Original article

Atazanavir exposure is effective during pregnancy regardless of tenofovir use

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Background: We studied the effect of pregnancy on atazanavir pharmacokinetics in the presence and absence of tenofovir.

Methods: This was a non-randomized, open-label, multicentre Phase IV study in HIV-infected pregnant women recruited from European HIV treatment centres. HIV-infected pregnant women treated with boosted atazanavir (300/100 mg or 400/100 mg atazanavir/ritonavir) as part of their combination antiretroviral therapy (cART) were included in the study. 24 h pharmacokinetic curves were recorded in the third trimester and postpartum. Collection of a cord blood and maternal sample at delivery was optional.

Results: 31 patients were included in the analysis, 21/31 patients used tenofovir as part of cART. Median (range) gestational age at delivery was 39 weeks (36–42). Approaching delivery 81% (25 patients) had an HIV viral load <50 copies/ml, all <1,000 copies/ml. Least squares means ratios (90% CI) of atazanavir pharmacokinetic parameters third trimester/postpartum were: 0.66 (0.57, 0.75) for AUC_{0-24h}, 0.70 (0.61, 0.80) for C_{max} and 0.59 (0.48, 0.72) for C_{24h}. No statistical difference in pharmacokinetic parameters was found between patients using tenofovir versus no tenofovir. None of the patients showed atazanavir concentrations <0.15 mg/l (target for treatment-naive patients). One baby had a congenital abnormality, which was not likely to be related to atazanavir/ritonavir use. None of the children were HIV-infected.

Conclusions: Despite 34% lower atazanavir exposure during pregnancy, atazanavir/ritonavir 300/100 mg once daily generates effective concentrations for protease inhibitor (PI)-naive patients, even if co-administered with tenofovir. 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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Introduction

The risk of mother-to-child transmission (MTCT) of HIV has been reduced by the introduction of combination antiretroviral therapy (cART), reducing the risk from 15–40% in the absence of therapy to <2% [1]. Since 2012, the Department of Health and Human Services (DHHS) perinatal guidelines have classified ritonavir-boosted atazanavir (ATV/r) as one of the preferred protease inhibitors (PIs) to be used during pregnancy [2]. The European AIDS Clinical Society guidelines [3] as well as the British HIV Association guidelines for the management of HIV infection in pregnant women report boosted lopinavir, saquinavir as well as atazanavir as compounds that are effective as the third agent in cART in pregnancy [4].

In the US, PIs are the most common third class of drugs (combined with NRTIs) used in pregnancy: up to 86% in 2009. In 2009, ATV/r use during pregnancy was much lower compared with lopinavir (LPV)/r use (20% versus 55%) [5]. The use of ATV/r during pregnancy may increase because ATV/r has been classified as the preferred PI to be used in pregnancy. Moreover, ATV is classified as FDA Pregnancy Category B indicating that animal reproduction studies failed to demonstrate risk to the foetus; whereas LPV/r is classified as FDA Pregnancy Category C, indicating that animal reproduction studies have shown an adverse effect on the foetus [2].

Sufficient numbers of first trimester exposures to ATV (n=746 up to July 2012) have been monitored by the Antiretroviral Pregnancy Register to have power to detect at least a twofold increase in risk of overall birth defects, but no such increases have been detected to date. A subset of the registry (all cases using ATV during pregnancy from 2002 onwards) was analysed for possible birth defects [6]. No pattern of birth defects suggestive of a common aetiology was observed.

During pregnancy human physiology alters, potentially affecting the pharmacokinetics (PK) of drugs. These changes include: decreased gastric emptying and motility, increased gastric pH, increased total body water and plasma volume, increased hepatic blood flow, alteration of cytochrome P450 activity, increased cardiac output, increased glomerular filtration and decreased protein binding. In most cases resulting in lower exposure of medication during pregnancy [7–9], this effect seems to be rather strong for boosted PIs [10,11].

Between 2005 and 2012 several studies were performed investigating the PK of ATV/r during pregnancy. A systematic review of these studies was recently published [12]. PK studies as well as studies on safety and efficacy were reported, including one study with an increased dose during the third trimester (400/100 mg once daily ATV/r). Most studies report lower exposure during pregnancy, with area under the curve (AUC) 21% (geometric mean ratio [GMR]) lower in the second and 21–33% lower in the third trimester of pregnancy. When combined with tenofovir disoproxil fumarate (TDF) in cART the decrease in exposure was even more pronounced (34%) [13]. However, not all PK studies performed during pregnancy showed decreased exposure: Ripamonti *et al*. [14] reported an AUC GMR (90% CI) of 0.93 (0.79, 1.08; third trimester versus postpartum).

Two intensive PK studies investigated an ATV dose increase in the third trimester of pregnancy. The increased dose (400/100 mg once daily) resulted in therapeutic concentrations in both studies, but also a doubling of maternal grade 3–4 hyperbilirubinaemia in one study [15,16].

The ATV product characteristics state that as ATV/r 300/100 mg once daily may not give sufficient exposure during the second and third trimester, therapeutic drug monitoring is recommended and dose increase if necessary. If TDF or an H2-receptor antagonist is needed, a dose increase to ATV/r 400/100 mg once daily with therapeutic drug monitoring may be considered. ATV/r should not be used by pregnant women also using TDF and an H2-receptor antagonist [17]. TDF use may play a bigger role in pregnancy because tenofovir/emtricitabine is considered a preferred NRTI backbone during pregnancy according to the recent changes in the DHHS perinatal guidelines [2].

Given that information on ATV PK during pregnancy and after pregnancy was not consistent, TDF was reported to decrease ATV levels during pregnancy to a greater extent, and ATV and TDF are considered preferred agents to be used during pregnancy, we studied the effect of pregnancy on ATV PK in the presence and absence of TDF.

Methods

This was a non-randomized, open-label, multicentre Phase IV study in HIV-infected pregnant women recruited from HIV treatment centres in Europe (PANNA network). The PANNA network is a European network of hospitals collecting PK curves of several antiretrovirals (ARVs) during pregnancy in a prospective study. In total, 17 hospitals are involved in the network; data in this publication were collected between February 2010 and May 2013.

The study was conducted in compliance with the principles of the Declaration of Helsinki. Informed consent was obtained from each participant before entering the study. The study was approved by the medical ethical committee from each individual centre involved and by the national authorities if applicable. The study was registered at ClinicalTrials.gov under number NCT00825929.

Here, we describe the PK of ATV/r in pregnancy compared with postpartum, with a focus on concomitant use of TDF. Patient eligibility included being HIV-infected, pregnant, at least 18 years of age at screening and treated with a cART regimen containing ATV for at least 2 weeks before the day of first PK curve evaluation (in the third

trimester of pregnancy). Patients were excluded if they had a past medical history or current condition that might interfere with drug absorption, distribution, metabolism or excretion or presented with grade III/IV anaemia (defined as haemoglobin <4.6 mmol/l or <7.4 g/dl) at screening.

Safety assessments and viral load

Blood samples for safety assessments and viral load were taken at screening and visits for PK blood sampling. Patients were asked for adverse events at each visit. Birth weight, congenital abnormalities and HIV status of the infants were collected.

PK blood sampling

PK curves (samples were taken predose, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h post-medication intake) were recorded during the third trimester (preferably at week 33) and at least 2 weeks postpartum (preferably 4–6 weeks postpartum). At delivery (if possible), a cord blood (CB) sample was taken and at the same time a blood sample from the mother was taken. A standard breakfast (650 kCal; 30g fat) was served prior to (observed) dosing on the PK days.

Analytical and PK methods

Concentrations of ATV and RTV in plasma were analysed by use of a validated (ultra) high-performance liquid chromatography method for the simultaneous quantitative determination of several HIV PIs in human plasma [18]. ATV and RTV lower limit of quantification (LLOQ) was 0.090 mg/l for atazanavir and 0.045 mg/l for ritonavir. The assays were externally validated through ACTG and KKGT [19,20].

PK parameters were determined using a non-compartmental model in WinNonlin/Phoenix version 6.3 (Pharsight Corporation, Mountain View, CA, USA). Concentrations below the LLOQ occurring before the first measurable concentration were set to zero, the first <LLOQ concentration at the end of the curve was set to 1/2 LLQ, subsequent concentrations were left empty. Area under the curve over a dosing interval ($AUC_{0\text{-}24h}$) using the trapezoidal rule, trough concentration (C_{24h}) defined as the sample taken at time point 24 h (or extrapolated from the last available concentration, using lambda, if the sample was missing), maximum concentration (C_{max}), elimination half-life (T_{half}), time of maximum concentration (T_{max}) and apparent clearance (CL/F, being the dose/AUC_{tau}) were determined per individual curve.

Statistical analysis data handling

Patients from whom a PK curve was taken during pregnancy were included in demographic, safety analyses and descriptive statistics of the PK parameters. Demographic data were summarized with descriptive statistics. Quantitative data were compared between patients with and without TDF co-treatment using the Mann–Whitney U test, categorical data were compared using the χ^2 test. PK parameters are reported as geometric means with 95% intervals (for 300/100 mg ATV/r dose only). Least squares means ratios (LSMRs) and 90% CIs of $AUC_{0\text{-}24h}$, C_{max}, C_{24h}, CL/F and T_{half} of third trimester versus postpartum were calculated. For geometric mean calculations patients using 400/100 mg ATV/r were excluded and for the LSMR calculations these patients were included. To indicate whether the PK parameters during pregnancy differed statistically significantly from the postpartum parameters, a mixed models test (using SPSS) was performed on the natural log (ln)-transformed parameters. 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. CB/maternal blood concentration ratios were determined and described.

Results

Thirty-six patients receiving ATV/r during pregnancy were enrolled in the study from 13 different sites from the PANNA network. Four of these patients dropped out before the first PK curve was taken: three delivered before the intensive sampling PK day (the gestational age [GA] was 28 weeks, 33 weeks and 40 weeks) and one withdrew consent. For one patient all plasma concentrations (for both ATV and RTV) were below LLOQ, indicating that the patient was not adherent to therapy and that intake of medication was apparently not supervised. These five patients were excluded from the analysis.

The characteristics and pregnancy outcome of the remaining patients (*n*=31) are presented in Table 1. Fourteen patients were White, 16 Black and 1 of mixed race. At the time of conception, 11 (35%) of the patients were treatment-naive and 13 patients used ATV/r and continued during pregnancy. The majority of the patients used ATV/r 300/100 mg once daily (94%), 2 patients used ATV/r 400/100 mg once daily. Twenty-one out of 31 patients used TDF. Other NRTIs taken were: emtricitabine (*n*=20), lamivudine (*n*=10), zidovudine (*n*=6) and abacavir (*n*=4). One patient also used raltegravir. Non-ARV concomitant substances possibly influencing ATV exposure was marijuana used by one patient. No statistical differences were observed between patients with TDF and without TDF in their backbone therapy (Table 1).

A total of 31 curves were collected in the third trimester (median 35 weeks GA) and 26 curves postpartum (median 6 weeks postpartum). Five patients did not have a postpartum curve for the following reasons: withdrawn consent (*n*=1), lost to follow-up (*n*=2), changed medication (*n*=1), plasma ATV levels <LLOQ (*n*=1) probably due to non-adherence.

Table 1. Subject characteristics

Variable	All patients (*n*=31)	Patients on ATV/r 300/100 mg with TDF (*n*=19)	Patients on ATV/r 300/100 mg without TDF (*n*=10)	*P*-value
Median age at delivery, years (range)	32 (18-44)	32 (20–42)	34 (24–44)	0.154[a]
Race/ethinicity				0.147[b]
White, *n* (%)	14 (45)	7 (37)	7 (70)	
Black, *n* (%)	16 (52)	12 (63)	3 (30)	
Other, *n* (%)	1 (3)	0	0	
Smoking, *n* (%)	6 (19)	2 (11)	4 (40)	0.098[b]
Alcohol use, *n* (%)	2 (6)	1 (5)	1 (10)	0.579[b]
Drug use, *n* (%)	3 (10)	0	3 (30)	
Treatment-naive at pregnancy start, *n* (%)	10 (32)	5 (26)	5 (50)	0.259[b]
Median ARV treatment duration before pregnancy, weeks (range)	259 (3–561)	223 (3–561)	306 (23–519)	0.405[a]
Conception on atazanavir, *n* (%)	13 (42)	10 (53)	3 (30)	–
Start atazanavir per trimester				
First trimester, *n* (%)	1 (3)	–	1 (10)	
Second trimester, *n* (%)	13 (42)	8 (42)	4 (40)	
Third trimester, *n* (%)	4 (13)	1 (5)	2 (20)	
ATV/r 300/100 mg once daily, *n* (%)	29 (94)[c]	–	–	–
Concomitant ARVs				–
NRTI: TDF, *n* (%)	21 (68)	–	–	
NRTI: emtricitabine, *n* (%)	20 (65)	–	–	
NRTI: lamivudine, *n* (%)	10 (32)	–	–	
NRTI: zidovudine, *n* (%)	6 (19)	–	–	
NRTI: abacavir, *n* (%)	4 (13)	–	–	
Integrase inhibitor: raltegravir, *n* (%)	1 (3)	1 (5)	0	
Third trimester (*n*=31)				
Median gestational age, weeks (range)	35 (28–38)	35 (32–38)	35 (28–37)	0.493[a]
Median weight, kg (range)	78 (56–139)	77.5 (55.5–136)	80.1 (63–139)	0.565[a]
HIV RNA undetectable				0.141[b]
<50 copies/ml, *n* (%)	25 (81)	13 (68)	10 (100)	
<200 copies/ml, *n* (%)	29 (94)	17 (89)	10 (100)	
Median CD4$^+$ T-cell count, copies/µl (range)	555 (196–1,333)	508 (196–1,333)	648 (360–1,170)	0.350[a]
Postpartum (*n*=25)				
Median time after delivery, weeks (range)	6 (3–10)	6 (3–10)[d]	6 (3–7)[e]	0.414[a]
Median weight, kg (range)	72 (51–126)	71 (51–89)	73 (56–126)	0.713[a]
HIV RNA undetectable				0.407[b]
<50 copies/ml, *n* (%)	21 (81)	14 (82)	7 (88)	
<200 copies/ml, *n* (%)	24 (92)	16 (94)	–	
Unknown, *n* (%)	1 (4)	–	1 (12)	
Median CD4$^+$ T-cell count, copies/µl (range)	653 (150–1,020)	620 (150–940)	689 (346–1,020)	0.816[a]
Pregnancy outcomes				
Median gestational age, weeks (range)	39 (36–42)	39 (36–42)	39 (36–41)	0.626[a]
Caesarean section				–
Yes, *n* (%)	18 (69)	13 (76)	5 (63)	
Unknown, *n*	2	1	1	
Median birth weight, g (range)	3,195 (2,230–4,350)	3,260 (2,290–4,350)	3,145 (2,710–3,500)	0.404[a]
Infant HIV DNA PCR status				–
Negative, *n* (%)	28 (90)	18 (95)	8 (80)	
Unknown, *n* (%)	3 (10)	1 (5)	2 (20)	

[a]Mann–Whitney U test. [b]χ^2 test. [c]Two patients on ritonavir-boosted atazanavir (ATV/r) 400/100 mg once daily. [d]*n*=17. [e]*n*=8. ARV, antiretroviral; TDF, tenofovir disoproxil fumarate.

Pharmacokinetics

Mean plasma concentration–time profiles of ATV 300/100 mg once daily with separate lines for TDF use and non-TDF use are presented in Figure 1. Summary statistics of the PK parameters are listed in Tables 2 and 3.

The $AUC_{0\text{-}24h}$, C_{max}, C_{24h} for ATV were, respectively, 34%, 30% and 41% lower during pregnancy compared with postpartum (intra-subject comparison) and 55%, 58% and 53% lower for RTV, respectively. For both compounds the steady-state apparent clearance (CLss/F) was increased during pregnancy (53% and 124% for ATV and RTV, respectively) and T_{half} tended to be shorter in the third trimester. No statistical difference in ATV $AUC_{0\text{-}24h}$, C_{max}, C_{24h}, T_{half} or CLss/F was found between patients (ATV 300/100 mg only) using TDF versus no TDF in the third trimester or postpartum (P>0.15 for all parameters; Table 3). Geometric mean (95% CI) ATV $AUC_{0\text{-}24h}$ in the third trimester was 32.08 (21.1, 48.7) h•mg/l without TDF and 28.8 (22.2, 37.4) h•mg/l with TDF, and ATV C_{24h} was 0.58 (0.32, 1.05) mg/l without and 0.44 (0.31, 0.62) mg/l with TDF co-treatment. Postpartum geometric mean (95% CI) ATV $AUC_{0\text{-}24h}$ was 49.2 (34.7, 69.8) h•mg/l without TDF and 46.1 (36.2, 58.6) h•mg/l with TDF, and ATV C_{24h} was 0.90 (0.47, 1.71) mg/l without and 0.89 (0.59, 1.32) mg/l with TDF.

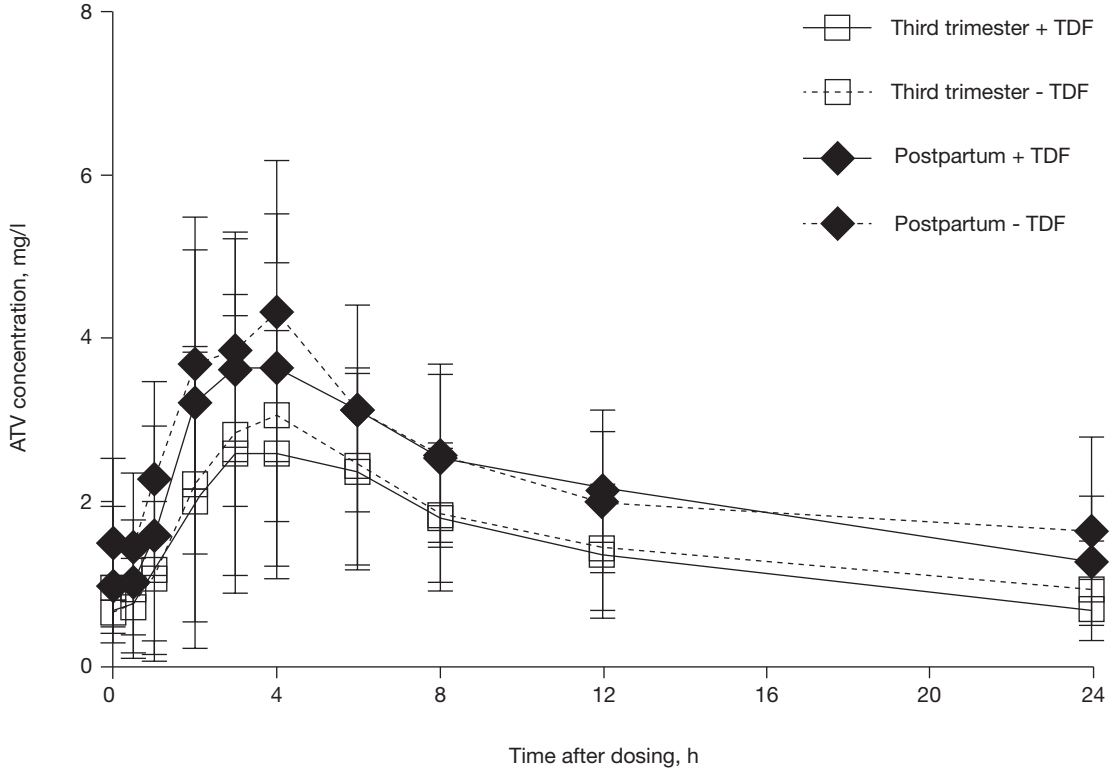
None of the patients had ATV concentrations below 0.15 mg/l (target for treatment-naive patients) in the third trimester or postpartum. For three patients, extrapolated third trimester C_{24h} concentrations would have been below 0.15 mg/l (that is, 0.130, 0.135 and 0.139 mg/l). The predose concentrations of these patients were well above 0.15 mg/l; two of these patients used TDF concomitantly.

Eighteen umbilical CB samples were collected with matching maternal blood samples. The median time between the reported last dose and delivery was 12 h (range 2–27); the median time between CB sample and maternal sample was 3 min (0–345). In five CB samples, ATV concentrations were undetectable; in one case the time between maternal and CB sample was 10 h, this sample was excluded from descriptive statistics. The median (range) ratio of CB/maternal blood was 0.20 (0.06–3.05; n=12) for ATV. For RTV all CB samples were <LLOQ.

Efficacy and safety

HIV viral load close to delivery (median 34 weeks GA) was undetectable in 25 (out of 31) women and detectable in 6 women: 68, 100, 120, 162, 290 and 402 copies/ml. One patient started cART in the second trimester, the other patients were on cART at conception. All of these patients used ATV/r 300/100 mg once daily and TDF concomitantly.

Figure 1. Mean atazanavir concentration–time profiles



Mean (±SD) concentration versus time curves for HIV-infected pregnant women using 300/100 mg ritonavir-boosted atazanavir (ATV/r) once daily during the third trimester and postpartum. Solid lines represent patients using tenofovir disoproxil fumarate (TDF) and dashed lines represent subjects not using TDF.

Table 2. Pharmacokinetic parameters 300/100 mg ATV/r once daily

	Third trimester[a] (*n*=29)	Postpartum[a] (*n*=25)	Third trimester/postpartum[b]	*P*-value[c]
Atazanavir				
$AUC_{0\text{-}24h}$, 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)	–	–
$C_{predose}$, mg/l	0.60 (0.46, 0.79)	0.92 (0.69, 1.23)	–	–
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
CL_{ss}/F, l/h	10 (8, 12)	6 (5, 8)	1.53 (1.34, 1.75)	<0.001
Ritonavir				
$AUC_{0\text{-}24h}$, mg•l/h	5.01 (4.09, 6.15)	11.68 (9.46, 14.42)	0.45 (0.37, 0.53)	–
C_{max}, mg/l	0.59 (0.46, 0.77)	1.50 (1.22, 1.86)	0.42 (0.34, 0.51)	–
T_{max}, h	4.0 (0.00–8.00)	4 (0–7.9)	–	–
C_{24h}, mg/l	0.036[d] (0.028, 0.045)	0.08[e] (0.060, 0.12)	0.47 (0.36, 0.62)	–
T_{half}, h	5 (4, 6)	5 (5, 6)	0.90 (0.78, 1.04)	–
CL_{ss}/F, l/h	20 (16, 24)	9 (7, 11)	2.24 (1.88, 2.68)	–

[a]Geometric mean (95% CI) except for time of maximum concentration (T_{max}): median (range). [b]Least squares mean (LSM) ratio (90% CI) includes one patient using 400/100 mg ritonavir-boosted atazanavir (ATV/r). [c]Mixed model analysis. [d]16 below lower limit of quantification (LLOQ), taken as 1/2 limit of quantification (LOQ), that is, 0.0225 mg/l. [e]5 below LLOQ, taken as 1/2 LOQ, that is, 0.0225 mg/l. $AUC_{0\text{-}24h}$, area under the curve over a dosing interval; CL_{ss}/F, apparent steady-state clearance; C_{max}, maximum concentration; $C_{predose}$, predose concentration; C_{24h}, trough concentration defined as the sample taken at time point 24 h (or extrapolated from the last available concentration, using lambda, if the sample was missing); T_{half}, elimination half-life.

Table 3. Pharmacokinetic parameters 300/100 mg ATV/r in presence and absence of TDF

	Third trimester plus TDF (*n*=19)[a]	Third trimester without TDF (*n*=10)[a]	*P*-value[b]	Postpartum plus TDF (*n*=17)[a]	Postpartum without TDF (*n*=8)[a]	*P*-value[b]	Third trimester/ postpartum plus TDF[c]	Third trimester/ postpartum without TDF[c]
Atazanavir								
$AUC_{0\text{-}24h}$, h•mg/l	28.8 (22.2, 37.4)	32.08 (21.1, 48.7)	0.624	46.1 (36.2, 58.6)	49.2 (34.7, 69.8)	0.735	0.65 (0.55, 0.78)	0.66 (0.53, 0.83)
C_{max}, mg/l	2.92 (2.21, 3.84)	2.93 (1.95, 4.40)	0.985	4.17 (3.42, 5.08)	4.58 (3.31, 6.34)	0.570	0.72 (0.60, 0.86)	0.65 (0.52, 0.82)
C_{24h}, mg/l	0.44 (0.31, 0.62)	0.58 (0.32, 1.05)	0.351	0.89 (0.59, 1.32)	0.90 (0.47, 1.71)	0.972	0.57 (0.43, 0.75)	0.64 (0.47, 0.87)
T_{half}, h	9 (8, 11)	12 (8, 17)	0.181	12 (10, 16)	12 (8, 18)	0.768	0.82 (0.68, 0.97)	1.00 (0.80, 1.26)

[a]Geometric mean (95% CI). [b]Independent *t*-test on ln-transformed parameters. [c]Least squares mean (LSM) ratio (90% CI) includes one patient using 400/100 mg ritonavir-boosted atazanavir (ATV/r). $AUC_{0\text{-}24h}$, area under the curve over a dosing interval; C_{max}, maximum concentration; C_{24h}, trough concentration defined as the sample taken at time point 24 h (or extrapolated from the last available concentration, using lambda, if the sample was missing); TDF, tenofovir disoproxil fumarate; T_{half}, elimination half-life.

The average GA at delivery was 39 weeks (range 36–42). Two children were born pre-term at 36 weeks and 36 weeks and 3 days. Birth weight of 26 children was reported, 2 had a low birth weight (<2,500 g), whereas 5 out of 26 were small for GA (reference 10th percentile of birth weight for GA by gender, US 1991). Twenty-eight children tested HIV-negative (PCR DNA after delivery) and the status of three children was unknown. One child had a congenital diaphragmatic hernia resulting in respiratory failure, septic shock and death. A relationship with the ARV medication used could not be ruled out, however, the closure of the pleuroperitoneal canal in the developing embryo occurs at approximately week 8 of pregnancy and the patient started antiretroviral therapy in week 18 of her pregnancy (ATV/r even later at week 21). Furthermore, this patient also used methadone since 2000 (also during this pregnancy).

Five patients developed a serious adverse event (SAE). One was the congenital abnormality described above. Five hospital admissions occurred (three patients) for several reasons: a patient thought the baby was not moving (the baby was born without problems); early contractions at 31.3 weeks GA (baby was born at GA 38.6 weeks) and urinary tract infection; tonic/clonic seizure and headache after delivery. All patients recovered. The final SAE was in a patient who had postnatal uterus agony, coagulapathy and postpartum haemorrhage, which prolonged hospital admission. She recovered within 1 week. The local investigators judged these SAEs not to be related to the cART given. Nine other patients reported adverse events, all were grade 1 or 2 and not or unlikely related to the cART given. No clinically relevant laboratory abnormalities were reported.

Pharmacokinetic – efficacy relationship

HIV viral loads were detectable for 6 patients around delivery. The Mann–Whitney U test did not reveal significant differences in third trimester ATV PK parameters ($AUC_{0\text{-}24h}$, C_{max}, C_{24h}, T_{half} or CLss/F) compared with the PK parameters of patients with an undetectable viral load around delivery (Table 3). One patient had an extrapolated C_{24h} <0.15 mg/l, with a predose concentration of 0.54 mg/l. Twenty-eight children were tested HIV-negative (PCR DNA after delivery) and the status of three children was unknown.

Discussion

In this study we evaluated the PK of ATV/r in the third trimester of pregnancy in the absence and presence of TDF in 31 pregnant HIV-infected patients.

In the third trimester of pregnancy a decrease in ATV $AUC_{0\text{-}24h}$, C_{max} and C_{24h} (34%, 30% and 41%, respectively) was observed as well as a marked decrease in RTV $AUC_{0\text{-}24h}$, C_{max} and C_{24h} (55%, 58% and 53%, respectively). Clearance (CLss/F) was markedly increased during pregnancy for both compounds (ATV 53% and RTV 124%).

Four previous studies report intensive PK of ATV during pregnancy [13,15,16,21]. Our findings are in-line with other groups reporting a decrease in exposure (ATV AUC during 300/100 mg ATV treatment) of 21% [15], 30% without TDF or 34% with TDF [13] in the third trimester of pregnancy versus postpartum or historical controls. None of the studies reported a significant decrease of C_{24h} concentrations during pregnancy, although we did find a statistically significant decrease. Despite this significant decrease of ATV C_{24h}, no concentrations below the target trough concentration of 0.15 mg/l were measured, indicating sufficient exposure for PI-naive patients.

For six patients a detectable HIV viral load was reported around delivery, although all were <1,000 copies/ml, this might be of concern. Five of these patients were treatment-experienced and all of them used ATV/r 300/100 mg once daily and TDF. Although all of these patients used TDF concomitantly, no statistically significant difference in PK parameters in the third trimester was observed for these patients compared with the patients with an undetectable HIV viral load and none showed ATV concentrations <0.15 mg/l. None of the children of the patients with a detectable viral load were HIV-infected.

In contrast to data reported by Mirochnick *et al*. [13], our study showed no statistical difference in $AUC_{0\text{-}24h}$, C_{max} or C_{24h} for patients (ATV 300/100 mg only) using TDF versus no TDF (in the third trimester or postpartum). Although the ATV product characteristics [17] and Taburet *et al*. [22] report decreased exposure to ATV if combined with TDF, some other studies do not find this effect (for which a mechanism has not been discovered) [23,24].

Furthermore, most studies investigating the PK of ATV during pregnancy [13,15,16] report the postpartum exposure to be unexpectedly higher compared with the non-pregnant population. ATV C_{max} and AUCs were found to be approximately 26–40% higher, and C_{trough} concentrations even twofold higher during the postpartum period than those observed historically in HIV-infected, non-pregnant patients. This finding is not confirmed in our study, as the postpartum ATV $AUC_{0\text{-}24h}$ of 47.0 h•mg/l and C_{max} of 4.29 mg/l observed in this study (with and without TDF combined) is in-line with historical data: ATV $AUC_{0\text{-}24h}$ of 44.2 h•mg/l and C_{max} of 4.47 mg/l [17].

The CB/maternal blood concentration ratio we found for ATV (0.20) is in-line with the CB/maternal blood concentration ratios reported in literature: ranging from 0.13 to 0.20 [25].

We did not analyse bilirubin concentrations in the mother or in the child. As this is a known side effect of ATV, this would have been interesting for safety purposes. However, as the bilirubin concentrations seem to be correlated to high plasma ATV concentrations, and the plasma ATV concentrations postpartum were in the 'normal range' and during pregnancy even lower, we do not think this is a major concern.

The mechanism behind the decreased exposure during pregnancy remains unclear, as C_{max} is decreased (indicating decreased absorption and/or increased volume of distribution) and the elimination (T_{half}) seems to be faster during pregnancy. As this study was performed under steady-state conditions, the half-life is difficult to determine accurately. We determined total ATV concentrations in plasma, not the unbound concentrations. During pregnancy protein binding is decreased, resulting in a higher free fraction, possibly (partly) compensating for the lower concentrations during pregnancy.

Despite 34% lower ATV exposure during pregnancy, 300/100 mg ATV/r seems to generate effective concentrations for PI-naive patients, even if co-administered with TDF. For treatment-experienced patients (with relevant PI resistance mutations) therapeutic drug monitoring of ATV should be considered to adapt the ATV/r dose on an individual basis.

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