

Atazanavir-based HAART in pregnancy

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Abstract

Background: Optimal antiretroviral exposure during pregnancy is critical to prevent MTCT of HIV. Pregnancy can alter antiretroviral pharmacokinetics. Our objective was to describe atazanavir (ATV) pharmacokinetics during pregnancy.
Methods: We performed intensive steady-state 24-hour pharmacokinetic profiles of ATV associated to AZT and 3TC (at standard doses) at 30-36 weeks gestation and 8-16 weeks postpartum. Maternal and umbilical cord blood samples were obtained at delivery. HPLC was used to measure ATV concentrations.
Results: 9 women completed antepartum evaluations. Their mean age was 31 years and their mean baseline CD4 count was 471 cells/mm³. HAART was started between 0 and 24 weeks of pregnancy (mean 13.7). The mean antepartum ATV AUC was 20.4 mg·h/l (SE 3.1), while the postpartum value was 33.5 mg·h/l (SE 3.9) with a mean antepartum ratio of 0.36 (SD 0.34), compared to a postpartum ratio of 2.7 (SE 0.4) compared to a postpartum value of 2.9 mg/ml (SE 0.4) for an antepartum ratio of 1.03 (SD 0.31). There was a 3.1 h antepartum and 2.8 h postpartum, while C_{trough} resulted of 6.2 mg/ml antepartum and 5.9 mg/ml postpartum. None of the considered measures was significantly different (P > 0.05) nor they were influenced by the women's BMI (mean 26.8 during and 24.5 after pregnancy). ATV mean concentration in the cord blood at delivery was 0.22 mg/ml (SD 0.15) and counted for 9.7% of the concomitant maternal blood concentration 2.3 mg/ml (SD 1.3). All mothers at delivery and 3 months after birth resulted HIV-RNA negative. None of them required phototherapy.
Conclusions: ATV concentrations during late pregnancy are similar to those obtained postpartum. No dose adjustments should be needed. Small amounts of ATV cross the placenta. An ATV based HAART is effective in preventing MTCT of HIV infection.

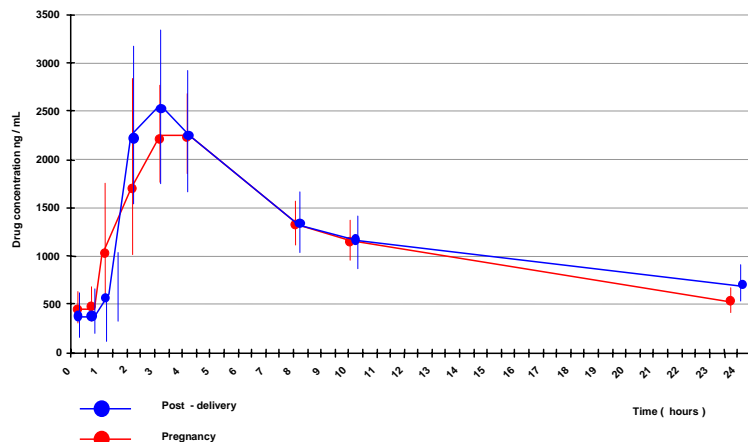
Data presented in this poster consider a population larger than that reported in the abstract. This larger casuality leads to the same conclusions of the abstract and adds sufficient statistical power

Introduction

When compared with postpartum, lower AUC and C_{trough} prepartum values have been reported for boosted LPV, boosted SQV, IDV and NFV. It is critical to understand the effect of pregnancy on absorption and disposition of different PIs, in order to ensure the best therapeutic choices and that adequate concentrations are achieved in the blood of pregnant women so to prevent the development of viral resistance and vertical transmission of the infection.

The primary purpose of this study was to evaluate if a standard boosted atazanavir dose produces adequate drug exposure during pregnancy. HIV-infected pregnant women receive HAART as soon as the HIV status is known (or continued in the case of a previously treated woman) if the woman's immunological status requires immediate treatment, otherwise HAART is delayed until the end of the first trimester of pregnancy. Women undergo elective caesarean resection. At birth the children receive one month AZT prophylaxis (2 mg/kg every 6 hours). Breast feeding is avoided.

Geometric least-squares mean atazanavir concentration-time curves, with bar indicating 95%CI



Baseline Characteristics of women and newborns. Clinical outcome.

Parameters	value
Number pregnant women	17
Ethnicity	
Black	9
White	7
Asian	1
CDC classification	
A1	4
A2	9
A3	3
B2	1
Mean age [years (SD)]	30.7 (5.2)
Mean baseline CD4 count [cells/μL (SD)]	420 (169)
Mean baseline HIV-RNA [copies/ml (SD)]	11,308 (17,194)
Initiation of HAART [mean pregnancy week (SD)]	12.3 (8.3)
Number of newborns	17
Sex	
Males	9
females	8
Mean gestational age [weeks (SD)]	37.2 (0.56)
Mean weight at birth [kg (SD)]	2.912 (0.195)
Number of newborns with HIV-RNA < 50 copies/ml	17*
Number of women with HIV-RNA < 50 copies/ml	17**

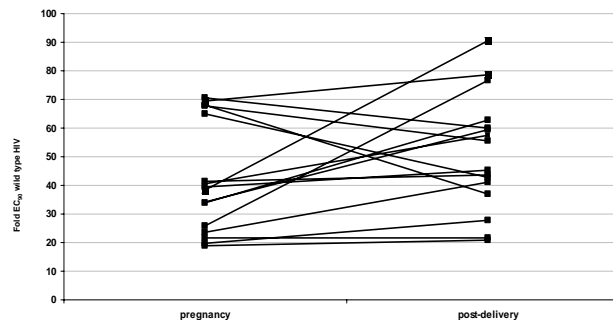
* at birth and 3 months after birth
 ** at prepartum evaluation, at delivery and at postpartum evaluation

Summary of pharmacokinetic parameters and their pre- postpartum ratios.

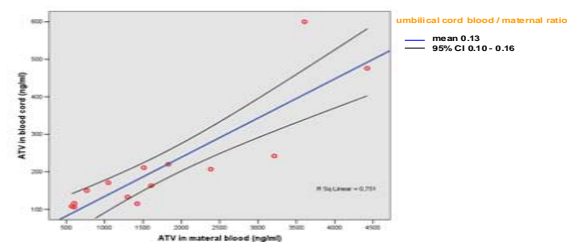
Parameters	Third trimester	Postpartum	Ante- postpartum ratio**
Mean* AUC ₀₋₂₄ [ng·h/l (95% CI)]	28,510 (23,765-34,200)	30,465 (24,440-37,960)	0.94 (0.80-1.11)
Mean* C _{max} [ng/ml (95% CI)]	2,591 (2,080-3,224)	2,878 (2,164-3,810)	0.94 (0.74-1.11)
Mean* C _{trough} [ng/ml (95% CI)]	486 (396-597)	514 (377-699)	0.96 (0.82-1.13)
Mean T _{1/2} [h (SD)]	10.0 (2.4)	10.6 (2.4)	
Mean T _{max} [h (SD)]	3.2 (1.6)	2.8 (0.8)	

* Mean is the geometric least-squares mean
 ** 90 % Confidence interval

Inhibitory Quotient (IQ). Ratio C_{trough} to atazanavir EC₉₀ for wild-type HIV (14 ng/ml).



Umbilical cord blood to maternal blood ratio at delivery.



Definition of equivalence.

According to the Center for Drug Evaluation and Research. Draft Guidance for Industry: Pharmacokinetics in Pregnancy: Study Design, Data Analysis, and Impact on Dosing and Labeling. Washington, DC: US Department of Health and Humans Services, Food and Drug Administration; October 2004.
<http://www.fda.gov/cder/guidance/5917dft.htm>

A pharmacokinetic parameter was defined as equivalent if the 90% Confidence Interval (CI) of the prepartum to the postpartum ratio of observed values fell between 0.80 and 1.25. For geometric means the CI was calculated as the antilog of the true mean of the log ratios

CONCLUSIONS

Atazanavir overall exposure at steady state during the third trimester of pregnancy is similar to that observed in the non-pregnant state.

Over the whole dosing interval therapeutic drug concentrations are well above the wild-type HIV IC₉₀ (approximately 40 folds).

Atazanavir crosses the placenta at a 13% ratio with clear positive linear correlation to maternal plasma levels. Consequently, even considering maternal C_{trough} levels the fetus exposure to atazanavir would fall into a therapeutic range roughly 4 folds higher than wild-type HIV IC₉₀. On the other hand, a limited, but still therapeutic, placental transfer of atazanavir may protect the fetus against the potential toxic effects of the drug.

Since pregnancy does not appear to alter plasma exposure to atazanavir, no dose adjustment is required in pregnant women.

Pharmacokinetic results suggest that a standard boosted atazanavir dose is a reasonable component of HAART during pregnancy.