# PHARMACOKINETICS OF RILPIVIRINE IN HIV-INFECTED WOMEN DURING PREGNANCY AND POSTPARTUM

CROI 2015
Poster #894

Mark Mirochnick[1], Anna H. Tran[2], Brookie M. Best[2], Edmund V. Capparelli[2], Alice Stek[3], Jiajia Wang[4], David Shapiro[4], Elizabeth Smith[5], Lynne Mofenson[6], Tim R. Cressey[7], Regis Kreitchmann[8], IMPAACT P0126s Protocol Team

[1]Boston University, Boston, MA, USA; [2]Univ. of California San Diego, San Diego, CA, USA; [3]University of Southern California, Los Angeles, CA, USA; [4]Harvard School of Public Health, Boston, MA, USA; [5]NIAID, Bethesda, MD, USA; [6]NICHD, Bethesda, MD, USA; [7]Chaing Mai University, Chaing Mai, Thailand; [8]Irmandade da Santa Casa de Misericordia de Porto Alegre, Porto Alegre, Brazil

## Abstract

Background: Rilpivirine (RPV), a 2nd generation non-nucleoside reverse transcriptase inhibitor, has increased absorption when taken with food and is primarily metabolized by cytochrome P450 3A4. During pregnancy, physiological changes including alterations in intestinal transit time and increased CYP 3A4 activity may impact systemic drug exposure. The impact of pregnancy on RPV pharmacokinetics (PK) is unknown.
Methods: IMPAACT Protocol P1026s is an ongoing, multicenter, non-blinded prospective study evaluating the PK of antiretrovirals (ARV) in pregnant HIV-infected women that included a cohort of US pregnant women receiving as part of clinical care combination ARV regimens including RPV 25 mg once daily with food. Intensive steady-state 24 hour PK profiles were performed during the 2nd trimester, 3rd trimester and 6-12 weeks postpartum. Maternal and umbilical cord blood samples were obtained at delivery. Plasma RPV concentrations were measured using liquid chromatography-mass spectrometry, with a lower limit of quantitation of 0.010 mcg/mL. The minimum target for RPV AUC24 was 0.88 mcg*hr/mL, the 10th percentile AUC for non-pregnant adults. Pairwise comparisons within each subject between time points were performed using a two-sided Wilcoxon signed rank test.
Results: RPV PK data were available for 26 women. PK parameters are presented in the table below as median (range). There were no significant differences in any PK parameters for the 2nd or 3rd trimester compared to postpartum. Mean (90% CI) for the ratio of 2nd or 3rd trimester to postpartum log-transformed pk parameters were 1.05 (0.78-1.32) and 1.01 (0.77-1.24) for AUC and 0.94 (0.69-1.18) and 0.91 (0.70-1.12) for C(24)h, respectively. Median (range) RPV concentrations (mcg/mL) in cord blood and maternal delivery samples, and their ratio were 0.054 (BQL (below quantitation limit) - 0.102), 0.103 (BQL – 0.234) and 0.53 (0.38 – 0.83). RPV was well tolerated by all study mothers. Viral load at delivery was below 400 copies/mL for 22 of 24 women and below 50 copies/mL for 17 of 24. No infants were HIV infected, but infection data through the final 24 week visit are only available for 7 infants.
Conclusions: No significant differences in RPV exposure during pregnancy and postpartum were observed. The standard RPV dose provides adequate RPV exposure during pregnancy.

## Introduction

- Rilpivirine is a second generation non-nucleoside reverse transcriptase inhibitor.
- It has increased absorption when taken with food and is primarily metabolized by cytochrome P450 3A4.
- During pregnancy, physiological changes include alterations in intestinal transit time and increased CYP 3A4 activity, which can impact systemic drug exposure.
- The impact of pregnancy on rilpivirine pharmacokinetics is unknown.

## Objectives

- To investigate the pharmacokinetics of rilpivirine during pregnancy and postpartum.
- To compare rilpivirine AUCs, clearance, and troughs during pregnancy and postpartum within the same HIV-positive patient.

## Methods

- International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Protocol 1026s (P1026s) is a Phase IV study of the pharmacokinetics and safety of ARV's, including a rilpivirine arm, in pregnant women.
- Thirty two 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.
- Plasma rilpivirine concentrations measured using liquid chromatography-mass spectrometry, with a lower limit of quantitation of 10 ng/mL.
- Target AUC was at least 0.88 mcg*hr/mL, which is the 10th percentile AUC for non-pregnant adults. Median AUC in nonpregnant adults is 2.1 mcg*hr/mL.
- Pairwise comparisons within each subject between time points were performed using a two-sided Wilcoxon signed rank test with $p < 0.05$ considered statistically significant.

## Results

Enrollment: 19 women in 2nd trimester, 31 in 3rd trimester, and 30 women postpartum had results available at the time of this analysis

Maternal Characteristics (n=32) - N (%) or Median (range):

- Ethnicity:
  White Non-Hispanic: 1 (3.1%) Black Non-Hispanic: 18 (56.3%)
  Hispanic: 12 (37.5%) Asian/Pacific Islander: 1 (3.1%)
- Age at Delivery (years): 26.8 (17.2-37.6)
- Weight at Delivery (kg): 90.7 (60.9-171)
- HIV RNA (copies/mL):
  2nd-trimester: 40 (20 - 2270) 3rd-trimester: 20 (20 - 48700)
  Delivery: 20 (16 - 48700) Post-partum: 40 (20 - 46536)
- HIV RNA at Delivery (copies/mL):
  < 50: 21/30 (70%)
  <400: 27/30 (90%)
- CD4+ Cell Count (cells/ μL):
  2nd-trimester: 593 (180 - 1080) 3rd-trimester: 557 (151 - 1277)
  Delivery: 550 (112 - 1149) Post-partum: 716 (185 - 1427)
- Concomitant ARV's: all received TDF/FTC; 5 also received ZDV and 1 received darunavir/ritonavir at some time during pregnancy

Infant Characteristics (n=30) ) - N (%) or Median (range) :

- Weight at Delivery (grams): 3095 (1570 - 4570)
- Gestational Age (weeks): 39 (32 - 41)
- Infant Infection Status:
  Uninfected: 21 (70%) Indeterminate/Pending: 9 (30%)

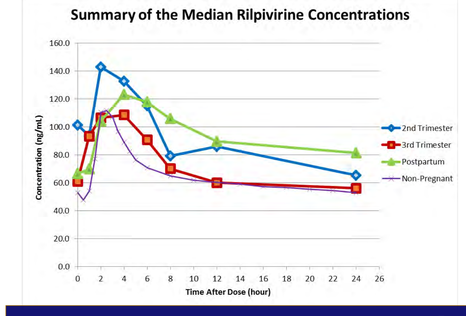
## Results (cont)

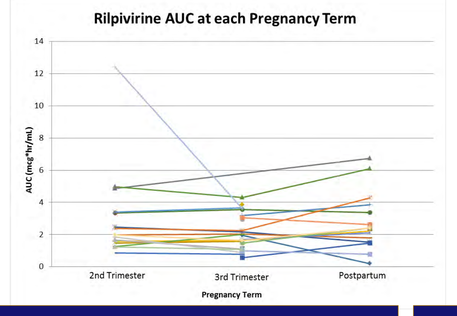
- Rilpivirine pharmacokinetic parameters showed high variability.
- The following pharmacokinetic parameters were different during pregnancy compared to postpartum:
  - $C_{24}$ and $AUC_{24}$ were reduced during 3rd trimester
  - $C_{24}$ was reduced during 2nd trimester
- When 2nd and 3rd trimester were compared, $C_0$ and $C_{min}$ were increased while $V_d$/F and T1/2 were reduced during the 2nd trimester
- AUC target was met in 15/16 (94%) of 2nd trimester women, 27/29 (93%) of 3rd trimester women and 23/26 (88%) of postpartum women for whom AUC could be calculated.
- Maternal plasma and umbilical cord samples are available for 9 women:
  Cord blood rilpivirine (ng/mL): 53.8 (<10.0 – 219.7)
  Maternal delivery plasma rilpivirine (ng/mL): 103.3 (<10.0 - 273.4)
  Cord blood/maternal plasma ratio: 0.55 (0.38-0.83)
- Rilpivirine was generally tolerated well. There were 4 maternal grade 3 or 4 AE's (2 anemia, 1 spinal headache, 1 tachycardia) and two lesser adverse events possibly attributed to rilpivirine exposure (1 oligohydramnios, 1 Grade 2 SGPT elevation). There were 4 infant grade 3 or 4 AE's (1 preterm birth; 1 neutropenia; 1 testicular torsion; 1 vomiting).

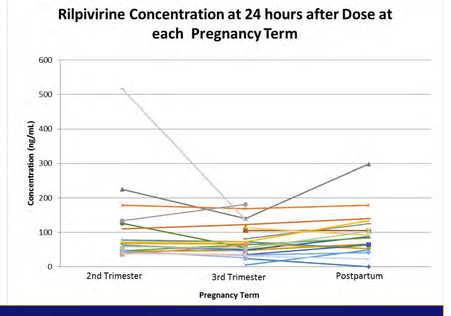
Median (range)

| Parameter | 2nd Trimester n = 19 | 3rd Trimester n = 31 | Postpartum n = 26 |
|---|---|---|---|
| $AUC_{24}$ (mcg*hr/mL) | 1.97 (0.87 - 12.40 ) | 1.70 (0.56 - 4.31) § | 2.39 (0.19 - 6.74) |
| $C_0$ (ng/mL) | 101 (31 - 550) * | 61 (<10 - 210) | 66 (<10 - 285) |
| $C_{max}$ (ng/mL) | 146 (43 - 669) | 146 (49 - 267) | 134 (48 - 407) |
| $T_{max}$ (hr) | 4 (0 - 6) | 4 (0 - 6) | 4 (0 - 8) |
| $C_{24}$ (ng/mL) | 65 (37 - 517) + | 56 (<10 -181) § | 81 (<10 - 299) |
| $C_{min}$ (ng/mL) | 68 (29 - 416) * | 52 (<10 - 136) | 58 (<10 - 200) |
| $T_{min}$ (hr) | 24 (0 - 24) | 1 (0 -24) | 5 (0 - 24) |
| $V_d$/F (L) | 750 (148 -12035) * | 1210 (155 -30626) | 695 (74 - 23571) |
| CL/F (L/hr) | 13 (2 - 29) | 15 (6 - 45) | 10 (4 - 133) |
| $T_{1/2}$ (hr) | 37 (5 - 552) * | 63 (7 - 836) | 35 (6 - 1375) |

+p<.05 2nd trimester vs postpartum; §p<.05 3rd trimester vs postpartum; *p<.05 2nd trimester vs 3rd trimester




## Conclusions

- Rilpivirine pharmacokinetics during pregnancy show extensive variability.
- While pregnancy affects some rilpivirine pharmacokinetic parameters and reduces rilpivirine exposure, AUC and Cmin remain well above targets in pregnant women receiving standard adult rilpivirine doses.
- No dosing adjustment is needed for rilpivirine during pregnancy.

## Acknowledgements

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. A. Tran was supported by the Predoctoral Research Training in Maternal and Pediatric Pharmacology grant, 1T35HD064385. Thanks to the patients and their families, the study team and the site personnel.