Pharmacokinetics, pharmacodynamics and pharmacogenetics of efavirenz 400 mg once daily during pregnancy and post-partum

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RUNNING TITLE: Efavirenz 400 in pregnancy

SUMMARY: We investigated efavirenz 400mg once-daily pharmacokinetics in pregnant women living with HIV and showed that efavirenz concentrations were maintained above those measured in patients on efavirenz 400mg in the ENCORE-1 study, suggesting that efavirenz 400mg can be used in pregnancy.

Some of the results of this study were presented at the 9th IAS Conference on HIV Science, 23-26 July 2017; Paris, France.

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Abstract

BACKGROUND: ENCORE-1 showed that efavirenz 400mg (EFV400) is as effective as the standard adult dose. WHO guidelines recommend EFV400 as an alternative first-line agent, with a disclaimer that no data exist on EFV400 during the third trimester of pregnancy (TT). Eliminating this caveat would allow wider use of EFV400. This study investigated the pharmacokinetics (PK), efficacy and *CYP2B6* pharmacogenetics in women living with HIV (WLWH) on EFV400 during TT and post-partum (PP).

METHODS: Open-label, two-centre study (UK and Uganda) conducted in WLWH receiving tenofovir disoproxil fumarate (TDF), emtricitabine (FTC) or lamivudine (3TC) and EFV 600mg with an undetectable viral load (VL), who switched to TDF/FTC/EFV400. Weekly therapeutic drug monitoring (TDM), steady-state PK 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 VL<50copies/mL at baseline, which was maintained throughout the study. No infant was HIV-infected. No WLWH were excluded from the study because of low EFV400 TDM results. Geometric mean (GM) ratios (TT/PP; 90%CI) of EFV400 C_{max}, AUC, and C_{trough} were 0.97 (0.85-1.10), 0.87 (0.76-0.99), 0.77 (0.65-0.91). Five/25 WLWH were slow metabolisers.

CONCLUSIONS: Although EFV400 PK parameters were slightly lower during TT versus PP, EFV concentrations were maintained above cut-off levels established by the study and those measured in ARV-naïve patients on EFV400 in ENCORE-1. All subjects maintained a VL<50, suggesting that EFV400 can be used in pregnant WLWH.

KEY WORDS: Low dose efavirenz, pharmacokinetics, pregnancy

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Introduction

The World Health Organization (WHO) recommends combination antiretroviral therapy (cART) for all pregnant women regardless of CD4+ T-lymphocyte count (CD4 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 (LMIC) 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) plus efavirenz 600 mg once daily (OD), the lower dose of 400 mg efavirenz OD is recommended as an alternative to the 600 mg OD dose [1]. Dose reductions achieved following successful dose optimization studies could result in benefits for individuals infected by HIV, by allowing access programmes to reach larger numbers of patients for the same public health expenditure, compensate for the finite global drug manufacturing capacity and address increasing demand [3].

Importantly, the ENCORE-1 study 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 central nervous system symptoms. Significantly fewer people taking the lower dose discontinued treatment due to adverse events [4]. Importantly, *CYP2B6* polymorphisms were associated with adverse events but not efficacy [5].

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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 co-administration in HIV/tuberculosis (TB) co-infected individuals.

The primary objective of this 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 to post-partum (PP).

The secondary objective was to describe the pharmacogenetics of *CYP2B6*, which is significantly associated with metabolic clearance of efavirenz [6].

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Methods

Study population and design

The study enrolled pregnant WLWH from two sites: the St. Stephen's Centre in London, UK 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 prior to 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 above 18 years, confirmation of HIV-infection status, CD4 count higher than 100 cells/mm^3, and viral load below 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 contra-indicated with efavirenz. Subjects were enrolled between gestational week 25 and 31. When switched to EFV 400 mg, women received Sustiva® 200 mg capsules (Bristol-Myers Squibb) in the UK, 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 drawn between 10 and 14 hours post-dose and analysed for efavirenz in real-time using a validated assay and results were reported to the study team for review. Viral load was tested bi-weekly and haematology and serum biochemistry at screening, baseline, and full PK visits.

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Stopping criteria were met if a viral load > 50 copies/mL was detected on two consecutive occasions or if efavirenz concentrations were below 800 ng/mL on three consecutive occasions. The 800 ng/mL study cut-off was derived by the receiver operating characteristic (ROC) curve analysis performed by Dickinson et al. within the pharmacokinetic sub-study of the ENCORE-1 study [5].

Participants were assessed for adverse events at each study visit. Adverse events were reported according to the Division of AIDS (DAIDS) grading scale (December 2004).

Full pharmacokinetic assessments

Serial blood samples were collected over 24 hours for measurement of efavirenz concentrations on two occasions: during TT (between 31-35 weeks of gestation) and after delivery (between three and 10 weeks PP), as maternal physiological conditions generally normalize to non-pregnant adult conditions within an average time of six weeks PP.

On sampling days, the pre-dose sample was drawn 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 post-dose.

At delivery, when possible, one maternal plasma sample and one umbilical cord blood sample were drawn after cord clamping.

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Efavirenz concentration assays and analysis

Samples for all full profile and London site TDM were analysed at the Jefferiss Research Trust Laboratories by a validated reversed-phase ultra-performance liquid chromatography (UPLC) method modified from a method previously published [7]. Efavirenz was measured at a wavelength of 246 nm. The lower limit of quantification was 250 ng/mL.

TDM samples collected in Kampala were analysed at the Infectious Diseases Institute Translational Laboratory using a previously described method (HPLC with ultraviolet detection) [8]. 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 [9].

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 from 0 to 24 hours (AUC_{0-24}).

All parameters were calculated using non-compartmental modelling techniques (WinNonlin Phoenix, version 7.0; Pharsight Corp, Mountain View, CA, USA). Descriptive statistics, including geometric mean (GM) and 95% confidence intervals (CI), were calculated for all parameters.

Within-subject changes of drug concentrations (TT *versus* PP) were assessed by calculating GM ratios (GMR) and 90% CI. The CI were first determined using logarithms of the individual GMR values and then expressed as linear values. The

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changes in parameters were considered significant when the CI for the GMR did not cross the value of one.

Inter individual variability in efavirenz pharmacokinetic parameters was expressed as a percentage coefficient of variation [CV, (standard deviation/mean) x 100].

Pharmacogenetics assays and analysis

Pharmacogenetic analysis involved two *CYP2B6* polymorphisms (516G>T and 983T>C) known to predict increased steady state efavirenz exposure [6,10,11]. Genomic DNA was extracted from whole blood collected at baseline after obtaining specific written consent for pharmacogenetic studies utilising the manufacturers protocol (E.Z.N.A Blood DNA Mini Kit, Omega Bio-tek, Norcross, GA). Extracted DNA was quantified using NanoDrop (ThermoFisher Scientific, Wilmington, DE). Genotyping of polymorphisms of primary interest (*CYP2B6* 516G>T [*CYP2B6*6*] and 983T>C [*CYP2B6*18*]) was accomplished using a real-time allelic discrimination polymerase chain reaction (PCR) with a DNA Engine Chromo4 System (Bio-Rad Laboratories, Hercules, CA). 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 (Wilmington, DE).

Allelic discrimination plots were obtained and genotype identification determined using Opticon Monitor version. 3.1 software (Bio-Rad Laboratories, Hercules, CA).

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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, two variant alleles (i.e. either 516 T/T, 983 C/C, or 516 G/T with 983 T/C).

Results

A total of 39 pregnant WLWH were screened (eight in London and 31 in Kampala). Thirteen women were excluded because of: detectable viral load (> 50 copies/mL, n=6), being outside of screening gestational age (n=2), being hepatitis B positive (n=1), non-compliance to study visits and procedures (n=2), having an haemoglobin < 10 g/dL (n=1) and one was enrolled in another study at Infectious Diseases Institute in Kampala. Thus, 26 were given efavirenz 400 mg at baseline. One woman was withdrawn 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 (eight 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 cut-off of 800 ng/mL on single occasions, with their

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remaining samples measured above this threshold. No subject was excluded from the study for low TDM results. The number of days from the EFV dose change to the TT full PK assessment ranged from 6 to 43, however only four women had an interval of less than 14 days (only two less than 10 days). On the full pharmacokinetic assessment days, efavirenz concentrations measured at 12 hours post dose, following observed dosing were all above the study established cut off 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 GMR (90% CI) of these 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% CI were within the constraints for bioequivalence of 80–125%, these were maintained for both C_{max} and AUC between the extended confidence interval of 70-143% for drugs meetings high variability criterion (CV>30%) [12].

Efavirenz pharmacogenetics

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

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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 plasma/maternal plasma were 0.71, 0.76, 0.57, and 0.84, respectively.

All women had a viral load below 50 copies/mL at baseline, which was maintained throughout the study (only two blips were observed, but confirmed as being < 50 copies/mL, when 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.

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Discussion

Therapeutic concentrations of efavirenz were maintained in this study despite a dose reduction from 600 mg OD 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 pre-determined cut-off selected by the study *a priori* and the threshold calculated from efavirenz concentrations in cART-naïve patients receiving efavirenz 400 mg OD in the ENCORE-1 study [4]. Further, dose reduction was observed to be safe in terms of maintenance of virus suppression, frequency and severity of maternal adverse events and in terms of prevention of vertical transmission of HIV 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 EFV 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 EFV, suggesting better tolerability (data not shown).

Furthermore, we could hypothesise that the 25% decrease in EFV C_{trough} measured during the TT versus PP is due to a change in EFV protein binding caused by a decrease of albumin during late stages of pregnancy (31%) and leading to a higher unbound fraction of EFV, which would result in lower total drug concentration measurements [13,14]. This change may not be of clinical relevance as it would indicate a modification of the equilibrium between total and unbound drug rather than a real drop in EFV 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 programmes will initiate efavirenz 400 mg as their first cART regimen. For ethical and safety considerations, the current study recruited

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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 likely be mitigated because efavirenz undergoes auto-induction and higher efavirenz concentrations in plasma have been noted at the start of efavirenz treatment, with mild reduction in efavirenz concentrations reported weeks to months after treatment initiation [15]. Importantly, efavirenz C_{trough} 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 [16,17]. In our study, only three women had a C_{trough} below 660 ng/mL and these 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 four women enrolled in London. Nonetheless, the cord plasma/blood plasma ratios measured in these four women on 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 metabolisers) 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

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management of adverse events related to efavirenz and potential cost-savings to national programmes [3]. By contrast, different efavirenz doses for different sub-populations 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 during PP, pregnant WLWH maintained concentrations above the cut-off 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.

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Acknowledgements

The authors would like to thank Anton Pozniak (SSAT, Chelsea and Westminster Hospital, London, UK), David Hawkins (SSAT, Chelsea and Westminster Hospital, London, UK), Andrew Hill (University of Liverpool, Liverpool, UK), Gary Maartens (University of Cape Town, Cape Town, South Africa), Polly Clayden (HIV i-Base), Annemiek de Ruiter (ViiV Healthcare and Guy's and St Thomas' NHS Foundation Trust, London, UK), for their advice on study design and being part of the protocol steering committee; Melynda Watkins and Paul Domanico from Clinton Health Access Initiative (CHAI) for their support on study design and completion; the research teams at St Stephen's AIDS Trust and the Infectious Diseases Institute for their hard work and the volunteers who took part in the study.

We are grateful to the NIHR BRC at Imperial College for its support of this study to Bryony Simmons for reviewing the statistical analysis.

Funding

This work was supported by research grants from Mylan and the St. Stephen's AIDS Trust.

Transparency declarations

ML has received research funding ViiV and Janssen. AO has received research funding from Merck, AstraZeneca, Pfizer, ViiV Healthcare and Janssen and consultancy for Merck and ViiV Healthcare. He is also co-inventor of patents relating to nanotechnology-based drug delivery systems. MB has received travel and research grants from and has been advisor for Janssen, Roche, ViiV, Bristol-Myers Squibb, Merck Sharp & Dohme, Gilead, Mylan, Cipla, Teva. All other authors have no potential conflicts to disclose.

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Table 1: Plasma efavirenz (EFV) pharmacokinetic (PK) parameters following the administration of efavirenz 400 mg once daily during the third trimester of pregnancy (TT) and at postpartum (PP).

	EFV GM (95% CI)		**GMR (90% CI)**
PK parameter	**TT**	**PP**	**TT/PP**
C_{max} (ng/mL)	2751 (2250-3363)	2767 (2250-3403)	0.97 (0.85-1.10)
GeoCV%	52%	52%	
C_{trough} (ng/mL)	1205 (878-1653)	1491 (1109-2005)	0.77 (0.65-0.91)
GeoCV%	89%	80%	
AUC_{0-24} (ng.h/mL)	39941 (30849-51713)	44109 (34620-56198)	0.87 (0.76-0.99)
GeoCV%	69%	62%	

GM = geometric mean, CI = confidence intervals, C_{max} = maximum concentration, AUC = area under the curve, C_{24} = 24 hour post-dose concentration, C_{trough} = 24 hour post-dose concentration.

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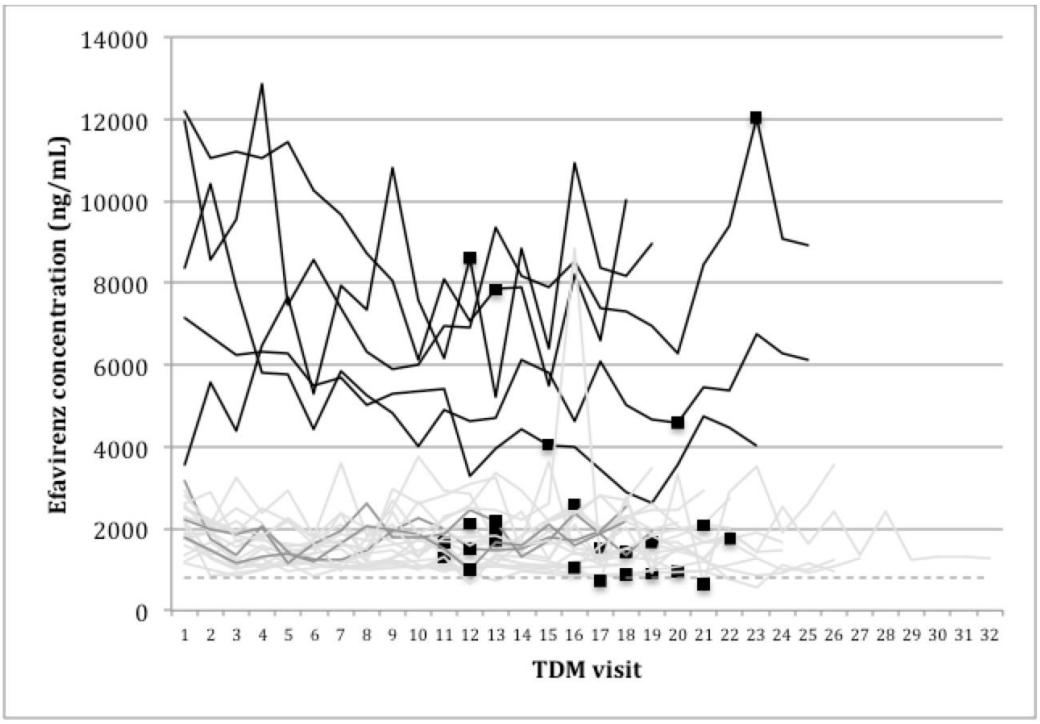
Legends to Figures

Figure 1: Efavirenz (EFV) therapeutic drug monitoring (TDM) results. Geometric mean is the dotted line. Black lines indicate those study participants who were slow metabolisers, dark grey, the intermediate metabolisers and light grey, the extensive metabolisers. The dashed grey straight line indicates the efavirenz concentration cut-off established by the study protocol at 800 ng/mL. The black squares indicate the time of delivery.

Figure 2: Geometric mean (GM) drug concentration-time curves of efavirenz following administration of efavirenz 400 mg OD during TT (grey line) and at PP (black line). Dotted lines represent 90% CI. The dashed grey straight line indicates the efavirenz concentration cut-off established by the study protocol at 800 ng/mL.

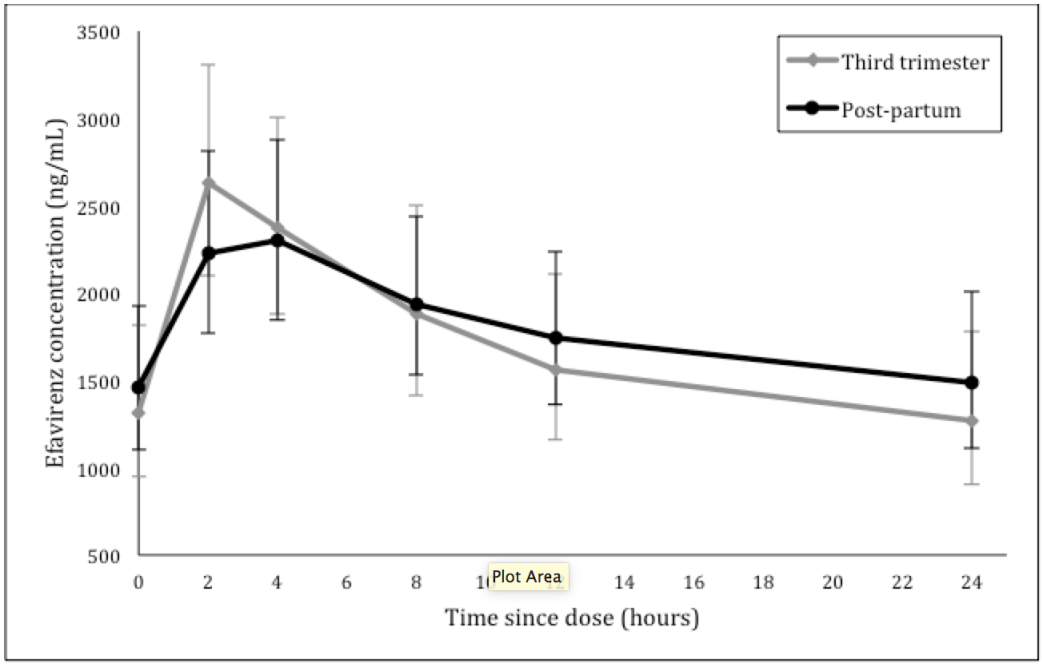
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Figure 1



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Figure 2



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