Antiretroviral therapy with indinavir 400 mg-ritonavir 100 mg twice daily containing regimen in HIV-1 infected women during pregnancy.

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Abstract:

We evaluated safety and efficacy of indinavir/ritonavir 400/100 mg bid based therapy in thirty-two HIV-infected women during pregnancy. Median indinavir trough concentration was 208 ng/mL during third trimester. At delivery, 26/28 women on indinavir/ritonavir had an HIV-RNA<200 copies/ml. No infant was HIV-infected. These data are encouraging for the use of this combination for PMTCT.
Protease inhibitors based combinations are the current standard of care in HIV-1 infected pregnant women in France (18). Published data describing indinavir (IDV) pharmacokinetic parameters in pregnant women are limited and suggest that IDV plasma concentrations may be suboptimal in pregnant women taking standard doses of IDV (7) (D. Wara, R. Tuomala, and Y. Bryson. PACTG 358: safety, pharmacokinetics and antiretroviral activity of indinavir, zidovudine (ZDV) and lamuvidine (3TC) in HIV-1 seropositive pregnant women and infants. Presented at the 2\textsuperscript{nd} Conference on Global Strategies for the Prevention of HIV Transmission from Mothers to Infants, Montreal, 1999, abstract 447). Thus, use of unboosted-IDV should be avoided during pregnancy (12, 15). We have previously shown the good efficacy and tolerance of a twice daily regimen containing indinavir/ritonavir (IDV/r) 400/100 mg in patients switching from standard IDV-containing regimen (6) and in patients initiating first-line treatment (4). The objective of this study was to describe maternal and new-born safety, tolerability and response to an IDV/r 400/100 containing regimen during antenatal period in HIV-1 infected pregnant women.

In a prospective, observational, pilot, open-label, single centre, non-comparative study, the efficacy and tolerability of a triple combination of two nucleoside analogues reverse transcriptase inhibitors (NRTI) plus IDV/r (400/100 mg bid) were evaluated in consecutive HIV-1 infected women in whom pregnancy was diagnosed before the third trimester. Patients were followed monthly, with clinical examination and biological assessments including plasma HIV-RNA (Amplicor HIV Monitor kit, Roche, Meylan, France, lower limit of quantification (LOQ) 200 copies/ml), and CD4
cell count. Steady-state IDV plasma trough concentrations ($C_{\text{trough}}$) were determined during the third trimester by high performance liquid chromatography coupled with UV detection (LOQ 5 ng/ml) (17). IDV $C_{\text{trough}}$ was determined during the month following delivery in a subset of women. The expected efficient $C_{\text{trough}}$ IDV was 120 ng/ml (1).

The mode of delivery was determined according to plasma VL, obstetrical history and personal decision. All women received ZDV intravenous infusion during labour or initiated 2 hours before elective Cesar section, and newborns received a six-week course of ZDV (0.2 mg/Kg four times a day) as recommended by French guidelines (18). All women received counselling on the risk of HIV-1 transmission through breastfeeding, and no woman reported breastfeeding her child. Infants were followed according to French guidelines (18).

Thirty-two women were enrolled in the study between September 2002 and October 2003, 84% of them were from sub Saharan Africa. Their baseline characteristics are summarized in Table 1. Eleven women (34%) were antiretroviral-naïve and started a first-line combination including IDV/r (400/100 mg bid) at a median gestational age of 20 weeks (range 3-30). Fourteen women (44%) were already receiving IDV/r (400/100 mg bid) for a median of nine months (range 1-16) before study entry, and the remaining pre-treated women were switched from NRTI combinations (n=4), or PI-containing combinations (n=3) to an IDV/r-containing regimen.

Treatment combination comprised a backbone of ZDV+3TC in 29/32 (91%) women. Twenty-eight out of 32 women (87%) completed their pregnancy on study treatment
and are included in the on-treatment analysis. The other four patients discontinued IDV/r for virologic failure (n=1), biological (n=1) or clinical (n=2) adverse events.

Plasma IDV C_{trough} during last trimester of pregnancy was available in 28 women included in the on-treatment analysis, with a median concentration of 162 ng/ml (range BLOQ-4852). IDV C_{trough} was below 5 ng/mL in 4/28 women, with undetectable plasma VL at delivery in three of them. An additional woman with IDV C_{trough} of 89 ng/ml reported adherence difficulties, and her VL was 3100 copies/ml at the time of delivery.

In a subset of 7 women, median IDV C_{trough} increased from 245 ng/ml (range 18 – 443) during the third trimester up to 440 ng/ml (range 222 – 1212) after delivery.

By on-treatment analysis, 26/28 women (93%) had plasma VL < 200 copies/ml at delivery on IDV/r. At the time of delivery, median CD4 cell count was 352/mm^3 (range 113-948).

Overall, clinical tolerance was satisfactory. Three women discontinued study treatment for moderate adverse events (grade 2 elevation in liver enzymes at Week 16 (W16) on IDV/r, xerosis at W12, and xerosis plus ingrowing toenail at W10). No nephrolithiasis was observed. There was no significant change in any of the biological parameters studied, including total bilirubin and creatininemia.

Pregnancy led to delivery of 33 living newborns (two pairs of twins) in 31/32 women exposed to IDV/r, with one spontaneous miscarriage at 11 weeks’ gestation (W5 on IDV/r). Twelve women had vaginal delivery, 18 had elective caesarean section, and one an emergency caesarean section. Median gestational age at delivery was 38 weeks (range 33-42), with 4 deliveries before 37 weeks’ gestation. Clinical examination was
normal in all 33 infants. Median newborns birth weight was 3000 g (range 2100-4600). Evolution of biological markers in infants between Day 4 (D4) and D30 of life is shown in Table 2. None of the children developed HIV infection.

Here we show that a twice daily regimen containing IDV/r 400/100 mg bid was efficacious on achieving or maintaining viral suppression in HIV-1 infected pregnant women, with a good tolerance. Physiological changes, including alteration in gastrointestinal transit time, increased total body water and fat, and increased metabolism can modify the pharmacokinetics of medications taken during pregnancy (9, 10). Previous studies demonstrated that plasma levels of unboosted IDV were low during the last trimester of pregnancy, due to a possible induction of IDV metabolism (8, 15). Interestingly, Kosel et al showed that this induction was offset when pregnant women were switched from standard IDV to IDV/r (800/100 mg bid) (8). However, the expected poor tolerability of IDV/r regimens using doses higher than 400/100 mg (2, 3, 13, 16), and our previous experience with the IDV/r 400/100 mg bid dosage made us evaluate this regimen during pregnancy. In our study, median plasma IDV C_{trough} was above the targeted cut-off trough concentration value of 120 ng/ml (1). Five out of twenty eight women had C_{trough} below 120 ng/ml, most likely due to lack or poor adherence rather than pregnancy-related physiological modifications. Median plasma IDV C_{trough} during last trimester was lower than that obtained in the two previous studies we conducted in HIV-infected men and non-pregnant women (4, 6). This suggests an increased induction of IDV metabolism or efflux membrane proteins or
physiological changes during pregnancy, which is supported by the two-fold increase in $C_{\text{trough}}$ after delivery in a subset of seven women.

Some authors suggested that antiretroviral drug-related side-effects are more frequent for some ARV in pregnant than in non-pregnant HIV-infected women (14). Our study regimen was well tolerated, with no severe adverse events reported. Haematological abnormalities reported in newborns are most likely related to ZDV bone marrow toxicity (5).

Finally, the IDV/r (400/100 mg bid) regimen costs about 50% less than the standard IDV regimen, a major advantage for pregnant women in countries with limited access to second generation PIs. Thus, this regimen may be an effective and available alternative to the use of nevirapine in prevention of mother-to-child transmission regarding the risk of emergence of drug-resistant viruses (11) and for women requiring an effective PI-containing second line regimen during pregnancy.
References:


Table 1: Baseline characteristics of pregnant women (n= 32) (BLOQ: below limit of quantification)

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<tr>
<td><strong>Median age (years)</strong></td>
<td>32 [20- 43]</td>
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<td><strong>Gestational age at entry (weeks)</strong></td>
<td>14 [3-31]</td>
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<td><strong>Median Viral Load (copies/ml)</strong></td>
<td>992 [BLOQ-140.000]</td>
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<td><strong>Median CD4 (cells/mm³)</strong></td>
<td>335 [112-828]</td>
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Table 2: Biological tolerance in new-borns at Day 4 and Day 30. (n=33)

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<th>Infant Day 4 median [range]</th>
<th>Infant Day 30 median [range]</th>
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<tr>
<td>Hemoglobin g/dl</td>
<td>13.4 [10.4-17.5 ]</td>
<td>9.9 [ 8.3-13.9 ]</td>
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<td>Neutrophilia /mm³</td>
<td>3993 [ 920- 9500 ]</td>
<td>1756 [773- 3825 ]</td>
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<td>Total bilirubin µmol/l</td>
<td>104 [14-194 ]</td>
<td>15 [ 4- 28 ]</td>
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<td>SGOT UI/ ml</td>
<td>46 [ 22- 69 ]</td>
<td>35 [23-87]</td>
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<td>Creatininemia µmol/l</td>
<td>53 [ 37-67 ]</td>
<td>33 [14- 56 ]</td>
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<tr>
<td>Lactatemia mmol/l</td>
<td>Not applicable</td>
<td>3.1 [ 1.4- 6.4]</td>
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