A comparison of the pharmacokinetics of tenofovir during pregnancy and post-partum

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1. INTRODUCTION

- Combination antiretroviral therapy (cART) has been shown to reduce HIV mother to child transmission (MTCT) from 15-40% to <2%.
- The most commonly used nucleoside reverse transcriptase inhibitors are zidovudine and lamivudine. However, the use of tenofovir (TDF)/emtricitabine during pregnancy is increasing to approximately 30% whereas zidovudine/lamivudine use decreased from 90% to 70%.
- During pregnancy 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 of medicines. In most cases, the net effect will be a decreased exposure.
- Sparse publications on pharmacokinetic parameters of chronic exposure to tenofovir concluded that exposure during pregnancy is lower, but not below the threshold target for most women.
- In 2008, a European network was established to study the pharmacokinetics of newly developed antiretroviral drugs in pregnant women (PANNA).
- Here we present data on third trimester exposure to tenofovir.

2. OBJECTIVES

- To describe the pharmacokinetics of tenofovir 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 with TDF (245mg QD) as part of their cART 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, 12, 24h) after supervised intake of 245mg TDF 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.
- Tenofovir plasma concentrations were determined and pharmacokinetic parameters were calculated.

4. RESULTS

Table 1: Clinical characteristics (n=22)

parameters		
age (years)	32.5	(19-44)
weight (kg)	77.5	(60.5-123)
cART (n)	ATV/r (6); DRV/r (5); LPV/r (2); SQV/r (2); FPV/r(1); RAL(3); NVP(3); EFV(1)	
NRTI (n)	Truvada® (20); Combivir®+tenofovir (1); zidovudine+tenofovir (1)	
race (black / caucasian)	11 / 11	
Delivery		
gestational age (weeks)	38	(35-42)
HIV-1 RNA <50 cps/mL	18 out of 22	(VL>50: 70; 130; 162; 525 copies/mL)
way of delivery (caesarian section / natural / unknown)	15 / 6 / 1	
Infant		
infant weight at birth (g)	3090	(2190-4350)
infant VL undetectable	22 out of 22	

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

4. RESULTS (continued)

- Paired (third trimester and post-partum) tenofovir plasma concentration curves were available from 19 women (14 also used a boosted protease inhibitor).
- One patient withdrew consent prior to the post-partum curve; for two patients not enough plasma was available for the post-partum curve.
- Two SAEs were reported: 1) hospital admission because she thought that the baby was not moving; 2) transfusion with packed cells to treat anaemia 24h post-partum; anaemia was attributed to blood loss during/post delivery. Both SAEs were pregnancy or delivery related and judged not to be related to the medication used.
- No HIV mother to child transmission was observed; none of the 22 children showed congenital abnormalities.

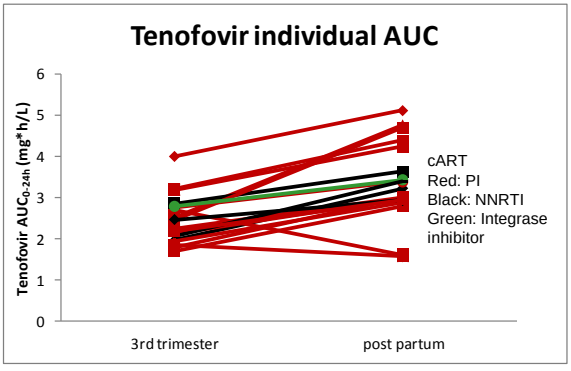
Pharmacokinetics

- During pregnancy (3rd trimester) the exposure to tenofovir is approximately 25% lower (AUC, C_{max} and C_{24h}). These results are independent of concomitant use of boosted protease inhibitor. Exposure post-partum was comparable to non-pregnant adults.
- The cord blood/maternal plasma ratio ranged from 0.66 to 1.10 (n=11). For one patient the cord blood concentrations were <LLOQ (0.015 mg/L).

Table 2: Tenofovir PK parameters

	Geometric mean (95% CI)		Geometric mean ratio (90% CI)
	3rd trimester (n=22)	post partum (n=19)	3rd trim/post partum
$AUC_{0\text{-}24h}$ (mg*h/L)	2.38 (2.15-2.64)	3.22 (2.77-3.75)	0.74 (0.67-0.83)
C_{24h} (mg/L)	0.049 (0.043-0.056)	0.067 (0.054-0.082)	0.76 (0.64-0.90)
C_{max} (mg/L)	0.268 (0.225-0.318)	0.350 (0.269-0.424)	0.77 (0.69-0.87)
t_{half} (h)	14.1 (12.7-15.7)	14.6 (12.5-17.0)	1.05 (0.91-1.20)
Placenta passage			
Cord blood / maternal blood ratio (n=11)			0.81 (0.66-1.10)

Figure 1: Tenofovir AUC_τ



5. CONCLUSIONS

- During pregnancy (third trimester) exposure to tenofovir is approximately 25% lower than post-partum.
- The decrease in exposure does not appear to be caused by (renal) clearance because t_{half} did not change. Potential causes for the decreased exposure are reduced absorption and/or increased volume of distribution.
- Despite this decrease in exposure, no children were infected.
- Tenofovir efficiently crosses the placenta.

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