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Multicenter Review of Protease Inhibitors in 89 Pregnancies

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Context: Despite the success of highly active antiretroviral therapy, the optimal approach for preventing perinatal HIV-1 transmission is not known.

Objective: A retrospective survey was conducted at six centers in the United States and Puerto Rico from January 1997 to October 1998 to evaluate the effects of protease inhibitor use during pregnancy on maternal and infant safety, prematurity rate, and frequency of perinatal HIV-1 transmission.

Results: In the study, 91 live infants, including 3 sets of twins, and 1 neonate who died shortly after birth were born to 89 women. HIV perinatal transmission rate in this series was 0 (95% confidence interval [CI], 0%–3%). Prematurity rate was 19.1%, comparable to rates in earlier reports of HIV-1–infected women. In multiple regression analysis, only cocaine use and premature rupture of membranes were associated with prematurity ($p = .03$ and .008, respectively). The gestational week during which the protease inhibitors were initiated was not found to be significantly associated with prematurity. Adverse maternal, obstetric, and infant events possibly related to protease inhibitors were uncommon.

Conclusions: Protease inhibitors appeared generally safe in mothers and infants in this series. No perinatal HIV-1 transmission occurred. Further prospective, controlled studies are needed to define the optimal management of HIV-1 in pregnancy.

Key Words: Perinatal transmission—Pregnancy—Protease inhibitors.

It is well known that antiretroviral treatment with zidovudine can significantly lower HIV perinatal transmission. Not until this year have data been published on the use of protease inhibitors (PI) during pregnancy (1–3). Concerns have been raised regarding a possible increase in prematurity and adverse events in infants in an abstract of a small series of Swiss women ($n = 16$) (4) and in an AIDS Clinical Trials Group (ACTG) protocol with ritonavir in pregnancy (5). The current standard of care for treatment of HIV-infected pregnant women is to consider therapy based on the needs of the mother in recognition of the unknown risks and benefits of newer therapies (6). Data are available demonstrating an association between lower perinatal transmission rates and lower maternal viral loads at the time of delivery (7,8). In view of these data, the recent reports demonstrating the benefit of cesarean section in decreasing perinatal transmission in the era prior to combination therapy (9–11), and those reports of increased morbidity with cesarean section (12,13), it is clear that more information is needed on the use of highly active antiretroviral therapy (HAART) including PIs during pregnancy to inform and counsel women on their options adequately.

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METHODS

A single invitation to participate in this collaborative effort was mailed or faxed to 21 centers known through HIV provider networks to

TABLE 3. *Maternal immunologic and virologic data*

	Average (range)
CD4 counts (cells/mm^3)	
Prior to antiretroviral therapy (n = 72)	381 (43–1100)
Last test before delivery (n = 67)	464 (33–858)
Change (n = 57)	+48 (−704–442)
Viral load ($\log_{10}$ copies/ml)	
Prior to antiretroviral therapy (n = 67)	4.23 (2.58–5.59)
Last test before delivery (n = 70)	2.83[a] (1.28–5.13)
Change (n = 54)	−1.23 (−2.95–0.86)

[a] 37 of 70 (53%) <400–500 copies/ml.

to be related to their antiretroviral therapy, including infection and preexisting medical conditions. Conditions that were possibly or likely related to therapy, included mild anemia, experienced by 8 women, and 1 with thrombocytopenia. Severe anemia was seen in 1 woman and considered to be secondary to zidovudine therapy, which required a packed red blood cell transfusion with a change in nucleoside therapy. Diarrhea and bradycardia were each seen in 1 woman. Hepatitis of uncertain etiology occurred in 1 woman but was not thought secondary to her antiretroviral therapy. She had been receiving zidovudine, zalcitabine, and nelfinavir for 7 months prior to conception. All medications were discontinued from weeks 19 to 22 of gestation due to nausea and vomiting. She resumed therapy at week 23 and remained on the same regimen 14 months after delivery without difficulty. Three women (3.3%) developed gestational diabetes. One woman whose antiretroviral therapy, including nelfinavir, was started at week 21 of gestation developed a postpartum cardiomyopathy and died 2 months after the delivery of twins.

Obstetric Outcomes

Most women (73%) delivered vaginally. A woman with asthma, insulin-dependent diabetes mellitus, and sickle cell trait experienced advanced preterm labor with cervical dilatation on admission. She subsequently had spontaneous ruptured membranes and delivered a live, nonviable 430-g infant at 22 weeks. Other obstetric adverse events included 4 women with oligohydramnios, 3 with preeclampsia, 2 with abruptio placentae, and 1 each with polyhydramnios and placenta previa.

Infant Outcomes

Excluding the infant who died after delivery at 22 weeks' gestation as already described, the average Apgar scores were 7 and 9. The average birth weight was 2948 g, with 77% of infants falling between the 25th and 75th percentiles on standard neonatal growth charts. A small number of infants (5.6%) had birth weights below the 5th percentile, including one set of twins. The average weights sorted by therapy with different PIs were not significantly different and are shown in Table 4. Three full-term infants were <2500 g, including one set of twins. The mean infant length was 48.7 cm with a mean head circumference of 33.4 cm. Infant adverse events are listed in Table 5. Anemia, hyperbilirubinemia, and upper respiratory infections were the most commonly seen problems. One infant has Down syndrome and one has a cleft lip and posterior urethral valves.

Prematurity

The gestational age was less than 37 weeks in 17 of 89 pregnancies, thus giving an overall prematurity rate of 19.1%, including two sets of twins born at 34 weeks', 4 days', and 35 weeks', 5 days' gestation, respectively. Of these, eight women delivered between 36 and 37 weeks' gestation and three women (3.4%) delivered at less than 34 weeks' gestation, including the woman whose child died shortly after birth. Most (15 of 17) women who had premature infants had known risk factors for prematurity including two who had previously given birth to twins and four others with histories of premature delivery. The two women with no known pregnancy-related risks included one with AIDS diagnosed on the basis of a CD4 cell count of <200 cells/mm^3 who delivered at 36 weeks and another asymptomatic HIV-positive woman who delivered at 36 weeks, 5 days' gestation. In the multiple logistic regression analysis (n = 80), only the maternal use of cocaine and premature rupture of membranes were associated with prematurity (adjusted odds ratio [OR], 7.4 [range, 1.2–44.2] and 9.8 [range, 1.8–53.6]; p = .03 and .008, respectively). Cigarette smoking, ethanol use, sexually transmitted diseases, bacterial vaginosis, history of premature delivery, placenta previa, abruptio placentae, polyhydramnios, preeclampsia, gestational diabetes, black race, HIV status, CD4 cells, viral load at delivery, and multiple gestation were not found to be associated. There were no differences in prematurity among women

TABLE 4. *Infants' outcomes in terms of birth weight by protease inhibitor*

Protease inhibitor	n	g
Indinavir	23	3116
Nelfinavir[a]	39	2824
Ritonavir	5	2805
Saquinavir[b]	34	3001

[a] Includes three sets of twins.
[b] Excludes 22-week, 430-g neonatal demise.

anemia was 12% and falls well within the range (14%–23%) seen in the infants born to women treated with placebo or zidovudine alone in the original AIDS Clinical Trials Group (ACTG) 076 protocol (24).

The prematurity rate (19.1%) and the low birth weight rate (20.6%) we report compares favorably with earlier data. In the Women and Infants Transmission Study (WITS) of 525 pregnancies, the gestational age was less than 37 weeks in 18.7% and the rate of low birth weight (<2500 g) was 18.7% (22). Employing the definition of prematurity used in the reporting of ACTG 076 (i.e., <36 weeks' gestation), the rate in this series is 10% (9 of 89), which is comparable with the rate of 8% in that large cohort (24).

This study has several limitations. That only 6 of 21 sites approached responded to the survey may bias the survey's results. Data on women from sites not responding to questionnaires are not available to allow comment on the generalizability of these findings. Our demographics suggest, however, that the population represented is typical of the overall population of HIV-infected pregnant women. Bias as the result of regional local practice patterns cannot be completely excluded. Data were obtained from retrospective chart reviews and therefore may be incomplete. Women who received PIs in this series represent a population of HIV-infected pregnant women for whom investigators considered combination therapy was indicated and these results may not be applicable to all women. Investigators included all eligible women from each site. Short-term infant data may also be incomplete due to inaccessibility to some study investigators of all infant data outside of the immediate peripartum period. This may have resulted in the underreporting of certain adverse events or concomitant diagnoses. No long-term data are available on maternal outcomes or infants' clinical outcomes following in utero exposure to PIs. CD4 cell and viral load data were not obtained in systematic or standardized manner and therefore cannot be used to assess the impact of these variables on maternal or infant outcomes.

CONCLUSIONS

In our series of HIV-infected women treated with PIs during pregnancy, no increase in prematurity was seen when compared with other studies involving HIV-infected women who were not treated with PIs. In this series, PIs appeared generally safe in mothers and infants. No perinatal HIV transmission occurred. Further prospective and large-scale investigations are warranted. Full discussions of the available data regarding cesarean sections and antiretroviral therapy during pregnancy should be part of antenatal care. Providers treating pregnant women with PIs are encouraged to register women with the Antiretroviral Pregnancy Registry (26).

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