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Efavirenz Pharmacokinetics during the Third Trimester of Pregnancy and Postpartum

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Abstract

Background—The impact of pregnancy on efavirenz pharmacokinetics is unknown.

Methods—International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1026s is an on-going, prospective, non-blinded study of antiretroviral pharmacokinetics in HIV-infected pregnant women that included a cohort receiving 600 mg efavirenz once daily as part of combination antiretroviral therapy. Intensive steady-state 24-hour blood sampling was performed during the third trimester and at 6–12 weeks postpartum. Maternal and umbilical cord blood samples were drawn at delivery. Pharmacokinetics targets were the estimated 10th percentile efavirenz AUC in non-pregnant historical controls (40.0 mcg.hr/mL) and a trough concentration of 1 mcg/mL.

Results—Twenty five women were enrolled during the third trimester: median (range) age was 29.3 (18.9–42.9) years, weight 69.0 (40–130) kg, gestational age 32.9 (30.1–38.7) weeks. Median (range) efavirenz AUC₀₋₂₄, C_{max} and C_{24hour} were 55.4 mcg.hr/mL (13.5–220.3), 5.4 mcg/mL (1.9–12.2) and 1.6 mcg/mL (0.23–8.13), respectively. Efavirenz AUC and C_{max} did not differ during pregnancy and postpartum but C_{24hour} was lower during the third trimester (1.6 vs. 2.1 mcg/mL, p=0.01). During the third trimester, 5 of 25 (20%) women had an efavirenz AUC below the target and 3 of 25 (12%) had a trough concentration below 1 mcg/mL. Efavirenz cord blood/maternal concentration ratio was 0.49 (0.37–0.74). All women had a HIV-1 RNA viral load less than 400 copies/mL at delivery and 19 (76%) had a viral load below 50 copies/mL. One child was perinatally HIV-infected. Three women were exposed to efavirenz throughout the first 6 weeks of

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pregnancy. EFV was well tolerated and among the 25 infants no congenital anomalies or newborn complications were reported.

Conclusions—Changes in efavirenz pharmacokinetics during pregnancy compared to postpartum are not sufficiently large enough to warrant a dose adjustment during pregnancy.

Keywords

efavirenz; pregnancy; pharmacokinetics; HIV; prevention of mother-to-child transmission of HIV

Introduction

The use of combination antiretroviral drugs regimens during pregnancy for HIV/AIDS treatment and/or the prevention of mother-to-child transmission of HIV are increasing following the rapid scale up of antiretroviral treatment programs. Recently, the World Health Organization (WHO) updated its HIV treatment guidelines to include efavirenz as a non-nucleoside reverse transcriptase inhibitor (NNRTI) option for treatment-naïve HIV-infected pregnant women after the first trimester. The restriction of efavirenz use during the first trimester is based on several case reports of congenital neural tube defects with first trimester exposure to efavirenz^{1, 2} which led the United States Food and Drug Administration (FDA) to classify efavirenz as a Class D drug ('evidence of human fetal risk'). As a consequence, efavirenz use in HIV-infected women of reproductive-age trying to conceive or not using effective contraception is also not recommended³.

To date, the impact of pregnancy on efavirenz pharmacokinetics (PK) is unknown. Physiological changes during pregnancy can significantly impact drug disposition. Efavirenz is primarily metabolized by the hepatic cytochrome 2B6 enzyme (CYP2B6)⁴ and temporal changes in hepatic drug-metabolising enzyme activities occur during pregnancy⁵. Several antiretroviral drugs metabolised via the hepatic cytochrome P450 enzymes have reduced exposure during pregnancy, particularly during the third trimester^{6, 7}.

Optimal antiviral exposure throughout pregnancy is critical to ensure maximal viral load suppression for the prevention of mother-to-child transmission of HIV and to prevent the selection of resistance. Thus, given the uncertainty regarding efavirenz drug exposure using the standard dose during pregnancy our aim was to investigate the pharmacokinetics of efavirenz during the third trimester of pregnancy and in the early postpartum period.

Materials and Methods

Study Population

International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network Protocol 1026s is an ongoing, multicenter, non-blinded, prospective study to evaluate the pharmacokinetics of antiretrovirals among pregnant HIV-infected women [ClinicalTrials.gov Identifier: NCT00042289]. This report includes women receiving efavirenz 600 mg once daily. For women enrolled in the United States, P1026s is a sub-study of P1025, a prospective cohort study of HIV-infected pregnant women receiving care at IMPAACT sites [NCT00028145].

Eligibility criteria for this efavirenz arm of P1026s were: initiating the standard dose of efavirenz (600 mg, once daily) as part of clinical care before the beginning of the 35th week of gestation. Exclusion criteria were: concurrent use of medications known to interfere with the absorption, metabolism or clearance of efavirenz, multiple gestation pregnancy, and clinical or laboratory toxicity that, in the opinion of the site investigator, would likely

require a change in the medication regimen during the study. Local institutional review boards approved the protocol at all participating sites and signed informed consent was obtained from all subjects prior to participation. Subjects continued to take their prescribed medications until postpartum blood sampling was completed. The choice of additional antiretrovirals and duration of treatment (i.e. continuation of ARV treatment) was determined by the subject's physician, who prescribed all medications and remained responsible for her clinical management throughout the study. Maternal and infant safety follow up continued until 24 weeks postpartum.

Women were enrolled during the third trimester. Pharmacokinetic sampling was performed between 30 and 36 weeks gestation and between 6 and 12 weeks postpartum. Efavirenz area under the concentration versus time curve (AUC_{0-24}) was calculated for each woman and compared to the efavirenz AUC_{0-24} in non-pregnant adult populations⁸. Each subject's physician was notified of the subject's plasma concentrations and AUC_{0-24} within two weeks of sampling. If the AUC_{0-24} was below the 10th percentile in non-pregnant adult populations (40.0 mcg.hr/mL), the physician was offered the option of discussing the results and possible dose modifications with a study team pharmacologist.

Clinical and laboratory monitoring

Maternal data accessed were: maternal age, ethnicity, weight, concomitant medications, CD4 cells count and plasma viral load assay results. Plasma viral load assays were performed locally at laboratories certified by the NIAID Virology Quality Assurance (VQA) program. Maternal clinical and laboratory toxicities were assessed through clinical evaluations (history and physical examination) and laboratory assays (ALT, AST, creatinine, BUN, albumin, bilirubin, hemoglobin) on each pharmacokinetic sampling day and at delivery. Infant data included birth weight, gestational age at birth, and HIV infection status. Infants received physical examinations at 24–48 hours, 4–21 days and 24 weeks after delivery. The study team reviewed toxicity reports on monthly conference calls, although the subject's physician was responsible for toxicity management. The Division of AIDS (DAIDS)/NIAID Toxicity Table for Grading Severity of Adult Adverse Experiences was used to report adverse events for study subjects⁹. All toxicities were followed through resolution.

Sample collection

Subjects were stable on their antiretroviral regimen for at least two weeks prior to pharmacokinetic sampling. Eight plasma samples were drawn at the third trimester and at the postpartum pharmacokinetic evaluation visits, starting immediately before an oral efavirenz dose and at 1, 2, 4, 6, 8, 12 and 24 hours post-dose. Efavirenz was given as an observed dose on an empty stomach (at least one hour before or two hours after a meal). Other information collected included the time of the two prior doses, the two most recent meals and maternal height and weight. A single maternal plasma sample and an umbilical cord sample after the cord was clamped were collected at delivery.

Drug assays

Efavirenz plasma drug concentrations were measured using a validated reversed-phase high-performance liquid chromatography (HPLC) method with ultraviolet detection at 245 nm. This HPLC method was validated using the AIDS Clinical Trials Group (ACTG) method validation guidelines over the concentration range of 0.78–10 mcg/mL¹⁰. Plasma samples with efavirenz concentrations >10 mcg/mL were diluted and re-assayed. The average accuracy was 91–104% and precision (inter- and intra-assay) was <12% of the coefficient of variation (CV). Overall extraction recovery from plasma was 99%. Plasma samples collected from women enrolled in Thailand were assayed at the PHPT-IRD laboratory at the

Faculty of Associated Medical Sciences, Chiang Mai University and samples collected from women enrolled in the United States were assayed at the Pediatric Clinical Pharmacology Laboratory at the University of California, San Diego. Both pharmacology laboratories participate in the AIDS Clinical Trial Group (ACTG), USA, Pharmacology Quality Control (Precision Testing) program, which performs standardized inter-laboratory testing twice a year¹¹.

Pharmacokinetic analyses

The pre-dose concentration ($C_{\text{pre-dose}}$), maximum plasma concentration (C_{max}), corresponding time (T_{max}), minimum plasma concentration (C_{min}), and 24 hour post-dose concentration ($C_{24\text{h}}$) were determined by direct inspection. AUC_{0-24} during the dose interval (from time 0 to 24 hours post-dose) for efavirenz was calculated using the trapezoidal rule. Apparent clearance (CL/F) from plasma was calculated as dose divided by AUC_{0-24} .

Statistical analyses

Target enrollment was at least 25 women with evaluable third trimester efavirenz pharmacokinetics. To prevent ongoing enrollment of subjects receiving inadequate dosing, enrollment was to be stopped early if six study subjects had third trimester efavirenz AUC_{0-24} below the estimated 10th percentile for the non-pregnant historical controls (40.0 mcg.hr/mL). The statistical rationale for this early stopping criterion has been previously described⁷. The number of subjects with AUC below 40.0 mcg.hr/mL and trough concentration below 1 mcg/mL, the suggested minimum target trough concentration, were determined during pregnancy and postpartum^{3, 12}. Efavirenz pharmacokinetic parameters during the third trimester and postpartum were compared at the within-subject level using 90% confidence limits for the geometric mean ratio of AUC_{0-24} , C_{max} and $C_{24\text{h}}$. When the true geometric mean of the ratio (the antilog of the true mean of the log ratios) of the pharmacokinetic parameters for pregnant and non-pregnant conditions has a value of 1, this indicates equal geometric mean pharmacokinetic parameters for the pregnant and non-pregnant conditions. If the 90% confidence intervals (CIs) are entirely outside the limits (0.8 and 1.25), the pharmacokinetic parameters for the pregnant and non-pregnant conditions are considered different. If, on the other hand, the 90% confidence limits are entirely within the limits (0.8, 1.25), the parameters are considered equivalent. If the 90% confidence interval overlaps with (0.8, 1.25), these data alone do not support any conclusions. Wilcoxon signed-rank test was used to assess the difference between third trimester and postpartum pharmacokinetic parameters. Descriptive statistics were calculated for pharmacokinetic parameters of interest during each study period.

Results

Subject Characteristics

Twenty five HIV-infected pregnant women, 21 Thai and 4 American, were enrolled. The clinical characteristics of the study population at the antepartum, delivery and 6–12 weeks postpartum visits are presented in Table 1. The majority of women initiated efavirenz after the first trimester of pregnancy. The median duration of efavirenz use at study entry (between 30 and 36 weeks gestation) was 6.7 weeks (interquartile range, IQR: 3.9 to 10.1). All 25 infants were live born and the median (range) birth weight was 3000 g (2300 to 4070).

Efavirenz pharmacokinetics

All 25 women completed both the third trimester and postpartum PK sampling. Antepartum pharmacokinetic assessments were performed at a median (range) gestational age of 33

weeks (30 to 39) and postpartum sampling at 7.9 weeks (2.0 to 14.1) after delivery. Median ($\pm$ IQR) efavirenz concentration versus time curves for the twenty five HIV-infected women receiving 600 mg of efavirenz once daily during the third trimester and postpartum are shown in Figure 1.

Efavirenz pharmacokinetic parameters during the third trimester and postpartum are presented in Table 2. The efavirenz AUC_{0-24} and C_{max} were not significantly different during the third trimester compared to postpartum. Efavirenz oral clearance (CL/F) was significantly higher during the third trimester compared to postpartum and the efavirenz concentration 24 hours after the dose (C_{24hour}) was also significantly reduced during the third trimester compared to postpartum (1.6 vs. 2.1 mcg.hr/mL, $p=0.0105$). The 90% confidence limits (90%CI) for the geometric mean ratio of the efavirenz pharmacokinetic parameters during the third trimester and postpartum (ante/post ratios) are also presented in Table 2. The median (range) efavirenz AUC and C_{24hour} were 54.5 mcg.hr/mL (29.2 to 220.3) and 1.42 mcg/mL (0.7 to 8.1), respectively, for the 21 women enrolled in Thailand, and 108.1 mcg.hr/mL (13.5 to 177.6) and 1.26 mcg /mL (0.3 to 6.3), respectively, for the 4 women enrolled in the United States.

Individual efavirenz AUC and C_{24hour} during the third trimester and postpartum are presented in Figure 2. Efavirenz AUC_{0-24} was below the study target (10th percentile for non-pregnant adults) in 5 women (20%) during the third trimester and 4 women (16%) during the postpartum period, with 3 women below the target at both time points (Table 2). Three women (12%) had an efavirenz C_{24hour} below the recommended efficacy threshold of 1.0 mcg/mL (0.23, 0.70 and 0.86 mcg/mL, Figure 2) during the third trimester. During the postpartum period, 2 women had an efavirenz C_{24hour} below 1.0 mcg/mL (0.31 and 0.66 mcg/mL, Figure 2). Of note, the women with the lowest C_{24hour} during pregnancy also had the lowest C_{24hour} postpartum. Three women with low efavirenz exposure during the third trimester had a dose increase to 800 mg once daily and PK sampling repeated and the efavirenz AUC increased to above the 10th percentile in 1 of the 3 women. Four women had efavirenz $AUC_{0-24} > 140$ mcg.h/mL during the third trimester.

Twenty-five pairs of maternal delivery and cord blood samples were collected. Two pair of maternal/cord blood samples had no detectable concentrations of efavirenz and were excluded. The median time interval between the last dose of efavirenz and delivery was 15.1 (4.0 to 24.7) hours. Maternal plasma EFV concentrations were 2.24 mcg/mL (0.99 to 7.57) at delivery and 1.05 mcg/mL (0.47 to 4.51) in the cord blood. The median ratio of cord blood/maternal delivery efavirenz concentration was 0.49 (0.37 to 0.74). Maternal delivery and cord blood efavirenz concentrations and their ratios are plotted as a function of the time interval between maternal dosing and delivery in Figure 3. At delivery, all 25 women had a HIV-1 RNA viral load less than 400 copies/mL and 19 of 25 women (76%) had a viral load below 50 copies/mL [4 subjects had 238, 215, 114 and 81 copies/mL; 2 subjects were reported as <400 and <80 cps/mL].

Infant HIV Status and Safety

At six months of age, twenty-two infants were confirmed HIV negative, one infant was confirmed HIV infected and the infection status for two infants were indeterminate. Both infants with indeterminate HIV status had HIV-DNA PCR negative results at 1 and 2 months of age and were presumed uninfected by the clinical care provider.

Clinical and laboratory information for the mother of the infected child are summarized below: antiretroviral naïve, started ZDV/3TC/EFV at 29 weeks 1 day gestation; CD4 cell count was 198 cells/mm³ and HIV-1 RNA viral load was 100,021 copies/mL (no viral resistance testing was performed). Intensive PK sampling was performed at 32 weeks

gestation and her efavirenz AUC and $C_{24\text{hour}}$ were 69.7 mcg.hr/mL and 1.6 mcg/mL, respectively, both above the study targets, and her HIV-1 viral load had decreased to 1,536 copies/mL. The baby was born at 37 weeks gestation by vaginal delivery (9.5 hours after membrane rupture). Maternal HIV-1 viral load at delivery was 238 copies/mL and efavirenz was detectable in the cord blood (0.89 mcg/mL). Infant prophylaxis included a single dose of nevirapine administered within 50 minutes of life and zidovudine for 1 week after delivery. Maternal postpartum PK sampling was performed 9 weeks after delivery and her efavirenz AUC and $C_{24\text{hour}}$ were comparable to those during the third trimester (59.3 mcg.hr/mL and 1.5 mcg/mL, respectively). Her HIV-1 viral load results were 73 and <40 copies/mL at 9 and 24 weeks postpartum. The mother reported that the infant was formula fed. The infant's HIV DNA PCR was negative at 2 and 10 days of life but positive at 1 and 2 months.

Efavirenz was tolerated well. There were 2 cases of premature rupture of membranes, 1 case of preterm labor and 1 case of gestational diabetes mellitus in the study population. Three women experienced adverse events (appendicitis, pleural effusion, 2 days fever); none were attributed to the maternal efavirenz treatment. Four women were exposed to efavirenz during the first trimester. Three women were receiving efavirenz prior to becoming pregnant and two of them continued to receive efavirenz throughout the first trimester, while one woman stopped efavirenz approximately 6 weeks after becoming pregnant but restarted efavirenz during the third trimester. One woman started EFV towards the end of the first trimester. The median duration of exposure during the first trimester was 73 days (12 to 98). No congenital anomalies or newborn complications were reported.

Discussion

Achieving optimal antiretroviral drug exposure during pregnancy is critical to ensure maximal HIV-1 viral load suppression to prevent mother-to-child transmission of HIV. The World Health Organization (WHO) HIV treatment guidelines now includes efavirenz-based combination antiretroviral therapy as a preferred first-line regimen for treating HIV-infected pregnant women after the first trimester. We found that standard efavirenz dosing of 600 mg once daily during the third trimester of pregnancy provides an exposure similar to that postpartum and in historical controls of non-pregnant adults.

The necessity to assess antiretroviral drug exposure during pregnancy is highlighted by several studies showing significant reductions in antiretroviral drug exposure with standard doses during pregnancy^{6,7}. Longer gastrointestinal emptying/transit times, reductions in gastric acid secretions, increases in body water, plasma volume, fat stores, and hepatic/renal blood flow, and temporal changes of hepatic metabolizing enzymes activities are among the physiological changes during pregnancy that can potentially impact a drugs disposition¹³. Efavirenz is metabolized via the hepatic cytochrome P450 enzymes, raising concerns regarding the risk of under exposure during pregnancy. However in our study, efavirenz AUC during the third trimester (55.4 mcg.hr/mL) was very similar to that reported in non-pregnant adults (58.1 mcg/hr/mL). Several women had an efavirenz drug exposure below the study target threshold of 40 mcg.hr/mL (10th percentile in non-pregnant adults) but this proportion was not above that expected within a non-pregnant population.

A major strength of the current study design is the ability to perform within-subject comparisons during pregnancy and postpartum. Efavirenz AUC and C_{max} were not significantly different during pregnancy and postpartum. While efavirenz Cl/F was increased and $C_{\text{pre-dose}}$ and $C_{24\text{hour}}$ were decreased during pregnancy compared to postpartum, the magnitude of the differences does not appear to be sufficient to warrant a dosing adjustment as 22 of 25 women (88%) achieved a trough concentration above the recommended

threshold of 1.0 mcg/mL. One woman had an AUC of 13.5 mcg.hr/mL and a $C_{24\text{hour}}$ of 0.23 mcg/mL during pregnancy which is well below the expected range in non-pregnant women; her AUC ante/post ratio of 0.56 was the largest change after delivery, suggesting that poor drug adherence prior to the PK sampling may have been a factor driving her individual results. Also, among the women with low trough concentrations during the third trimester, increasing the efavirenz dose from 600 to 800 mg once daily did not automatically ensure that target trough concentrations were achieved. In fact, both women who had an efavirenz trough concentration <1.0 mcg/mL and had a dose increase did not subsequently achieve target trough concentrations. Clearly, other factors may also be contributing to the low drug concentrations, particularly drug adherence, so it is difficult to conclude if a dose increase to 800 mg once daily should be routinely recommended in this situation. Thus, the decision for an efavirenz dose increase based on plasma drug concentration data should be taken on an individual basis. By study design, the efavirenz dose was reduced to the standard dose immediately following delivery but it could be argued that a woman who has had a dose increase during pregnancy should continue at the same dose until 6–12 weeks postpartum when the efavirenz concentrations are similar to those in non-pregnant adults.

Among the other non-nucleoside reverse transcriptase inhibitors, pharmacokinetic data during pregnancy are available for nevirapine and etravirine. In a study of chronic nevirapine use in US women during the second and third trimesters of pregnancy the mean nevirapine antepartum/postpartum AUC ratio was 0.90 (90% CI: 0.80–1.02)¹⁴. More recently, in a study of Ugandan pregnant women receiving nevirapine-based antiretroviral therapy the nevirapine AUC and $C_{12\text{hour}}$ was reduced by 20% during the third trimester compared to postpartum¹⁵. In a preliminary report on the pharmacokinetics of the newer NNRTI etravirine in 4 women, etravirine exposure during the third trimester was similar to that in non-pregnant adults¹⁶. Host genetic polymorphisms can impact the pharmacokinetics of antiretroviral drugs¹⁷. The homozygous variant allele of the *CYP2B6 516G>T* gene polymorphism is associated with higher efavirenz exposure¹⁸ and the frequency of this allele varies between different ethnic populations, ranging from 3.4% in Caucasians, 6.7% in Hispanic and 20% in African Americans. The majority of the women in the current study were Thai and the frequency of the *CYP2B6 516 TT* allele is 10.3% in HIV-infected Thai women¹⁹. Four women (16%) in our study had relatively high efavirenz exposures with AUC ranging from 146 to 220 mcg.hr/mL, consistent with the 516 TT genotype.

To date, efavirenz use in HIV-infected women during pregnancy and women of childbearing potential has been limited due to concerns of congenital neural tube defects following first trimester exposure. In a preclinical study, major central nervous systems anomalies were observed in 3 of 20 infants born to pregnant cynomolgus monkeys treated with efavirenz⁸. Analysis of prospective data from the antiretroviral pregnancy registry between January 1989 and 2010 found that birth defects occurred in 14 of 546 live births (2.6%, 95%CI 1.4 to 4.3%) with efavirenz first trimester exposure²⁰. One of these reported defects was a neural tube defect (neural tube closes by about 4 weeks after conception). Sufficient numbers of efavirenz first trimester exposures reported within the registry allows the exclusion of a 2-fold increase in overall common birth defects. A recent systemic review and meta-analysis of observational cohorts reported a non-significant relative risk of 0.87 for overall birth defects among women exposed to efavirenz during the first trimester of pregnancy compared with exposure to other antiretroviral drugs²¹. However, the authors cautioned that to identify an increased incidence of rare defects such as neural tube defects (prevalence of approximately 0.1%) several thousand first trimester exposures are needed to exclude an increased risk, thus data are still insufficient to draw conclusions about neural tube defects with efavirenz exposure in the first trimester. Three of the 25 women enrolled in the current

study were exposed to efavirenz throughout the first 6 weeks of pregnancy and no congenital anomalies or newborn complications were reported.

Efavirenz readily crosses the placenta in animal studies. Maternal and fetal blood concentrations in pregnant rabbits and cynomolgous monkeys are equivalent, while in pregnant rats fetal concentrations exceeded maternal concentrations²². In our subjects, the median ratio of cord blood to maternal blood efavirenz concentrations was 49%. This ratio is lower than that achieved following nevirapine exposure during pregnancy (~93%) but higher than with protease inhibitors (normally below 20%)^{6, 7, 23}. Although the efavirenz cord blood concentrations are below maternal concentrations throughout the dosing interval, virologically suppressive concentrations appear to be achieved in the fetus.

A limitation of the study is that the majority of women (84%) enrolled were Thai. Determining the optimal antiretroviral dose for HIV-infected pregnant women has shown to be population specific. For example larger reductions in lopinavir exposure during the third trimester of pregnancy have been observed in US women compared with Thai women.^{24, 25} Given the lack of impact of pregnancy of efavirenz exposure in the current study it is unexpected that a major impact will be observed in different populations but additional data in more diverse populations, including those with different frequencies of the *CYP2B6 516 TT* genotype, would be reassuring.

In conclusion, although efavirenz oral clearance is increased and pre-dose and trough concentrations are decreased during the third trimester compared to postpartum, efavirenz exposure during pregnancy following standard dosing appears adequate compared to historical data in non-pregnant adults and using within-subject ante/postpartum comparisons. With international and national antiretroviral treatment guidelines increasingly recommending efavirenz as an option in pregnant women after the first trimester, these data support the use of standard efavirenz dosing during pregnancy.

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Figure 1. Median ($\pm$ interquartile range) concentration versus time curves for HIV-infected pregnant women using 600 mg, once daily, during the third trimester and postpartum. Dashed line represents the typical 50th percentile concentrations in non-pregnant historical patients.

Figure 2.

Individual efavirenz (a) AUC and (b) C_{24 hour} for HIV-infected pregnant women using 600 mg, once daily, during the third trimester and postpartum. **Note:** Dashed line represents (a) the 10th percentile AUC (40 mcg.hr/mL) in non-pregnant historical patients and (b) suggested minimum target trough concentration (1 mcg/mL).

Figure 3.

(a) Maternal delivery and cord blood efavirenz concentrations plotted against the interval between maternal dosing and delivery. Filled circles represent maternal plasma efavirenz concentration at delivery and open triangles represent cord blood efavirenz concentrations; (b) Maternal/cord blood efavirenz concentrations ratio plotted against the interval between maternal dosing and delivery. Filled circles represent the ratio of cord blood to maternal delivery efavirenz concentration.

Table 1

Characteristics of women during the third trimester of pregnancy, at delivery and at 6- 12 weeks postpartum, and the infant characteristics at delivery.

	Median (Range) or # of Subjects (%)
3rd Trimester (n=25)	
Age (years)	29.3 (18.9 – 42.9)
Weight (kg)	69.0 (40.0 – 130.0)
Gestational Age (weeks)	32.9 (30.1 – 38.7)
CD4+ cell count (cells/ μ L)	413 (141 – 1045)
HIV-1 RNA (copies/mL)	≤ 40 (≤ 40 – 1536)
HIV1 RNA ≤ 50 cps/mL	18/25 (72%)
Other ARVs: ZDV/ d4T / 3TC / FTC / TDF / LPV-r / fAPV-r	18 / 1 / 20 / 5 / 9 / 1 / 1
Race/Ethnicity: <i>Black / Hispanic / Asian / Mixed</i>	1 (4%) / 2 (8%) / 21 (84%) / 1 (4%)
Duration of efavirenz use (weeks)	6.7 (2.4 – 199)
Delivery (n=25)	
Weight (kg)	71.5 (43.0–132.0)
Gestational Age (weeks)	38.7 (36.7–41.3)
HIV-1 RNA (copies/mL)	≤ 40 (≤ 40 – <400)
HIV-1 RNA ≤ 50 cps/mL	19/25 (76%)
Postpartum (n=25)	
Weight (kg)	60.0 (37.0 – 125.0)
Timing of PK Sampling (weeks)	7.9 (2.0 – 14.1)
Infants (n=25)	
Infant Weight at Birth (g)	3,000 (2300 – 4070)

Table 2

Efavirenz pharmacokinetics parameters during the third trimester of pregnancy and postpartum.

	3 rd Trimester (n=25)	Postpartum (n=25)	GM Ratio (90%CI) 3 rd trimester/postpartum
Efavirenz (EFV)[#]			
AUC ₀₋₂₄ (mcg.hr/mL)	55.4 (13.5 to 220.3)	58.3 (22.7 to 214.4)	0.97 (0.83 to 1.13)
C _{max} (mcg/mL)	5.44 (1.90 to 12.22)	5.10 (1.96 to 11.42)	1.11 (0.99 to 1.24)
T _{max} (median, hours)	2.0 (1.0 to 6.0)	2.0 (2.0 to 8.0)	0.88 (0.75 to 1.04)
C _{predose} (mcg/mL)	1.57 (0.39 to 7.34)	1.74 (<0.078 to 7.92) *	1.03 (0.78–1.36)
C _{24hour} (mcg/mL)	1.60 (0.23 to 8.13)	2.05 (0.31 to 8.43) *	0.88 (0.73–1.06)
CL/F (L/hr)	10.8 (2.7 to 44.4)	10.3 (2.8 to 26.4) *	1.03 (0.89–1.21)
Met EFV AUC ₀₋₂₄ Target [^]	20/25 (80%)	21/25 (84%)	NA
Met EFV C ₂₄ Target [^]	22/25 (88%)	23/25 (92%)	NA

[#] Values: Median (range) unless otherwise stated.

GM: Geometric Mean; 90%CI: 90% Confidence Interval;

AUC: Area under the curve; CL/F: apparent oral clearance.

[^] AUC₀₋₂₄ Target is 40.0 mcg.hr/mL: estimated 10th percentile for non-pregnant adults; C₂₄ Target is 1.0 mcg.hr/mL: recommended minimum threshold

* p<0.05, 3rd trimester compared to PP; Wilcoxon signed rank test

NA: Not Applicable