A Comparison of the Pharmacokinetics of Darunavir, Atazanavir and Ritonavir during Pregnancy and Post-partum

Nijmegen Institute for Infection, Inflammation & Immunity

Angela P.H. Colbers
Department of Pharmacy
Radboud University Nijmegen MC
PO Box 9101
6500 HB Nijmegen
The Netherlands
Tel: +31-24-3616405
e-mail: a.colbers@akf.umcn.nl

Angela Colbers[1], José Moltó[2], Jelena Ivanovic[3], Carmen Hidalgo Tenori[4], Katharina Weizsäcker[5], Ineke van der Ende[6], David Hawkins[7], Graham Taylor[8], Tariq Sadiq[9], David Burger[1], on behalf of the PANNA network

[1]Department of Pharmacy, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [2] "Lluita contra la Sida" Foundation, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [3]National Institute for Infectious Diseases "L. Spallanzani", Rome, Italy; [4]Hospital Universitario Virgen de las Nieves Granada, Granada, Spain; [5]CHARITÉ Berlin, Berlin, Germany; [6] Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands; [7]Chelsea & Westminster Hospital, London, UK; [8]St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK; [9]St George's hospital, London, UK

Poster #: 1013

ABSTRACT (updated)

- **Background**: It is important to achieve effective concentrations of antiretroviral drugs in the blood to prevent treatment failure and the development of resistance. During pregnancy physiological changes take place influencing the pharmacokinetics (PK) of medicines. Mostly, the net effect will be a decreased exposure during pregnancy. Very limited data are available on the PK behavior of darunavir (DRV) during pregnancy and placental passage and for atazanavir (ATV) the data have been interpreted inconsistently. In 2008, a European network was established to study the pharmacokinetics of newly developed antiretroviral drugs during pregnancy (PANNA). We present data on 3rd trimester exposure to DRV, ATV and ritonavir (RTV, used as booster).
- **Materials & Methods**: Patients treated with DRV/RTV (600mg/100mg BID or 800mg/100mg QD) or ATV/RTV (300mg/100mg QD) during pregnancy were screened and a pharmacokinetic curve (t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24h) was taken in the 3rd trimester and at least 2 weeks post-partum. Where possible a cord blood sample and matching maternal blood sample were taken at delivery. Safety and antiviral efficacy were evaluated.
- **Results**: Paired plasma concentration curves (3rd trimester and post-partum) were available for 6 patients on DRV; 13 patients on ATV and 19 patients using RTV as booster. For DRV, geometric means ratios (GMR) + 90% confidence interval (CI) of PK parameters 3rd trimester/post-partum DRV were: 0.64 (0.47-0.86) for AUC_{tau}; 0.71 (0.49-1.03) for C_{max}; 0.45 (0.22-0.91) for C_{last}. For ATV GMRs (90% CI) were: 0.67 (0.53-0.83) for AUC_{tau}, 0.71 (0.56-0.91) for C_{max}; 0.67 (0.46-0.97) for C_{24h}. For RTV GMRs (90% CI) were: 0.47 (0.35-0.64) for AUC_{tau}; 0.41 (0.31-0.55) for C_{max}. For DRV 2/9 patients showed concentrations below the target concentration (0.55 mg/L) in the 3rd trimester, compared to none on ATV (target 0.15 mg/L).
  The ratio of cord blood/maternal plasma concentrations ranged from 0.11-0.67 for ATV (n=7) and was <0.076 for DRV (n=5); for RTV all cord blood samples were <LOQ (n=12). All children were HIV uninfected, no birth defects were reported.
- **Conclusions**: Exposure to DRV, ATV and RTV was significantly lower during pregnancy (third trimester) than post-partum, with the most important effect for the boosting agent RTV. This is in line with previously reported exposure to protease inhibitors. Transplacental passage of ATV, DRV and RTV is low. Evidence-based recommendations for ARVs in pregnancy are urgently needed.

1. INTRODUCTION

- During pregnancy physiological changes cause a decreased exposure to the HIV protease inhibitor lopinavir. Very limited data are available on the pharmacokinetic behavior of darunavir (DRV) during pregnancy and placental passage and for atazanavir (ATV) the data have been interpreted inconsistently.
- The PANNA network has been established to describe the pharmacokinetics of anitretroviral agents in the third trimester of pregnant HIV-infected women in comparison to post-partum pharmacokinetics (www.pannastudy.com).
- A secondary objective is 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.

2. METHODS

- This is part of a non-randomized, open-label, parallel-group, multi-center phase-IV study in HIV-infected pregnant women recruited from 17 HIV treatment centers in Europe.
- Here, we report on pregnant HIV-infected patients treated with DRV/RTV or ATV/RTV as part of their cART.
- Blood was collected for a 12h or 24h pharmacokinetic curve (t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24h) after supervised intake of the medication 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.
- DRV, ATV and RTV plasma concentrations were determined by a validated UPLC method, pharmacokinetic parameters were calculated using WinNonlin version 5.2.
- Paired samples t-test was performed on the log-transformed data (using SPSS 18.0).

3. RESULTS

- For 9 HIV-infected women who used DRV/RTV during pregnancy (6 on DRV/RTV 800/100mg QD; 3 on DRV/RTV 600/100mg BID) data are available. For ATV/RTV 300/100mg QD data are available of 13 women.
- Three patients on DRV/RTV 800/100mg QD withdrew consent for the post partum curve or stopped using the medication after delivery.
- Cord blood and maternal samples are available for 5 patients on DRV and 7 patients on ATV.

Table 1: Demographics

parameters		
age (years)	33.5	(20-45)
weight (kg)	75	(63-135)
NRTI (n)	Truvada® (12); Combivir® (4); Kivexa® (3); Combivir®+tenofovir (3); none (1; DRV/r monotherapy)	
Raltegravir (n)	5	
race (black / caucasian)	9 / 13	
Delivery		
gestational age (weeks)	38.4	(34.4-40.0)
HIV-1 RNA <50 cps/mL	17 out of 22	(VL>50: 70; 162; 242; 525; 28711 copies/mL respectively)
way of delivery (caesarian section / natural)	20 / 2	
Infant		
infant weight at birth (g)	3050	(2290-4350)
infant VL undetectable	22 out of 22	

Median (range) for continuous variables, n for categorical variables. Kivexa® = Epzicom®

Table 2: Pharmacokinetic parameters

	Atazanavir (300/100mg QD)		Darunavir (600/100mg QD)		Darunavir (800/100mg BD)	
	3rd trimester (n=13)	post partum (n=13)	3rd trimester (n=6)	post partum (n=3)	3rd trimester (n=3)	post partum (n=3)
AUC_{0-tau} (mg*h/L)	31.2 (21.5-45.5)	46.9 (35.9-61.3)	46.8 (30.7-71.4)	76.2 (61.3-84.8)	36.8 (20.6-65.8)	51.8 (30.9-86.7)
C_{last} (mg/L)	0.59 (0.37-0.96)	0.88 (0.53-1.48)	0.64 (0.30-1.37)	2.07 (1.38-3.10)	2.05 (1.11-3.78)	2.41 (1.07-5.42)
C_{max} (mg/L)	2.92 (2.00-4.27)	4.09 (3.25-5.15)	4.96 (3.20-7.75)	6.25 (4.59-8.51)	4.42 (1.77-11.00)	6.90 (3.58-13.30)
t_{half} (h)	11.18 (8.57-14.54)	11.36 (8.54-15.12)	9.19 (5.09-16.58)	15.83 (6.58-38.10)	7.08 (4.32-11.61)	6.23 (2.15-18.10)

* Geometric means + 95% confidence intervals

Figure 1: Individual AUC_{0-tau}

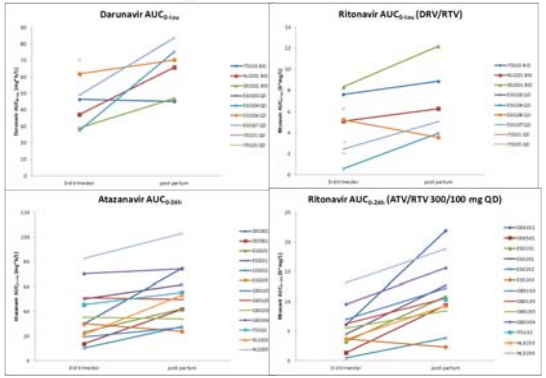

Table 3: Geometric mean ratios (90% CI)

Geometric mean ratio (90% confidence interval)			
	darunavir (n=6)	atazanavir (n=13)	ritonavir (n=18)
AUC_{0-tau} (mg*h/L)	0.64 (0.47-0.86)*	0.67 (0.53-0.83)*	0.47 (0.35-0.64)*
C_{last} (mg/L)	0.45 (0.22-0.91)	0.67 (0.46-0.97)	0.46 (0.28-0.74)*
C_{max} (mg/L)	0.71 (0.49-1.03)	0.71 (0.56-0.91)*	0.41 (0.31-0.55)*
t_{half} (h)	0.82 (0.45-1.51)	0.98 (0.77-1.25)	0.97 (0.83-1.12)

* Significant difference paired samples t-test (on log-transformed data)

Table 4: Cord blood / maternal blood ratios

	Darunavir (n=5)	Atazanavir (n=7)	Ritonavir (n=12)
Cord blood / maternal blood ratio	CB all <LOQ	0.23 (0.11-0.67)	CB all <LOQ

3. RESULTS (continued)

Pharmacokinetics

- Exposure (AUC_{tau}) during pregnancy to DRV, ATV and RTV was 36, 33 and 53% lower than post-partum.
  The decreased exposure could be caused by an increased volume of distribution or decreased absorption. Because the half life seems to be similar during and after pregnancy, increased elimination is less likely to be the reason for thr decreased exposure.
- Concomitant use of tenofovir (used by 14 patients (8 on DRV and 6 on ATV) seemed not to have influenced the DRV or ATV exposure. Raltegravir was concomitantly used with DRV only, no interaction was expected. All other concomitant medication used was not expected to interact with DRV or ATV.
- The PK parameters as determined post-partum are in line with the reference values for DRV and ATV.
- For DRV 2/9 patients showed concentrations below the target concentration (0.55 mg/L) in the 3rd trimester, compared to none on ATV (target >0.15 mg/L).

Safety

- One SAE was reported: a patient (on ATV/RTV) was admitted to the hospital because she thought the baby was not moving. She was admitted for safety reasons and observation only. This was not judged to be medication related.
- No congenital abnormalities have been reported.
- Two weeks prior to delivery one patient showed still a substantial viral load: (28,711 copies/mL in the third trimester). This patient was thought to be non-compliant and had observed drug intake until delivery. The child was born uninfected.

4. CONCLUSIONS

- Exposure to DRV, ATV and RTV was significantly lower during pregnancy (third trimester) than post-partum, with the most important effect for the boosting agent RTV. This is in line with previously reported exposure to protease inhibitors.
- Transplacental passage of ATV, DRV and RTV is low.
- Evidence-based recommendations for ARVs in pregnancy are urgently needed.

panna

UMC St Radboud

Presented at the 19th Conference on Retroviruses and Opportunistic Infections, March 5-8, 2012; Seattle.