Atazanavir in Pregnancy - Transplacental Transfer and Neonatal Hyperbilirubinaemia

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Background
The transplacental passage of antiretrovirals (ARVs) including Atazanavir (ATV) is well documented however the extent of this transfer and its effects on the neonate are poorly understood. ATV is known to cause elevated bilirubin levels in adults and so could contribute to hyperbilirubinaemia in neonates exposed to the drug in utero. The aim of this study is to evaluate the transplacental diffusion of ATV and determine the incidence of hyperbilirubinaemia in the neonate.

Methods
Fetal cord blood of infants exposed to ATV in utero were assessed for both ATV and bilirubin concentrations. These were compared to maternal levels at time of delivery.

In addition neonatal bilirubin levels in the first 24hrs of life were measured. Demographic and birth outcome data were also gathered.

Data was analysed using SPSS V20.

Results
Study population
15 women were enrolled in the study (16 infants 14 singleton and a twin pair). 6 women were on ATV prior to conception while 9 commenced treatment between 19 – 33 wks gestation (median 15 wks, range 13-18.4).

All women received standard dose ATV (300mg OD) boosted with ritonavir (100mg OD). The NRTI backbones were Truvada (n=9); Combivir (n=4) or Kivexa (n=2). 3/15 women were ART naive. 13/15 women achieved HIV RNA <50 cpm at time of delivery. 2 women had a detectable viral load of 108cpm and 633cpm respectively.

Mean birth weight was 3.3kg [range 2.0-4.7]; 2 babies were pre-term (twins at 35 wks); the remainder were > 37 wks gestation.

ATV pharmacokinetics
Maternal and cord ATV concentrations were available for 15 mother-baby pairs (Figure 1) Considerable variations in maternal ATV concentrations at delivery were noted and were most likely attributable to the differences in time since last dose.

The median maternal ATV concentration was 1250 ng/ml [range <48-3441], with 13/15 greater than the MEC of 150ng/ml. Detectable ATV levels were present in 12/15 cord samples (median 223 ng/ml [range <48-531]), 8/12 were greater than the MEC 150ng/ml, 3 were borderline.

Linear regression analysis showed a significant correlation between maternal blood and cord blood ATV concentrations (R² = 0.632, P<0.001).

The mean ratio of maternal blood concentration to cord blood concentration was 0.14 (95% CI 0.08 -0.20).

Hyperbilirubinaemia
The median maternal serum total bilirubin concentration at delivery was 23.5 mol/ml [range 6-102]; median cord blood total bilirubin concentration was 34 mol/ml [range 15-89] and median neonatal total bilirubin concentration was 60 mol/ml [range 19-146].

Excluding 1 infant with an indirect bilirubin level of 146 mol/ml at 27 hours age, a significant correlation was noted between neonatal unconjugated bilirubin concentration and both maternal serum unconjugated bilirubin concentration (R² = 0.693, P=0.022) and cord unconjugated bilirubin concentrations (R² = 0.759, P<=0.001). (Figure 2).

There was no correlation between ATV level and bilirubin concentration.

No cases of hyperbilirubinaemia were noted.

Conclusion
Transplacental transfer of ATV may offer additional protection to the neonate against mother-to-child transmission of HIV, with therapeutic levels observed in the majority of cord blood samples here.

Although no cases of hyperbilirubinaemia were observed in this small cohort, further larger scale studies into the effects of ATV on the fetus and neonate are needed.

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