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Association Between HIV in Pregnancy and Antiretroviral Therapy, Including Protease Inhibitors and Low Birth Weight Infants

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ABSTRACT

Objective: To determine the incidence of low birth weight infants born to HIV seropositive women and to demonstrate any effects of antiretroviral therapy on birth weight.

Methods: Retrospective review of all obstetrical medical records from January 1, 1995 through June 30, 1998 to identify HIV seropositive women. We evaluated their antiretroviral therapy, CD4 counts, and birth weights of their newborns. We conducted detailed review of the clinical and laboratory findings for the HIV-infected untreated patients, women who received ZDV antepartum alone, and those who received PIs as part of antiretroviral treatment.

Results: The frequency of low birth weight infants was significantly increased in HIV seropositive compared to HIV seronegative parturients. Low birth weight infants were more frequent among HIV infected women with lower CD4 counts but the association was not statistically significant. Women who received no antepartum treatment, antepartum only ZDV, and those treated with PIs had significantly more low birth weight infants than did comparison groups. HIV seropositive women also had high frequencies of several obstetrical risk factors for low birth weight infants.

Conclusion: The present study showed a significantly increased frequency of low birth weight infants among HIV infected women and especially the subgroups of infected women who received no antepartum treatment, antepartum ZDV only, and those treated with PIs. This association, however, may be related to the presence of many other preterm obstetrical risk factors noted in this study. Increasing numbers of HIV seropositive women are being treated with PIs according to the Centers for Disease Control (CDC) guidelines. If PIs are a cause of low birth weight infants, women taking these drugs may have incremental risk of low birth weight. Infect. Dis. Obstet. Gynecol. 8:94–98; 2000. © 2000 Wiley-Liss, Inc.

KEY WORDS
protease inhibitors (PIs); antiretroviral drugs; pregnancy; HIV

The Pediatric AIDS Clinical Trials Group (ACTG) protocol 076 study demonstrated a very significant reduction in vertical transmission of human immunodeficiency virus (HIV) with the use of zidovudine (ZDV) monotherapy (25.5% to 8.3%).[1] The study group of women was treated antepartum and intrapartum, and the neonates were also treated after birth. Despite this remarkable result of perinatal pharmacotherapy on vertical transmission of HIV in pregnancy, many questions remain. One such question concerns the possible adverse effects of the antiretroviral drugs to mothers and infants. The U.S. Public Health Service Task Force currently recommends combination

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therapy including the use of protease inhibitors (PIs) in pregnant women.[2] However, at the Twelfth World Congress on AIDS in Geneva, 1998, Lorenzi reported that PIs may contribute to premature birth.[3] This resulted in a temporary moratorium on the use of PIs in ACTG clinical trials involving pregnant women.[4] Since low birth weight is the major source of newborn morbidity and mortality, and since premature birth is thought to be a risk factor for perinatal transmission,[5–11] identifying an association with HIV therapy is critically important. We reviewed the Washington Hospital Center experience with HIV seropositive pregnant women to determine the frequency of low birth weight in various cohorts; those patients who were untreated and those who were treated with various antiretroviral drugs.

MATERIALS AND METHODS

Medical records from all obstetrical patients from January 1, 1995 through June 30, 1998 were reviewed to identify individuals who had confirmed positive serological tests for HIV and recorded birth weights of all infants. Clinical and laboratory data were reviewed for patients who received no treatment, those who received intrapartum ZDV only, ZDV antepartum only, patients who received combination therapy, patients who received both antepartum and intrapartum ZDV, and patients who received PIs as part of combination therapy. Statistical tests included, where appropriate, the Chi-square test and the two-tailed Fisher's exact test.

RESULTS

From January 1, 1995 through June 30, 1998, 10,635 infants were born at the Washington Hospital Center. A total of 1809 low birth weight infants (2500 gm), including 368 infants less than 500 gm, were born alive during this period. When the less than 500 gm infants are excluded, the true number of low birth weight infants is 1441. A total of 107 infants were identified as being born to HIV seropositive women, of whom 29 infants were low birth weight by the above criteria (Table 1). The frequency of low birth weight infants was significantly increased in the HIV seropositive women (29 of 107) (27.1%) compared to the HIV seronegative women (1412 of 10,160)(13.9%) ($P \leq 0.001$).

CD4 counts were available for 72 patients within 2 months prior to delivery. Thirteen women had CD4 counts of 200 or less, and 5 delivered low birth weight infants (38%). Thirty-five women had CD4 counts between 200 to 500 and 9 delivered low birth weight infants (26%). Twenty-five women had CD4 counts of 500 or greater and only 3 had low birth weight infants (12%). These data suggest a stepwise association between lower CD4 levels and increased rates of low birth weight infants; however, statistical significance was not achieved.

TABLE 1. Antiretroviral therapy, type, and low birth weight infants

Antiretroviral therapy	Number of patients	Low birth weight infants (%)
No treatment	9	4 (44.4)
Intrapartum only		
ZDV[a]	13	6 (46.1)
Antepartum only		
ZDV	9	5 (55.5)
ZDV + HIVIG/IVIG[b]	1	0 (0)
ZDV + PI[c]	1	1 (100)
Subtotal	11	6 (54.5)
Antepartum + intrapartum		
ZDV (A + I)[d]	51	8 (15.7)
ZDV (A + I) + NVP[e] (I)	1	0 (0)
ZDV (A + I) + HIVIG/IVIG (A)	8	0 (0)
ZDV (A + I) + 3TC[f] (A)	6	2 (33.3)
ZDV (A + I) + 3TC (A) + NVP (I)	2	1 (50)
ZDV (A + I) + 3TC (A) + D4T[g] (A)	1	0 (0)
ZDV (A + I) + 3TC (A) + PI (A)	3	2 (66.6)
ZDV (A) + NVP (I)	2	0 (0)
Subtotal	74	13 (17.6)
TOTAL	107	29 (27.1)

[a]ZDV = Zidovudine.
[b]HIVIG/IVIG = High titer HIVIV immunoglobulin or IV immunoglobulin.
[c]PI = Protease inhibitor.
[d]A = Antepartum; I = Intrapartum.
[e]NVP = Nevirapine.
[f]3TC = Lamivudine.
[g]D4T = Stavudine.

The effect of antiretroviral treatment on birth weight was determined for several subgroups (Table 2). The patients who received no treatment were combined with those that were treated intrapartum only since it is unlikely that therapy intrapartum has an effect on birth weight (Group A). The patients, who were treated antepartum only were combined with those treated antepartum + intrapartum because antepartum therapy potentially has an effect on birth weight (Group B). The frequency of low birth weight infants was significantly higher among Group A women (no antepartum antiretroviral treatment) (45.4%) compared to

TABLE 2. Antiretroviral treatment subgroups—time treated in pregnancy and low birth weight infants

Treatment subgroups	Number of patients	Low birth weight infants (≤2500 gm)
A. No treatment and intrapartum only treatment	22	10 (45.4%)
B. All treatments, antepartum and antepartum + intrapartum	85	19 (22.3%)
C. Protease inhibitors along with other treatments, antepartum and antepartum + intrapartum	4	3 (75%)
D. No protease inhibitors. All other treatments antepartum and antepartum + intrapartum	81	16 (19.7%)

Group B women (antepartum antiretroviral treatment) (22.3%) (P = 0.03).

For the Group A women we compared those who had infants weighing ≤2500 gm with those who had infants weighing >2500 gm (Table 3). A high frequency of obstetrical risk factors was observed, and these were particularly increased in the low-birth-weight weight group. The frequency of preterm infants, prolonged rupture of membranes, and infrequent prenatal care was higher in the ≤2500-gm infants. Cocaine abuse, HIV first diagnosed during intrapartum hospital stay, advanced stage of AIDS (C3), and fetal death in utero were similar for the two birth weight groups. Viral load and CD4 determinations were too infrequent to assess.

We noted that the women who received antepartum only ZDV monotherapy had a high frequency of low birth weight infants (55.5%) (Table 1). We compared the patients who had infants weighing ≤2500 gm with those who had infants weighing >2500 gm (Table 4). Four of the 5 low birth weight infants were also preterm. Three of these 5 women had each previously delivered at least 2 other preterm babies. These 3 also had multiple sexually transmitted diseases. An additional one of these patients delivered a dead fetus secondary to abruptio placenta at 31 weeks gestation. The frequency of precipitous deliveries, prolonged rupture of membranes, infrequent prenatal care, cocaine abuse, HIV first identified during labor, and advanced AIDS were similar for the two birth weight groups.

TABLE 3. No antepartum treatment (Group A); obstetrical risk factors for two birth weight groups

	Birth weight ≤2500 gm	Birth weight >2500 gm
Number of patients	10	12
Preterm (≤36 weeks gestation)	10	2
Premature rupture of membranes	6	NA
Prolonged rupture of membranes	6	2
Infrequent prenatal care (≤2 visits)	9	3
Cocaine abuse	5	7
HIV first diagnosed intrapartum	3	1
Advanced aids (C3)	2	0
Fetal death in utero	0	1

TABLE 4. Antepartum only ZDV; obstetrical risk factors for two birth weight groups

	Birth weight ≤2500 gm	Birth weight >2500 gm
Number of patients	5	4
Preterm (≤36 weeks gestation)	4	0
Premature rupture of membranes	1	NA
Prior preterm deliveries	3	0
STDS ≥2 during pregnancy	3	0
Fetal death in utero	1	0
Precipitous deliveries	4	3
Prolonged rupture of membranes (≥24 hours)	0	0
Infrequent prenatal care (≤2 visits)	1	1
Cocaine abuse	2	1
HIV first identified intrapartum	0	0
Advanced AIDS (C3)	0	0

PIs were given along with other antiretroviral drugs in the antepartum and antepartum + Intrapartum category to four patients (Table 2, Group C). Three of these 4 patients delivered low birth weight infants who were also preterm. Other antiviral treatments without PIs were given antepartum and antepartum + intrapartum to 81 women of which 16 delivered low birth weight infants (Table 2, Group D). The frequency of low birth weight infants was significantly higher in the PIs treated Group C (75%) compared to the no PIs Group D (19.7%) (P = 0.033).

Table 5 demonstrates the clinical and laboratory findings for the 4 patients in group C who were treated with PIs. The 3 patients who had low birth weight infants had several obstetrical risk factors associated with low birth weight and preterm birth including prolonged premature rupture of membranes (2 patients), advanced AIDS CDC category 3 (2 patients), chorioamnionitis (2 patients), oligo-

TABLE 5. Antiretroviral chemotherapy including protease inhibitors (Group C); clinical and laboratory findings

	Birth weight ≤2500 gm			Birth weight >2500 gm
	Patient 1	Patient 2	Patient 3	Patient 4
Birth weight	1400 gm	810 gm	780 gm	3630 gm
Weeks gestation	31 6/7	27 4/7	26 4/7	40
Length of rupture of membranes	4 d	0 hr	4 d	3 hr
CDC staging	C3	C3	A1	A2
Prenatal complications	Premature ROM Chorioamnionitis	Oligohydramnios Severe IUGR and PIH	Premature ROM Chorioamnionitis	None
Behavioral history	Tobacco, IV heroin, ETOH	None	Tobacco, cocaine, ETOH	Tobacco
CD4 count	1/20 wks = 1 2/22 wks = 6 (PI start) 3/27 wks = 28	1/6 wks = 16	1/8 wks = 546 (PI start) 2/19 wks = 583 3/25 wks = 570	1/12 wks = 396
Viral load	1/20 wks = 49756 2/22 wks = 49759 (PI start) 3/27 wks = 521	1/6 wks = 360544 2/24 wks = 3131 (2 wks post PI start)	1/8 wks <400 (PI start) 2/19 wks <400 3/25 wks <400	Not done

hydramnios (1 patient), and cocaine or heroin abuse (2 patients). Two of these 3 patients showed significant decreases in viral load after the introduction of PIs. These patients, however, did not show significant increases in CD4 counts. One patient had undetectable viral load throughout the period of study and similar data was not available for the fourth and only full term patient.

DISCUSSION

Preterm birth is responsible for 70% of all fetal and neonatal deaths in the United States.[12] Our experience at the Washington Hospital Center suggested that there was a high rate of low birth weight, preterm births among HIV seropositive women. We therefore examined the potential association between low birth weight and HIV seropositive parturients. We found that the frequency of low birth weight infants among the HIV group was significantly greater than the rate of low birth weight infants among uninfected women.

We investigated CD4 levels to determine an association with the increased rate of low birth weight infants in our HIV seropositive patients. A stepwise association between lower CD4 levels and increased rates of low birth weight infants was noted, however, this association did not achieve statistical significance. We then studied the association of antepartum therapy on birth weight and found that the women who had no antepartum antiretroviral therapy had a statistically significant increase in low birth weight infants, compared to treated patients. Untreated women, however, also had obstetrical factors that are associated with low birth weight, including an increased frequency of preterm infants, preterm rupture of membranes, and infrequent prenatal care.

Next we analyzed women who received antepartum only ZDV since they also seemed to have a high rate of low birth weight infants. Most of these women also had many of the obstetrical factors that are associated with low birth weight and preterm infants. Incidentally, 4 of 22 women who received no antepartum therapy were diagnosed as HIV seropositive while hospitalized for preterm labor or premature ruptured membranes.

We evaluated our patients who received PIs as part of their therapy, and found that their preterm birth rate was 75%, (3 of 4) which was significantly higher compared with other treated patients. These women, however, also had a high frequency of obstetrical risk factors for low birth weight, preterm birth including prolonged, premature rupture of membranes, advanced AIDS, chorioamnionitis, oligohydramnios, and cocaine and heroin abuse. It should be noted that at the time of the study, PIs were generally reserved for patients with more advanced HIV disease.

A cause and effect relationship between PIs and low birth weight, as first suggested by Lorenzi,[3] is speculative. However, these drugs are known to have many metabolic side effects including nephrolithiasis, hyperlipemia, hepatic metabolic alterations, and glucose intolerance.[13] For example,

both nelfinavir and ritonavir decrease the plasma concentration of exogenously administered ethinylestradiol.[14,15] The mechanism seems to be by the PI induction of the hepatic P450 cytochrome enzyme system. We would offer a hypothesis that perturbations in the pregnancy milieu caused by the effect of PIs on estrogen and/or progesterone metabolism by PIs could lead to preterm labor.[16]

In conclusion, we found a significantly increased rate of low birth weight infants in our HIV seropositive patients, especially among those women who did not receive antepartum antiretroviral treatment and women who had antepartum only ZDV. We also identified a significant association between low birth weight and the use of PIs compatible with the observation of Lorenzi et al. Women who did not receive antepartum antiretroviral treatment, women who received antepartum ZDV only, and women who received PIs, also had a high frequency of obstetrical risk factors, which may have been responsible for the observed increased frequency of low birth weight infants.

The concern about the use of PIs in pregnant women based on Lorenzi's data, was confirmed by the present study. Because of the high rates of obstetrical risk factors for low birth weight in the pregnancies in HIV seropositive patient groups studied, additional studies are needed to determine the possible role of obstetrical factors compared to antiretroviral drugs including PIs in relation to low birth weight and preterm births.

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