Effect of Prenatal Zidovudine on Disease Progression in Perinatally HIV-1–Infected Infants

*Ricardo S. de Souza, †Orlando Gómez-Marín, †Gwendolyn B. Scott, ‡Silvia Guasti, §Mary Jo O’Sullivan, §Ricardo Hugo Oliveira, and †Charles D. Mitchell

*Universidade de Caxias do Sul, Caxias do Sul, Brazil; †University of Miami School of Medicine, Miami, Florida, U.S.A.; ‡Fundac¸a˜o Municipal de Sau´de de Niteroi, Niteroi, Brazil; and §Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

Objective: To determine the influence of prenatal zidovudine (ZDV) prophylaxis on the course of HIV-1 infection in children by comparing the clinical outcome of infants born to HIV-1–seropositive mothers who did versus those who did not receive ZDV during pregnancy.

Methods: Medical records of HIV-1–seropositive mothers and their infants were reviewed retrospectively. Participants were divided according to maternal ZDV use: no ZDV (n = 152); ZDV (n = 139). The main outcome measure was rapid disease progression (RPD) in the infant, defined as occurrence of a category C disease or AIDS-related death before 18 months of age.

Results: HIV vertical transmission rates were significantly different (no ZDV versus ZDV: 22.3% versus 12.2%; p = .034). Among infected infants, the RPD rate was 29.4% in the no ZDV group compared with 70.6% in the ZDV group (p = .012), and prematurity was significantly associated with a higher risk of RPD (p = .027).

Conclusions: The rate of RPD was significantly higher among perinatally infected infants born to HIV-infected mothers treated with ZDV than among infected infants born to untreated mothers. The decreased proportion of infected infants with nonrapid disease progression in the former group might be related to the ability of ZDV to block intrapartum transmission preferentially and also to nonrapid disease progression resulting from intrapartum transmission.

Key Words: Perinatal HIV-1 infection—Rapid disease progression—Timing of transmission—Prematurity—Zidovudine.

The course of vertically acquired HIV-1 infection is characterized by two distinct patterns (1–5): rapid progression of disease (RPD) and nonrapid progression of disease (NRPD). RPD, which occurs in 20% to 30% of perinatally infected infants, presents during the first months of life usually with CD4⁺ lymphocyte depletion and the occurrence of an AIDS-defining event. In contrast, NRPD is characterized by gradual development of immunodeficiency over several years with a pattern of morbidity and mortality similar to that in infected adults.

Many factors have been proposed to explain these divergent patterns of disease progression including timing of transmission (2,6,7), maternal health status (8,9), maternal virus load at delivery (10), gestational age (11), genetic susceptibility (12), and intrinsic characteristics of the virus (13,14). A relationship between high HIV-1 RNA virus load early in life and rapid disease progression has also been described in perinatally infected children (15–19).

The AIDS Clinical Trial Group (ACTG) Protocol 076 demonstrated the ability of zidovudine (ZDV) (given during pregnancy, delivery, and to the infant) to reduce perinatal transmission by 67% (20). Prior to the an-
nouncement of these results during February of 1994, ZDV was not routinely recommended as prophylaxis during pregnancy and the choice of a particular regimen was based on maternal clinical indications and patient acceptance.

Although the specific mechanisms regarding how the ACTG 076 regimen exerts its beneficial effects are not clear, it is assumed that ZDV primarily acts to block mother-infant transmission around the time of birth (20,21). This assumption has been bolstered by data from a trial conducted in Thailand (22). In that study, an abbreviated ZDV regimen, (oral ZDV beginning at 36 weeks’ gestation and continuing through labor, with no neonatal component), reduced the risk of perinatal HIV transmission by approximately 50% (from 18%–9%). A more recent report from New York also demonstrated the efficacy of abbreviated regimens in reducing the rates of perinatal transmission when ZDV was restricted either to the prenatal period, the intrapartum period, or when begun during the first 48 hours of life (23). Despite these advances, approximately 5% of perinatally exposed infants whose mothers are treated with ZDV are nonetheless infected with HIV-1. Whether prenatal ZDV therapy can affect the infants’ virus load or the course of disease progression is not known.

For the present analysis, data from HIV infected mothers and their infants born between January 1990 and December 1994 were used to assess the effect of prenatal ZDV treatment on the course of disease among infected infants. This cohort of mother-infant pairs provided a unique opportunity to study the effect of ZDV on disease progression in children when the drug was initiated at different periods during gestation as compared with infected infants born to untreated mothers. The demonstration of such an effect may help to elucidate the mechanisms involved in the transmission of HIV-1 from mother to infant.

METHODS

The University of Miami/Jackson Memorial Hospital (UM/JMH) is a large, tertiary care urban medical facility that serves the population of Miami-Dade County, Florida. In response to the growth of the HIV-1 epidemic, the UM Perinatal Network was established in 1990 to provide prenatal and postpartum medical care to mother-infant pairs affected by HIV-1. This infrastructure has been used to conduct several perinatal research studies. The HIV-1–infected women included in the present study attended the UM Perinatal Network during pregnancy and were evaluated along with their infants at regular intervals. Maternal clinical and laboratory data collected during pregnancy included CD4+ and CD8+ T-lymphocyte counts, a detailed obstetric questionnaire, physical examination, and HIV-1 disease staging. Symptomatic HIV-1 infection or AIDS was considered present in the mother if there were clinical symptoms of HIV infection or presence of an AIDS defining condition, according to the 1993 AIDS case definition, prior to birth (24). The prepartum maternal absolute CD4+ cell count closest to delivery was used in the analyses. All women were counseled not to breastfeed.

Infants were evaluated at delivery, 2 weeks of age, 4 to 6 weeks of age, 4 to 6 months of age, and every 3 months thereafter until the age of 2 years. During each of these visits, a physical examination was conducted, relevant medical history was obtained and laboratory tests were performed.

Study Population

The medical records of 403 infants and their HIV-1–seropositive mothers, who were observed on a follow-up basis in the Special Immunology Perinatal Clinic and delivered between January 1, 1990, and December 31, 1994, were reviewed retrospectively. Eligible study participants were not enrolled in any ACTG protocol. In total, 291 mother-infant pairs were included in the final analysis after excluding 43 mother-infant pairs whose infant’s HIV-1 status remained indeterminate or unknown by the time of the analysis, 36 mother-infant pairs who received only intrapartum or postnatal ZDV, 27 mother-infant pairs in whom the infant was born as a result of a second pregnancy (25 singleton and 1 twin pregnancy), 3 second born twins, and 3 infected infants lost to follow-up prior to 18 months of age.

Participants were divided according to their ZDV regimen. The no ZDV group consisted of mother-infant pairs who did not receive ZDV either prior to or during pregnancy, the delivery, or during the first 6 weeks of life. The ZDV group consisted of mother-infant pairs treated with ZDV for a minimum of 7 days prior to delivery with doses as specified in the current U.S. Public Health Service Guidelines. Mother-infant pairs in the ZDV group received one of the following combinations: prenatal ZDV only; prenatal and intrapartum ZDV; prenatal and postnatal ZDV; or prenatal, intrapartum and 6 weeks of postnatal ZDV.

Prenatal ZDV alone was prescribed initially for those women who had a clinical indication for ZDV and/or a CD4+ count <500 cells/mm³. The potential risks and benefits of such therapy were reviewed with the mother and her consent was documented. Prenatal plus intrapartum ZDV therapy was a common regimen beginning in 1992. From March 1, 1994 (following the announcement of the Protocol 076 results) until the end of December of the same year, all mothers who consented received both prenatal plus intrapartum ZDV while their infants received postnatal ZDV for the first 6 weeks of life.

Definitions

Perinatal HIV-1 Infection was defined according to U.S. Centers for Disease Control and Prevention (CDC) criteria (25). Noninfected infants were those who either satisfied CDC criteria for seroreversion, or who had two or more negative results to HIV-1 DNA polymerase chain reaction assays or viral cultures with at least one being done at 1 month of age or older and the second being done at 4 months of age or older.

Rapid progression of HIV-1 disease (RPD): occurrence of a CDC class C clinical event or AIDS related death by 18 months of age

Nonrapid progression of HIV-1 disease (NRPD): absence of any RPD endpoint by 18 months of age

Timing of initiation of prenatal ZDV: two different analyses were performed to assess the effect of this variable. In the first analysis, a cut-off point of 28 weeks was chosen because this was the median gestational age at the time of starting ZDV/placebo in the ACTG 076 protocol (19). In the second analysis, the cut-off point selected was 36 weeks, the gestational age of initiation of ZDV in the Thailand study (22).

Drug use during pregnancy was determined by self-report as use of one
or more of the following drugs: marijuana, cocaine, crack cocaine, heroin, methadone, alcohol, or cigarettes.

Statistical Analyses

Statistical analyses were performed using SAS (26). Prior to any analyses, the normality of the distribution of the continuous variables was assessed and, if necessary, either the data were transformed or nonparametric methods were used. Independent groups were compared using Student’s t-test or the Mann-Whitney test. To assess associations between discrete variables, χ² analyses were used and, whenever appropriate, odds ratios (ORs) and their 95% confidence intervals (CI) were calculated. For 2×2 tables, p values reported are those corresponding to χ² with continuity correction. Paired groups were compared using either matched-pairs Student’s t-tests, the signed rank test, or McNemar’s test.

Multiple stepwise logistic regression was used to assess the factors associated with vertical transmission and, within the subgroup of infected infants, factors associated with RPD. Univariate analyses of the time from birth to disease progression were performed by the Kaplan-Meier survival method (27), and the survival curves for different subgroups were compared by the log-rank test (28). Multivariate analyses to test the effects of covariates on time to disease progression were performed by using the Cox regression proportional hazards model (29). Throughout, data are reported as mean ± standard deviation (SD).

Selection Bias Assessment

Second-born twins (n = 3) and infants of second pregnancies that occurred during the study period (n = 27) were arbitrarily excluded from the analyses to preserve the statistical independence of the data. Our analyses (data not presented) showed that including in the study second-born, instead of first-born, infants would not have changed substantially any of the results.

Also excluded from the analyses were 46 mother-infant pairs because the infant’s HIV infection status was unknown (n = 43), or the infant was lost to follow-up (n = 3). Comparisons of these 46 mother-infant pairs versus the 291 mother-infant pairs included in the analyses (data not presented) showed no significant differences with respect to any maternal or infant characteristics.

RESULTS

Treatment Groups

Of 291 mother-infant pairs included in the final analyses, 152 received no antiretroviral therapy during pregnancy (no ZDV group). The remaining 139 pairs received ZDV as part of one of the following regimens: prenatal ZDV alone (36 of 139, 26%); prenatal and intrapartum ZDV (58 of 139, 41%); prenatal and postnatal ZDV (8 of 139, 6%); or prenatal, intrapartum, and postnatal ZDV (37 of 139, 27%). Mother-infant pairs receiving one of these regimens were combined and are referred to as the ZDV group.

Maternal Characteristics

The overall HIV-1 transmission rate was 17.5% (51 of 291). Among treated mothers 12.2% (17 of 139) transmitted the virus to their infants, whereas 22.4% (34 of 152) of the untreated mothers transmitted the virus to their infants (OR, 0.48; 95% CI, 0.26–0.91; p = .025). Maternal age at delivery ranged from 14 to 42 years, mean ± SD = 27.3 ± 6.1, median = 27 years. Seventy-three (25.0%) gave birth to premature babies (≤37 weeks gestation); 62.1% (180 of 290) had ruptured membranes for 4 hours or less; and 216 (74.2%) delivered vaginally.

Most of the mothers (226 of 273 or 82.8%) had CD4+ counts ≥200 cells/mm³. Clinical symptoms of HIV infection or AIDS were present in 50 (17%) and drug use was recorded in 55 mothers (18.9%). Length of ZDV therapy was known for 131 of 139 treated mothers, its distribution was highly skewed with a range of 7 to 1286 days, a median of 87, and a mean of 113.1 ± 167. Comparisons of treatment groups with respect to maternal characteristics are shown in Table 1. Significant differences between the two groups were found for absolute CD4+ counts, duration of ruptured membranes, and rate of perinatal transmission. The larger number of mothers with a CD4+ count <199 cells/mm³ in the ZDV group resulted from these mothers having more advanced stages disease and thus were more apt to receive ZDV.

Infant Characteristics

Among infants, there was approximately the same number of boys (147 or 50.5%) and girls (144 or 49.5%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No ZDV group</th>
<th>ZDV group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Black</td>
<td>123 (52.3)</td>
<td>112 (47.7)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>29 (51.8)</td>
<td>27 (48.2)</td>
<td></td>
</tr>
<tr>
<td>CD4 count</td>
<td></td>
<td></td>
<td>.005</td>
</tr>
<tr>
<td>&lt;199 cells/mm³</td>
<td>14 (29.8)</td>
<td>33 (70.2)</td>
<td></td>
</tr>
<tr>
<td>≥200 cells/mm³</td>
<td>121 (53.5)</td>
<td>105 (46.5)</td>
<td></td>
</tr>
<tr>
<td>Premature birth</td>
<td></td>
<td></td>
<td>.476</td>
</tr>
<tr>
<td>&lt;37-wk gestation</td>
<td>35 (48.0)</td>
<td>38 (52.0)</td>
<td></td>
</tr>
<tr>
<td>≥37-wk gestation</td>
<td>117 (53.7)</td>
<td>101 (46.3)</td>
<td></td>
</tr>
<tr>
<td>Ruptured membranes</td>
<td></td>
<td></td>
<td>.025</td>
</tr>
<tr>
<td>&lt;4-hr duration</td>
<td>84 (46.7)</td>
<td>96 (53.3)</td>
<td></td>
</tr>
<tr>
<td>≥4-hr duration</td>
<td>67 (60.9)</td>
<td>43 (39.1)</td>
<td></td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Vaginal</td>
<td>113 (52.3)</td>
<td>103 (47.7)</td>
<td></td>
</tr>
<tr>
<td>Cesarean</td>
<td>39 (52.0)</td>
<td>36 (48.0)</td>
<td></td>
</tr>
<tr>
<td>Infant’s HIV-1 status</td>
<td></td>
<td></td>
<td>.034</td>
</tr>
<tr>
<td>Infected</td>
<td>34 (66.7)</td>
<td>17 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Noninfected</td>
<td>118 (49.2)</td>
<td>122 (50.8)</td>
<td></td>
</tr>
</tbody>
</table>

* ZDV group = prenatal only, prenatal + intrapartum, prenatal + intrapartum + postnatal, prenatal + postnatal.

The p values from χ² analysis of 2×2 tables.
Their birth weight ranged from 845 to 6033 g with a median of 3169 and a mean of 3115.1 ± 654.2. Infected and uninfected infants did not differ in rate of prematurity (23.5% versus 25.4%; \( p = .917 \)).

During the first 18 months of follow-up, 22 of 51 infected infants, or 43%, met the criteria for RPD: 13 developed category C diseases and 9 died of AIDS-related illnesses. Although in the whole group prematurity was not associated with treatment (Table 1), it was significantly associated with higher risk of RPD when the analyses were restricted to infected infants (OR, 5.3; 95% CI, 1.4–26.3; \( p = .027 \); Table 2).

**Maternal Zidovudine Use and Disease Progression**

Neither maternal CD4+ cell counts (Table 2) nor maternal symptoms related to HIV were associated with disease progression in infected infants (data not shown). In contrast, the risk of RPD was clearly related to maternal treatment: the proportion of infants with RPD was 29.4% (10 of 34) in the no ZDV group compared with 70.6% (12 of 17) in the ZDV group (OR, 0.17; 95% CI, 0.04–0.73; \( p = .012 \); Fig. 1; Table 2).

Results of multiple logistic regression for infected infants showed that both maternal ZDV treatment and prematurity were independently associated with RPD (treated versus nontreated: OR, 7.20; 95% CI, 1.49–34.87; \( p = .014 \); gestational age ±37 versus >37 weeks: OR, 13.63; 95% CI, 1.67–111.07; \( p = .015 \)). Maternal CD4+ count, also included in the model, was not significantly associated with rapid progression (\( \leq 199 \) cells/mm\(^3\) versus \( \geq 200 \) cells/mm\(^3\); OR, 0.34; 95% CI, 0.04–2.72; \( p = .31 \)).

The duration of prenatal ZDV therapy was analyzed to assess the effect of its varying lengths and the potential of ZDV resistance. Neither the mean nor median duration of ZDV therapy was significantly different (analysis of variance [ANOVA] \( p = .753 \); Kruskal-Wallis \( p = .527 \)) among mothers of infants with RPD (mean ± SD, median: 131.3 ± 170.3, 87), with NRDP (57.5 ± 56.1, 33) or noninfected infants (114.1 ± 169.6, 90).

Time to RPD diagnosis was analyzed using both Kaplan-Meier survival methods and Cox regression. As shown in Figure 1A, the time to development of RPD in perinatally infected children was consistently shorter for infants in the ZDV compared with those in the no ZDV group (log-rank \( p = .004 \)). RPD was three times more likely in preterm versus term infants (risk ratio [RR], 2.7, \( p = .032 \);) and twice as likely for infants born to mothers with versus without clinical symptoms (RR, 2.0; \( p = .145 \)).

After adjusting for prematurity and maternal clinical characteristics, RPD was three times more likely to occur in infants born to treated compared with findings in untreated mothers (RR = 2.8; \( p = .021 \)).

We also assessed the potential effect of timing of prenatal initiation of ZDV on the time to RPD diagnosis by performing a Kaplan-Meier analysis at two different timepoints during gestation. The first analysis compared the clinical course of infants born to untreated mothers

<table>
<thead>
<tr>
<th>TABLE 2. Zidovudine (ZDV) treatment, maternal characteristics, and risk of rapid HIV-1 disease progression among infected infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal characteristic</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>ZDV regimen</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes(^b)</td>
</tr>
<tr>
<td>Gestational age</td>
</tr>
<tr>
<td>(&lt;37 \text{ wk})</td>
</tr>
<tr>
<td>(&gt;37 \text{ wk})</td>
</tr>
<tr>
<td>CD4 counts</td>
</tr>
<tr>
<td>(&lt;199 \text{ cells/mm}^3)</td>
</tr>
<tr>
<td>(&gt;200 \text{ cells/mm}^3)</td>
</tr>
<tr>
<td>Ruptured membranes</td>
</tr>
<tr>
<td>(&lt;4\text{-hr duration})</td>
</tr>
<tr>
<td>(&gt;4\text{-hr duration})</td>
</tr>
<tr>
<td>Mode of delivery</td>
</tr>
<tr>
<td>Vaginal</td>
</tr>
<tr>
<td>Cesarean</td>
</tr>
</tbody>
</table>

\(^a\) Continuity corrected \( \chi^2 \) \( p \) values except for CD4 count.

\(^b\) Includes prenatal only, prenatal + intrapartum, prenatal + intrapartum + postnatal, and prenatal postnatal.

\(^*\) Fisher’s exact test two-tailed \( p \) value.

CI, confidence interval.
versus mothers who started ZDV at or before 28 weeks’ gestational age versus after 28 weeks’ gestational age. Kaplan-Meier survival curves for this analysis are shown in Figure 1B. From this figure, it is evident that there is no difference between the two ZDV treatment subgroups and also that the no ZDV group is significantly different from either of the two treatment subgroups. For the second analysis, a cut-off point of 36 weeks’ gestational age was used instead of 28 weeks. The results of this second analysis are identical to those in the first analyses, and the corresponding survival curves are shown in Figure 1C.

Further analysis of specific clinical findings in infants with RPD in the two treatment groups showed similar median age at onset of the first category C event (data not shown), and also similar frequencies and percentages of infants developing a particular first C event.

**DISCUSSION**

Our results suggest that maternal treatment with ZDV may influence the course of disease among perinatally infected infants. In this retrospective study, the risk of RPD was five to six times higher among infants born to treated compared with untreated mothers. This relationship remained after controlling for other maternal characteristics (maternal CD4+ count, gestational age, duration of rupture of membranes, and maternal clinical symptoms of HIV infection).

The overall proportion of perinatally infected infants who developed RPD by 18 months of age was 43%. The proportion of infected infants with RPD was higher among those born to treated mothers compared with infants born to untreated mothers (12 of 17 or 70.6% versus 10 of 34 or 29%; \( p = .01; \) Table 2; Fig. 2). The median age at onset and types of category C events were similar for infants with RPD in the ZDV and no ZDV groups (data not shown).

Since the introduction of the working definition of intratuterine and intrapartum transmission proposed by Bryson et al. (30), many studies have associated intrauterine infection with rapid progressive disease in perinatally infected children (\( n = 51 \)) without rapid progressive disease (RPD). (A) Continuous line, no zidovudine (ZDV) (\( n = 34 \)); dashed line, ZDV (\( n = 17 \)); log-rank test \( p \) value = .0044. (B) Continuous line, no ZDV (\( n = 34 \)); dashed line, ZDV started after 28 weeks’ gestation (\( n = 7 \)); dotted line, ZDV started at or before 28 weeks’ gestation (\( n = 8 \)); log-rank test \( p \) value = .0035. (C) Continuous line, no ZDV (\( n = 34 \)); dashed line, ZDV started after 36 weeks’ gestation (\( n = 5 \)); dotted line, ZDV started at or before 36 weeks’ gestation (\( n = 10 \)); log-rank test \( p \) value = .0049. Two cases were missing information on date of initiation of ZDV prophylaxis.
natally infected infants. According to the definition, an infant is considered as infected in utero if there is an HIV-1–positive culture or DNA polymerase chain reaction (PCR) test in a sample drawn within the first 48 hours of life. Intrapartum transmission is assumed if there is a negative culture or PCR test in the first week of life, followed by a positive sample before 3 months of life. Kuhn et al. (31) reported that maternal ZDV was effective in reducing intrapartum infection and that intrauterine infected infants had a twofold risk of progression to AIDS or death by 12 months of age compared with intrapartum infected infants.

If ZDV is primarily effective in preventing intrapartum transmission and if NRPD develops as a result of this mode of transmission (while RPD develops as a result of intrauterine transmission), then ZDV should preferentially decrease the proportion of infected infants with NRPD. This is, in fact, what we observed. The respective proportions of infected infants with RPD versus NRPD in the treated group (71% versus 29%) was the reverse of what was observed in the non treated group (29% versus 71%, Table 2).

A similar relationship between maternal ZDV monotherapy and disease progression in perinatally infected children has been suggested in a study from Italy (32). However, that report did not control for important maternal factors associated with disease progression, such as maternal clinical and immunologic status at delivery. Although frequency of RPD in the treated group (70.6%) was higher than the frequency reported in the Italian study (57%), it was within the 95% CI reported by the Italian investigators (40.9%–74.3%).

Although it is possible that transmission may have occurred prior to the initiation of ZDV therapy, the median duration of therapy was similar among all groups of mothers irrespective of whether their infants were infected (and developed RPD versus NRPD). Only 1 mother of an infant with RPD was treated with ZDV for more than 180 days. Both these observations lessen the possibility that ZDV resistance was a confounding factor in our analyses. The actual length of ZDV treatment was not associated with either the risk of transmission or the rate of RPD. This did not change when analyses were performed comparing initiation of maternal therapy at 28 weeks’ gestation or less (Fig. 1B) and 36 weeks’ gestation (Fig. 1C). The lack of any difference in efficacy for regimens initiated during the second or the third trimester of pregnancy has been previously noted by both Connor et al. (19) and Blanche et al. (33).

Prematurity was also shown in this study to be associated independently with a higher risk of rapid disease progression. Although prematurity was not associated with treatment in the whole group (Table 1), prematurity was significantly associated with a higher risk of RPD when the analyses were restricted to infected infants (OR, 5.3; 95% CI, 1.4–26.3; p = .027). This finding is
consistent with the assumption that intrauterine infection may be associated with RPD. Prematurity as a risk factor for RPD has been suggested in earlier studies. Data from a prospective study among a cohort of HIV-1–infected women in New York City suggested that perinatally infected infants born prematurely have more severe disease (11). If the fetal immune system is affected by HIV-1 when it is relatively immature, as a result of either intrauterine infection or prematurity, it may be less apt to control viral replication, and this might explain the propensity to develop RPD. Premature infants may be at higher risk for intrapartum transmission (21) because of increased permeability of the skin or gastrointestinal mucosa, and immature humoral and/or cellular immunity.

Our study may be limited by its retrospective nature and by the sizable number (almost 50) of mother-infant pairs enrolled into AIDS Clinical Trials Group protocols who were not included in the present study. The analyses included mother-infant pairs enrolled before and after the beneficial effects of ZDV prophylaxis were announced and include women who used this agent either as therapy or for the prevention of transmission. Although we did not assess the use of chemoprophylaxis for *Pneumocystis carinii* pneumonia (PCP) in infants, the similar median age at onset and similar types of category C events for infants with RPD in the ZDV and no ZDV groups (data not shown), imply that this information would not have affected the likelihood of RPD in our study. All efforts were made to control for bias. We were not able to assess the significance of the detection of virus within the first 48 hours of life as this testing was not being done during the period of this study. Despite these shortcomings, the similarities between our findings and other reports (30,32) support our conclusions.

Early reports have documented both an increasing frequency of ZDV use during pregnancy and a decreasing number of new cases of perinatal infection in the United States and elsewhere (34,35). The ability of gestational ZDV to reduce the frequency of perinatal transmission has now been documented in several reports (36–38). The clinical ramifications of our findings are twofold. First, if ZDV monotherapy preferentially decreases intrapartum transmission without affecting intrauterine transmission, then more effective regimens that can prevent intrauterine transmission need to be developed. Second, because of the increased risk of RPD, highly active antiretroviral therapy should definitely begin at an early age for any perinatally infected infant born to a treated mother.

Acknowledgments: This study was supported in part by the Fogarty International Center of the U.S. National Institutes of Health and NIDA grant 2R01DA06556-08S2 to O. Gómez-Marin.

REFERENCES


19. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-


