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Effective Exposure to Atazanavir during Pregnancy, Regardless of Tenofovir Use

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ABSTRACT

- **BACKGROUND**: Atazanavir with low-dose ritonavir boosting moved from an alternative protease inhibitor to a preferred protease inhibitor for use in antiretroviral-naive pregnant women. The package insert recommends an atazanavir (ATV) dose increase in the 2nd and 3rd trimester of pregnancy if tenofovir (TDF) or an H2 receptor antagonist is used concomitantly. Conflicting data exist about the influence of TDF on ATV concentrations, and therefore also for the necessity to increase the ATV dose in the 2nd and 3rd trimester of pregnancy if used with TDF.
- **METHODOLOGY**: Patients treated with ATV/r (300/100mg QD) during pregnancy had intensive steady-state 24-hour PK profiles in the 3rd trimester and at least 2 weeks postpartum. Geometric mean ratios (GMR) and 90% confidence intervals (CI) were calculated for PK parameters 3rd trimester/postpartum. PK parameters with and without TDF co-treatment were compared by an independent t-test.
- **RESULTS**: 29 patients were included in the analysis, 11 were treatment naive at conception. 15 patients were black and 14 Caucasian. Paired PK curves (3rd trimester and postpartum) were available for 25 patients. 19/29 patients used TDF as part of the combination antiretroviral therapy.
  Median gestational age at delivery was 39 (36-42) weeks. Approaching delivery 76% had an HIV viral load <50 cps/mL, all <1000 cps/mL.
  GMR (90% CI) of ATV PK parameters 3rd trimester/postpartum were: 0.65 (0.56-0.74) for AUC; 0.69 (0.60-0.79) for C_{max}; 0.58 (0.47-0.71) for C_{24h}. No statistical difference in AUC was found between patients using TDF vs no TDF: GM (95%CI) 3rd trimester 28.9 mg*h/L (22.2-37.4) vs 32.1 mg*h/L (21.1-48.7); postpartum 46.1 (36.2-58.7) vs 49.2 mg*h/L (34.7-69.8). None of the patients showed ATV concentrations <0.15 mg/L (target for treatment naive patients). One baby had a congenital diaphragmatic hernia resulting in respiratory failure, septic shock and death. A relationship with ATV/r is not likely, because ATV/r was started in week 21 of pregnancy, whereas the closure of the pleuroperitoneal canal occurs around week 8 of pregnancy. None of the children were HIV infected.
- **CONCLUSIONS**: Despite 35% lower ATV exposure during pregnancy, 300/100mg ATV/r seems to generate effective concentrations for PI naive patients, even if co-administered with TDF. For experienced patients therapeutic drug monitoring of ATV should be considered to adapt the ATV/r dose on an individual basis.

1. INTRODUCTION

- The risk of mother to child transmission (MTCT) of HIV has been reduced by the introduction of combination antiretroviral therapy (cART), decreasing the risk from 15-40% to <2%.
- DHHS perinatal guidelines classify ritonavir boosted atazanavir (ATV/r) as one of the preferred protease inhibitors (PI) to be used during pregnancy.
- During pregnancy physiological changes cause a decreased exposure to most HIV protease inhibitors.
- Information on ATV pharmacokinetics during pregnancy and after pregnancy was not consistent. Furthermore tenofovir (TDF) was reported to decrease ATV levels during pregnancy to a greater extent.

Objective

- To study the effect of pregnancy on ATV pharmacokinetics in presence and absence of TDF.

2. METHODS

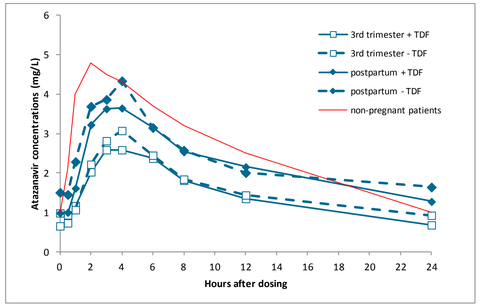
- This was a non-randomized, open-label, multi-centre phase-IV study in HIV-infected pregnant women recruited from HIV treatment centres in Europe (PANNA network: www.pannastudy.com). The PANNA network is a European network of hospitals collecting pharmacokinetic curves of several ARVs during pregnancy in a prospective study.
- Here, we report on pregnant HIV-infected patients treated with 300/100mg ATV/r QD (with and without TDF) as part of their cART.
- Blood was collected for a 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.
- Target ATV trough concentration is defined as 0.15 mg/L (suggested minimum target trough concentration for ART-naive patients suggested in Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents).
- Safety and antiviral parameters were evaluated.
- ATV and RTV plasma concentrations were determined by validated UPLC method, pharmacokinetic parameters were calculated using Phoenix/WinNonlin version 6.3.
- Mixed linear model analysis was performed on the log-transformed data (using Phoenix). PK parameters (ln-transformed) with and without TDF co-treatment were compared by an independent t-test. The non-parametric test for independent samples: Mann Whitney U was used to determine a difference in PK parameters for patients with and without a detectable viral load around delivery.

Table 1: Demographics

	all patients (n=31)	patients on ATV/r 300/100mg with TDF (n=19)	patients on ATV/r 300/100mg without TDF (n=10)
Age at delivery (years)	32 (18-44)	32 (20-42)	34 (24-44)
Race/ethinicity			
White (n (%))	14 (45%)	7 (37%)	7 (70%)
Black (n (%))	16 (52%)	12 (63%)	3 (30%)
Other (n (%))	1 (3%)	0	0
Conception on atazanavir (N (%))	13 (42%)	10 (53%)	3 (30%)
Start atazanavir per trimester (N (%))	1 (3%) 1st trim; 13 (42%) 2nd trim; 4 (13 %) 3rd trim	8 (42%) 2nd trim; 1 (5 %) 3rd trim	1 (10%) 1st trim; 4 (40%) 2nd trim; 2 (20 %) 3rd trim
Atazanavir/r 300/100mg QD (N (%))	29 (94%); 2 on 400/100mg	-	-
Third trimester (n=31)		(n=19)	(n=10)
Gestational age (weeks)	35 (28-38)	35 (32-38)	35 (28-37)
Weight (kg)	78 (56-139)	77.5 (55.5-136)	80.1 (63-139)
HIV-RNA undetectable <50 (n (%))	25 (81%) / <200: 29 (94%)	13 (68%) / 17 (89%)	10 (100%) / 10 (100%)
CD-4 count (copies/uL)	555 (196-1333)	508 (196-1333)	648 (360-1170)
Post partum (n=25)		(n=17)	(n=8)
Time after delivery (weeks)	6 (3-10)	6 (3-10)	6 (3-7)
Weight (kg)	72 (51-126)	71 (51-89)	73 (56-126)
HIV-RNA undetectable <50 (n (%))	21 (81%) / <200: 24 (92%) / u	14 (82%) / 16 (94%)	7 (88%) / 1 unk (12%)
CD-4 count (cells/uL)	653 (150-1020)	620 (150-940)	689 (346-1020)
Pregnancy outcomes			
Gestational age (weeks)	39 (36-42)	39 (36-42)	39 (36-41)
Caesarian section	18 (69%); 2 unk	13 (76%); 1 unk	5 (63%); 1 unk
Birth weight (grams)	3195 (2230-4350)	3260 (2290-4350)	3145 (2710-3500)
Infant HIV DNA PCR negative (n (%))	28 (90%) / 3 unk (10%)	18 (95%) / 1 unk (5%)	8 (80%) / 2 unk (20%)

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

Figure 1: Mean ATV concentrations



3. RESULTS

- Data are available for 29 HIV-infected women who used 300/100mg ATV/r QD during pregnancy data are available.

Pharmacokinetics

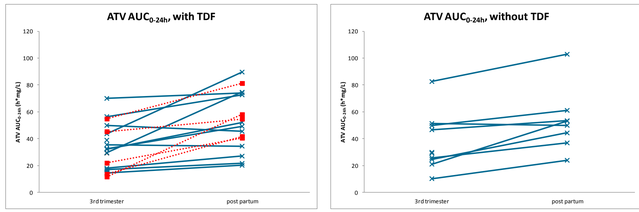
- Paired PK curves (3rd trimester and postpartum) were available for 25 patients.
- Exposure (AUC_{tau}) during pregnancy (3rd trimester) to ATV was 34% lower than post-partum (see Figures 1&2), p=0.084.
- No statistical difference in pharmacokinetic parameters was found between patients using tenofovir vs no tenofovir.
- None of the patients showed atazanavir concentrations <0.15 mg/L (target for treatment naive patients).
- The median ratio of cord blood/maternal plasma concentrations was 0.20 (0.06-3.05; n=12).

Table 2: Pharmacokinetic parameters

	Third Trimester*	Postpartum*	GM Ratio (90% CI)** Third Trimester / Postpartum	p-value***
Atazanavir	(n=29)	(n=25)		
$AUC_{0\text{-}24h}$ (h*mg/L)	29.9 (24.3-36.8)	47.0 (39.1-56.6)	0.66 (0.57-0.75)	<0.001
C_{max} (mg/L)	2.92 (2.36-3.61)	4.29 (3.67-5.02)	0.70 (0.61-0.80)	<0.001
T_{max} (h)	3 (0-6)	3 (1-7.9)		
C_{24h} (mg/L)	0.48 (0.36-0.65)	0.89 (0.65-1.22)	0.59 (0.48-0.72)	<0.001
t_{half} (h)	10 (9-12)	12 (10-15)	0.87 (0.76-1.00)	0.109
Atazanavir plus TDF	(n=19)	(n=17)		
$AUC_{0\text{-}24h}$ (h*mg/L)	28.8 (22.2-37.4)	46.1 (36.2-58.6)	0.65 (0.55-0.78)	
C_{max} (mg/L)	2.92 (2.21-3.84)	4.17 (3.42-5.08)	0.72 (0.60-0.86)	
C_{24h} (mg/L)	0.44 (0.31-0.62)	0.89 (0.59-1.32)	0.57 (0.43-0.75)	
t_{half} (h)	9 (8-11)	12 (10-16)	0.82 (0.68-0.97)	
Atazanavir without TDF	(n=10)	(n=8)		
$AUC_{0\text{-}24h}$ (h*mg/L)	32.08 (21.1-48.7)	49.2 (34.7-69.8)	0.66 (0.53-0.83)	
C_{max} (mg/L)	2.93 (1.95-4.40)	4.58 (3.31-6.34)	0.65 (0.52-0.82)	
C_{24h} (mg/L)	0.58 (0.32-1.05)	0.90 (0.47-1.71)	0.64 (0.47-0.87)	
t_{half} (h)	12 (8-17)	12 (8-18)	1.00 (0.80-1.26)	

* Geometric mean (95% confidence interval); except for Tmax: median (min-max)
** GMR includes one patiënt using 400/100mg ATV/r
*** mixed model analysis

Figure 2 Individual pharmacokinetic values



blue : VL undetectable; **red**: VL detectable

3. RESULTS (continued)

Safety and efficacy

- One baby had a congenital diaphragmatic hernia resulting in respiratory failure, septic shock and death. A relationship with ATV/r is not likely, because ATV/r was started in week 21 of pregnancy, whereas the closure of the pleuroperitoneal canal occurs around week 8 of pregnancy.
- None of the children was HIV infected.
- HIV VL was detectable for 6 patients around delivery. 3rd trimester ATV PK parameters did not significantly differ compared to the PK parameters of patients with an undetectable VL around delivery (p-values ranging from 0.212-0.384).

Discussion

- The decreased exposure in the 3rd trimester is in line with previously published data, however, the absence of a stronger decrease when TDF was used concomitantly was not seen before.
- The PK parameters as determined post-partum are in line with the reference values for ATV.

4. CONCLUSIONS

- Despite 34% lower atazanavir exposure during pregnancy, atazanavir/ritonavir 300/100mg QD generates effective concentrations for protease inhibitor naive patients, even if co-administered with tenofovir.
- Transplacental passage of atazanavir is low.
- For treatment experienced patients (with relevant PI resistance mutations) therapeutic drug monitoring of atazanavir should be considered to adapt the atazanavir/ritonavir dose on an individual basis.

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