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A Comparison of the Pharmacokinetics of Raltegravir during Pregnancy and Postpartum

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ABSTRACT

- **BACKGROUND**: During pregnancy physiological changes take place which can influence the pharmacokinetics (PK) of antiretroviral agents and lead to decreased drug exposure. Effective plasma concentrations are important to prevent treatment failure, development of resistance and mother-to-child transmission. According to perinatal guidelines raltegravir (RAL) can be used in pregnant HIV infected women in special circumstances, because safety and PK information is limited. The use of RAL in late pregnancy for women who have a high viral load (VL) has been suggested because of its ability to rapidly suppress VL. More data on the PK behaviour and safety of RAL during pregnancy are needed to be able to recommend its use in this setting.
- **METHODOLOGY**: An open-label, multi-centre phase IV study in HIV infected pregnant women recruited in HIV treatment centers in Europe (PANNA Network). Patients treated with RAL 400 mg BID during pregnancy had intensive steady-state12-hour PK profiles in the 3rd trimester and at least 2 weeks postpartum. Where possible a cord blood (CB) and matching maternal blood samples were taken at delivery to asses placental transfer. Safety and virological efficacy were evaluated.
- **RESULTS**: Fourteen patients (8 Black, 6 Caucasian) were included in the analysis of which 5 patients were treatment naive at conception. Paired PK curves (3rd trimester and postpartum) were available for 12 and 3rd trimester only for two patients. Treatment with RAL was started during pregnancy in 11/14 women, of which 5 were in the 3rd trimester. RAL was combined with a PI-based regimen in 9/14 patients. Median (range) gestational age at delivery was 38 weeks (36-41); birth weight was 3115 (2300-3730) gm. Approaching delivery 10/14 patients had a VL <50 cps/mL, all were <1,000 cps/mL. No SAEs were reported. None of the children were HIV infected and no birth defects were reported. Geometric mean ratios (90% CI) of RAL PK parameters 3rd trimester/postpartum were: 0.77 (0.59-1.00) for $AUC_{0\text{-}12h}$; 0.83 (0.55-1.25) for C_{max}; 0.54 (0.28-1.05) for C_{12h}. Geometric mean (95% CI) for $AUC_{0\text{-}12h}$, C_{max} and C_{12h} in the 3rd trimester were: 4.95 (3.01-8.13) mg*h/L, 1.40 (0.74-2.65) mg/L and 0.054 mg/L (0.032-0.091) mg/L respectively. One patient in the 3rd trimester (and none postpartum) had a C_{12h} level below the suggested threshold of 0.020 mg/L which was associated with failure to achieve an undetectable VL in QDMRK. The median (range) ratio of CB/maternal RAL concentrations (n=8), was 1.24 (0.13-4.53).
- **CONCLUSIONS**: The slight decrease observed in exposure to RAL during 3rd trimester compared to postpartum is not considered to be of clinical importance. RAL was well tolerated during pregnancy without causing congenital abnormalities. RAL efficiently crosses the placenta.

1. INTRODUCTION

- Mother-to-child HIV transmission (MTCT) is the most common route of HIV infection among infants and children.
- Combination antiretroviral therapy (cART) is considered the standard of care for the prevention of perinatal transmission in the United States and Europe.
- Regimens including the HIV-1 integrase inhibitor raltegravir can be considered for use in special circumstances when preferred or alternative agents cannot be used (DHHS Perinatal guidelines).
- The use of raltegravir in pregnant women who present late (> 28 weeks gestational age) or whose HIV RNA load is not undetectable at third trimester has been suggested because raltegravir has been shown to rapidly reduce HIV RNA load.
- Pregnancy is associated with considerable physiological changes which may influence the pharmacokinetics of raltegravir and lead to decreased drug exposure.
- More data on the pharmacokinetic behaviour and safety of raltegravir during pregnancy are needed to be able to recommend its use in this setting.
- **Objective:** To study the effect of pregnancy on the pharmacokinetics of raltegravir and its safety and efficacy in pregnant HIV infected women.

2. METHODS

- This was a non-randomized, open-label, multi-centre phase-IV study in HIV infected pregnant women recruited from HIV treatment centres in Europe (PANNA network: www.pannastudy.com). The PANNA network is a European network of hospitals collecting pharmacokinetic curves of several ARVs during pregnancy in a prospective study.
- We enrolled HIV infected pregnant women (aged ≥ 18 years) who were on a cART regimen containing raltegravir 400 mg twice daily.
- Pharmacokinetic (PK) assessment took place in the 3rd trimester (approximately at week 33) and at least two weeks postpartum (approximately 4-6 weeks postpartum).
- Blood samples for PK assessment were collected during a 12-hour period at 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 12 hours after observed intake of 400 mg of raltegravir with breakfast.
- Where possible umbilical cord blood (CB) and matching maternal blood samples were obtained at delivery to asses placental transfer.
- Safety and virological efficacy were evaluated.
- Raltegravir plasma concentrations were analyzed by use of a validated high-pressure liquid chromatography (HPLC) with a lower limit of quantification of 0.014 mg/L.
- Pharmacokinetic parameters were determined using a mixed linear model on the log-transformed data in Phoenix/WinNonlin version 6.3.
- Geometric means ratios (GMRs) and 90% confidence intervals (CI) of raltegravir $AUC_{0\text{-}12h}$, C_{max}, C_{12h} and t_{half} of 3rd trimester versus postpartum (= reference) were calculated.
- This trial is registered at ClinicalTrials.gov, number NCT00825929.

3. RESULTS

Table 1: Patient characteristics

General (n=14)		
Age at delivery (years)		31 (22-44)
White; black [n (%)]		8 (57%); 6 (43%)
Treatment naive at conception [n (%)]		5 (36%)
Conception on raltegravir [n (%)]		3 (21%)
Start raltegravir per trimester		2 (14%) 1st trim; 4 (29%) 2nd trim; 5 (36%) 3rd trim
Concomitant ARVs [n (%)]:	NRTI	11 (79%); TDF+FTC 7 (50%), AZT+3TC 2 (14%)
	PI	9 (64%); DRV/r 7 (50)%; ATV/r 1 (7%); LPV/r 1 (7%)
	Other	4 (29%)
Third trimester (n=14)		
Gestational age (weeks)		33 (31-39)
Weight (kg)		73 (49-90)
HIV RNA undetectable <50 cps/mL [n (%)]		11 (79%) / < 400 cps/mL: 14 (100%)
CD4 count (cells/uL)		497 (120-1086)
Postpartum (n=12)		
Time after delivery (weeks)		6 (4-9)
Weight (kg)		65 (43-78)
HIV RNA undetectable <50 cps/mL [n (%)]		10 (83%) / <400 cps/mL: 11 (92%); one 650 cps/mL
CD4 count (cells/uL)		337 (130-1041)
Pregnancy outcomes (n=14)		
Gestational age (weeks)		38 (36-41)
Caesarian section [n(%)]		8 (57%)
Infant birth weight (grams)		3115 (2300-3730)
Infant HIV DNA PCR negative [n(%)]		14 (100%)

Median (range) for continuous variables, n for categorical variables.

3. RESULTS (continued)

- For 14 HIV infected women who used raltegravir 400 mg twice daily during pregnancy data are available.
- Treatment with raltegravir was started during pregnancy in 11/14 women (79%), of which 5 started in the 3rd trimester (36%), see Table 1.
- In 6/14 patients (43%) raltegravir was part of quadruple cART. These patients started raltegravir in the 2nd or 3rd trimester.

Pharmacokinetics

- Evaluable paired PK curves (3rd trimester and postpartum) were available for 12 patients. Two patients had 3rd trimester curves only and for one patient the postpartum curve was incomplete and therefore not evaluable.
- Exposure ($AUC_{0\text{-}12h}$) to raltegravir during pregnancy (3rd trimester) was 33% lower than postpartum (see Figure 1 and Table 2).
- Individual exposure to raltegravir in 3rd trimester and postpartum shows considerable intra- and intersubject variability (see Figure 2).
- C_{12h} plasma concentrations in 3rd trimester were approximately 50% lower compared to postpartum [GMR (90% CI): 0.54 (0.28-1.05)].
- One patient in the 3rd trimester (and none postpartum) had a C_{12h} level below the suggested threshold of 0.020 mg/L which was associated with failure to achieve an undetectable HIV RNA load in QDMRK study. This patient had an HIV RNA load of 74 cps/mL at PK assessment during the 3rd trimester visit and an undetectable HIV RNA load at the day of delivery.
- The median ratio (range) of cord blood/maternal plasma concentrations was 1.24 (0.13-4.53; n=8).

Figure 1: Mean raltegravir concentrations

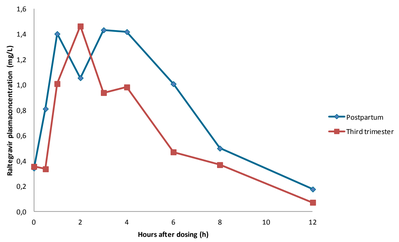


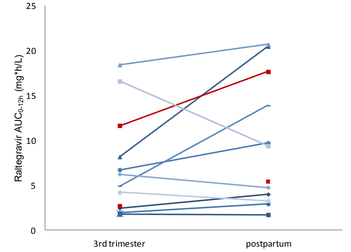
Table 2: Pharmacokinetic parameters

	Third Trimester* (n=13)	Postpartum* (n=12)	GM Ratio (90% CI)** Third Trimester / Postpartum
$AUC_{0\text{-}12h}$ (h*mg/L)	4.95 (3.01-8.13)	7.08 (4.16-12.05)	0.77 (0.59-1.00)
C_{max} (mg/L)	1.40 (0.74-2.65)	1.83 (0.95-3.55)	0.83 (0.55-1.25)
T_{max} (h)	2.0 (0-8.0)	3.4 (0-7.8)	
C_{12h} (mg/L)	0.05 (0.03-0.09)	0.10 (0.05-0.20)	0.54 (0.28-1.05)
t_{half} (h)	2.5 (1.7-3.5)	2.5 (1.6-3.7)	1.02 (0.55-1.25)

* Geometric mean (95% confidence interval); except for Tmax: median (min-max)
** mixed model analysis

3. RESULTS (continued)

Figure 2: Individual raltegravir $AUC_{0\text{-}12h}$ values third trimester vs. postpartum



Blue: undetectable HIV RNA load during or close to delivery
Red: detectable HIV RNA load (> 50 to <400 cps/mL) during or close to delivery

Safety and efficacy

- None of the children were HIV infected and no birth defects were reported.
- No SAEs were reported.
- HIV RNA load was detectable for 3 patients around delivery. None of these patients had an HIV RNA load above 400 cps/mL and their C_{12h} levels (if available) were not below the suggested threshold of 0.020mg/L.

Discussion

- The mean exposure to raltegravir ($AUC_{0\text{-}12h}$) as determined postpartum is in line with historical control values (6.3 h*mg/L; Markowitz et al, JAIDS 2006).
- It is well known that the pharmacokinetics of raltegravir displays large intersubject variability, which was observed in our study as well.
- Our data show that raltegravir is started late in pregnancy in one third of the patients and is part of a quadruple regimen in almost half of the patients.

4. CONCLUSIONS

- The slight decrease observed in exposure to raltegravir during 3rd trimester compared to postpartum is not considered to be of clinical importance given the large inter- and intrasubject variability in raltegravir pharmacokinetics.
- Raltegravir was well tolerated during pregnancy without causing congenital abnormalities.
- Raltegravir efficiently crosses the placenta.

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