

1. INTRODUCTION

- During pregnancy it is important to achieve effective concentrations of antiretroviral drugs in the blood to prevent treatment failure and the development of resistance.
- Physiological changes take place, influencing the pharmacokinetics of medicines. In most cases, the net effect will be a decreased exposure during pregnancy.
- Until now only limited data are available about the pharmacokinetic behavior of raltegravir during pregnancy and whether the drug passes the placenta.
- In 2008, a European network was established to study the pharmacokinetics of newly developed antiretroviral drugs in pregnant women (PANNA).
- We present preliminary data on third trimester exposure to raltegravir.

2. OBJECTIVES

- To describe the pharmacokinetics of raltegravir in the third trimester of pregnant HIV-infected women in comparison to post-partum pharmacokinetics.
- To describe the safety of the antiretroviral agents during pregnancy and the efficacy in terms of viral load response of the mother and prevention of mother to child transmission.

3. METHODS

- This is part of a non-randomized, open-label, parallel-group, multi-center phase-IV study in HIV-infected pregnant women recruited from HIV treatment centers in Europe.
- Patients treated with raltegravir (400mg BID) during pregnancy were included in the study.
- Blood was collected for a 12h pharmacokinetic curve (t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12h) after supervised intake of 400mg raltegravir with food in the third trimester. At least 2 weeks post-partum intensive PK sampling was repeated.
- Where possible a cord blood sample and matching maternal blood sample were taken at delivery.
- Safety and antiviral efficacy were evaluated.
- Raltegravir plasma concentrations were determined and pharmacokinetic parameters were calculated.

4. RESULTS

- Up till now 6 women were included who used raltegravir 400mg BID.
- One patient withdrew consent prior to the post partum curve.
- None of the 6 children showed congenital abnormalities.

Table 1: Clinical characteristics

3rd trimester (n=6)		
age (years)	32.5	(29-44)
weight (kg)	66.2	(56.0-78.5)
gestational age (weeks)	34.1	(32.7-35.3)
CD4+ cell count (cells/ μ L)	240	(151-837)
HIV-1 RNA <50 cps/mL	4 out of 5	(1 ptnt 242 cps/mL; 1 ptnt missing)
other ARVs TDF / FTC / ZDV / 3TC / DRVr / LPVr / ATVr	5 / 4 / 1 / 1 / 4 / 1 / 1	
race (black / caucasian)	3 / 3	
Delivery (n=5)		
gestational age (weeks)	37.8	(34.1-38.7)
HIV-1 RNA <50 cps/mL	3 out of 5	(1 ptnt 99 cps/mL; 1 ptnt 62 cps/mL)
way of delivery (caesarian section / natural)	4 / 2	
Post partum (n=5)		
weight (kg)	63.2	(56.0-70.0)
weeks after delivery	8.6	(4.6-12.9)
Infant		
infant weight at birth (g)	2970	(2030-3360)
infant VL undetectable	5 out of 5	(1 child not known)

Values are n for categorical variables and median (range) for continuous variables.

Pharmacokinetics

Figure 1 shows matched individual raltegravir AUCs in the third trimester and post partum. Table 2 shows median (range) of the pharmacokinetic parameters and of the ratio's of the parameters in the third trimester compared to post partum.

Figure 1 Raltegravir AUC,

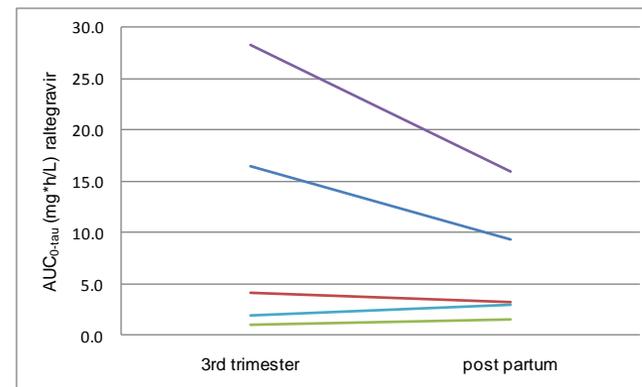


Table 2: Raltegravir PK parameters

	3rd trimester (n=6)	post partum (n=5)	ratio (n=5)
AUC _{0-12h} (mg*h/L)	4.14 (1.85-28.32)	5.42 (2.92-16.02)	1.26 (0.66-1.77)
C _{12h} (mg/L)	0.09 (0.02-0.33)	0.15 (0.05-0.28)	1.61 (0.21-2.33)
C _{max} (mg/L)	0.79 (0.38-9.67)	1.04 (0.44-4.03)	1.44 (0.44-2.40)
	conc maternal at delivery (mg/L)	conc. cord blood (mg/L)	cord blood / maternal plasma ratio
GB0201	0.615	0.628	1.02
IT0103	0.063	0.073	1.16

5. CONCLUSIONS

- In this small population (n=6) exposure to raltegravir was not lower during pregnancy (third trimester) than post-partum. This is in contrast to a number of other antiretroviral agents, especially protease inhibitors.
- Raltegravir efficiently crosses the placenta.
- These results need to be confirmed in a larger group of patients.