Etravirine Pharmacokinetics During Pregnancy and Postpartum

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Abstract (Updated)

Background: Maintaining therapeutic concentrations of antiretrovirals (ARVs) throughout pregnancy is critical to prevent perinatal transmission and maternal resistance development. Physiological changes during pregnancy may alter the pharmacokinetics (PK) of prescribed medicines, particularly those metabolized by cytochrome (CYP) P450 enzymes. To date, no studies have reported etravirine (ETV) PK during pregnancy. ETV is metabolized by and inhibits or induces CYP 3A4, 2C9 and 2C19. The goal was to determine ETV PK parameters during the 2nd and 3rd trimesters compared to the same subjects postpartum and to historical non-pregnant controls.

Methods: P1026s is an ongoing, multi-center, multi-arm, prospective PK study of HIV-1 infected pregnant women on ARVs for routine care. This arm enrolled women on ETV 200 mg twice daily. The PANNA Study is a similar design, enrolling in European countries. Steady-state 12-hour ETV profiles were obtained in the 2nd and 3rd trimesters, and at 4-12 weeks postpartum. Maternal and cord blood samples were collected at delivery. The P1026s minimum target steady-state ETV 12-hour AUC was 2.5 µg*hr/mL (10th percentile in non-pregnant historical controls). The 50th percentile AUC in non-pregnant controls is 4.4 µg*hr/mL, and a suggested minimum concentration from the GRACE trial is 0.16 mg/L. Paired PK parameters were compared with the Wilcoxon signed-rank test at a significance of $p<0.05$.

Results: Five, 13 and 9 women completed 2nd trimester, 3rd trimester, and postpartum PK evaluations. Median (range) age was 26 (19-43) years. Seven patients were black; 7 Hispanic; and 1 Caucasian. At delivery 9/11 patients had an HIV viral load <50 copies/mL. One subject took ETV 400 mg once daily; her oral clearance (CL/F), Vd/F, AUC_{12}, and half-life values are included in the summary data, while individual concentrations were excluded. ETV PK parameters are presented below (Table 3). The median (range) ratio of cord blood/maternal plasma concentrations (n=6) was 0.76 (0.19-4.25). Eleven children were HIV uninfected (n=6), indeterminate (n=2) or negative based on best available data (n=3); for one child results are pending.

Conclusions: While second trimester and postpartum ETV PK were similar to non-pregnant adult PK, third trimester ETV exposure was significantly higher than postpartum and historical controls. The metabolism of ETV is complex; pregnancy, ETV itself and other drugs alter the activity of these pathways. The increase in third trimester ETV exposure may be due to decreases in CYP2C19 activity or altered absorption. No ETV dose change is needed during pregnancy.

Introduction

- During pregnancy physiological changes cause decreased exposure to many antiretrovirals. No data are available on the pharmacokinetic behavior of etravirine (ETV) during pregnancy, nor on placental passage.
- Both the IMPAACT P1026 protocol and the PANNA network have been established to describe the pharmacokinetics of antiretroviral agents in HIV-infected pregnant women in comparison to post-partum pharmacokinetics (www.impaactgroup.org and www.pannastudy.com).
- ETV is a non-nucleoside reverse transcriptase inhibitor indicated for treatment of HIV-1 in treatment-experienced adults with resistant viral strains. The recommended ETV dose (for non-pregnant adults) is 200mg BID.
- The goal was to determine ETV exposure in the 2nd and 3rd trimesters of pregnancy compared to postpartum and historical controls.

Methods

- Data presented were collected in two studies: PANNA "Pharmacokinetics of Antiretroviral Agents in HIV-infected Pregnant Women" and IMPAACT study P1026 "PK Properties of ARV Drugs During Pregnancy" (ClinicalTrials.gov identifiers NCT00825929 and NCT00042289).
- Both studies are non-randomized, open-label, parallel-group, multi-center phase-IV studies in HIV-infected pregnant women. PANNA recruits patients from HIV treatment centres in Europe; IMPAACT recruits patients from sites in the US, South America, Thailand and Africa.
- Both studies recruited pregnant HIV-infected women receiving ETV as part of their cART. One subject took 400 mg QD; all other subjects took 200 mg BID.
- For the QD-dosed subject, only Cl/F, Vd/F, $t_{1/2}$, and AUC_{12} (AUC_{24} divided by 2) were included in summary statistics.
- Blood was collected for a 12h pharmacokinetic curve (t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12 ± 24h) after supervised intake of the medication in the 2nd trimester, 3rd trimester, and at least 2 weeks post-partum, using the same ETV dose. Where possible a cord blood sample and matching maternal blood sample were taken at delivery.
- Median ETV trough concentration in non-pregnant adult studies was 275 ng/mL, and median AUC was 4.4 mcg*hr/mL.
- ETV plasma concentrations were determined by validated LC/MS/MS or UPLC methods; pharmacokinetic parameters were calculated with standard noncompartmental methods. Wilcoxon signed rank tests compared parameters between time points.

Demographics

Table 1. Subject Demographics (n=15)

Parameter	Median (Range)
Age at 3rd Trimester (years)	26 (19 – 43)
Weight at 3rd Trimester (kg)	77 (48 – 102)
Race - Black; Hispanic; Caucasian	7; 7; 1
Other ARVs – Raltegravir; Ritonavir; Emtricitabine; Tenofovir; Darunavir; Zidovudine; Lamivudine; Lopinavir; Maraviroc	8; 8; 5; 5; 5; 4; 4; 3; 1
HIV RNA < 50 copies/mL at Delivery	9/11
CD4+ Cell Count at Delivery (cells/mm^3)	394 (107-610)
Gestational Age at Delivery	38 (36 – 42)
Birth Weight (grams)	3200 (2620 – 3800)
Infant Infection Status: Uninfected/Indeterminate/Negative per best data; Pending	11; 1

Results

Figure 1. Median Etravirine Concentrations

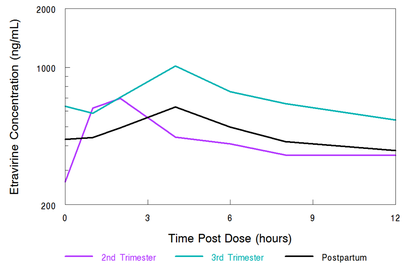
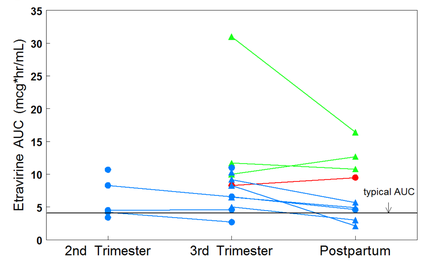
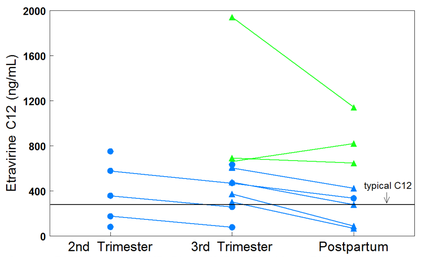


Figure 2. Etravirine AUCs



Green = PANNA subjects BID; Red = PANNA subject QD (AUC_{24} ÷ 2);
Blue = IMPAACT subjects BID; Triangles = boosted PI; Circles = no PI

Figure 3. Etravirine C12h Concentrations



Green = PANNA subjects BID; Blue = IMPAACT subjects BID;
Triangles = boosted PI; Circles = no PI

Table 2. Placental Passage (n=6)

Parameter	Median (Range)
Cord Blood Concentration	222 (68 – 2890)
Maternal Plasma Concentration	339 (188 – 680)
Cord Blood/Maternal Plasma Ratio	0.76 (0.19 – 4.25)

- Data were available from 2nd trimester (n=5), 3rd trimester (n=13) and postpartum (n=9; Table 1).
- Etravirine had high placental passage (Table 2).
- Etravirine maximum and 12-hour concentrations were higher and clearance was lower in the 3rd trimester of pregnancy compared to postpartum (Table 3, Figures 1 – 3). 3rd trimester AUC trended towards being significantly increased compared to postpartum. All other parameters were similar between the 2nd trimester, 3rd trimester and postpartum.
- Exposure did not differ between subjects taking or not taking: 1) DRV/r (n=5), 2) DRV/r or LPV/r (n=8).
- 3/5 (60%) subjects in the 2nd trimester, 11/11 (100%) subjects in the 3rd trimester, and 8/9 (89%) subjects postpartum had AUCs above the 10th percentile in non-pregnant historical controls.
- 1 subject in 3rd trimester and 1 other subject postpartum had pre-dose concentrations below detection, suggesting non-adherence.
- Two women reported grade 3 adverse events: fever and high glucose concentration.
- Three infants had congenital anomalies; skin tag on ear, bilateral double 5th toe, and patent foramen ovale with right to left shunt and right ventricular hypertrophy. Four infants had Grade 3 or 4 laboratory abnormalities of glucose (n=1), potassium (n=1) and absolute neutrophil count (n=3).

Table 3. Etravirine Pharmacokinetic Parameters

Parameter	2nd Trimester, n = 5	3rd Trimester, n = 13	Postpartum, n = 9
AUC_{12} (mcg*hr/mL)	4.5 (3.4 - 10.7)	8.3 (2.7 – 31.0)	5.7 (2.1 - 16.4)
C_0 (ng/mL)	261 (69 - 1053)	635 (<5 - 2640)	430 (<5 - 1210)
C_{max} (ng/mL)	696 (442 - 1053)	1023 (264 - 3470)*	631 (301 - 1600)
T_{max} (hr)	2 (0 - 8)	4 (2 - 6)	4 (1 - 4)
C_{12} (ng/mL)	356 (80 - 750)	540 (77 - 1940)*	378 (67 - 1140)
C_{min} (ng/mL)	253 (69 - 750)	473 (<5 - 1940)	378 (<5 - 1140)
T_{min} (hr)	12 (0 - 12)	1.5 (0 -12)	6 (0 - 12)
V_d/F (L)	1439 (337 - 27878)	432 (154 - 3563)	657 (225 - 1758)
CL/F (L/hr)	44 (19 - 59)	24 (7 - 74)*	35 (12 - 95)
$T_{1/2}$ (hr)	45 (5 - 435)	10 (6 - 82)	23 (5 - 37)

*p<0.05 for 3rd Trimester versus Postpartum

Discussion and Conclusions

- Unlike other cytochrome P450 (CYP) 3A4 substrates, etravirine exposure trends towards being higher in the 3rd trimester compared to postpartum, while 2nd trimester and postpartum exposure are similar to non-pregnant historical controls.
- Etravirine is metabolized by CYP 3A4, 2C9 and 2C19, which have increased (3A4, 2C9) or decreased (2C19) activities in pregnancy. Decreased etravirine exposure with concomitant DRV/r or LPV/r was not observed in this small study.
- Etravirine transplacental passage is high.
- More data are needed on etravirine in pregnancy to make dosing recommendations.

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