Rilpivirine Female Genital Tract Concentrations in Pregnant and Postpartum Women

Poster #439

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Introduction

- Genital tract concentrations of antiretrovirals (ARVs) may play a key role in the success of oral ARVs used for pre-exposure prophylaxis in HIV-uninfected women and for prevention of perinatal transmission of HIV.
- Viral shedding in the female genital tract may be incompletely suppressed even when plasma HIV-1 RNA is below detection.
- Rilpivirine is a second generation NNRTI licensed for use in antiretroviral naïve adults with HIV-1 RNA less than 100,000 copies/mL. It is dosed as a 25 mg once daily, single-tablet regimen, either as an individual tablet (Edurant) or co-formulated with tenofovir-DF and emtricitabine (Complera).
- Female genital tract concentrations of rilpivirine with chronic oral dosing have not been described in pregnant or non-pregnant women.

Objectives

- To investigate the female genital tract concentrations of rilpivirine with chronic oral dosing.
- To compare rilpivirine female genital tract concentrations between pregnancy and postpartum.

Methods

- International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Protocol 1026s (P1026s) is a Phase IV study of the pharmacokinetics and safety of ARVs, including a rilpivirine arm, in pregnant women.
- Twenty-four US women receiving combination ARV therapies including rilpivirine at the standard 25mg dose once daily as part of clinical care were enrolled into the study.
- Pharmacokinetic evaluations were done during the second trimester (20-26 weeks of gestation), third trimester (30-38 weeks of gestation), and postpartum (6-12 weeks after giving birth).
- Plasma samples collected at 0, 1, 2, 4, 6, 8, 12, and 24 hours post-dose, and cervicovaginal fluid (CVF) samples were collected by direct aspiration at 0, 1, 2 and 4 hours post-dose.
- Plasma and CVF rilpivirine concentrations were measured using liquid chromatography-mass spectrometry; lower limits of quantitation were plasma = 10 ng/mL and CVF = 1 ng/mL.
- Pairwise comparisons within each subject between time points were performed using a two-sided Wilcoxon signed rank test with $p < 0.10$ considered statistically significant.

Results

- Clinical characteristics and pregnancy outcomes of the 24 participants are shown in Table 1.
- Median plasma and cervicovaginal fluid (CVF) concentrations at each time point are shown in Figures 1A-1C and Table 2.
- For all time points combined, rilpivirine concentrations were 70 ng/mL (23 – 121) in CVF and 92 ng/mL (49-147) in plasma.
- The CVF-to-plasma $AUC_{(0-4)}$ ratios were significantly higher in the 2nd and 3rd trimesters of pregnancy compared to postpartum (Figures 2A-2B, Table 2).
- CVF and Plasma $AUC_{(0-4)}$s were moderately correlated antepartum and weakly correlated postpartum (Figure 3).
- Three of 189 (1.6%) plasma samples in two women were below the quantitative limit; the corresponding CVF concentrations were also below quantitation. Seventeen additional CVF concentrations out of 189 (10.6%) were below quantitation in 13 women.

Characteristics

Table 1. Participant Characteristics

Maternal Demographics (n=24)	N (%) or Median (Range)
Age at Delivery (years)	26.8 (17.2 – 37.6)
Weight at Delivery (kg)	92 (60.9 – 131.8)
Race/Ethnicity White; Black; Hispanic	1 (4%); 12 (50%); 11 (46%)
2nd Trimester	
Gestational Age	23.6 (21.7 – 26.7)
HIV-1 RNA ≤ 50 copies/mL	7/10 (70%)
CD4 (cells/mm³)	565 (293 – 828)
3rd Trimester	
Gestational Age	33.6 (29.3 – 35.0)
HIV-1 RNA ≤ 50 copies/mL	14/17 (82%)
CD4 (cells/mm³)	554 (297 – 1147)
Postpartum	
Weeks After Delivery	9.3 (6.1 – 12.4)
HIV-1 RNA ≤ 50 copies/mL	13/18 (72%)
CD4 (cells/mm³)	693 (185 – 1180)
Pregnancy Outcomes	
Gestational Age (weeks)	38.9 (32.3 – 41.4)
Birth Weight (grams)	3075 (1570 – 4570)
Infection Status: Uninfected by best available data	24/24 (100%)

Figure 1A. 2nd Trimester Rilpivirine Curves

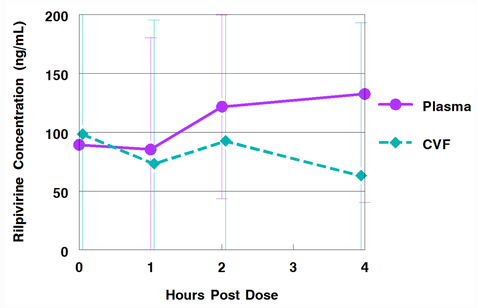


Figure 1B. 3rd Trimester Rilpivirine Curves

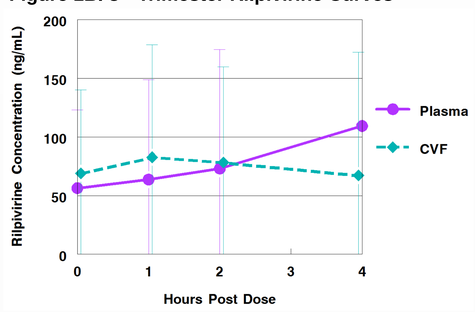


Figure 1C. Postpartum Rilpivirine Curves

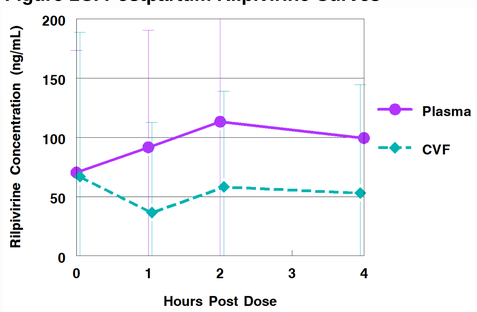


Figure 2A. CVF/Plasma AUC Ratio by Participant

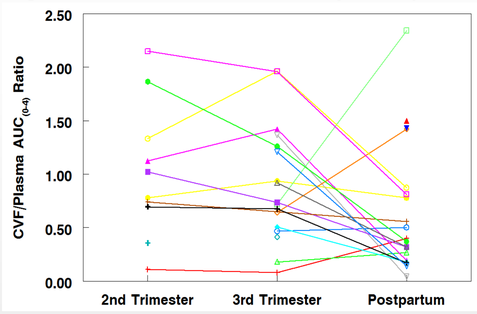


Figure 2B. CVF/Plasma AUC Ratio by Visit

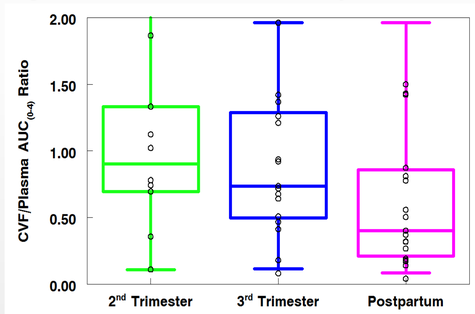


Figure 3. CVF and Plasma AUC Correlations

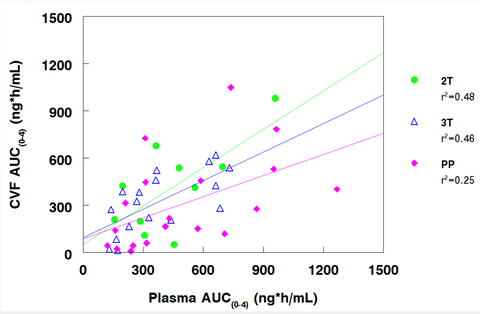


Table 2. Rilpivirine CVF and Plasma Pharmacokinetics

Parameter Median (IQR)	2nd Trimester (n=10)	3rd Trimester (n=17)	Postpartum (n=19)
CVF AUC (ng*h/mL)	419 (176-578)	325 (185-491)	217 (61-456)
Plasma AUC (ng*hr/mL)	409 (263-627)	327 (185-646)	410 (238-738)
CVF:Plasma AUC Ratio	0.90* (0.61-1.46)	0.74** (0.49-1.32)	0.40 (0.19-0.87)

*2nd Trimester vs. Postpartum, p=0.02; **3rd Trimester vs. Postpartum, p=0.07

Discussion & Conclusions

- With chronic oral dosing during pregnancy, rilpivirine female genital tract concentrations are similar to plasma concentrations over the first four hours of the dosing interval.
- CVF rilpivirine concentrations, similar to plasma concentrations, are highly variable.
- The median CVF rilipivirine concentration was more than 100 fold above the protein-free EC_{90} for rilpivirine (0.66 ng/mL). Binding proteins are lower in the genital tract than in plasma; hence, protein-free EC_{90} may be more reflective of inhibitory concentrations.
- CVF concentrations appear higher during both the 2nd and 3rd trimesters of pregnancy compared to postpartum.
- Female genital tract concentrations of rilpivirine are likely to achieve inhibitory concentrations and contribute to viral suppression in that compartment.

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