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Antiretroviral Therapy with a Twice-Daily Regimen Containing 400 Milligrams of Indinavir and 100 Milligrams of Ritonavir in Human Immunodeficiency Virus Type 1-Infected Women during Pregnancy▽

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We evaluated the safety and efficacy of a twice daily regimen containing 400 mg of indinavir and 100 mg of ritonavir in 32 human immunodeficiency virus (HIV)-infected women during pregnancy. The median indinavir trough concentration was 208 ng/ml during the third trimester. At delivery, 26 of 28 women on indinavir-ritonavir had HIV RNA levels of <200 copies/ml. No infant was HIV infected. These data are encouraging for the use of this combination for prevention of mother-to-child transmission of HIV.

Protease inhibitor (PI)-based combinations are the current standard of care for human immunodeficiency virus type 1 (HIV-1)-infected pregnant women in France (18). Published data describing indinavir (IDV) pharmacokinetic parameters for 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, presented at the 2nd Conference on Global Strategies for the Prevention of HIV Transmission from Mothers to Infants, Montreal, Canada, 1999). Thus, use of unboosted IDV should be avoided during pregnancy (12, 15). We have previously shown the good efficacy and tolerability of a twice daily (BID) regimen containing 400 mg of IDV and 100 mg of ritonavir (hereafter referred to as IDV/r 400/100 mg BID) in patients switching from a standard IDV-containing regimen (6) and in patients initiating a first-line treatment (4). The objective of this study was to describe, in terms of effects on mothers and newborns, the safety and tolerability of and responses to an IDV/r 400/100 mg BID regimen during the antenatal period in HIV-1-infected pregnant women.

In a prospective, observational, pilot, open-label, single-center, noncomparative study, the efficacy and tolerability of a triple combination of two nucleoside reverse transcriptase inhibitors and IDV/r 400/100 mg BID were evaluated for consecutive HIV-1-infected women in whom pregnancy was diagnosed before the third trimester. The patients were followed monthly with clinical examinations and biological assessments, including plasma HIV RNA (lower limit of quantification [LOQ], 200 copies/ml; Amplicor HIV monitor kit; Roche, Meylan, France) and CD4 cell counts. Steady-state IDV plasma trough concentrations (C_{trough} values) were determined during the third trimester by high-performance liquid chromatography coupled with UV detection (LOQ, 5 ng/ml) (17). IDV C_{trough} was determined during the month following delivery for a subset of women. The expected efficient IDV C_{trough} was 120 ng/ml (1).

The mode of delivery was determined according to plasma viral load (VL), obstetrical history, and personal decision. All women received intravenous zidovudine (ZDV) infusions initiated during labor or 2 h before elective caesarean section, and newborns received a 6-week course of ZDV (0.2 mg/kg of body weight four times a day), as recommended by French guidelines (18). All women received counseling 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, and 84% of them were from sub-Saharan Africa. Their baseline characteristics were as follows: median age, 32 years (range, 20 to 43); gestational age at entry, 14 weeks (range, 3 to 31); median VL, 992 copies/ml (range, below LOQ to 140.000); and median CD4 count, 335 cells/mm^3 (range, 112 to 828). 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 to 30). Fourteen women (44%) were already receiving IDV/r 400/100 mg BID for a median of 9 months (range, 1 to 16) before study entry, and the remaining pretreated women were switched from nucleoside reverse tran-

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TABLE 1. Biological tolerance in newborns at D4 and D30 ($n = 33$)[a]

Time point	Median (range) for indicated biological marker in infants					
	Hemoglobin (g/dl)	Neutrophilia (no. of cells/mm^3)	Total bilirubin (μmol/liter)	SGOT (IU/ml)	Creatininemia (μmol/liter)	Lactatemia (mmol/liter)
D4	13.4 (10.4–17.5)	3,993 (920–9,500)	104 (14–194)	46 (22–69)	53 (37–67)	NA
D30	9.9 (8.3–13.9)	1,756 (773–3,825)	15 (4–28)	35 (23–87)	33 (14–56)	3.1 (1.4–6.4)

[a] SGOT, serum glutamic oxalacetic transaminase; NA, not applicable; IU, international units.

scriptase inhibitor combinations ($n = 4$) or PI-containing combinations ($n = 3$) to an IDV/r-containing regimen.

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

Plasma IDV C_{trough} values during the last trimester of pregnancy were available for 28 women included in the on-treatment analysis, with a median concentration of 162 ng/ml (range, below LOQ to 4,852). IDV C_{trough} values were below 5 ng/ml in 4 of 28 women, with undetectable plasma VLs at delivery in 3 of them. An additional woman, with an IDV C_{trough} of 89 ng/ml, reported adherence difficulties, and her VL was 3,100 copies/ml at the time of delivery.

In a subset of seven women, the median IDV C_{trough} increased from 245 ng/ml (range, 18 to 443) during the third trimester to 440 ng/ml (range, 222 to 1,212) after delivery.

According to on-treatment analysis, 26 of 28 women (93%) had plasma VLs of <200 copies/ml at delivery on IDV/r. At the time of delivery, the median CD4 cell count was 352/mm^3 (range, 113 to 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], xerosis at W12, and xerosis plus ingrown toenail at W10 on IDV/r). No nephrolithiasis was observed. There was no significant change in any of the biological parameters studied, including total bilirubin and creatininemia levels.

Pregnancy led to delivery of 33 living newborns (two pairs of twins) in 31 of 32 women exposed to IDV/r, with one spontaneous miscarriage at 11 weeks of gestation (at W5). Twelve women had vaginal deliveries, 18 had elective caesarean sections, and 1 had an emergency caesarean section. The median gestational age at delivery was 38 weeks (range, 33 to 42), with four deliveries before 37 weeks of gestation. Clinical examinations were normal for all 33 infants. The median newborn birth weight was 3,000 g (range, 2,100 to 4,600). The evolution of biological markers in infants between day 4 (D4) and D30 of life is shown in Table 1. None of the children developed HIV infection.

Here, we show that a BID regimen containing IDV/r 400/100 mg was efficacious for achieving or maintaining viral suppression in HIV-1-infected pregnant women, with a good tolerability. 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, possibly due to an induction of IDV metabolism (8, 15). Interestingly, Kosel et al. showed that this induction was offset when pregnant women were switched from a standard IDV regimen to an IDV/r 800/100 mg BID regimen (8). However, the expected poor tolerability of IDV/r regimens using doses higher than 400 mg of IDV and 100 mg of ritonavir (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, the median plasma IDV C_{trough} was above the targeted cutoff C_{trough} of 120 ng/ml (1). Five out of 28 women had C_{trough} values below 120 ng/ml, most likely due to a lack or inadequacy of adherence rather than pregnancy-related physiological modifications. The median plasma IDV C_{trough} during the last trimester was lower than that obtained in the two previous studies that we conducted with HIV-infected men and nonpregnant women (4, 6). This suggests an increased induction of IDV metabolism or efflux membrane proteins or physiological changes during pregnancy, which are supported by the twofold increases in C_{trough} after delivery in a subset of seven women.

Some authors suggested that antiretroviral-drug-related side effects are more frequent for some AIDS-associated retroviruses in pregnant than in nonpregnant HIV-infected women (14). Our study regimen was well tolerated, with no severe adverse events reported. The hematological abnormalities reported to occur 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 extended-spectrum PIs. Thus, this regimen may be an effective and available alternative to the use of nevirapine in the prevention of mother-to-child transmission with regard to the risk of emergence of drug-resistant viruses (11) and for women requiring an effective PI-containing second-line regimen during pregnancy.

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