ABSTRACT. Background. Infants with perinatally acquired human immunodeficiency virus type 1 (HIV-1) infection have widely variable courses. Previous studies showed that a number of maternal and infant factors, when analyzed separately, are associated with infant HIV-1 disease progression. In this study, clinical, virologic, and immunologic characteristics in the mothers and infants were examined together to determine the predictors of disease progression by 18 months of age and the associations with rapid progression during the first 6 months of life.

Methods. One hundred twenty-two HIV-1-infected women whose infants were HIV-1 infected were identified from the Women and Infants Transmission Study (WITS) cohort. WITS is a longitudinal natural history study of perinatal HIV-1 infection carried out at 6 sites in the continental United States and in Puerto Rico. The women were enrolled during pregnancy and their infants were enrolled at the time of delivery and followed prospectively by a standardized protocol. Virologic and immunologic studies were performed in laboratories certified by National Institutes of Health-sponsored quality assurance programs. Maternal factors in pregnancy were used as potential predictors of infant disease progression (progression to Centers for Disease Control and Prevention [CDC] Clinical Class C disease or death by 18 months of age) or as correlates of progression at <6 months of age. Infant factors defined during the first 6 months of life were used as potential predictors of progression during 6 to 18 months of age and as correlates of progression at <6 months of age.

Results. Progression by 18 months of age occurred in 32% of infants and by 6 months of age in 15%.

Maternal characteristics that, by univariate analysis, were significant predictors of infant disease progression by 18 months of age were elevated viral load, depressed CD4+, and depressed vitamin A. CD8+%, CD8+ activation markers, zidovudine (ZDV) use, and gestational age at delivery were not. When examined in a combined multivariate analysis of maternal characteristics, only vitamin A concentration independently predicted infant progression.

Infant characteristics during the first 6 months of life that, by univariate analysis, were associated with disease progression included elevated mean viral load at 1 to 6 months of age, depressed CD4+%, CDC Clinical Disease Category B, and growth delay. Early HIV-1 culture positivity (<48 hours), CD8+%, CD8+ activation markers, and ZDV use during the first month of life did not predict progression. Multivariate analysis of infant characteristics showed that the only independent predictors were progression to CDC Category B by 6 months of age (odds ratio [OR], 5.80) and mean viral load from 1 to 6 months of age (OR, 1.99).

The final combined maternal and infant analysis included the significant maternal and infant characteristics in a multivariate analysis. It showed that factors independently predicting infant progression by 18 months of age were progression to CDC Category B by 6 months of age (OR, 5.80) and elevated mean HIV-1 RNA copy number at 1 to 6 months of age (OR, 1.99).

The characteristics associated with rapid progression to CDC Category C disease or death by 6 months of age were also examined. The only maternal characteristic associated with progression by 6 months in multivariate analysis was low maternal CD4+. The infant characteristics associated with progression by 6 months of age in multivariate analysis were depressed mean CD4+% from birth through 2 months and the presence of lymphadenopathy, hepatomegaly, or splenomegaly by 3 months. Infant ZDV use was not associated with rapid progression.

Conclusion. The strongest predictors of progression by 18 months are the presence of moderate clinical symptoms and elevated RNA copy number in the infants in the first 6 months of life. In contrast, progression by 6 months is associated with maternal and infant immune suppression, and the presence of infant clinical symptoms. The difference suggests that the key pathogenetic mechanisms responsible for progression may vary with age. These observations help provide direction for future pathogenesis research and assist in clinical care. Pediatrics 2000;105(1). URL: http://www.pediatrics.org/cgi/content/full/105/1/e8; human immunodeficiency virus type 1, infant, maternal, disease progression.

ABBR VIATIONS. HIV-1, human immunodeficiency virus type 1; AIDS, acquired immunodeficiency syndrome; WITS, Women and Infant Transmission Study; CDC, Centers for Disease Control and Prevention; ZDV, zidovudine; PCR, polymerase chain reaction; ACTG, AIDS Clinical Treatment Group; NIAID, National Institute of Allergy and Infectious Disease; VQA, Viral Quality Assurance program; IUPM, infectious units per million cells; OR, odds ratio.
Infants with perinatally acquired human immunodeficiency virus type 1 (HIV-1) infection have widely variable disease courses and lengths of survival. Approximately 15% to 20% of infected untreated infants progress rapidly to acquired immunodeficiency syndrome (AIDS) and death by 4 years of age. Understanding the factors that predict progression is critical to both delineate the pathogenesis of HIV-1 infection and to develop and implement aggressive therapeutic regimens.

Most previous smaller studies concentrated on examining individual maternal and infant factors associated with rapid progression. The Women and Infants Transmission Study (WITS), a large prospectively acquired cohort of HIV-1-infected women and their infants, offers a unique opportunity to examine the multifactorial nature of maternal and infant factors that jointly contribute to rapid progression. This analysis of the WITS cohort reports on both maternal and infant factors that predict progression between 6 and 18 months of age and progression before 6 months of age.

METHODS

Description of the Study Protocol

WITS is a multicenter, longitudinal study of the natural history of HIV-1 infection in pregnant HIV-1-infected women and their infants. The institutional review board approved the study protocol at each study site, and written informed consent was obtained from all participants before study entry. The study sites include Massachusetts (subsites in Boston and Worcester), New York (centers in Manhattan and Brooklyn), Texas (Houston), Puerto Rico (San Juan), and Illinois (Chicago).

Pregnant women were enrolled at any time during pregnancy, and were seen for study visits and blood sampling at entry, 25 ± 2 weeks’ gestation, 34 ± 2 weeks’ gestation, and at delivery. Clinical and laboratory evaluations of the infants were performed at <7 days of life and at 1, 2, 4, 6, 9, 12, and 18 months of age and every 6 months thereafter. Bayley evaluations of mental and physical development were performed at 4, 9, and 12 months of age and every 6 months thereafter until 30 months of age.

Definitions

Infant HIV-1 infection status was defined according to the WITS definition detailed previously. In summary, ≥2 positive HIV-1 culture results of peripheral blood mononuclear leukocytes at any age were required to categorize an infant as infected. An infant was categorized as uninfected if the infant had ≥2 negative culture results from ≥1 month of age, at least 1 negative culture result at ≥6 months of age, and no positive culture results. A small number of infants could not be automatically classified according to the algorithm and were reviewed individually by a committee of WITS investigators who considered all clinical and laboratory data. If a definite infection category could not be established, they were excluded from the analysis.

Progression by 18 months of age was defined as attaining Centers for Disease Control and Prevention (CDC) Clinical Category C condition or dying by 18 months of age. Nonprogressors were required to have reached the 18-month visit window (>12 months) without progression. We also examined factors contributing to progression by 6 months of age, because these factors might be different from those affecting progression by 18 months of age. Therefore, a separate analysis of progression by 6 months of age was performed and was defined as attaining CDC Clinical Category C or dying by 6 months of age.

Hard drug use was defined as reported previously. Maternal use of hard drugs (cocaïne, heroin/opiates, methadone, and injection drug use) was evaluated using maternal self-report at each visit and urine toxicology on specimens collected at enrollment and delivery.

Study Cohort Composition

The analysis was performed using data from study visits before December 1, 1996. At this time, 161 infants were defined as HIV-1-infected. Three infants who had older siblings enrolled in WITS and 36 infants who had <17 months of follow-up without having met the criteria for disease progression were excluded.

Of the mother–infant pairs, 122 were available for the primary analysis of maternal factors predicting progression by 18 months of age. For these, 39 infants (32%) had progression between birth and 18 months of age. The longest follow-up was 6 years.

The secondary analysis of infant factors predicting progression by 18 months of age, predictors were always defined before outcomes and the infant had to either have attained 6 months of age or died of an AIDS-related illness. Therefore, 18 infants who did not meet these criteria were eliminated in the analysis resulting in a sample of 104 infants.

For the analysis of progression by 6 months of age, 18 infants met the criteria for rapid progression and 104 did not.

Until 1994, zidovudine (ZDV) was only given for the treatment of symptomatic maternal disease. In March 1994, the results of the successful perinatal trial of the use of ZDV to prevent HIV-1 transmission became available. Thereafter, all pregnant women enrolled in WITS were counseled about the use of ZDV following the US Public Health Service guidelines for the prevention of HIV-1 transmission to their infants. Of the 102 mother–infant pairs who had the information recorded, 28% used ZDV during pregnancy and infancy.

Laboratory Methods

Blood samples for plasma storage were drawn into specimen tubes containing heparin anticoagulant. Samples for lymphocyte phenotyping were drawn into specimen tubes containing ethylenediaminetetraacetic acid anticoagulant. Separation of the plasma usually occurred within 6 hours of drawing but occasionally samples were held for up to 24 hours. The plasma was stored at −70°C until assayed.

Viral load was determined using a commercially available HIV-1 RNA polymerase chain reaction (PCR) assay according to the manufacturers instructions as described previously (Amplicor HIV-1 Monitor Test; Roche Molecular Systems, Inc, Somerville, NJ). The RNA was extracted from heparinized plasma samples using the silica extraction method of Boom et al. The laboratories performing the assay were fully certified by the AIDS Clinical Trials Group (ACTG) National Institute of Allergy and Infectious Diseases (NIAID) Viral Quality Assurance Program (VQA). Standard samples from the quality assurance program also were included in each run. The lower limit of quantification was 400 HIV-1 RNA copies/mL of plasma. Values <400 copies/mL were arbitrarily assigned a value of 400.

Lymphocyte phenotyping was performed using standardized technology and reagents at each site. Each site participated in the ACTG/NIAID-sponsored quality assurance program as well as a special WITS quality assurance program. In the analysis, the respective count (%) during the first 6 months of life was used, because, in contrast to absolute counts, there is minimal variation in CD4% during the first 6 months of life.

HIV-1 viral cultures were performed using the standard ACTG protocol for quantitative culture. Qualitative cultures were performed on a few occasions early in the study. All sites participated in the ACTG/NIAID VQA program. Results were reported as infectious units per million cells (IUPM).

Maternal vitamin A levels were assayed in the laboratory of Dr Richard Semba using high performance liquid chromatography on hexane-extracted stored plasma specimens.

Statistical Methods

Unless otherwise stated, maternal factors measured during pregnancy were summarized by taking the mean (eg, CD4% or vitamin A) or geometric mean (eg, HIV-1 RNA and IUPM) over all values during pregnancy before analysis. Similarly, unless stated otherwise, measurable infant factors were summarized by taking the mean (eg, CD4% or geometric mean (eg, HIV-1 RNA) over 1 to 6 months of age. Univariate analysis to assess categorical covariates as predictors of progression by 18 months of age was performed using Fisher’s exact test for dichotomous or unordered categorical covariates and the Mantel extension test for ordered
Progressors are infants progressing by 18 months of age, nonprogressors are infants not progressing by 18 months of age. Other factors that were not predictive (P > .05) were culture positivity, mean CD8⁺, mean CD8⁺ CD38⁺, mean CD8⁺ HLA-DR⁺, hard drug use, ZDV use during pregnancy, and gestational age.

categorical covariates. The Wilcoxon rank–sum statistic was used to compare the distributions of continuous covariates across those who progressed by 18 months of age and those who did not.

Multivariate analyses used logistic regression.‡ Adjusted comparisons were initially examined separately for maternal and infant factors. Factors significantly predicting progression by 18 months of age from the above models then were evaluated together. The estimated logistic regression coefficients were transformed into odds ratios (ORs). For ordered categorical covariates such as quartiles of infant mean CD4⁺, RNA copy number, and grouped maternal CD4⁺ (<14%, 15%–28%, and ≥29%), the ORs correspond to the increase in the odds of disease progression by 18 months of age associated with being in adjacent categories. The same statistical methods were used for assessing factors associated with progression by 6 months of age although maternal and infant factors were not analyzed together because of small sample size.

RESULTS

Overall, 32% of 122 HIV-1-infected infants progressed to CDC Clinical Category C or death between birth and 18 months of age. The most common first events that resulted in a Category C categorization were encephalopathy and Pneumocystis carinii pneumonia. Of the rapid progressors with a Category C condition, 6 died between 6 and 18 months of age, and 3 died with no preceding Category C event.

To understand the factors predicting progression by 18 months of age, possible maternal and infant factors were initially examined individually. The significant individual maternal and infant factors then were examined in multivariate models of maternal and of infant factors and, finally, the predictors were examined in a model that combined maternal and infant factors.

Maternal Characteristics Predicting Progression by 18 Months of Age

The viral load during pregnancy was higher, CD4⁺ % lower and plasma vitamin A lower in pregnant women whose infants had progression by 18 months of age compared with those who did not (P = .052). Sixty-seven percent of infants whose mothers had CD4⁺ % <14% at delivery, 32.1% with CD4⁺ % 14% to 28%, and 12.8% with CD4⁺ >29% had progression by 18 months of age (P = .001; Fisher’s exact test, 2 tail; n each group 12, 56, and 39, respectively). The median vitamin A was 33.4 μg/dL in women whose infants had progression by 18 months of age, compared with 37.7 μg/dL in women whose infants did not (P = .029; Wilcoxon).

Maternal factors that did not predict infant progression by 18 months of age included CD8⁺%, CD8⁺ CD38⁺ and HLA-DR⁺, gestational age, hard drug use, and ZDV use during pregnancy. The positive maternal predictors for progression by 18 months of age in the univariate analysis (viral load, CD4⁺%, and vitamin A) then were examined together in a logistic regression analysis. Of these maternal factors, only maternal vitamin A concentration independently predicted infant progression by 18 months of age (P = .015; OR for adjacent quartile categories = .57; Table 2).

Infant Characteristics Predicting Progression by 18 Months of Age

The viral copy number was higher, CD4⁺ % lower, CDC Clinical Disease Category more advanced, and growth delayed in those infants who had progression by 18 months of age (Table 3). The mean RNA PCR copy number at 1 to 6 months of age in rapidly progressing infants was 701 455, compared with 164 816 (P < .001). The proportion of infants with disease progression by 18 months of age in the lowest quartile of CD4⁺ % was 37.5%, compared with 15.0% in the highest (P = .022). Advancement to CDC Clinical Category B (moderate HIV-1-related symptoms) by 6 months of age predicted progression.

**TABLE 1.** Maternal Characteristics That Predict Infant Disease Progression to CDC Category C or Death Before 18 Months of Age

<table>
<thead>
<tr>
<th>Predictor in Pregnancy of Progression by 18 Months</th>
<th>Nonprogressors/Progressors</th>
<th>Median Value of Predictors of Nonprogressors Versus Progressors</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral RNA PCR – mean log₁₀ HIV-1 RNA</td>
<td>72/36</td>
<td>4.447 vs 4.533</td>
<td>.052</td>
</tr>
<tr>
<td>HIV-1 co-culture (mean IUPM)</td>
<td>51/27</td>
<td>1.940 vs 3.538</td>
<td>.020</td>
</tr>
<tr>
<td>Immune CD4⁺ %</td>
<td>78/39</td>
<td>26.8% vs 20.3%</td>
<td>.002</td>
</tr>
<tr>
<td>Clinical Vitamin A</td>
<td>62/32</td>
<td>37.7 μg/dL vs 33.4 μg/dL</td>
<td>.029</td>
</tr>
</tbody>
</table>

**TABLE 2.** Logistic Regression Models: Maternal Antenatal Characteristics and Risk of Progression by 18 Months of Age in HIV-1-Infected Infants

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unadjusted Models</th>
<th>Adjusted Model†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (mean by quartile)‡</td>
<td>.66 (.44, .99) .040*</td>
<td>.57 (.36, .89) .015*</td>
</tr>
<tr>
<td>RNA PCR (mean copies/mL by quartile)‡</td>
<td>1.53 (1.05, 2.24) .027*</td>
<td>—</td>
</tr>
<tr>
<td>Mean CD4⁺ % (&lt;14% vs 14%–28% vs ≥29%)‡</td>
<td>.38 (.19, .74) .005*</td>
<td>—</td>
</tr>
<tr>
<td>n in model</td>
<td>94–117</td>
<td>91</td>
</tr>
</tbody>
</table>

* OR (95% confidence interval) P value.
† OR (95% CI) and P value adjusted for other 2 variables.
‡ The OR correspond to the increase in the odds of progression by 18 months of age associated with being in the higher versus the adjacent lower quartile/category of the risk factor.
Predicting Progression by 18 Months of Age

In the final combined maternal and infant analysis, the significant maternal and infant predictors of progression were incorporated into a multivariate model. The factors that remained significantly associated with progression by 18 months of age in this model were infant progression to CDC Category B by 6 months of age ($P = .002$; OR: 5.80) and quartile of the averaged infant HIV-1 RNA copy number between 1 and 6 months of age ($P = .009$; OR for adjacent categories: 1.99).

Disease Progression by Six Months of Age

For this analysis, infants experiencing death or progression to CDC Category C disease by 6 months of age were examined ($n = 18$), and all others were classified as not having disease progression by 6 months of age ($n = 104$).

Of the maternal factors, only depressed maternal CD4+ % during pregnancy ($P = .025$; OR for adjacent categories: 4.31) was significantly associated with progression by 6 months of age after adjusting for other covariates (mean antenatal vitamin A by quartile, mean antenatal log HIV-1 RNA copy number, and HIV-1 culture results).

Of the infant factors, only the mean CD4+ % from birth through 2 months of age and the presence of lymphadenopathy, hepatomegaly, or splenomegaly by 3 months of age were independently associated with disease progression by 6 months of age in a multivariate analysis ($P = .014$ and .035, respectively). Other infant factors that were significantly associated only in univariate analysis included mean log HIV-1 RNA copy number at 1 and 2 months of age and mean CD8+ HLA-DR+ % from birth through 2 months of age ($P < .002$). Eighteen percent of the 22 who used ZDV in the first month of life had progression by 6 months of age, whereas 14.2% of the 99 infants who did not use ZDV had progression by 6 months ($P = .009$; Fisher’s exact test).

A combined maternal and infant multivariate analysis was not performed because of the limited num-
number of the infants experiencing disease progression by 6 months of age.

**DISCUSSION**

Identification of HIV-1-infected infants at greatest risk of disease progression by 18 months of age has important utility both for understanding the pathogenesis of perinatal HIV-1 disease and targeting aggressive early treatment strategies toward high risk infants. Although there is a large body of literature describing individual associations with disease progression, few studies have had the statistical power to simultaneously examine the contribution of both maternal and infant factors to disease progression using multivariate analysis. Using the WITS database of 122 infected infants and their mothers and multivariate modeling, we evaluated multiple maternal and infant characteristics to identify those that predict disease progression by 18 months of age.

In this study, we utilized events occurring during the first 6 months of life as the landmark predictors of disease progression during 6 and 18 months of age. We also described the characteristics associated with rapid disease progression or disease progression occurring by 6 months of age. This approach is in contrast to those using time-varying covariates that relate the risk of disease progression to current patient characteristics rather than to characteristics measured during the landmark observation period. A separate report on the time varying covariate approach in the infants was presented elsewhere (12th World AIDS Conference; June 28, 1998, to July 3, 1998; Geneva, Switzerland; Abstract 13368).

We found that, of all the maternal predictors of infant disease progression by 18 months of age, only depressed maternal plasma vitamin A during pregnancy was independently significant. Deficiency of maternal vitamin A is associated with an increased risk of HIV-1 transmission, intercurrent infection in HIV-1-uninfected or HIV-1-infected infants, and mortality. The increased risk of these adverse outcomes may be attributable to decreased maternally derived stores of vitamin A in the infant. However, when examined in the combined multivariate analysis, it was not significant.

Among the few multivariate studies in the literature on maternal factors and infant rapid progression, advanced maternal HIV disease during pregnancy and high viral load late in pregnancy or shortly after delivery were independently associated with infant disease progression. Maternal vitamin A was not examined in these studies. In agreement with our results, others have found that low CD4+ count (<500 per mm3), use of ZDV and the duration of rupture of the membranes were not associated with disease progression (Lambert G, Weedon J, Thea DM, et al; XI International Conference on AIDS; July 7, 1996, to July 12, 1996; Vancouver, Canada; Abstract WE.C.3461; page 138; Abstract Book 2). Infant characteristics expressed during the first 6 months of life also predicted progression during the next year of life. Despite the numerous associations reported in univariate analysis in both the current study and in the literature, only high viral load during 1 to 6 months of life and clinical disease progression to CDC Category B independently predicted progression by 18 months of age.

In the final combined multivariate model that included maternal and infant characteristics, only the infant viral load from 1 to 6 months of life and progression to CDC Category B independently predicted progression by 18 months of age. None of the maternal factors independently predicted progression by 18 months of age. Thus, the intensity and lack of control of infection in the infant as manifest by the viral load and target organ disease expression (organomegaly or adenopathy) seemed to be the primary predictors of disease progression.

We also found that the factors associated with disease progression by 6 months of age were not the same as those predicting disease progression by 18 months of age. In the WITS cohort, rapid progression was associated with immune suppression as evidenced by depressed maternal CD4+ % during pregnancy and lower infant CD4+ % from birth through 2 months of age and the presence of lymphadenopathy, hepatomegaly, or splenomegaly. However, it was not associated with elevated viral load as was seen with disease progression after 6 months of age. Thus, disease progression by 6 months of age seemed to be associated with disruption of the immune system while disease progression by 18 months is characterized by high viral loads irrespective of CD4+ %.

We speculate that this difference could be predicted by the observation that virologic, immunologic, and clinical characteristics during primary infection are different from in later infection. For example, the predictive value of HIV-1 RNA levels for disease progression in infected adults is greatest after the patient has achieved a steady-state level following the initial stage of primary infection. Similarly, in acute perinatal infection, the risk of rapid progression during the first 6 months of life may be governed more by the beginning and relatively ineffective immune response of the neonate to HIV-1 infection than by viral load at birth or during the first month of life.

**CONCLUSION**

In summary, this analysis of 122 infected infant–mother pairs identified multiple predictors of progression by 18 months of age (early infant clinical symptoms and elevated RNA copy number) and associations with progression by 6 months (depressed maternal and infant CD4+ % and early clinical symptoms). These observations should help provide direction for additional research on HIV-1 pathogenesis and assist health care providers in targeting intensive therapy toward those HIV-1-infected infants at highest risk for early morbidity and death.

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REFERENCES

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