Abstract # 754

Substantially Lower Rilpivirine Plasma Concentrations during Pregnancy

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on behalf of the PANNA network

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1. BACKGROUND

- It is important to achieve effective blood concentrations of antiretroviral drugs to prevent treatment failure and the development of resistance. The physiological changes during pregnancy influence the pharmacokinetics of drugs. In most cases this process results in a decreased exposure during pregnancy. Limited data are available on rilpivirine pharmacokinetics during pregnancy and on the placental passage of rilpivirine. Another study by the IMPAACT group, reported that rilpivirine exposure was lower during pregnancy compared with postpartum and highly variable. Ninety percent of women had minimum concentrations above the protein binding-adjusted EC90 for rilpivirine (0.0122 mg/L).
- In 2008, a European network was established to study the pharmacokinetics of newly developed antiretroviral drugs during pregnancy (PANNA).

Objectives:

1. Here we present preliminary data on third trimester exposure to rilpivirine and cord blood concentrations at delivery.
2. To describe the safety of the antiretroviral agents during pregnancy and monitor viral load response and pregnancy outcomes.

2. METHODS

- Data presented were collected in the PANNA study: “Pharmacokinetics of Antiretroviral Agents in HIV-infected Pregnant Women” (Europe) (ClinicalTrials.gov identifier NCT00825929).
- Non-randomized, open-label, parallel-group, multi-center phase-IV studies in HIV-infected pregnant women. PANNA recruits patients from HIV treatment centers in Europe.
- Here, we report on pregnant HIV-infected patients treated with rilpivirine 25mg once daily as part of their cART.
- Blood was collected for 24h pharmacokinetic curve (t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24h) after observed intake of the medication in the third trimester. After at least 2 weeks continuation of therapy post-partum, intensive PK sampling was repeated. Where possible a cord blood sample and matching maternal blood sample were taken at delivery to estimate placental transfer.
- Safety and antiviral parameters were evaluated.
- Total rilpivirine plasma concentrations were determined with a validated UPLC method and an LLOQ of 0.0063 mg/L.
- Pharmacokinetic parameters were calculated using Phoenix (Certera®) version 6.3. Bioequivalence analysis was conducted using Phoenix.

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3. RESULTS

- Sixteen HIV-infected pregnant women were included in this analysis.
- Subject characteristics per trimester and pregnancy outcomes are shown in Table 1.

Pharmacokinetics

- Mean concentration-time profiles of RPV 25mg QD during third trimester and postpartum are shown in Figure 1. The reference concentration-time profile is based on the study from Lamorde, 2015, including 15 patients using 25mg RPV.
- GM pharmacokinetic parameters of RPV 25mg QD in third trimester and postpartum are shown in Table 2.
- GM ratios and 90% confidence intervals (90%CI) of pharmacokinetic parameters of RPV 25mg QD in third trimester compared to postpartum are shown in Table 2.
- Individual pharmacokinetic parameters after RPV 25mg QD administration during third trimester and postpartum are shown in Figure 2.

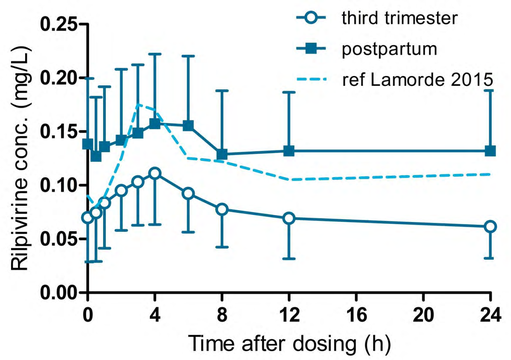
Table 1: Subject characteristics and pregnancy outcomes

General (n=16)	
Age (years)	29 (18-36)
Black; white; Asian; other [n (%)]	10 (63%); 3 (19%); 2 (13%); 1 (6%)
Treatment naive at conception [n (%)]	1 (6%)
Conception on RPV [n (%)]	13 (81%)
Eviplera use [n(%)]	16 (100%)
Concomitant ARVs [n (%)]	2 (13%): Lopinavir/ritonavir 1 (6%); zidovudine iv at delivery 1 (6%)
Third trimester (n=16)	
Gestational age (weeks)	33.4 (30.9-37.1)
Weight (kg)	81 (58-122)
HIV RNA undetectable <50 cps/mL [n (%)]	16 (100%)
CD4 count (cells/uL)	580 (159-1078), n=15, 1 unknown
Postpartum (n=15)	
Time after delivery (weeks)	6.3 (3.0-13.6)
Weight (kg)	82 (58-121)
HIV RNA undetectable <50 cps/mL [n (%)]	14 (93%); 1 unknown
CD4 count (cells/uL)	700 (340-1040)
Pregnancy outcomes (n=16)	
Gestational age (weeks)	40 (37-42)
Caesarian section [n(%)]	5 (31%); 2 unknown
Infant birth weight (grams)	3423 (2340-4470)
Low body weight (<2500 g) [n(%)]	1 (6%)
Small for gestational age [n(%)]	3 (19%)*
Infant HIV DNA PCR negative [n(%)]	15 (96%); 1 unknown

Median (range); or number (percentage)
ARVs: antiretrovirals, NRTI: nucleoside/nucleotide reverse transcriptase inhibitors
** SGA small for gestational age, based on Fenton graph, 2003*

3. RESULTS (continued)

Figure 1: Mean (±%CV) concentration-time profile after administration of RPV 25mg QD during third trimester and postpartum



Pharmacokinetics (continued)

- Two out of 16 patients had a sub-therapeutic C_{0h} (< 0.04 mg/L) in the third trimester (0.039 mg/L and 0.030 mg/L respectively), no sub-therapeutic levels were observed postpartum.
- The median (range, n=5) ratio of cord blood/maternal plasma RPV concentrations was 0.5 (0.35-0.81).

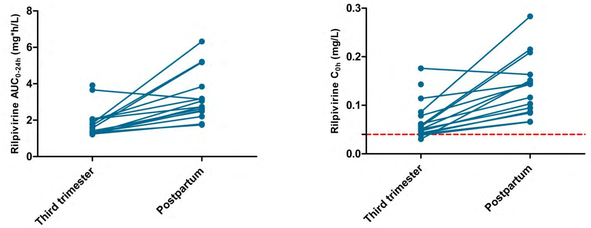
Table 2: Total RPV 25mg QD geometric mean (%CV) pharmacokinetic parameters in third trimester and postpartum and geometric mean ratios (90% CI)

Pharmacokinetic Parameters	Third Trimester (n=16)	Postpartum (n=15)	GM Ratio (%) [90% CI] Third trimester / postpartum
$AUC_{0\text{-}24h}$ (h*mg/L)	1.71 (37)	3.04 (39)	55 (46-66)
C_{max} (mg/L)	0.11 (36)	0.17 (34)	65 (55-76)
T_{max} (h)	3.02 (0.5-6.08)	5.95 (0-11.9)	
C_{0h} (mg/L)	0.06 (53)	0.13 (45)	47 (38-58)
C_{min} (mg/L)	0.05 (50)	0.10 (42)	51 (41-63)
CL/F (L/h)	14.77 (38)	8.23 (39)	184 (154-220)

Tmax: median (min-max)

3. RESULTS (continued)

Figure 2: RPV 25mg QD individual pharmacokinetic parameters during third trimester and postpartum.



Red line represents suggested therapeutic concentration of 0.04 mg/L.

Safety

- One SAE was reported: admission to the hospital because of irregular contractions, the SAE was judged not to be related to rilpivirine. In total 13 adverse events were reported by 8 patients. None were judged to be related to rilpivirine.
- No children were HIV-infected, no birth defects were reported. No major safety concerns were observed.
- No preterm births were observed, one baby with low body weight (<2500 g) at birth and three (19%) children small for gestational age.

4. CONCLUSIONS

- In this study exposure to RPV was about 50% lower in the third trimester of pregnancy, however, in this limited number of patients, this did not lead to detectable maternal VL or MTCT.
- It is important that RPV is taken with a meal during pregnancy and we would advice TDM in the third trimester to avoid sub-therapeutic exposure.

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