A Comparison of the Pharmacokinetics of Maraviroc during Pregnancy and Postpartum

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ABSTRACT (updated)

- **Background**: Effective plasma concentrations of antiretroviral drugs (ARV) are important to prevent both treatment failure and development of resistance. During pregnancy physiological changes take place influencing the pharmacokinetics (PK) of medicines. Mostly, the net effect is decreased exposure during pregnancy. Currently no data are available on the PK behavior of maraviroc (MVC) during pregnancy, nor on placental passage.
- **Materials & Methods**: Patients treated with MVC during pregnancy had intensive steady-state 12-hour PK profiles in the 2nd (if possible), 3rd trimester and at least 4 weeks postpartum. Cord blood samples and matching maternal blood samples were taken at delivery. We present data on MVC PK in the 3rd trimester compared to postpartum and on transplacental passage. The data were collected in two different studies: P1026 (US) and PANNA (Europe).
- **Results**: Paired PK curves (3rd trimester and postpartum) were available for 9 patients. One also had a 2nd trimester curve. Three additional patients had 3rd trimester but no postpartum evaluations available. At the 3rd trimester visit the duration of MVC treatment ranged from 16-244 weeks.
  Patients used MVC 150mg BID (8), 300mg BID (3) or 300mg QD (2). Ten patients used a boosted protease inhibitor (PI) regimen, 7 patients used raltegravir (in 6 cases added to the MVC/PI regimen). Median gestational age at delivery was 39 (37-41) weeks. Approaching delivery 9/10 patients had an HIV viral load <50 cps/mL. 7 patients were black; 4 hispanic; 1 mixed race and 1 caucasian.
  Geometric mean ratios (90% confidence interval) of MVC PK parameters 3rd trimester/postpartum were (n=9): 0.79 (0.63-0.98) for AUC; 0.79 (0.61-1.00) for C_{max}; 0.85 (0.72-1.01) for C_{last}. 2/12 and 1/9 patients had C_{last} concentrations below the target concentration (50 ng/mL) in the 3rd trimester and postpartum respectively.
  The median ratio of cord blood/maternal plasma concentrations (n=8) was 0.33 (0.03-0.56). Eight children were HIV uninfected; for 5 children results are pending.
- **Conclusions**: Exposure to MVC was 21% lower during pregnancy (3rd trimester) than postpartum. This is in line with previously reported data from other CYP3A substrates such as PIs. Transplacental passage of MVC is low. More data on MVC use in pregnancy are needed to make dosing recommendations. In the meantime, viral load should be closely monitored and therapeutic drug monitoring may be useful.

1. INTRODUCTION

- During pregnancy physiological changes cause a decreased exposure to emtricitabine, tenofovir, efavirenz and most HIV protease inhibitors (PI). No data are available on the pharmacokinetic behavior of maraviroc (MVC) during pregnancy, nor on placental passage.
- Both the IMPAACT P1026 protocol and the PANNA network have been established to describe the pharmacokinetics of anitretroviral agents in HIV-infected pregnant women in comparison to post-partum pharmacokinetics (www.impaactgroup.org and www.pannastudy.com).
- MVC is a CCR5 co-receptor antagonist indicated for combination antiretroviral treatment of adults infected with only CCR5-tropic HIV-1. The recommended MVC dose for (non-pregnant adults) is 300mg BID and 150mg BID when given with potent CYP3A inhibitors (e.g. PI's).
- A secondary objective is to describe the safety of the antiretroviral agents during pregnancy and monitor viral load response of the mother and prevention of mother to child transmission.

2. METHODS

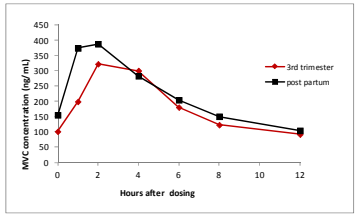
- Data presented were collected in two studies: PANNA "Pharmacokinetics of Antiretroviral Agents in HIV-infected Pregnant Women" (Europe) and IMPAACT study P1026 "PK Properties of ARV Drugs During Pregnancy" (US, Argentina) (ClinicalTrials.gov identifiers NCT00825929 and NCT00042289).
- Both studies are non-randomized, open-label, parallel-group, multi-center phase-IV studies in HIV-infected pregnant women. PANNA recruits patients from HIV treatment centres in Europe; IMPAACT recruits patients from sites in the US, South America, Thailand and Africa.
- Here, we report on pregnant HIV-infected patients treated with MVC 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 second and third trimester. At least 2 weeks post-partum intensive PK sampling was repeated, using the same MVC dose. Where possible a cord blood sample and matching maternal blood sample were taken at delivery.
- Target MVC trough concentration is defined as 50 ng/mL (suggested minimum target trough concentration for ART-experienced patients suggested in Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents).
- Safety and antiviral parameters were evaluated.
- MVC plasma concentrations were determined by validated LC/MS/MS methods, pharmacokinetic parameters were calculated using Phoenix/WinNonlin version 6.3. Mixed linear model analysis was performed on the log-transformed data (using SPSS 18.0).

Table 1: Demographics

	median	range
3rd trimester (n=13)		
age (years)	24	(20-41)
weight (kg)	74.6	(59.9-127.8)
gestational age (weeks)	33.6	(30.6-37.3)
CD4+ cell count (cells/µL)	378	(39-1030)
HIV-1 RNA <50 cps/mL	10 out of 13	(VL>50: 516; 648; 1234 copies/mL)
Other ARVs: Combivir ; Truvada ; Tenofovir ; Abacavir ; Lamivudine; Etravirine; Darunavir/r ; Kaletra ; Raltegravir ; Entuvirtide	4 ; 3 ; 2 ; 1 ; 1; 1 ; 10 ; 1 ; 7 ; 1	
race (black ; hispanic ; caucasian ; mixed)	7 ; 4 ; 1 ; 1	
Delivery (n=13)		
gestational age (weeks)	38.9	(37.3-41.4)
HIV-1 RNA <50 cps/mL	9 out of 10	(VL>50: 5110 copies/mL, 3 unknown)
way of delivery (caesarian section ; natural)	8 ; 4	
Post partum (n=9)		
weight (kg)	69.4	(56.1-121.7)
weeks after delivery	7	(4.3-13.1)
CD4+ cell count (cells/µL)	519	(149-1184)
HIV-1 RNA <50 cps/mL	8 out of 10	(VL>50: 96; 391 copies/mL respectively)
Infant (n=13)		
infant weight at birth (g)	3290	(2430-3730)
infant VL undetectable ; pending	8 ; 5	

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

Figure 1: Mean MVC concentrations



3. RESULTS

- For 13 HIV-infected women who used MVC during pregnancy (8 on MVC 150mg BID + PI; 2 on MVC 300mg BID; 1 on 300mg MVC BID + PI and 2 on MVC 300mg QD + PI) data are available.

Pharmacokinetics

- Paired PK curves (3rd trimester and postpartum) were available for 9 patients (6 on MVC 150mg BID; 1 on 300mg MVC BID+PI; 1 on MVC 300mg BID and 1 on MVC 300mg QD). One also had a 2nd trimester curve. One patient was excluded from PK analyses due to poor compliance.
- Geometric mean ratios were based on all patients with paired PK curves.
- PK descriptive statistics and concentration-time plots were based on patients using MVC 300mg BID or MVC 150mg BID + PI (n=9 for 3rd trimester and n=7 for post partum curves).
- Exposure (AUC_{tau}) during pregnancy (3rd trimester) to MVC was 21% lower than post-partum (see Figures 1&2), p=0.084.
- 2/12 patients showed concentrations (C_{last}) below the target concentration (50 ng/mL) in the 3rd trimester, compared to 1/9 postpartum.
- The median ratio of cord blood/maternal plasma concentrations (n=6) was 0.33 (0.03-0.56).

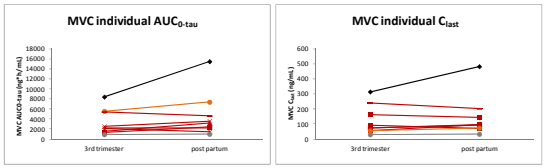
Table 2: Pharmacokinetic parameters

	Geometric mean (95% confidence interval)			
	2nd trimester (n=1)	3rd trimester (n=9)	post partum (n=7)	Geometric mean ratio (90% confidence interval)
AUC_{0-12h} (ng*h/mL)	3199	2146 (908-5427)	2402 (990-4620)	0.79 (0.63-0.98)
C_{12h} (ng/mL)	64.4	73.6 (29.7-239)	94.0 (33.4-201)	0.85 (0.72-1.01)
C_{max} (ng/mL)	598.3	339 (214-890)	464 (238-933)	0.79 (0.61-1.00)
T_{max} (h)	2	2.0 (1.0-4.0)	1.5 (0.8-4.0)	-
t_{half} (h)	3.69	5.67 (3.03-8.81)	6.92 (3.80-9.74)	0.95 (0.74-1.23)

Safety

- One SAE was reported during pregnancy: psychiatric hospitalization due to depression.
- No congenital abnormalities have been reported.

Figure 2 Individual pharmacokinetic values



red: 150mg MVC BID+PI; **black**: 300mg MVC BID+PI; **grey**: 300mg MVC BID; **orange**: 300mg MVC QD +PI

3. RESULTS (continued)

Discussion

- 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 the decreased exposure.
- The PK parameters as determined post-partum are in line with the published values for MVC 300mg BID.

4. CONCLUSIONS

- Exposure to MVC was 21% lower during pregnancy (3rd trimester) than postpartum. This is in line with previously reported data from other CYP3A substrates such as PIs.
- Transplacental passage of MVC is low.
- More data on MVC use in pregnancy are needed to make dosing recommendations. In the meantime, viral load should be closely monitored and therapeutic drug monitoring may be useful.

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