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Pharmacokinetics and Safety of Indinavir in Human Immunodeficiency Virus-Infected Pregnant Women▽†

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Human immunodeficiency virus-infected women ($n = 16$) received indinavir (800 mg three times a day) plus zidovudine plus lamivudine from 14 to 28 weeks of gestation to 12 weeks postpartum. Two women and eight infants experienced grade 3 or 4 toxicities that were possibly treatment related. Indinavir area under the plasma concentration-time curve was 68% lower antepartum versus postpartum, suggesting increased intestinal and/or hepatic CYP3A activity during pregnancy.

Current antiretroviral guidelines recommend triple combination highly active antiretroviral therapy during pregnancy for the treatment of the mother and the prevention of mother-to-infant transmission of human immunodeficiency virus (HIV) (4). During pregnancy, physiological changes occur that have the potential to change the pharmacokinetics of drugs (8) and hence lead to decreased virologic efficacy. This study was initiated to determine the pharmacokinetics and safety of indinavir (IDV), coadministered with zidovudine (ZDV) and lamivudine (3TC), in HIV-infected women during pregnancy and postpartum.

Women with a singleton, uncomplicated pregnancy between 14 and 28 weeks of gestation according to menstrual and ultrasound dating were enrolled after signing institutional human subjects committee-approved informed consent statements. Exclusion criteria included prior treatment with a protease inhibitor of >3 weeks, nonnucleoside reverse transcriptase inhibitor use within 3 weeks, >3 weeks of prior 3TC usage unless taken for >3 months with a stable HIV RNA and $CD4^+$ cell count, or intolerance to ZDV or 3TC. Women received 800 mg IDV three times daily according to standard instructions with ZDV (300 mg twice a day or 200 mg three times daily) and 150 mg 3TC twice daily through 12 weeks postpartum. During labor, IDV was temporarily discontinued, oral 3TC was continued, and ZDV was given intravenously (7). Infants received orally 2 mg/kg 3TC twice daily and 2.6 mg/kg ZDV three times daily (or 2.0 mg/kg intravenously every 8 h) until 6 weeks. Infants did not receive IDV because of the concern for increases in indirect bilirubin concentrations.

Maternal and infant study visits for safety and efficacy evaluations occurred every 1 to 2 weeks antepartum, at delivery, at 6 and 12 weeks postpartum, and at 1, 6, 12, and 24 weeks of life, respectively. Adverse events were graded according to the National Institute of Allergy and Infectious Diseases Division of AIDS toxicity grading tables (1). Maternal blood samples for IDV pharmacokinetics were obtained predose and at 0.5, 1.0, 1.5, 2, 4, 6, and 8 h postdose at 30 to 32 weeks of gestation and 6 weeks postpartum. Infant IDV plasma concentrations were obtained at birth and at 1, 2, 4, and 6 h of life. IDV plasma concentrations (as free base) were determined by a high-performance liquid chromatography-UV and, at later stages of the study, by the more sensitive high-performance liquid chromatography-mass spectrometry assay (University of California at San Diego PACTG Pharmacology Laboratory). For both assays, the inter- and intra-assay precision had a <13% coefficient of variation, and the accuracy had a <13% deviation from the expected. Pharmacokinetic parameters were estimated by noncompartmental analysis of the IDV plasma concentration-time profiles (WinNonLin 3.0; Pharsight, CA). With a sample size of 10 evaluable mothers, the study had approximately 80% power to show "equivalence" of maternal postpartum and antepartum area under the plasma concentration-time profiles (AUCs; defined as having a 90% confidence interval [CI] of the ratio of the geometric mean of antepartum to postpartum AUC in the range of 0.67 to 1.50).

Baseline characteristics of the 16 HIV-infected pregnant women and their infants and the adverse effects they experi-

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TABLE 1. Summary of the baseline characteristics of women and infants enrolled in the study as well as their experience of adverse events

Characteristic	Total
Women	
No. of patients	16
Race/ethnicity	
Black, non-Hispanic	15 (94%)
Hispanic	1 (6%)
Median (range) age (yr)	24.9 (19–36)
Median (range) gestational age at enrollment (wk)	18 (14–26)
Prior antiretroviral use	
Yes	8[a]
No	8
Median (range) $CD4^+$ cell count	372 (135–647)
Median (range) HIV-1 RNA (log_{10} copies/ml)[b]	4.1 (<2.7–5.0)[c]
Median (range) weight (kg)	71 (57–109)
No. who completed study evaluations	15[d]
No. who discontinued study treatment prior to delivery	2[d,e]
Adverse events	48 in 15 women
Possibly treatment related[f]	11
Grade 3 flank pain	1
Grade 3 abdominal pain	1
Grade 4 flank pain	2
Infants	
No. of patients (1 male, 14 female)	15
Median (range) gestational age at birth (wk)	38 (35–41)[g]
Median (range) birth weight (kg)	3.15 (2.27–3.57)[g]
No. with two negative HIV DNA PCR results	13[h]
No. who completed study treatment	13[i]
Adverse events	45 in 13 infants
Possibly treatment related[f]	8
Grade 3 anemia	1
Grade 2/3 neutropenia	3
Grade 2/3 neutropenia and grade 2 anemia	2
Grade 3 neutropenia and grade 4 hypoglycemia	1
Grade 2 neutropenia, grade 3 anemia, and grade 3 bilirubinemia	1

[a] Five of these women had received ZDV for 4 to 7 months during a prior pregnancy. Of the remaining three, one received ZDV for 1 month, one received stavudine and 3TC for 7 months, and one received ZDV and 3TC plus nelfinavir for 2 weeks prior to study entry.
[b] Available for 15 women.
[c] Three patients had baseline HIV RNA of <2.7 log 10 copies/ml (<400 copies/ml).
[d] One patient stopped study medication after 4 weeks of treatment following an episode of pyelonephritis, hematuria, and persistent grade 3/4 abdominal flank pain. She refused further contact 6 weeks prior to delivery.
[e] One patient stopped study medication after 2 weeks of treatment due to grade 2 nausea and vomiting but completed all study assessments.
[f] Of these, grade 3/4 adverse events are listed below.
[g] Two infants were preterm (<37 weeks gestation): one was born at 35 weeks of gestation with a low birth weight of 2.27 kg but appropriate for gestational age, and the other was born at 36 weeks of gestation with a birth weight of 3.05 kg. No other infants had a low birth weight (i.e., <2.5 kg).
[h] There was incomplete information on the remaining two infants.
[i] One infant did not receive study treatment and another discontinued treatment at 2 weeks of age at the request of the mother.

enced are provided in Table 1. Maternal adverse effects were similar in type and magnitude to those seen in nonpregnant individuals taking the same regimen (13). Although two women had flank pain, renal ultrasound did not show kidney stones and there was no crystalluria. The major adverse event noted in infants was bone marrow suppression, previously described in infants receiving ZDV (7). Of note, none of the women or their infants experienced grade 2 or higher episodes of indirect hyperbilirubinemia.

Among the 14 women who remained on study treatment through delivery and postpartum, the mean CD4 count increased from 358 cells/mm^3 at baseline to 505 cells/mm^3 at delivery (n = 12) and 605 cells/mm^3 at 12 weeks postpartum ($P < 0.001$). Among the 12 women who had HIV-1 RNA evaluations at de-

TABLE 2. Geometric mean (95% CI), GMR, and arithmetic mean of the postpartum (6.3 ± 0.8 weeks) and antepartum (31.1 ± 2.4 weeks) indinavir pharmacokinetic parameters in HIV-1-infected women

Time point or ratio	Parameter (geometric and arithmetic mean values)[a]											
	$AUC_{(0\text{-}8)}$ (μg · min/ml)		CL/F (ml/min)		CL/F (ml/min/kg)		C_{max} (μg/ml)		T_{max} (min)		C_{min} (ng/ml)	
	Geometric (95% CI)	Arithmetic (±SD)	Geometric (95% CI)	Arithmetic (±SD)	Geometric (95% CI)	Arithmetic (±SD)	Geometric (95% CI)	Arithmetic (±SD)	Geometric (95% CI)	Arithmetic (±SD)	Geometric (95% CI)	Arithmetic (±SD)
Antepartum	341 (187, 621)	459 (322)	2,354 (1,290, 4,297)	3,558 (3,796)	29.6 (17.0, 51.7)	41.5 (40.1)	3.07 (1.53, 6.16)	4.37 (2.77)	95 (65, 138)	111 (72)	25.5 (4.4, 149.1)	128 (127)
Postpartum	1,285 (927, 1,781)	1,429 (707)	624 (450, 864)	697 (369)	8.6 (6.7, 11.2)	8.8 (4.0)	8.57 (6.49, 11.33)	9.27 (3.81)	97 (69, 136)	113 (87)	96.7 (13.8, 675.5)	806 (1,548)
Postpartum: antepartum[b]	3.77 (1.95, 7.28)		0.26 (0.14, 0.50)		0.29 (0.16, 0.54)		2.79 (1.29, 6.04)		1.02 (0.60, 1.75)		3.80 (1.03, 13.99)	

[a] CL_F, oral clearance, where F is bioavailability; C_{max}, maximum concentration of drug in plasma; T_{max}, time to reach maximum plasma concentration; C_{min}, minimum concentration in plasma at the end of the dosing interval.
[b] Geometric mean ratio.

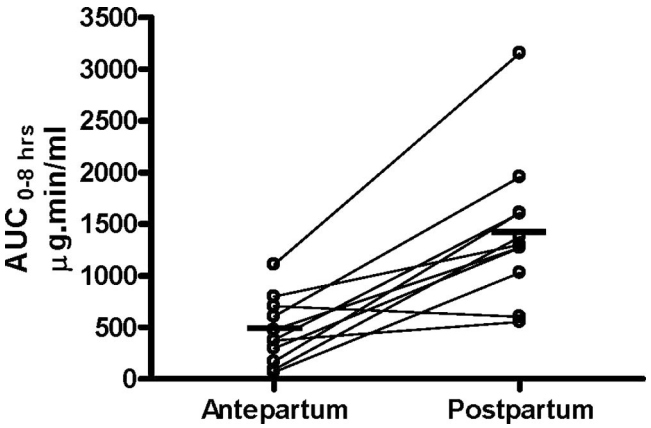

FIG. 1. Area under the plasma concentration-time curves (AUC_{0-8}) of indinavir in all but two women were lower antepartum versus postpartum. The horizontal solid line represents the arithmetic mean AUC_{0-8} values for the antepartum and postpartum periods.

livery, the number with levels less than 400 copies/ml increased from 4 (33%) at baseline to 10 (83%) at delivery.

Eleven women had complete, evaluable pharmacokinetic profiles (Table 2). Except for time to reach maximum plasma concentration (T_{max}), 95% confidence intervals for the geometric mean ratios (GMR) comparing postpartum to antepartum pharmacokinetic parameters did not encompass one, indicating that these parameters were significantly different postpartum versus antepartum. The postpartum pharmacokinetic parameters and their variability were comparable to those in nonpregnant women (AUC from time 0 to 8 h [AUC_{0-8}], 1,124 ± 540 μg · min/ml; maximum concentration of drug in plasma, 8.37 ± 3.97 μg/ml; B.-Y. Nguyen, personal communication). Therefore, we conclude that the antepartum pharmacokinetics of IDV differ from those in nonpregnant HIV-1-infected women. Cord IDV plasma concentrations were evaluated from eight mother/infant pairs: they were below the assay limit of quantification for six, gave no detectable peak in one, and had a concentration of 39.9 ng/ml in one.

The reduced exposure (AUC_{0-8}) to protease inhibitors during pregnancy observed here (Fig. 1; Table 2) and by others (6–10) can be explained by several mechanisms. During pregnancy, the bioavailability (including the amount absorbed) of the drug may be lower, or the clearance of the drug may be increased. The oral clearance of IDV could be increased due to an increase in the free fraction of the drug in plasma due to pregnancy. However, this is unlikely, as IDV is not highly bound to plasma proteins (~60% protein bound). Therefore, its plasma protein binding would have to be reduced to almost zero during pregnancy to produce the change in oral clearance observed in our study. Such a change is physiologically unrealistic. Since IDV and the other protease inhibitors are predominately cleared by cytochrome P-450 (CYP) 3A4/5 metabolism (3, 5, 12) and P-glycoprotein efflux (3, 5, 12), their clearance through these pathways may be increased during pregnancy. Others have also suggested that intestinal and/or hepatic CYP3A activity is increased during pregnancy (10, 11). In the pregnant mouse, hepatic, but not intestinal, CYP3A activity and expression is increased, while hepatic and intestinal P-glycoprotein expression is unaffected (9). Based on these studies, we propose that increased intestinal and/or hepatic activity of CYP3A activity is the most reasonable explanation for the enhanced oral clearance of protease inhibitors during pregnancy. Such an increase has significant ramifications for designing appropriate dosing regimens for pregnant women receiving narrow-therapeutic-window drugs cleared extensively by CYP3A. CYP3A enzymes clear more drugs on the market than any other drug-metabolizing enzyme. Therefore, we predict that dosing regimens of CYP3A-cleared drugs such as the anti-rejection drugs (e.g., cyclosporine), anti-epileptics (e.g., carbamazepine), cardiovascular agents (e.g., nifedipine), or antimicrobials (e.g., clarithromycin) will need to be adjusted upwards during pregnancy.

Although viral suppression was documented in the majority of women who participated in this study, two women did not have viral suppression at delivery, one of which had very low exposure to IDV. There are significant concerns that utilizing dosing regimens of antiretrovirals yielding low plasma drug concentrations during pregnancy may be associated with lack of viral suppression as well as the development of resistance mutations (2, 6). It is possible that using standard doses of protease inhibitors for pregnant women could result in unnecessary cases of vertical transmission, with an additional concern for transmission of genotypically resistant virus to the infant. Antiretroviral agents utilized during pregnancy should be used in doses adequate to achieve plasma drug concentrations known to suppress the virus.

Since initiating this study, drug therapy of the HIV-infected pregnant woman has evolved (http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf). The addition of low-dose ritonavir to IDV for dose "boosting" has been utilized in nonpregnant adults. Although the use of IDV during pregnancy is infrequent, based on these results, further study of the pharmacokinetics and safety of the combination of IDV plus ritonavir during pregnancy is warranted to provide an alternative agent for pregnant women intolerant of or not responding to other anti-HIV protease inhibitor regimens.

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