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Efavirenz pharmacokinetics during pregnancy and infant washout

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Abstract

Background: Limited data exist on efavirenz pharmacokinetics in HIV-positive pregnant women and neonatal washout.

Methods: HIV-infected pregnant women receiving 600 mg efavirenz once daily had intensive steady-state 24-hour pharmacokinetics profiles during the second trimester (2T), third trimester (3T) and 6–12 weeks postpartum (PP). Maternal and umbilical cord blood samples were drawn at delivery and neonatal washout pharmacokinetics were determined. Therapeutic targets were the estimated 10th percentile efavirenz area under the concentration-time curve (AUC) in non-pregnant historical controls (40.0 mcg.hr/mL) and a trough concentration ($C_{24\ hour}$) of 1 mcg/mL. Data were prospectively collected within two trials: IMPAACT P1026s (United States) and PANNA (Europe).

Results: Among 42 women studied, 15, 42 and 40 had efavirenz pharmacokinetic data available in 2T, 3T and PP, respectively. Median (range) 3T age 33 (20.7–43.5) years, weight 74 (50–132) kg, and gestational age 33.4 (28.4–37.9 weeks). Efavirenz AUC during the third trimester (60 ug*h/mL) was similar to that reported in non-pregnant adults (58 ug*h/mL). Exposure in the

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Disclosure statement

The authors report no conflicts of interest related to this work.

second trimester was lower, but within the 0.80–1.25 range. C_{24} concentrations during pregnancy, were lower compared to historical controls on 600mg EFV, however, they were similar to the C_{24} concentrations after equally potent dose of 400mg EFV. Cord blood/maternal plasma concentration ratio (range) was 0.67 (0.36–0.95). Among 23 infants with washout data available, median (interquartile range) elimination half-life was 65.6 hours (40.6– 129). HIV RNA viral load at delivery were <400 and <50 copies/mL for 96.7% and 86.7% of women, respectively. In 3T and PP, respectively, 8 /41 (19%) and 6/40 (15%) had AUC below target; 7/41 (17%) and 3/39 (8%) had C_{24} below target.

Conclusions—Efavirenz exposure was similar during pregnancy compared to postpartum, C_{24} was in line with C24 after 400mg equipotent efavirenz dosing. Efavirenz readily crossed the placenta and infant elimination half-life was over twice that of maternal participants.

Introduction

Efavirenz is the most widely used non-nucleoside reverse transcriptase inhibitor (NNRTI) and is recommended as part of combination antiretroviral treatment for HIV/AIDS in several adult treatment guidelines [1–3]. The World Health Organization (WHO) mother-to-child HIV prevention (PMTCT) guidelines include efavirenz as part of the first-line antiretroviral therapy (ART) regimens for treatment of HIV-infected pregnant women and this recommendation has been followed by several countries [3,4]. The past restriction of efavirenz use in women who are planning to become pregnant in prior US guidelines was based on few case reports of congenital neural tube defects with first trimester exposure to efavirenz [5,6], leading the United States Food and Drug Administration (FDA) to originally classify efavirenz as a Class D drug (evidence of human fetal risk) [7]. In 2014, a systematic review and meta-analysis of observational cohorts reported birth outcomes among women exposed to efavirenz during the first trimester. Twenty-three studies met the inclusion criteria and the analysis found no increased risk of overall birth defects among 2026 women exposed to efavirenz during first trimester (n = 44, 1.63% 95% CI 0.78–2.48%) compared with exposure to other antiretroviral drugs.[8] Efavirenz now has a descriptive risk summary rather than a pregnancy classification and is an alternative in US guidelines [1].

Physiological changes during pregnancy can substantially impact drug disposition. Efavirenz is primarily metabolized by the hepatic cytochrome 2B6 enzyme (CYP2B6) [9] and temporal changes in hepatic drug-metabolizing enzyme activities occur during pregnancy [10]. Several antiretroviral drugs metabolized via the hepatic cytochrome P450 enzymes have reduced exposure during pregnancy, particularly during the third trimester [11,12]. Data are scarce on the impact of pregnancy on efavirenz pharmacokinetics. The IMPAACT P1026s trial has previous assessed efavirenz pharmacokinetics during pregnancy but this primarily included Thai women [13]. In these women increased efavirenz clearance and lower trough concentrations during pregnancy was observed but the magnitude of changes were small and not likely clinically significant. A cohort study of South African HIV pregnant women with and without tuberculosis co-treatment evaluated efavirenz pharmacokinetics and described increased clearance during pregnancy [14]. Lower efavirenz and lopinavir/ritonavir exposure were described in underweight pregnant women with food insecurity when compared to well nourished women in a clinical trial in Uganda [15].

Efavirenz has been shown to cross the placenta [13] but no data on the washout pharmacokinetics of efavirenz in neonates are available

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 viral resistance. Thus, given the uncertainty regarding efavirenz drug exposure using the standard dose during pregnancy across different geographical regions our aim was to investigate the pharmacokinetics of efavirenz 600 mg QD during pregnancy and in the early postpartum period in non-Thai women, and efavirenz washout pharmacokinetics in their infants.

Materials and Methods

Study Population

The data reported were prospectively collected in two clinical trials: (1) PANNA "Pharmacokinetics of Antiretroviral Agents in HIV-infected Pregnant Women" (ClinicalTrials.gov identifier:) and (2) IMPAACT P1026s "Pharmacokinetics Properties of ARV Drugs During Pregnancy" (). Both studies are parallel-group, multi-center phase-IV studies in HIV-infected pregnant women. PANNA recruits pregnant women from HIV treatment centers in Europe and IMPAACT P1026s recruits pregnant women from sites in the USA, South America and Africa.

Patient eligibility included being HIV-infected, pregnant, ≥18 years of age at screening and treated with an ART regimen containing efavirenz (600 mg, once daily) as part of clinical care for ≥ 2 weeks before the day of the first pharmacokinetic evaluation. Participants continued to take their prescribed medications throughout pregnancy and until postpartum PK blood sampling was completed. Participants were excluded if they had a past medical history, concurrent condition or use of medication that might interfere with drug absorption, distribution, metabolism or elimination (such as renal or hepatic failure) or presented grade II-IV anemia at screening (PANNA specific) or multiple gestation pregnancy (P1026s specific). Local institutional review boards approved the protocol at all participating sites and signed informed consent was obtained from all participants prior to participation. The choice of additional antiretrovirals and duration of treatment (i.e. continuation of ART) was determined by the participant'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.

Each participant's physician was notified of the participant'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 (P1026s specific).

Clinical and Laboratory Monitoring

Inclusion screening consisted of: medical history, physical examination, serum biochemistry and hematology, HIV-1 RNA vial load and CD4+ T-cell count. Laboratory safety

assessments were performed at site. Blood samples for safety assessments were taken at visits for pharmacokinetic blood sampling and at delivery. Participants were asked for adverse events at each visit and serum biochemistry, hematology, HIV-1 RNA load and CD4+ T-cell count were measured. The HIV-status of the infants was assessed per standard of care. The study team reviewed toxicity reports on monthly conference calls, although the participant'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 participants [16]. All toxicities were followed through resolution. Infants were considered HIV uninfected if they had at least 2 negative HIV nucleic acid tests, one after age one month and one after age four months.

Sample Collection

The 24-hour intensive pharmacokinetic profiles were performed in the second trimester, third trimester and at 6 to12 weeks postpartum. Blood samples were drawn immediately before an efavirenz dose and at 1, 2, 4, 6, 8, 12 and 24 hours post-dose. PANNA participants had additional blood samples drawn at 0.5 and 3 hours post-dose. At each PK visit efavirenz was administered as an observed dose on an empty stomach (at least one hour before or two hours after a meal) in P1026s and with a meal in PANNA. 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. P1026s newborns who were not breastfeeding had four plasma samples collected to evaluate efavirenz washout pharmacokinetics at 2–10 hours, 18–28 hours, 36–72 hours and 5–9 days after birth.

Efavirenz concentration assays

Efavirenz plasma drug concentrations were analyzed by 2 centers. The PANNA samples were analyzed at the Radboud University Medical Center, Department of Clinical Pharmacy, Nijmegen, The Netherlands, and the P1026s samples at the Pediatric Clinical Pharmacology Laboratory, University of California, San Diego. Both laboratories used a validated reversed-phase high performance liquid chromatography (HPLC) method with ultraviolet detection at 245 nm. The lower limits of quantification were 0.05 mg/L (PANNA) and 0.039 mcg/L (P1026s). The linear calibration ranges in plasma were 0.2–20.0 mg/L. Both pharmacology laboratories participate in the AIDS Clinical Trial Group pharmacology quality control (precision testing) program in the United States, which performs standardized inter-laboratory testing twice a year [17].

Pharmacokinetic analyses

The pre-dose concentration (C_0), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), minimum plasma concentration (C_{min}), and 24 hour post-dose concentration (C_{24}) 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 $AUC_{0–24}$. Half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$; λ_z is the elimination rate constant derived from the terminal slope of the log concentration versus time curve. For participants with pre-dose concentrations below the assay quantification limit (indicating probable non-adherence),

single-dose AUC from time 0 to infinity was estimated as $AUC_{0–24}$ plus the C_{24} divided by λ_z. Undetectable concentrations were set at half the lower limit of quantification to calculate summary statistics.

Statistical Analyses

The numbers of participants with efavirenz 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. Descriptive statistics were calculated for pharmacokinetic parameters of interest during each study period. Efavirenz pharmacokinetic parameters during the second trimester and third trimester were compared with those postpartum at the within-participant level using a Wilcoxon signed-rank test, with a two-sided p-value <0.10 considered statistically significant. Within-participant geometric mean ratios (GMR) and 90% confidence intervals (CI) were calculated for efavirenz pharmacokinetic parameters in pregnant versus non-pregnant conditions to estimate the range of pharmacokinetic changes between the two conditions that would be consistent with the observed data and assess clinical importance, to inform dosing recommendations. GMRs and CIs between 0.80 and 1.25 (representing a PK parameter during pregnancy remaining within 80–125% of the postpartum value, in line with standard bioequivalence criteria) were considered to indicate pregnancy effects that were not clinically important. Cord blood: maternal blood concentration ratios were determined and recorded. Infant gestational age and birthweight were summarized with twins counted as one infant and their data averaged.

Results

Participant Characteristics

Forty-two pregnant women taking efavirenz 600 mg once daily were enrolled in the study. The clinical characteristics per trimester and pregnancy outcomes are presented in Table 1. All women gave birth to live infants, 41 singletons and one pair of twins. Among infants with data available, the median (range) gestational age at birth was 38 weeks of pregnancy (32 – 41 weeks) and the median (range) birth weight was 3,162 g (1,875–4,365 g).

Efavirenz Pharmacokinetics

Fifteen, 42 and 40 women completed second trimester, third trimester and postpartum pharmacokinetic sampling. The median efavirenz concentration versus time curves are shown in Figure 1 and efavirenz pharmacokinetic parameters during each of these three sampling periods are presented in Table 2. When comparing second and third trimester with postpartum, $AUC_{0–24}$ did not differ significantly and the 90% CI for the $AUC_{0–24}$ GMR was within the 0.80 to 1.25 range for the second trimester and just outside the range (0.90–1.32) for the third trimester. C_{24} and C_{min} were statistically significantly lower in the third trimester than postpartum but C12 was not significantly lower. EFV C_{max} was higher in the third trimester than postpartum. The 90% CI for C_{24} and C_{min} were just outside the 0.80–1.25 range, while C12 was within the range. The 90% CIs for C_{max} were within the 0.80–1.25 range for the second trimester, and C_{max} was higher than postpartum in the third trimester (1.01–1.56). One participant had extremely low postpartum concentrations. In a sensitivity analysis excluding this participant's data, the third trimester 90% CIs for the C_{24},

$C_{min,}$ and C_{max} GMRs all excluded 1.0 [GMR (90% CI: 0.84 (0.78, 0.89) for $C_{24,}$ 0.78 (0.65, 0.93) for C_{min}, and 1.12 (1.03, 1.21) for C_{max}]; the CI for C_{max} was within the 0.80 to 1.25 range but the CI for C_{24} and C_{min} extended below 0.80, indicating that a clinically important decrease in C_{24} and C_{min} could not be ruled out.

Median third trimester and postpartum GM AUCs were 60.0 and 62.7 ug*h/mL respectively, compared to historical control AUC of 67.2 ug*h/mL after 600 mg dosing [18]. Median second trimester AUC was lower (47.3 ug*h/mL), with high variation (range, 30.8–138.4 ug*g/mL), comparable to AUC after 400mg EFV dosing in historical controls of 49.2 ug*h/mL. [18]. Median C_{max} during pregnancy and postpartum were comparable to that seen in historical data (3.67 ug/mL). [18]. EFV C_{24} was lower during pregnancy compared to postpartum. The median postpartum C_{24} of 1.94 ug/mLwas equivalent to that seen in non-pregnant adults. [18].

Individual efavirenz AUC and C_{24} during second, third trimester and postpartum are presented in Figure 2. Efavirenz AUC $_{0–24}$ was below the study target (10^{th} percentile for non-pregnant adults) in 3/15 women (20%) during the second trimester, in 8/42 women (19%) during the third trimester and in 6/40 (15%) during the postpartum period. No women had an EFV C_{12} (mid-dose) below the proposed target of 1.0 mg/L during the second trimester or third trimester of pregnancy. The proportion of women with a C_{24} below 1.0 mcg/mL were 2/15 (13%), 7/42 (17%) and 3/40 (8%) during second trimester, third trimester and postpartum, respectively.

Seventeen pairs of maternal and cord blood were collected at delivery. Median (range) maternal plasma efavirenz concentrations at delivery were 1.43 mcg/mL (0.68 to 5.95) and 0.95 mcg/mL (0.40–3.99) was obtained in the cord blood; the median ratio of cord blood to maternal blood was 0.67 (range, 0.36–0.95). In 23 infants whose pharmacokinetic samples were obtained after birth, the median efavirenz C_{max} was 1.2 mcg/mL (range, 0.5–3.5) at median 20.2 hours (range, 2.5–165.2) after birth. Concentrations at 9 days of life are shown in Figure 3 and Table 3. At the final washout sample (between 5–9 days of life) 22 samples assayed still had measurable efavirenz (above 0.039 mcg/mL). The median (IQR) infant efavirenz half life was 65.6 hours (40.6–128.7). None of the mothers were breastfeeding.

Maternal and Infant HIV Status and Safety

At delivery 29 out of 30 (96.7%) women had HIV-1 RNA viral load less than 400 copies/mL and 26 of 30 (86.7%) women had viral load below 50 copies/mL. Seven women experienced adverse events grade 3 or greater: one case of premature rupture of membranes and preterm delivery, three cases of pregnancy-induced hypertension, two cases of postpartum hemorrhage, one pyelonephritis, one case of acute liver failure. This participant presented with fulminant hepatitis and was using efavirenz for seven months before the event. She received a liver transplant and changed her antiretroviral regimen with good outcome. This event was considered as possibly related to efavirenz.

Two congenital abnormalities were reported and were judged by the study team as possibly related to efavirenz: bilateral ulnar postaxial polydactyly and edema of penis head. Grade 3 or greater adverse events were reported for 8 infants and included prematurity, neonatal

sepsis, urinary tract infection, low glucose, respiratory distress and congenital syphilis. At six months of age, thirty infants were confirmed HIV negative, and the infection status for eleven infants were indeterminate or pending results. Infant characteristics at birth are described in Table 1.

Discussion

Achieving optimal antiretroviral drug exposure during pregnancy is critical to obtain maximal viral load suppression to prevent HIV mother-to-child transmission. Efavirenz-based regimens have been widely used during pregnancy in several countries. We found that standard efavirenz dosing of 600 mg once daily during the second and third trimesters among women with wide racial diversity provides an exposure similar to that during the early postpartum period and historical controls of non-pregnant adults. The necessity to assess antiretroviral exposure during pregnancy is highlighted by several studies showing reduced drug exposure with standard doses. Longer gastrointestinal emptying/transit times, reductions in gastric acid secretions, increases in body water, plasma volume, fat stores, and hepatic/renal blood flow, temporal changes in hepatic metabolizing enzymes activities are among the physiological changes during pregnancy that can potentially impact drug disposition. However, in our study, efavirenz median AUC during the second and third trimesters were not different from postpartum and were similar to that reported in non-pregnant adults. [19], exposure in the second trimester was within the 0.80–1.25 range, exposure in the third trimester was similar, or even higher than postpartum (90% CI 0.90–1.32). C_{24} concentrations during the second and third trimester pregnancy were lower compared to postpartum but were similar to the C_{24} concentrations seen in the ENCORE1 study with the equally potent dose of 400mg [18].

Efavirenz readily crossed the placenta achieving in our participants, with a median ratio of cord blood to maternal concentration of 67%. Median half-life in neonates in our study was 65.6 hours (8.7 to 245), which is over twice that of maternal participants. This may be related to metabolic processes that are often immature at birth, which can lead to a reduced clearance and a prolonged half-life for drugs where cytochrome P450 enzyme metabolism is a primary route for elimination, such as efavirenz [20]. The prolonged neonatal washout elimination of efavirenz may contribute to the efficacy of neonatal prophylaxis against HIV transmission with infant efavirenz dosing in the first weeks of life and make it difficult to precisely determine breast milk transfer of efavirenz during this period. There was a small observed increase in neonatal plasma concentration in some infants following delivery. One explanation for this could be the rapid loss of water and relative increase in albumin (and drug) levels, with a corresponding drop in the fraction of unbound drug. Such temporal changes could lead to a transient increase in total plasma concentrations in neonates following delivery. Infant washout pharmacokinetic data has not been previously described. This information may be helpful to design an EFV-based intervention for infants who might benefit from initiation of therapy shortly after birth.

A major strength of our study is the ability to perform within-participant comparisons during pregnancy and postpartum. Efavirenz AUC was not clinically significant lower during pregnancy. C_{max} was higher during the third trimester compared to postpartum, whereas C_{24}

was lower during second and third trimester compared to postpartum, but these effects were similar to or above the exposure and C24 observed in the ENCORE1 study. Another strength of this study is the combination of data from the PANNA and P1026s studies, which provided a sample with wide geographic diversity, including women from South America, USA, South Africa and European countries. A limitation of our study is that our sample size was too small to allow assessment of the impact of maternal and infant genetic variation on maternal and neonatal efavirenz exposure, as had been demonstrated in nursing mothers and their breastfed infants [21]. Another weakness is that the opportunistic recruitment of women who were already taking efavirenz selects women who are responding to and not experiencing adverse effects from this regimen at the time of enrollment. This selection bias overestimates positive outcomes and underestimates adverse events. Some of the women in the study experienced adverse events, including one who developed acute liver failure that required a liver transplant. Mild liver toxicity with resolution after stopping therapy is described in few women using efavirenz but fulminant hepatitis rarely occurred [22, 23].

In summary, although efavirenz exposure did not fall in the bioequivalence ranges, exposure in pregnancy was sufficient, as third trimester AUCs were similar to non-pregnant AUCs. C24 efavirenz concentrations were marginally lower during pregnancy, but exposures were deemed sufficient to meet the therapeutic target during pregnancy and no dose adjustment is needed. Standard 600 mg daily efavirenz dosing during pregnancy is adequate to obtain high rates of viral suppression and prevent HIV mother-to-child transmission.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. DHHS.Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 2017; https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.
2. BHIVA. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015; http://www.bhiva.org/Guidelines.aspx.
3. WHO.Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV infection 2016; http://www.who.int/hiv/pub/arv/arv-2016/en/.
4. de Ruiter A, Taylor GP, Clayden P, et al. British HIV Association guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). HIV Med. 2014;15 Suppl 4:1–77.
5. De Santis M, Carducci B, De Santis L, Cavaliere AF, Straface G. Periconceptional exposure to efavirenz and neural tube defects. Arch Intern Med. 2002;162(3):355.
6. Fundaro C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. AIDS. 2002;16(2):299–300. [PubMed: 11807320]
7. DHHS.Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. 2016; https://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.
8. Ford N, Mofenson L, Shubber Z, et al. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. AIDS. 2014;28Suppl 2:S123–131. [PubMed: 24849471]
9. Ward BA, Gorski JC, Jones DR, Hall SD, Flockhart DA, Desta Z. The cytochrome P450 2B6 (CYP2B6) is the main catalyst of efavirenz primary and secondary metabolism: implication for HIV/AIDS therapy and utility of efavirenz as a substrate marker of CYP2B6 catalytic activity. J Pharmacol Exp Ther. 2003;306(1):287–300. [PubMed: 12676886]
10. Tracy TS, Venkataramanan R, Glover DD, Caritis SN,National Institute for Child H, Human Development Network of Maternal-Fetal-Medicine U.Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy. Am J Obstet Gynecol. 2005;192(2): 633–639. [PubMed: 15696014]
11. Kreitchmann R, Best BM, Wang J, et al. Pharmacokinetics of an increased atazanavir dose with and without tenofovir during the third trimester of pregnancy. J Acquir Immune Defic Syndr. 2013;63(1):59–66. [PubMed: 23392467]

12. Cressey TR, Urien S, Capparelli EV, et al. Impact of body weight and missed doses on lopinavir concentrations with standard and increased lopinavir/ritonavir doses during late pregnancy. J Antimicrob Chemother. 2015;70(1):217–224. [PubMed: 25261418]
13. Cressey TR, Stek A, Capparelli E, et al. Efavirenz pharmacokinetics during the third trimester of pregnancy and postpartum. J Acquir Immune Defic Syndr. 2012;59(3):245–252. [PubMed: 22083071]
14. Dooley KE, Denti P, Martinson N, et al. Pharmacokinetics of efavirenz and treatment of HIV-1 among pregnant women with and without tuberculosis coinfection. J Infect Dis. 2015;211(2):197–205. [PubMed: 25081933]
15. Bartelink IH, Savic RM, Mwesigwa J, et al. Pharmacokinetics of lopinavir/ritonavir and efavirenz in food insecure HIV-infected pregnant and breastfeeding women in Tororo, Uganda. J Clin Pharmacol. 2014;54(2):121–132. [PubMed: 24038035]
16. The Division of AIDS (DAIDS) Standardized Toxicity Table for Grading Severity of Adult Adverse Experiences. . 2004 http://rsc.tech-res.com.
17. Holland DT, DiFrancesco R, Stone J, et al. Quality assurance program for clinical measurement of antiretrovirals: AIDS clinical trials group proficiency testing program for pediatric and adult pharmacology laboratories. Antimicrob Agents Chemother. 2004;48(3):824–831. [PubMed: 14982771]
18. Dickinson L, Amin J, Else L, et al. Pharmacokinetic and Pharmacodynamic Comparison of Once-Daily Efavirenz (400 mg vs. 600 mg) in Treatment-Naïve HIV-Infected Patients: Results of the ENCORE1 Study. Group. Clinical Pharmacology and Therapeutics 2015:98(4):406–16. [PubMed: 26044067]
19. Sustiva Package Insert Bristol-Myers Squibb Compani; Princepton, NJ 2004.
20. Lu H, Rosenbaum S. Developmental pharmacokinetics in pediatric populations. J Pediatr Pharmacol Ther. 2014;19(4):262–276. [PubMed: 25762871]
21. Olangunju A, Bolaji O, Amara A, et al. Breast milk pharmacokinetics of efavirenz and breastfed infants' exposure in genetically defined subgroups of mother-infant pairs: an observational study. Clin Infect Dis. 2015 8 1;61(3):453–63 [PubMed: 25882300]
22. Elsharkawy AM, Schwab U, McCarron B, et al. Efavirenz induced acute liver failure requiring liver transplantation in a slow drug metaboliser. J Clin Virol. 2013;58(1):331–333. [PubMed: 23763943]
23. Sonderup MW 1, Maughan D, Gogela N, et al. Identification of a novel and severe pattern of efavirenz drug-induced liver injury in South Africa. AIDS. 2016 6 1;30(9):1483–5 [PubMed: 26959511]

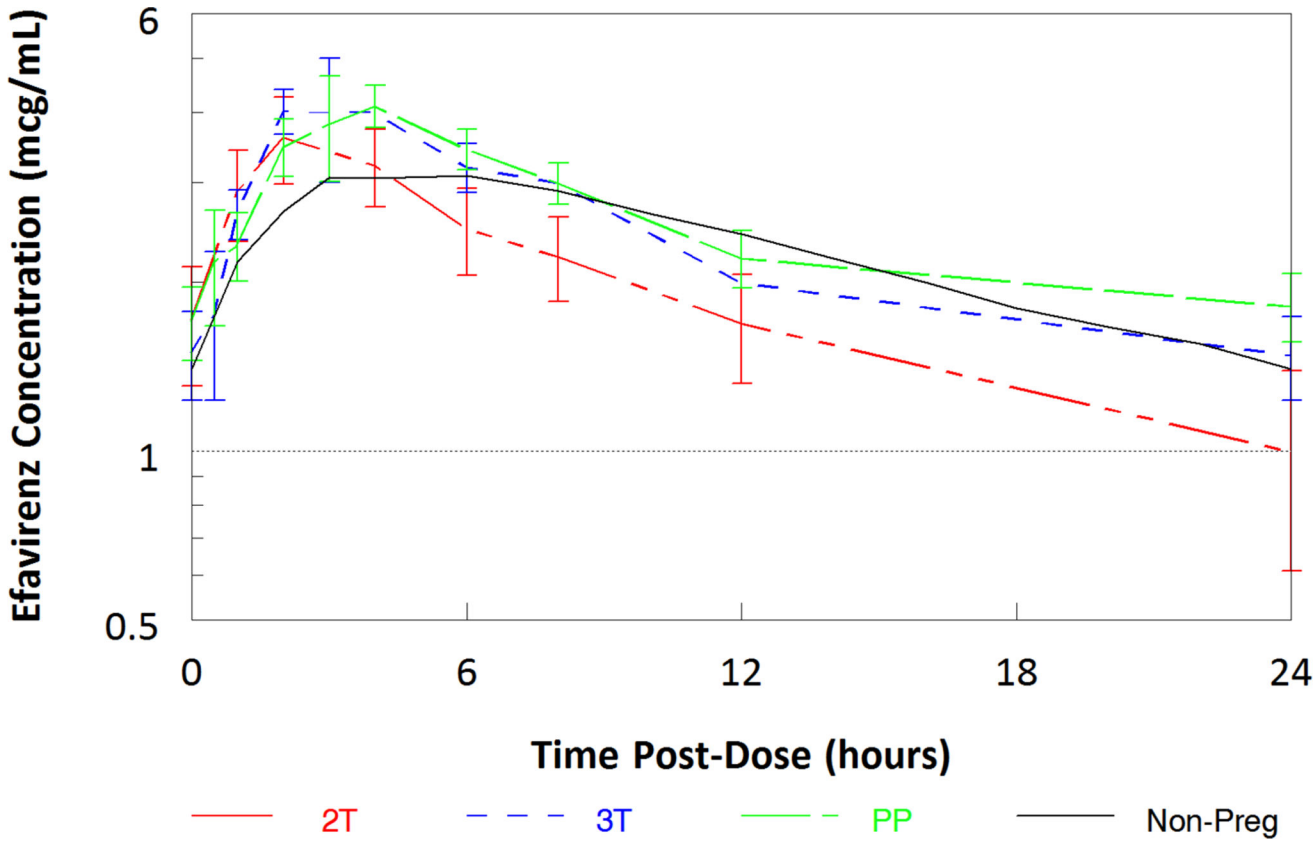
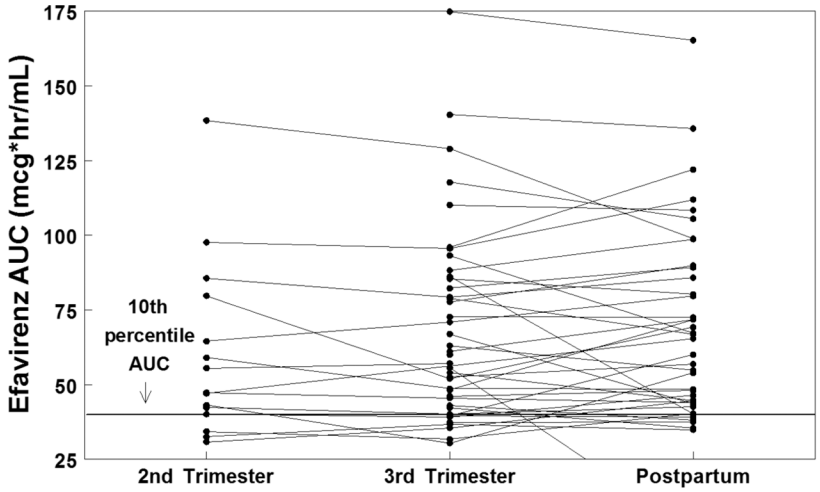


Figure 1.

Median concentration versus time curves for Efavirenz (600 mg once daily) during the second trimester, third trimester and postpartum. Solid line represents the reference 50th percentile concentrations in non-pregnant historical patients [19]



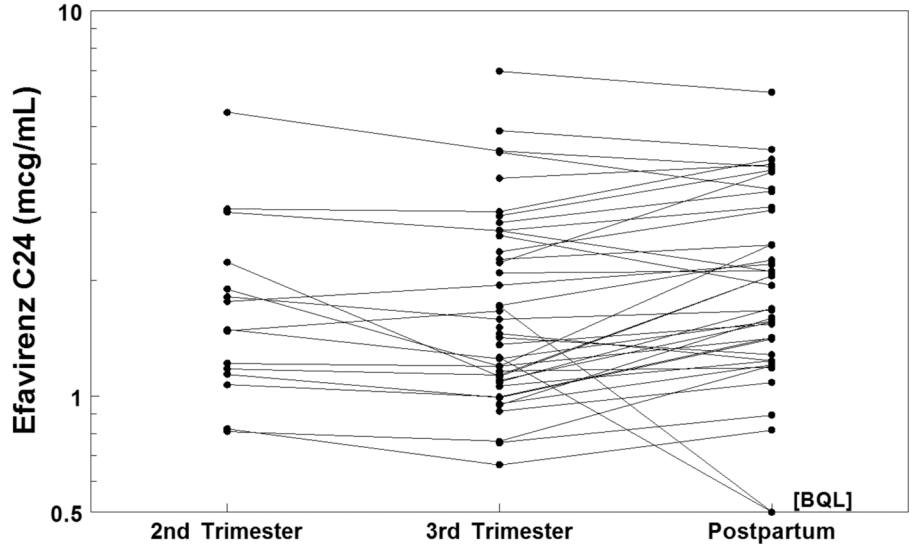


Figure 2.

Individual efavirenz (a) AUC and (b) $C_{24\ hour}$ for women using 600 mg once daily, during the second, third trimester and postpartum. The 10^{th} percentile AUC is 40 mcg*hr/mL in non-pregnant historical patients. BQL=below the quantitation limit.

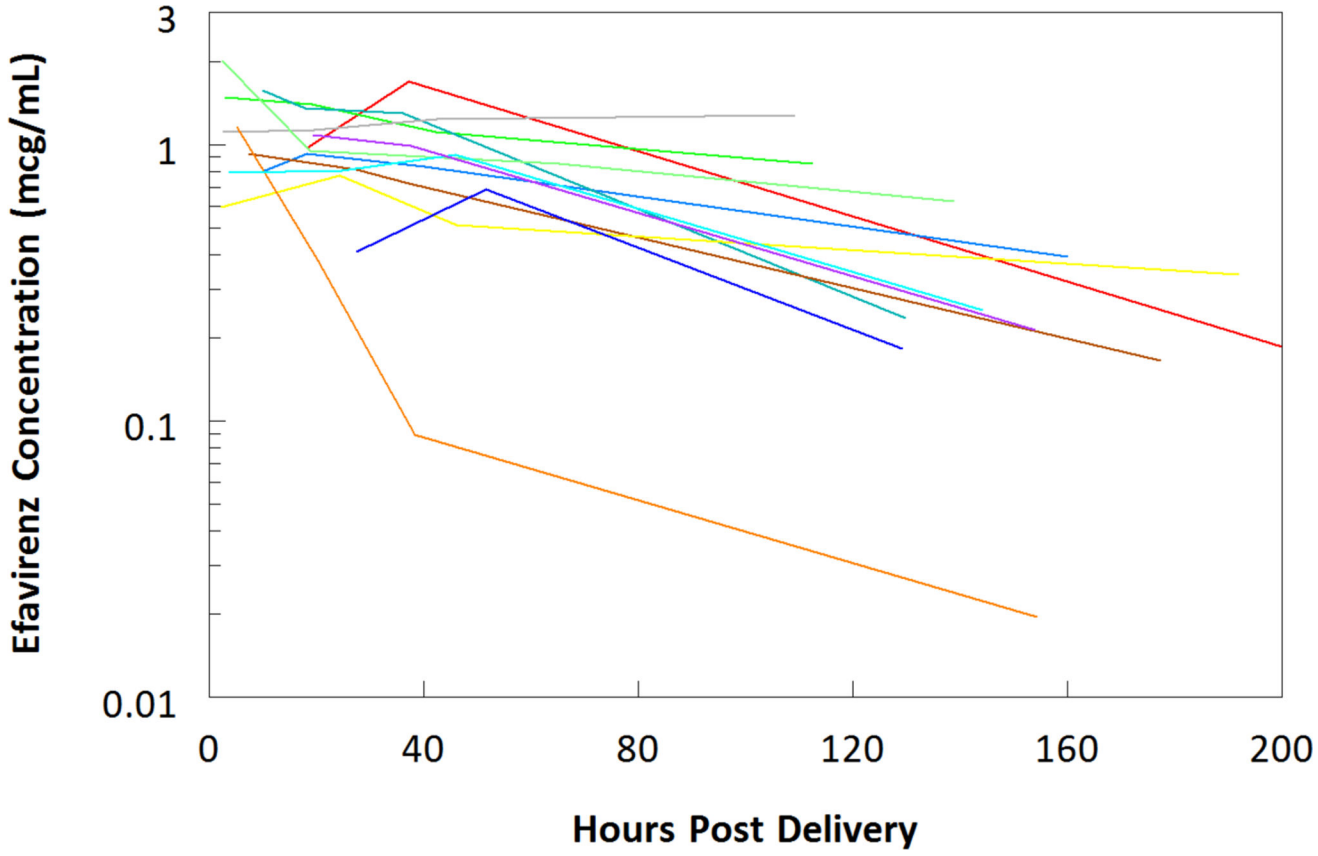


Fig 3.

Infant Washout: Efavirenz concentration vs. time after birth. The line represents individual concentration at each sampling time point.

Table 1

Patient Characteristics

Characteristic	N (%)	Median (range)
Patients included	42 (27 IMPAACT; 15 PANNA)	
Age (years) at delivery		33 (2–44)
Country		
USA	11 (26.2)	
PANNA (Europe)	15 (35.7)	
Brazil	12 (28.6)	
Argentina	1 (2.4)	
South Africa	3 (7.1)	
Race/ethnicity		
Black or African American	30 (71)	
Caucasian/White	10 (24)	
Other	2 (5)	
Concomitant medications at third trimester PK evaluation		
Zidovudine	3	
Lamivudine	14	
Emtricitabine	25	
Tenofovir	37	
Lopinavir	1	
CD4+ at delivery (cells/μL)	28	521(166–975)
Delivery plasma HIV-1 RNA concentration (copies/mL)	30	40 (20–628)
Undetectable (< 400)	29 (96.7)	
(<50)	26 (86.7)	
Pregnancy outcome *		
Gestational age at delivery (weeks)	33	38.9 (32–41)
Infant birth weight (grams)	40	3,162(1,875–4,365)

* Average data for twins was used and twins count one infant demographics

Table 2.

Maternal Efavirenz Pharmacokinetic Parameters, Median (Inter-Quartile Range, IQR)

Parameter	2nd trimester (N=15)	2T vs PP (N=14)		3rd trimester (N=42)	3T vs PP (N=40)		Postpartum (N=40)
		GMR [90% CI]	p-value		GMR [90% CI]	p-value	
AUC_{0-24} (µg*hr/mL)	47.30 (40.10, 79.70)	0.94 [0.85, 1.03]	0.241	60.02 (42.96, 85.40)	1.09 [0.90, 1.32]	0.837	62.70 (43.75, 87.51)
C_{max} (µg/mL)	3.87 (2.82, 5.67)	1.05 [0.94, 1.18]	0.296	5.13 (3.62, 5.90)	1.26 [1.01, 1.56]	0.007*	4.41 (3.38, 5.79)
C_{min} (µg/mL)	1.47 (0.96, 2.23)	0.86 [0.76, 0.97]	0.104	1.36 (1.059, 2.57)	0.86 [0.68, 1.10]	0.010*	1.60 (1.19, 2.67)
C_{12h} (µg/mL)	1.69 (1.37, 3.12)	0.89 [0.81, 0.97]	0.119	1.99 (1.50, 3.02)	1.00 [0.83, 1.21]	0.071	2.21 (1.72, 3.27)
C_{24h} (µg/mL)	1.49 (1.14, 2.23)	0.87 [0.78, 0.97]	0.079*	1.48 (1.10, 2.61)	0.92 [0.77, 1.09]	0.01*	1.94 (1.28, 3.09)
CL/F (L/hr)	12.69 (7.53, 14.96)	1.07 [0.97, 1.18]	0.104	10.00 (7.03, 14.00)	0.91 [0.76, 1.11]	0.691	9.59 (6.86, 13.72)
$T_{1/2}$ (hr)	27.82 (16.95, 34.98)	0.66 [0.47, 0.93]	0.191	32.71 (25.22, 49.14)	0.96 [0.82, 1.12]	0.285	34.67 (25.40, 59.62)
N (%) above 10th percentile nonpregnant AUC	12/15 (80.0%)			33/41(80.5%)			34/40 (85%)

*P<0.10, Wilcoxon signed rank test

GMR: Geometric Mean Ratio; 90%CI: 90% Confidence Interval; AUC: Area under the curve; CL/F: apparent oral clearance.

Table 3.

Efavirenz Infant Washout after delivery

Characteristic	Total (N=23) Median (Q1, Q3)
$T_{1/2}$ (hours)	N=18 65.6 (40.6, 128.7)
C_{max} (mcg/mL)	N=22 1.2 (0.9, 1.5)
T_{max} (hours after birth)	N=20 20.2 (6.3, 45.4)
Concentration at 2–10 hours after birth (mcg/mL)	N=18 1.1 (0.8, 1.5)
Concentration at 18–28 hours after birth (mcg/mL)	N=21 1.0 (0.8, 1.2)
Concentration at 36–72 hours after birth (mcg/mL)	N=20 0.9 (0.6, 1.4)
Concentration at 5–9 days after birth	N=22 0.4 (0.2, 0.9)