

## Abstract: 1

*Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations*



## Placental transfer of antiretroviral drugs in HIV-infected women : a retrospective study from 2002 to 2009.

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**Background:** The rate of mother-to-child transmission (MTCT) of HIV-1 is as low as 0.5% in non-breast-feeding mothers who delivered at term while receiving HAART with a plasma RNA < 500 c/mL in the French ANRS perinatal cohort. The degree of fetal exposure depends largely on the amount of placental transfer of drugs. The TDM of antiretroviral drugs (ARV) in HIV-infected pregnant women was used to detect adherence difficulties or intolerance.

**Objectives:** to evaluate the *in vivo* maternofetal transfer of ARV used to prevent MTCT based on the determination of concentrations in different compartments of the maternofetal unit.

**Materials & Methods:** paired maternal and cord blood and amniotic fluid samples were collected at delivery from HIV-1 infected women to determine steady-state plasma concentrations of ARV using HPLC coupled with UV-PDA or fluorimetric detection. Results from gemellary pregnancy were excluded from the study. The *in vivo* placental transfer of ARV was calculated as the ratio of cord (CP) to maternal plasma (MP) concentrations. Median ratio are presented and compared to the results of the *ex vivo* double perfusion of placental cotyledon reported in the literature. Other *in vivo* transfer ratio including amniotic fluid (AF) concentrations were calculated as AF/MP and AF/CP in a subgroup of patients.

**Results:** A total of 354 paired CP and MP were obtained from HIV-1 infected women (31.4 yrs) between 2002 and 2009. Among them, 65 had an AF sample collected. The main triple ARV combination found was LPV/r + ZDV/3TC (43%). CP/MP ratio were: ZDV (with pre-labour infusion 1.1, n=195 and without 1.67, n=78); 3TC (1.2, n=267); ABC (0.8, n=37); ddI (1.0, n=21); TFV (0.7, n=20); IDV (0.65, n=19); RTV (0.15, n=294); LPV (0.13, n=204); NFV (0.13, n=14); M8 (0.23, n=14); SQV (0.03, n=30); APV (0.21, n=12); NVP (0.81, n=21) and T20 (0.01, n=5). These *in vivo* results were statistically associated to the *ex vivo* results using the double perfusion of placental cotyledon ( $R^2=0.42$ ;  $p=0.04$ ) and related to the respective plasma protein binding percentage ( $R^2=0.79$ ;  $p<0.0001$ ). Other determinant factors for a poor placental transfer were the high liposolubility ( $\log P>2.8$ ) and high Molecular Weight (T20~4565 Da). AF/MP, CP/MP and AF/CP ratio were: ZDV (with pre-labour infusion: 2.8, 0.8, 2.0, n=31 and without: 3.49, 1.23, 3.0, n=7), 3TC (10.7, 1.4, 6.1, n=37), ABC (7.4, 0.6, 8.8, n=2), TFV (6.6, 0.1, 8.5, n=2), IDV (1.0, 0.2, 8.6, n=19), LPV (0.14, 0.12, 1.0, n=31), RTV (0.18, 0.15, 1.0, n=52), NFV (0.47, 0.12, 3.9, n=3), M8 (1.0, 1.0, 1.0, n=3) APV (0.2, 0.14, 1.4, n=2), T20 (0.2, 0.02, 8.9, n=2).

**Conclusions:** Triple drug regimens reported in this study were in accordance with the successive French Guidelines to prevent MTCT. High transfer of NRTI, NVP and IDV in cord blood (Ratio > 0.7) was found regarding to their low protein binding, low liposolubility and low Molecular Weight. The *ex vivo* model of double perfusion of placental cotyledon might be a good predictor of the *in vivo* placental transfer. Because of high placental transfer, NRTI accumulation in amniotic compartment was found.

*No conflict of interest*