Lopinavir/ritonavir in pregnancy

Introduction

Studies in pregnant women continue to document altered pharmacokinetics of lopinavir/ritonavir (LPV/r) during pregnancy.

We hereby present some abstracts about increase LPV/ dose during pregnancy and pregnancy outcomes.

Modification of LPV/r dose is unlikely to be required for PI-naive pregnant women; however, in pregnant women who have previously received a PI, therapeutic drug monitoring and/or empirical increasing of the dose can be considered.

They investigated 145 HIV-infected women, including 74 pregnant women and they saw that pregnancy associated with a gestational age >15 weeks and delivery were found to increase LPV clearance by 39% and 58%, respectively.

With the standard 400 mg twice-a-day regimen, the probability of reaching the 1 mg/L target trough concentration for protease inhibitor (PI)-naive patients was 99% for non-pregnant women and 96% for pregnant women.

An important decrease in the probability of achieving the 5.7 mg/L target trough concentration for "salvage therapy" (i.e., in patients already treated with PIs) was observed in 55% of non-pregnant women and this decrease was even greater for pregnant women (21%). Raising the LPV dose to 600 mg twice daily increased these probabilities to 87% and 53% for non-pregnant and pregnant women, respectively.

In conclusion the authors suggest that modification of the LPV dose is unlikely to be required for PI-naive pregnant women; however, in pregnant women who have previously received a PI, therapeutic drug monitoring and/or empirical increasing of the dose should be considered.
LPV increased during pregnancy

At department of Pediatrics, Boston University School of Medicine, Mirochnick M et al (JID 2008, 200(5):485-91) looked at LPV exposure during the third trimester of pregnancy and 2 weeks postpartum with a higher LPV/r dose.

Women included in a cohort received LPV/RTV 400/100 mg twice daily during the second trimester and 533/133 mg twice daily during the third trimester through 2 weeks postpartum. Intensive steady state 12-hour pharmacokinetic profiles were performed during the third trimester and at 2 weeks postpartum and were optional.

Twenty-six HIV-infected pregnant women were studied. Median LPV area under the plasma concentration-time curve (AUCs) for the second trimester, third trimester, and postpartum were 57, 88, and 152 microg.h.mL, respectively.

Median minimum LPV concentrations were 1.9, 4.1, and 8.3 microg/mL.

In conclusion the higher LPV/r dose (533/133 mg) provided LPV exposure during the third trimester similar to the median AUC (80 microg.h.mL) in nonpregnant adults taking standard doses. However, the AUC on this increased dose at 2 weeks postpartum was considerably higher.

These data suggest that the higher LPV/r dose should be used in third trimester pregnant women; that it should be considered in second trimester pregnant women, especially those
who are protease inhibitor experienced; and that postpartum LPV/r dosing can be reduced to standard dosing by 2 weeks after delivery.

Gender, pregnancy and ARVs drug dosing

A review published in *Curr Opin HIV AIDS 2008, 3(3):277-82* by Best BM & Capparelli EV from University of California, outlined the influences of gender and pregnancy on drug disposition, and described the available antiretroviral pharmacokinetic data and dosing recommendations in these groups. Recent studies in pregnant women continue to document altered exposure of different classes of drugs during pregnancy. While new information shows that tenofovir exposure is significantly decreased during pregnancy, the magnitude of the decrease will not likely necessitate dose changes, similar to other nucleoside reverse

Recent studies in pregnant women continue to document altered exposure of different classes of drugs during pregnancy. While new information shows that tenofovir exposure is significantly decreased during pregnancy, the magnitude of the decrease will not likely necessitate dose changes, similar to other nucleoside reverse transcriptase inhibitors. In contrast, standard doses of LPV/r in the third trimester showed markedly decreased exposure, and they suggested that higher doses of this co-formulated agent should be given to women during the third trimester. Likewise, nelfinavir exposure using the new 625-mg tablets is also decreased during pregnancy, and higher doses should be considered in the third trimester.

In summary, the majority of antiretrovirals studied have altered pharmacokinetics during pregnancy. Understanding the extent of these changes is necessary to recommend dose changes during pregnancy when appropriate. The correct dose is critical to maintain efficacy and safety of these agents for both the mother and the fetus. Innovative study designs are needed to facilitate the study of antiretrovirals during pregnancy.

The team reported the pharmacokinetics of standard LPV/r dosing (400/100 mg twice daily) in the immediate and early postpartum period when initiated during labor.

In 16 human immunodeficiency virus-infected Thai women, the median (range) LPV area under the concentration-time curve and maximum and minimum concentrations in plasma were 99.7 (66.1 to 180.5) microg x h/ml, 11.2 (8.0 to 17.5) microg/ml, and 4.6 (1.7 to 12.5) microg/ml, respectively, at 41 (12 to 74) h after delivery. All of the women attained adequate LPV levels through 30 days postpartum.

Given the approximately 50% reduction in LPV exposure during the third trimester compared to that of nonpregnant women, it is perhaps surprising that standard LPV/r dosing resulted in adequate LPV exposure for all of the women in this study. However, the authors said that two factors may have accounted for this difference.

- First, the inverse correlation between body weight and LPV concentrations;
- Second, the timing of LPV initiation, i.e., antepartum versus intrapartum.

It is unclear how long the physiological changes affecting LPV exposure during pregnancy persist postpartum. Thus, the lower body weight and the timing of LPV/r treatment initiation in the study reported here may facilitate higher LPV concentrations.
Azria E et al (Antivir The. 2009;14(3):423-32) looked at adverse outcomes of LPV/r exposure during pregnancy. Data on 100 consecutive HIV-1-infected women receiving LPV/r during pregnancy and who delivered after 15 weeks gestational age between January 2003 and June 2007 in a single centre in France were analysed. For each HIV-1-infected woman, two uninfected women matched by age, parity and geographical origin were selected among patients delivering during the same period. Preterm delivery, vasculoperinatal complications, gestational glucose intolerance and post-partum complication rates were compared between cases and controls. Factors associated with preterm delivery and post-partum complications were assessed by a logistic regression model.

Rates of vasculoperinatal complication and gestational glucose intolerance were not higher among HIV-1-infected women than in controls. Preterm delivery was higher in HIV-1-infected women (21%) than in controls (10%; P<0.01).

In HIV-1-infected women, preterm delivery was associated with HIV-1 RNA level > or =50 copies/ml at delivery (adjusted odds ratio 6.15, 95% confidence interval 1.83-20.63; P=0.003). No association was found between occurrence of preterm delivery and LPV/r exposure before 14 weeks gestation.

In conclusion in this population of HIV-1-infected pregnant women receiving LPV/r, the risk of preterm delivery was higher than in HIV-1-uninfected controls.
Evolution in the treatment of HIV in pregnancy: 6 years perspective in Italy

Data from the National Program on Surveillance on Antiretroviral Treatment in Pregnancy in Italy (AIDS Patient Care STDS. 2009 Jul;23(7):513-20) were grouped per calendar year, and changes in antiretroviral treatment, population characteristics, maternal immunovirologic status and newborn clinical parameters were analyzed. A total of 981 HIV-infected mothers who delivered between 2002 and 2008 were evaluated. The proportion of women receiving at least three antiretroviral drugs at delivery increased significantly from 63.0% in 2002 to 95.5% in 2007-2008, paralleled by a similar upward trend in the proportion of women who achieved complete viral suppression at third trimester (from 37.3 in 2002 to 80.9 in 2007-2008; p < 0.001).

The co-formulation of zidovudine plus lamivudine remained the most common nucleoside backbone in pregnancy, even if a significant increase in the use of tenofovir plus emtricitabine was observed in more recent years. Starting from 2003, nevirapine prescription declined, paralleled by a significant rise in the use of protease inhibitors (PI), which were present in more than 60% of regimens administered in 2007-2008. Nelfinavir was progressively replaced by ritonavir-boosted PIs, mainly LPV.

No significant changes in preterm delivery, Apgar score, birth weight, and birth defects were observed during the study period, and the rate of HIV transmission remained below 2%.

These data demonstrate a significant evolution in the treatment of HIV in pregnancy. Constant improvements in the rates of HIV suppression were observed, probably driven by the adoption of stronger and more effective regimens and by the increasing options available for combination treatment.