

# Steady State Pharmacokinetic of Ritonavir-boosted Atazanavir in 31 Pregnant Women before and after Delivery.

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Abstract N. T-113

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## Abstract

**Background:** Pregnancy can alter the pharmacokinetics (PK) of several protease inhibitors, potentially requiring dose adjustment. The aim was to describe atazanavir/ritonavir (ATV/r) pharmacokinetic before and after delivery.  
**Methods:** An intensive steady-state 24-hours PK profiles of ATV/r given OD (with AZT/3TC BID) in the third trimester of pregnancy and at least 4 weeks postpartum was carried out. Paired maternal and umbilical cord blood samples were collected at delivery. ATV concentrations were measured by a validated HPLC method (limit of quantification 20 ng/ml).  
**Results:** Thirty-one women (17 previously described, 52% white) completed the ante/postpartum evaluations. Mean age ( $\pm$ SD) was 29 (5) years, median (IQR) baseline CD4 count was 413 (354-616) cells/ml, median (IQR) viral load was 8357 (1057-16200) copies/ml for patients with detectable viremia.  
In pre- and post-partum evaluations (figure 1), respectively, the PK parameters were as follows: ATV GM AUC 0-24 (range) was 29848 (7477-74008) vs 32389 (10229-71971) ng-h/ml, ( $p=0.48$ ), the ATV GM Cmax (range) was 2680 (636-6128) vs 3070 (683-10412) ng/ml, ( $p=0.13$ ), and the ATV GM C24h (range) was 439 (109-989) vs 405 (25-1944) ng/ml, ( $p=0.18$ ). Median Tmax (IQR) was 3 (2-4) vs 2 (2-3) hours. The mean ( $\pm$ SD) ATV fetal/maternal ratio was 0.14 (0.07). One baby required phototherapy for 2 days and all tested HIV RNA negative at 1-year follow up.  
**Conclusions:** Dose adjustment for ATV/r is not required during pregnancy as ATV PK profiles are similar during the third trimester and postpartum. Transplacental passage of ATV was confirmed to be low.

## Background

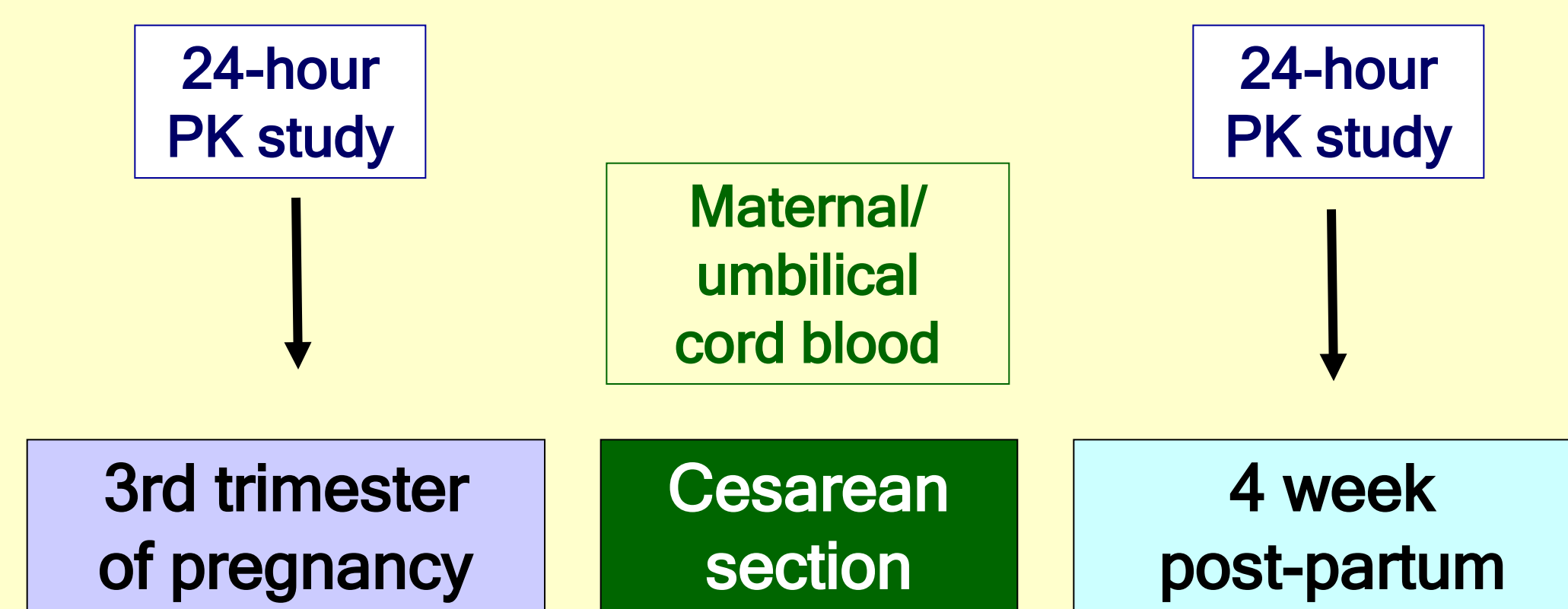
1. Antiretroviral therapy during pregnancy proved very effective in preventing the mother-to-child transmission (MTCT) of HIV-1 (1).
2. Pregnancy may alter the disposition of many drugs, particularly in the third trimester. Several protease inhibitors (PIs) require dose adjustment during the 3rd trimester, in order to compensate for the reduced plasma exposure (1, 2).
3. The virological failure during ATV-containing regimen is driven by ATV Cmin with a recommended threshold of 150 ng/ml (DHHS guidelines).
4. Our previous study (4) showed not difference in ATV PK parameters between pre- and post-partum in 17 women, although others reported a reduced ATV plasma exposure during the third trimester, suggesting to increase the daily dose from 300 to 400 mg (5-7).
5. ATV PK showed a high interindividual variability, so the sample size of PK studies is crucial to draw general recommendations. For this reason, we extended the enrollment to additional pregnant women.

## Objectives

- **Primary objective:**  
to assess:  
- the pharmacokinetic profile of ATV in pregnant women before and after partum.
- **Secondary objectives:**  
to assess:  
- the safety, toxicity and tolerability of ATV/r in pregnant patients  
- the ATV transplacental passage  
- the antiviral efficacy as maternal viral suppression and MTCT of HIV-1

## Methods

### Study Design



Patients were given (AZT+3TC) BID combined with ATV/rtv 300mg/100mg at morning time, according to genotype testing. Switch in the NRTI-backbone was permitted at anytime.

### Pharmacokinetics

- A steady-state 24h intensive PK study was carried out during the 3rd trimester of pregnancy and >4 weeks following delivery. PK parameters were derived by noncompartmental analysis using the WinNonlin software: Cmax, Tmax, Cmin (12h postdose), AUC (0-12), C0 and T1/2. Blood samples were collected at time 0, 0.5, 1, 2, 3, 4, 8, 10, 24h post dose. Maternal and umbilical cord plasma were collected at delivery to assess the ATV placental transfer.
- ATV concentrations in stored plasma samples were determined by a validated high-performance liquid chromatography (HPLC) method with limit of quantitation above 20 ng/ml (8).

### Safety

- Patients' visits were planned at baseline and every two months (unless differently required) before delivery and at least 4 weeks after partum for physical examination, viro-immunological tests and laboratory profiles. Virological and serological testing for babies were performed at delivery, every 3 months and up to the disappearance of HIV antibodies. All newborns received AZT for 6-weeks, as well as formula feeding.

### Statistics

- Point estimates for GM, CV%, median and range are reported, with 90%CI as appropriate.

## Results

Table 1: Demographics

	Number
Total patients (patients previously described, Ref 4)	31 (17)
Age, mean ( $\pm$ SD), years	29 ( $\pm$ 5)
<b>Ethnicity</b>	
Caucasian	11
African (Sub-Saharan)	15
Other	4
Week of gestation starting HAART, median (IQR)	13 (10-18)
CD4 count at entry, median (IQR), cells/ml	413 (354-616)
Antiretroviral naïve, N (%)	20 (64)
Patients with HIV RNA < 50 copies/ml at entry HIV RNA at entry, median (IQR), copies/ml	6 8,357 (1,057-16,200)
Switch in NRTI-backbone during pregnancy	2
HCV / HBV coinfection	2/2

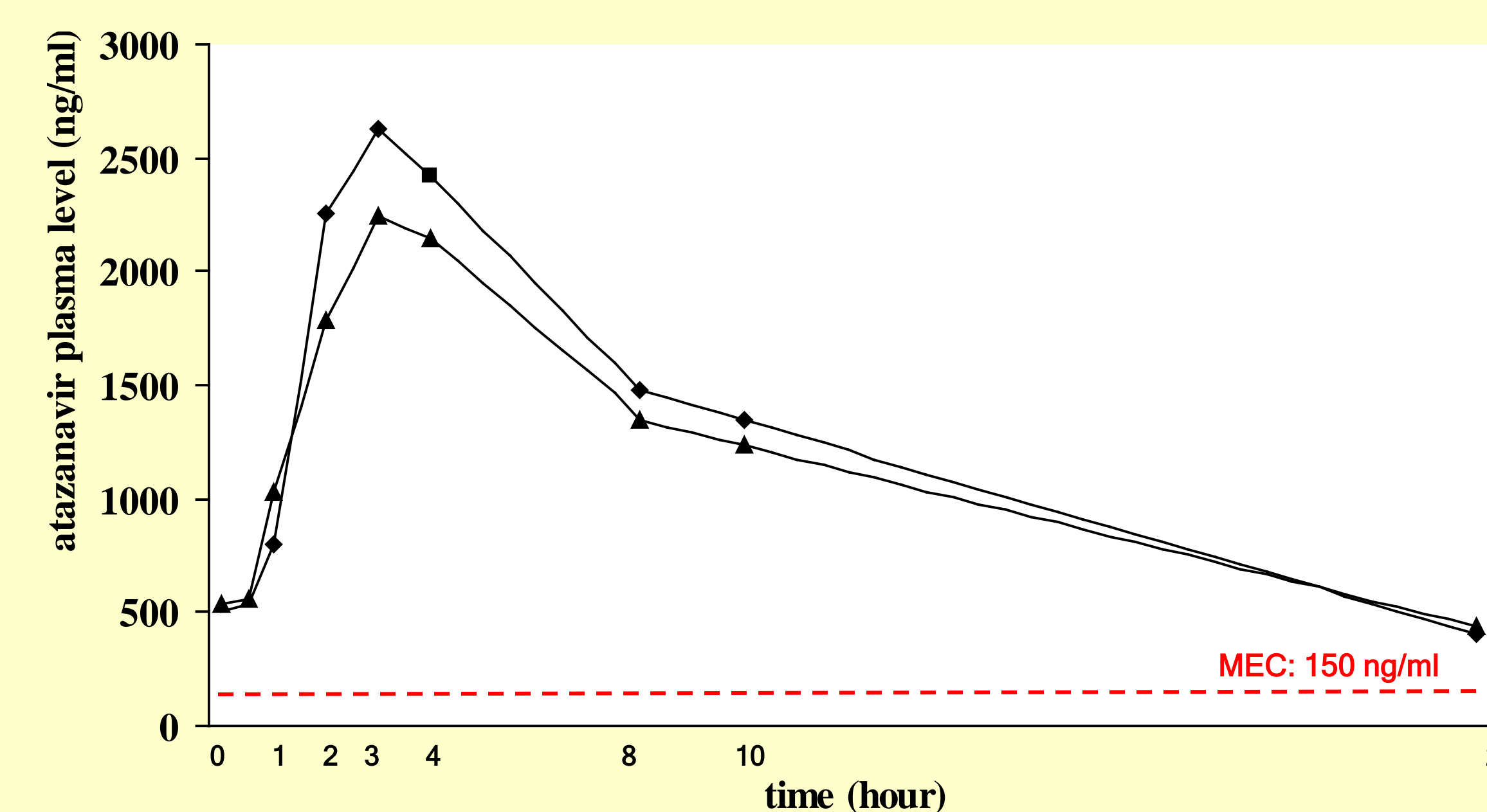
## Results

Table 2: ATV pharmacokinetic parameters in 31 pregnant women

	3rd trimester (N=31)	Postpartum (N=31)	Ratios of adjusted GM (post/pre-) point estimates (90%CI)
<b>Cmax (ng/ml)</b> GM (%CV) (range)	2,680 (59) (636-6,128)	3,070 (70) (683-10,412)	1.13 (0.96 - 1.34)
<b>AUC 0-24h (ng-h/ml)</b> GM (%CV) (range)	29,848 (53) (7,477-74,008)	32,389 (48) (10,229-71,971)	1.08 (0.93 - 1.26)
<b>C24h (ng/ml)</b> GM (%CV) (range)	439 (58) (109-989)	405 (121) (25-1,944)	0.83 (0.69 - 1.23)
<b>Tmax (hour)</b> Median (min-max)	3 (2-4)	2 (2-3)	-

ATV= atazanavir, GM= geometric mean, CV= coefficient of variation, IQR= interquartile C24h is defined as plasma concentration 24 hours post dose.

Figure 1: Plasma concentration-time profile for ATV (Geometric Means)



Post-partum PK evaluation was done after a median (IQR) of 7 (6-8) weeks. All women had detectable ATV C24h in both pre- and post-partum evaluation.

In pre-partum, only 1 (3.2%) patient had ATV C24h below the MEC (namely: 109 ng/ml), while in post-partum, 3 (9.6%) patients had ATV C24h below the MEC (namely: 25, 43, 51 ng/ml).

Mean ( $\pm$ SD) Body Mass Index at time of pre- and post-partum PK evaluation was 26 ( $\pm$ 3) and 23 ( $\pm$ 3) Kg/m<sup>2</sup>, respectively.

Table 3: ATV concentration in maternal and umbilical cord.

Number of paired samples	26
Time after dosing, median (IQR), hour	6 (5-6)
Umbilical cord blood, ng/ml GM, (CV%), range	237 (65) 90 - 620
Maternal plasma at delivery, ng/ml GM, (CV%), range	1,698 (61) 4,423 - 571
Fetal/maternal ratio	0.14

ATV= atazanavir, GM= geometric mean, CV= coefficient of variation.

## Results

- All women underwent a planned cesarean section and received the morning dose of ATV on the day of delivery.
- Median (IQR) gestational age at delivery was 38 weeks (IQR: 37-39).
- Median (IQR) neonatal weight at birth was 2970 (2785-3115) gr.
- A total of 3 newborns required 2-day phototherapy for clinical jaundice.
- All babies were healthy, no clinically significant adverse event was reported.
- No Case of MTCT of HIV-1 occurred (undetectable HIV RNA >1 year).

### Safety and tolerability

No unexpected and clinically significant adverse events were reported in 31 pregnant women. Table 4 shows the main lab parameters. Maximum value for total bilirubin was 7.4 mg/dl.

Table 4 : variation of laboratory tests before and after delivery.

	Hgb	Total bilirubin	AST	ALT	GGT	CPK	Amylase
Normal value	<15 g/dl	<1.3 mg/dl	<46 IU/L	<46 IU/L	<30 IU/L	<186 IU/L	<94 IU/L
Prepartum mean ( $\pm$ SD)	11 (1)	2 (2)	23 (7)	15 (5)	12 (5)	85 (74)	95 (31)
Postpartum mean ( $\pm$ SD)	12 (1)	2 (1)	21 (6)	19 (8)	20 (17)	103 (68)	79 (28)

## Conclusions

1. The Cmin, AUC and Cmax of ritonavir-boosted ATV were not significantly different between pre- and post-partum phase, so dose adjustment for ATV/r in pregnancy is not required.
2. Transplacental passage was low (mean fetal/maternal ratio was 0.14), but cord blood ATV concentration was always detectable.
3. All women and newborns had undetectable HIV RNA at delivery and no case of MTCT of HIV-1 occurred in the newborns.
4. ATV/r, in combination with AZT/3TC, was well tolerated in pregnant women.

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