeting high variability criterion (coefficient of variation, >30%) [13].

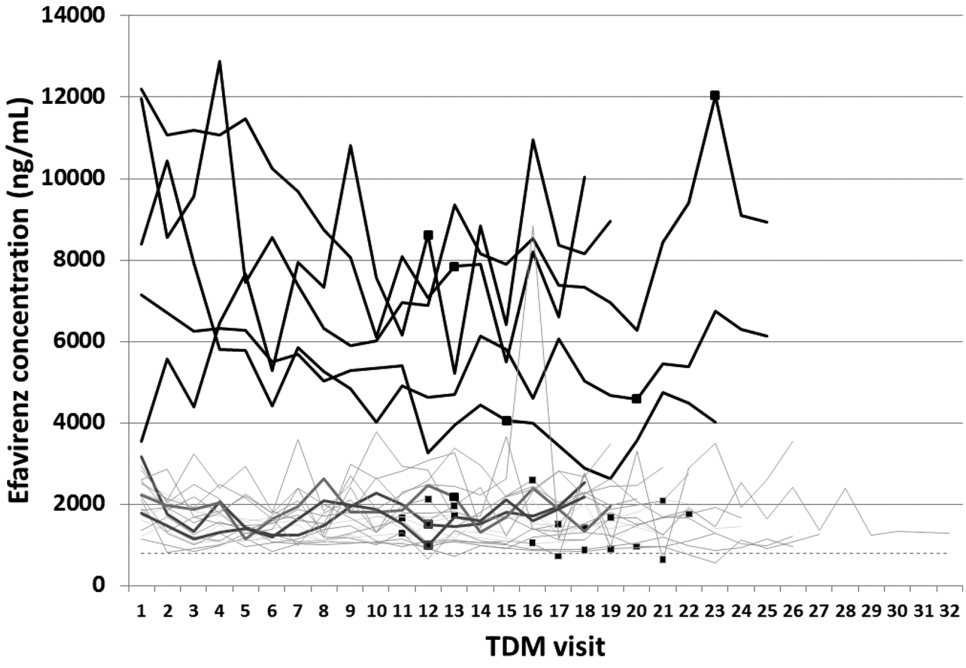

Figure 1. Efavirenz therapeutic drug monitoring (TDM) results. The dotted line represents the geometric mean; black lines, study participants who were slow metabolizers; dark gray, intermediate metabolizers; light gray, extensive metabolizers; horizontal dashed gray line, efavirenz concentration cutoff established by the study protocol (800 ng/mL); black squares, time of delivery.

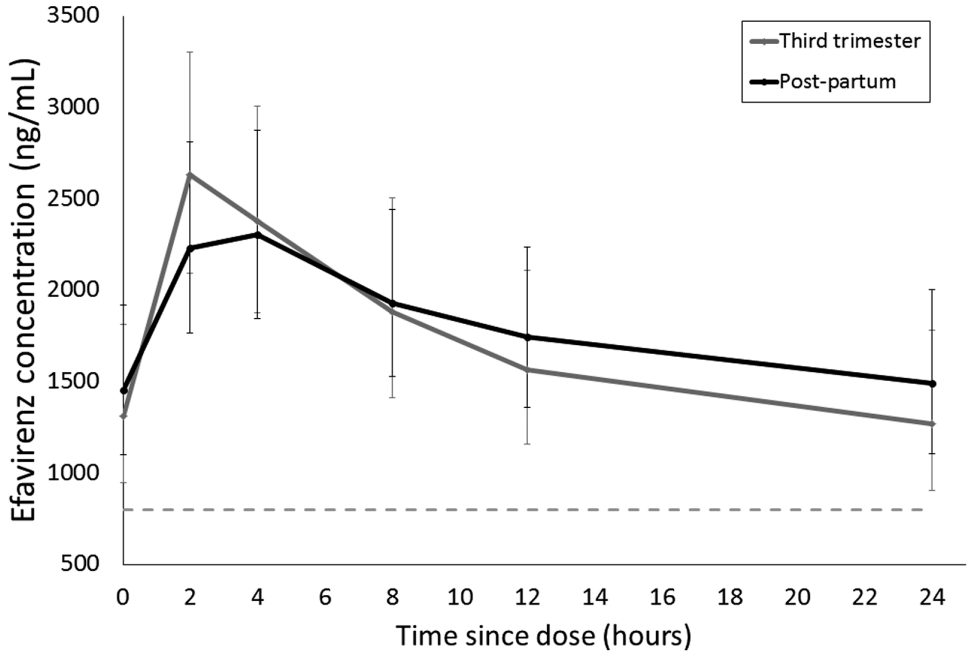

Figure 2. Geometric mean drug concentration–time curves of efavirenz after administration of efavirenz 400 mg once daily during the third trimester and post-partum. Dotted lines represent 90% confidence intervals; horizontal dashed gray line, efavirenz concentration cutoff established by the study protocol (800 ng/mL).

Efavirenz Pharmacogenetics

Among the 25 subjects who completed the study, 17 were extensive, 3 were intermediate, and 5 were slow metabolizers. The relationship between efavirenz TDM results and metabolizer status is illustrated in Figure 1, where the slow metabolizers are highlighted. As expected, slow metabolizers showed higher efavirenz concentrations throughout the study, but, importantly, extensive metabolizers maintained concentrations >800 ng/mL and an undetectable viral load.

Maternal and Infant Outcomes and Adverse Events

Four umbilical cord plasma samples were collected with matching maternal plasma samples at delivery. Efavirenz concentrations in the cord plasma were 2040, 755, 370, and 1087 ng/mL, with corresponding concentrations in the maternal plasma samples of 2886, 991, 653, and 1301 ng/mL, respectively. The corresponding ratios of cord to maternal plasma were 0.71, 0.76, 0.57, and 0.84, respectively.

All women had a viral load <50 copies/mL at baseline, which was maintained throughout the study (only 2 blips were observed, but values were confirmed as being <50 copies/mL, when testing was repeated). None of the infants was HIV infected. Efavirenz 400 mg OD was well tolerated during pregnancy, with no grade 3 or 4 laboratory abnormalities.

DISCUSSION

Therapeutic concentrations of efavirenz were maintained in this study despite a dose reduction from 600 to 400 mg OD in late pregnancy. Although efavirenz 400 mg OD parameters were slightly lower during TT versus PP, efavirenz concentrations were maintained above the predetermined cutoff selected by the study a priori and the threshold calculated from efavirenz concentrations in cART-naive patients receiving efavirenz 400 mg OD in the ENCORE1 study [4]. Furthermore, dose reduction was observed to be safe in terms of maintenance

Table 1. Plasma Efavirenz Pharmacokinetic Parameters After Administration of Efavirenz 400 mg Once Daily During the Third Trimester of Pregnancy and Post-Partum

	Third Trimester		Post-Partum		GMR for Third Trimester/Postpartum Exposure (90% CI)
Pharmacokinetic Parameter	Efavirenz GM (95% CI)	GeoCV, %	Efavirenz GM (95% CI)	GeoCV, %	
C_{max}, ng/mL	2751 (2250–3363)	52	2767 (2250–3403)	52	0.97 (.85–1.10)
C_{trough}, ng/mL	1205 (878–1653)	89	1491 (1109–2005)	80	0.77 (.65–.91)
AUC_{0-24}, ng·h/mL	39 941 (30 849–51 713)	69	44 109 (34 620–56 198)	62	0.87 (.76–.99)

Abbreviations: AUC_{0-24}, area under the plasma concentration curve from 0 to 24 hours; CI, confidence interval; C_{max}, maximum observed plasma concentration; C_{trough}, plasma concentration measured 24 hours after the observed dose; GeoCV, geometric coefficient of variation; GM, geometric mean; GMR, GM ratio.

of virus suppression, the frequency and severity of maternal adverse events, and the prevention of vertical HIV transmission to infants. Our data strongly suggest that efavirenz 400 mg OD can be considered as an alternative to efavirenz 600 mg OD in pregnant WLWH. Importantly, we did not see any differences in efavirenz tolerability by CYP2B6 genotype result; however, most women who took part in the study asked the investigator whether they could continue with the 400 mg dose of efavirenz, suggesting better tolerability (data not shown).

We could also hypothesize that the 25% decrease in efavirenz C_{trough} measured during TT versus PP is due to a change in efavirenz protein binding caused by a decrease in albumin during late stages of pregnancy (31%) and leading to a higher unbound fraction of efavirenz, which would result in lower total drug concentration measurements [14, 15]. This change may not be clinically relevant because it would indicate a modification of the equilibrium between total and unbound drug rather than a real drop in efavirenz plasma concentrations.

Women enrolled in the study were already established on cART. If efavirenz 400 mg OD is accepted for use in pregnancy, women identified as HIV positive as part of antenatal care screening programs will start efavirenz 400 mg as their first cART regimen. For ethical and safety considerations, the current study recruited women who were already established on an efavirenz 600 mg dose and who had suppressed viral load results. However, the risk of low concentrations during the accumulation phase of efavirenz dosing will probably be mitigated, because efavirenz undergoes autoinduction and higher plasma efavirenz concentrations have been noted at the start of efavirenz treatment, with mild reduction in concentrations reported weeks to months after treatment initiation [16]. Importantly, efavirenz C_{trough} values during TT were mainly within ranges of those measured for efavirenz 600 mg OD during TT, where the lowest C_{trough} has been shown to range between 230 and 660 ng/mL [17, 18]. In our study, only 3 women had a C_{trough} <660 ng/mL; these values were 614, 642, and 644 ng/mL, and they were associated with an undetectable viral load.

Unfortunately, cord plasma was collected at delivery in only 4 women enrolled in London. Nonetheless, the cord plasma/blood plasma ratios measured in these 4 women receiving efavirenz 400 mg OD were within those reported in the literature for efavirenz 600 mg OD [17].

All study participants were of African origin, representative of the demographics of the HIV pandemic in which women of African origin represent the highest percentage of mother-to child-transmissions worldwide [2]. From a pharmacological perspective, genetics rather than race is associated with drug exposure, and the impact of race is predicated by variation in the frequency of polymorphisms present in racial groups. Of relevance to this study, genetic polymorphisms known to be associated with lower concentrations of efavirenz (extensive metabolizers) did not result in efavirenz concentrations below the threshold.

In developing countries, cART containing efavirenz 600 mg OD is the most widely used regimen. Transition to regimens containing 400 mg OD is feasible because of the availability of fixed dose combination formulation, familiarity of clinicians with the management of adverse events related to efavirenz and potential cost savings to national programs [3]. By contrast, different efavirenz doses for different subpopulations would be cumbersome to implement in terms of health worker training and would increase the potential for medication and dispensing errors. Our data suggest that the restriction on the use of efavirenz 400 mg in pregnancy can be safely removed.

In conclusion, this pharmacokinetic study has demonstrated that, although efavirenz concentrations during TT are slightly lower than PP concentrations, pregnant WLWH maintained concentrations above the cutoff levels measured in prospective pharmacokinetic studies irrespective of their *CYP2B6* genotype [5]. Furthermore, these women maintained an undetectable viral load, ensuring that HIV was not transmitted from the mother to the child.

Notes

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Potential conflicts of interest. M. L. has received research funding from ViiV and Janssen. A. O. has received research funding from Merck, AstraZeneca, Pfizer, ViiV, and Janssen: has consulted for Merck and ViiV; and is also a coinventor of patents relating to nanotechnology-based drug delivery systems. M. B. has received travel and research grants from and has been an advisor for Janssen, Roche, ViiV, Bristol-Myers Squibb, Merck Sharp & Dohme, Gilead, Mylan, Cipla, and Teva. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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