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## OBSTETRICAL FACTORS AND THE TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 FROM MOTHER TO CHILD

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**Abstract Background.** A substantial proportion of perinatally acquired infections with the human immunodeficiency virus type 1 (HIV-1) occur at or near delivery, which suggests that obstetrical factors may have an important influence on transmission. We evaluated the relation of such factors and other variables to the perinatal transmission of HIV-1.

**Methods.** The Women and Infants Transmission Study is a prospective, observational study of HIV-1-infected women who were enrolled during pregnancy and followed with their infants for three years after delivery. We studied obstetrical, clinical, immunologic, and virologic data on 525 women who delivered live singleton infants whose HIV-1-infection status was known as of August 31, 1994.

**Results.** Among mothers with membranes that ruptured more than four hours before delivery, the rate of transmission of HIV-1 to the infants was 25 percent, as

compared with 14 percent among mothers with membranes that ruptured four hours or less before delivery. In a multivariate analysis, the presence of ruptured membranes for more than four hours nearly doubled the risk of transmission (odds ratio, 1.82; 95 percent confidence interval, 1.10 to 3.00;  $P=0.02$ ), regardless of the mode of delivery. The other maternal factors independently associated with transmission were illicit-drug use during pregnancy (odds ratio, 1.90; 95 percent confidence interval, 1.14 to 3.16;  $P=0.01$ ), low antenatal CD4+ lymphocyte count (<29 percent of total lymphocytes) (odds ratio, 2.82; 1.67 to 4.76;  $P<0.001$ ), and birth weight <2500 g (odds ratio, 1.86; 1.03 to 3.34;  $P=0.04$ ).

**Conclusions.** The risk of transmission of HIV-1 from mother to infant increases when the fetal membranes rupture more than four hours before delivery. (N Engl J Med 1996;334:1617-23.)

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**H**UMAN immunodeficiency virus type 1 (HIV-1) may be transmitted from mother to infant during the antepartum, intrapartum, or postpartum period. Immunologic, virologic, obstetrical, and other maternal factors influence transmission, but their relative contributions are difficult to assess. Most research has focused on measures of maternal immunocompetence, immunologic response to the virus, viral load, and viral

phenotype.<sup>1-12</sup> Relatively few studies have examined the role of obstetrical factors and their effect on transmission.<sup>1,2,13-15</sup> Increasing evidence indicates that a substantial proportion of infants acquire their infections at or near delivery.<sup>16-20</sup> We examined the relation between obstetrical factors and mother-to-infant transmission of HIV-1 among women and infants followed prospectively in the multicenter Women and Infants Transmission Study.

## METHODS

### Study Protocol

HIV-1-infected women have been enrolled in the Women and Infants Transmission Study from December 1989 to the time of this writing. This analysis included data corresponding to visits through August 31, 1994, at institutions in New York City, Chicago, Massachusetts, and San Juan, Puerto Rico. Women could enter the study at any time during pregnancy and for up to seven days after delivery. Infants were enrolled at birth. Because outcomes in infants born to the same mother may be related, we restricted the analyses in this report to the first live singleton birth after the mother's enrollment.

Women were seen at entry, within two weeks before or after weeks 25 and 34 of pregnancy (unless the women were enrolled later), at delivery, two and six months post partum, and every six months thereafter. At each visit a detailed questionnaire was administered, venous blood was collected for immunologic studies and HIV-1 culture, and a general physical examination, including a pelvic examination, was

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\*Additional participants in the Women and Infants Transmission Study are listed in the Appendix.

performed. At delivery or shortly thereafter, a member of the study team visited the mother, collected additional specimens, prepared an abstract of the medical record of the pregnancy and delivery, and examined and collected venous blood from the newborn.

The infants were seen at birth or shortly thereafter and at 1, 2, 4, 6, 9, 12, 15, 18, 24, 30, and 36 months of age. At each visit, blood was obtained for HIV-1 culture and immunologic studies.

The women were counseled about the risk of transmitting HIV-1 to their infants through breast-feeding. Only five women in the study were known to have breast-fed their infants, and those children were not infected. The study protocol was approved by the institutional review board at each participating institution. Informed, witnessed written consent was obtained from the women before entry into the study.

### Laboratory Analysis

HIV-1 serologic status was determined by a commercially available enzyme-linked immunosorbent assay, with confirmation by the Western blot assay. Lymphocyte subgroups were quantitated by standard techniques of flow cytometry using monoclonal antibodies. All laboratories analyzing lymphocytes were certified by the AIDS Clinical Trials Group and participated in the quality-assurance program of the National Institute of Allergy and Infectious Diseases. Blood was collected for HIV-1 culture in tubes treated with heparin and transported to a local laboratory at room temperature immediately after the samples were drawn, and peripheral-blood mononuclear cells were separated within 18 hours with Ficoll-Hypaque centrifugation. When the study began, HIV-1 cultures were performed qualitatively, but in October 1991 quantitative methods of culture were introduced and used to study all samples obtained from babies six months of age or less and from infected babies over that age. Throughout the study, the laboratory protocols of the AIDS Clinical Trials Group were followed with standard modifications for pediatric samples.<sup>21,22</sup> Details of the qualitative and quantitative methods of culture have been reported elsewhere.<sup>23</sup> During the study, the viral-culture laboratories participated in the AIDS Clinical Trials Group virologic quality-assurance program and were certified to perform qualitative and quantitative cultures as these certifications became available.

### Definitions

The criteria of the AIDS Clinical Trials Group<sup>21</sup> were used to classify cultures qualitatively as positive or negative. Because there is no generally accepted definition of a positive quantitative culture in an infant, such cultures were defined as positive if the contents of two or more wells tested positive.

Illicit-drug use during pregnancy was determined by self-reports and toxicologic testing of urine samples. A mother was considered to have used illicit drugs if she reported doing so, regardless of the results of urine tests. Toxicologic assays of maternal urine samples were performed on specimens collected at entry, during labor, or immediately post partum. Positive tests were confirmed by gas chromatography-mass spectrometry if the women denied using drugs. Because *in vitro* studies have shown that HIV replication is enhanced by cocaine and opiates,<sup>24-26</sup> our study focused on cocaine, heroin and other opiates, methadone, and injection drugs. For the purposes of the analysis, these drugs were studied in combination and described as "hard" drugs.

We examined relative levels of CD4+ and CD8+ lymphocytes during pregnancy, expressed as percentages of total lymphocytes rather than absolute counts, because the former are associated with less variation<sup>27,28</sup> and are less likely to change in response to alterations in blood volume, typically seen during pregnancy.<sup>29,30</sup> The means of all available antenatal measurements were used. When we used the "low-ess" method,<sup>31</sup> the cutoff points for CD4+, 14 percent and 29 percent, corresponded in the study cohort to absolute CD4+ counts of 225 and 512 cells per cubic millimeter, respectively, and the cutoff point for CD8+, 50 percent, corresponded to an absolute count of 800 cells per cubic millimeter. The infection status of the infants was determined with the following working definition of HIV-1 infection.<sup>23</sup> Infants with two or more peripheral-blood cultures positive for HIV-1 were defined as infected. Infants with no positive cultures and two or more negative peripheral-blood cultures, including one obtained at the age of one month or older and one obtained at six months of age or older, were classified as uninfected. Because an infant had to be at least six months old to be classified as uninfected, infants under six months of age were excluded from the analysis. Nine infants who each had a sin-

**Table 1. Characteristics of the Women Enrolled in the Study, According to Whether They Were Included in the Final Analysis.\***

| CHARACTERISTIC                    | WOMEN INCLUDED (N = 525) | WOMEN NOT INCLUDED (N = 351) |
|-----------------------------------|--------------------------|------------------------------|
| Age at enrollment (yr)            |                          |                              |
| Mean $\pm$ SD                     | 27.5 $\pm$ 5.2           | 27.9 $\pm$ 5.3               |
| Median                            | 27                       | 28                           |
| Range                             | 15-44                    | 14-44                        |
| Race or ethnic group (% of women) |                          |                              |
| White                             | 15.6                     | 13.5                         |
| Black                             | 40.3                     | 44.1                         |
| Hispanic                          | 39.8                     | 36.2                         |
| Other                             | 4.3                      | 6.2                          |
| Median no. of pregnancies         | 3                        | 3                            |
| Median no. of prior live births   | 2                        | 2                            |
| Nulliparity (% of women)          | 11.5                     | 10.4                         |
| Hard-drug use (% of women)†       | 41.8                     | 35.4                         |
| Mean CD4+ level (% of women)      |                          |                              |
| <14%                              | 7.1                      | 14.7                         |
| 14-28%                            | 43.0                     | 42.9                         |
| $\geq$ 29%                        | 49.9                     | 42.3                         |
| Zidovudine use (% of women)       | 22.8                     | 33.6                         |

\*For certain variables the study samples did not include all the women, because of missing data.

†Hard drugs were defined as heroin and other opiates, cocaine, methadone, and other injection drugs.

gle positive culture were classified as uninfected because they were consistently negative by the polymerase-chain-reaction (PCR) assay, remained asymptomatic, were immunologically normal, and were HIV-1-negative on serologic testing (by enzyme immunoassay and the Western blot assay) at the age of 15 months or more. Twenty-four infants with indeterminate HIV status (i.e., those under 15 months of age who had a single positive culture and those who died before either study criterion could be met) were excluded from the analysis.

### Statistical Analysis

Rates of HIV-1 transmission were compared in an unadjusted analysis by Fisher's exact test<sup>32</sup> for dichotomous or unordered categorical covariates and the Cochran-Armitage trend test<sup>33</sup> for ordered categorical covariates. The multivariate analysis used logistic regression,<sup>34</sup> Mantel-Haenszel tests for stratified two-by-two tables,<sup>33</sup> and a stratified Cochran-Armitage trend test. Crude and adjusted estimated risk ratios, calculated with a stratified Cochran-Mantel-Haenszel estimator,<sup>33</sup> and odds ratios from multivariate logistic-regression models<sup>34</sup> were used to express the effect of a covariate on HIV-1 transmission. The nonparametric lowess method<sup>31</sup> was used to estimate the probability of HIV-1 transmission as a function of the duration of ruptured membranes and to explore the relation between absolute and relative CD4+ and CD8+ lymphocyte levels.

In each analysis, women or infants for whom there was missing information on any variable used were excluded from the analysis of that variable. All tests were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance.

### RESULTS

Among the 876 women enrolled in the study as of August 31, 1994, 665 gave birth to live singleton infants. The remaining 211 pregnancies resulted in twins (16 women); stillbirth, miscarriage, or abortion (97 women); or an unknown birth outcome (61 women, approximately 60 percent of whom were still pregnant on the cutoff date); or the woman died or was lost to follow-up during the pregnancy (37 women). Of the 665 mother-infant pairs considered, 116 were excluded from the study because the infants had not been followed for at least six months, and another 24 were excluded because the infants' infection status was unknown at the time

of the analysis. This left 525 mother–infant pairs in the analysis, including 104 infected infants (20 percent). In the final analysis, abstracts containing information on obstetrical variables during pregnancy were available for 509 of the 525 mothers (97 percent), and information on the duration of ruptured membranes was available for 487 of the 525 (93 percent).

Table 1 compares the characteristics of the 525 women included in the analysis with those of the 351 not included. The two groups were similar with respect to age, race or ethnic group, median numbers of pregnancies and live births, the proportion who were nulliparous, use of hard drugs (as defined in the Methods section), mean percentage of CD4+ cells, and zidovudine use. When the 487 mother–infant pairs included in the analysis of the duration of ruptured membranes were compared with the 38 pairs for whom those data were not available, the two groups were similar with respect to the variables shown in Table 1, except that the women for whom data on the duration of ruptured membranes were missing were older, had lower CD4+ lymphocyte counts, and had a higher prevalence of drug use.

Table 2 shows the rate of transmission of HIV-1 from mother to infant according to selected maternal variables. The sample size varied depending on the number of women for whom data were available for a particular variable. In the univariate analysis, HIV-1 transmission was significantly associated with a low level of CD4+ cells (<29 percent), a high level of CD8+ cells ( $\geq 50$  percent), a positive HIV-1 culture at delivery, prematurity, low birth weight, longer duration of ruptured membranes, premature rupture of membranes (that is, before the onset of labor), premature rupture of membranes in a preterm delivery (that is, before 37 weeks' gestation), use of hard drugs during pregnancy, the presence of chorioamnionitis, and maternal age of at least 30 years. Table 2 also shows the prevalence of various characteristics of the mother–infant pairs.

In the univariate analysis, the use of zidovudine was not associated with a reduction in rates of HIV-1 transmission. Caution must be used in interpreting the data

Table 2. Univariate Analysis of Maternal Variables Possibly Related to HIV-1 Transmission.

| VARIABLE                           | NO. OF PATIENTS STUDIED | NO. INFECTED (%) | RELATIVE RISK (95% CONFIDENCE INTERVAL) | P VALUE |
|------------------------------------|-------------------------|------------------|---|---------|
| Exposure to blood                  |                         |                  |   |         |
| During labor*                      |                         |                  |   |         |
| No                                 | 430                     | 86 (20)          | 1.0                                     | 0.27    |
| Yes                                | 77                      | 11 (14)          | 0.71 (0.40–1.27)                        |         |
| During delivery†                   |                         |                  |   |         |
| No                                 | 300                     | 56 (19)          | 1.0                                     | 0.82    |
| Yes                                | 207                     | 41 (20)          | 1.06 (0.74–1.52)                        |         |
| Gestational age (wk)               |                         |                  |   |         |
| $\geq 37$                          | 427                     | 76 (18)          | 1.0                                     | 0.02    |
| <37                                | 98                      | 28 (29)          | 1.61 (1.10–2.33)                        |         |
| Birth weight (g)                   |                         |                  |   |         |
| $\geq 2500$                        | 392                     | 66 (17)          | 1.0                                     | <0.001  |
| <2500                              | 90                      | 30 (33)          | 1.98 (1.37–2.85)                        |         |
| Chorioamnionitis                   |                         |                  |   |         |
| No                                 | 495                     | 92 (19)          | 1.0                                     | 0.04    |
| Yes                                | 11                      | 5 (45)           | 2.45 (1.25–4.79)                        |         |
| Rupture of membranes               |                         |                  |   |         |
| Spontaneous                        | 267                     | 49 (18)          | 1.0                                     | 0.82    |
| Artificial                         | 231                     | 45 (19)          | 1.06 (0.74–1.53)                        |         |
| Before onset of labor              |                         |                  |   |         |
| No                                 | 306                     | 48 (16)          | 1.0                                     | 0.06    |
| Yes                                | 93                      | 23 (25)          | 1.58 (1.02–2.45)                        |         |
| During preterm delivery‡           |                         |                  |   |         |
| No                                 | 361                     | 58 (16)          | 1.0                                     | 0.01    |
| Yes                                | 38                      | 13 (34)          | 2.13 (1.29–3.51)                        |         |
| Duration (hr)                      |                         |                  |   |         |
| <1                                 | 158                     | 21 (13)          | 1.0                                     | <0.001  |
| 1–4                                | 123                     | 18 (15)          | 1.10 (0.61–1.97)                        |         |
| 5–12                               | 114                     | 24 (21)          | 1.58 (0.93–2.70)                        |         |
| 13–24                              | 50                      | 9 (18)           | 1.35 (0.66–2.76)                        |         |
| >24                                | 42                      | 19 (45)          | 3.40 (0.20–5.72)                        |         |
| $\leq 4$                           | 281                     | 39 (14)          | 1.0                                     | 0.002   |
| >4                                 | 206                     | 52 (25)          | 1.82 (1.25–2.64)                        |         |
| Duration of labor (hr)             |                         |                  |   |         |
| $\leq 6$                           | 154                     | 25 (16)          | 1.0                                     | 0.32    |
| 7–12                               | 116                     | 30 (26)          | 1.59 (0.99–2.56)                        |         |
| 13–24                              | 94                      | 12 (13)          | 0.79 (0.42–1.49)                        |         |
| >24                                | 31                      | 3 (10)           | 0.60 (0.19–1.85)                        |         |
| Mode of delivery                   |                         |                  |   |         |
| Vaginal                            | 410                     | 76 (19)          | 1.0                                     | 0.57    |
| Cesarean                           | 98                      | 21 (21)          | 1.16 (0.75–1.78)                        |         |
| Hard-drug use during pregnancy§    |                         |                  |   |         |
| No                                 | 305                     | 48 (16)          | 1.0                                     | 0.008   |
| Yes                                | 219                     | 56 (26)          | 1.62 (1.15–2.29)                        |         |
| Cigarette smoking during pregnancy |                         |                  |   |         |
| No                                 | 227                     | 41 (18)          | 1.0                                     | 0.38    |
| Yes                                | 297                     | 63 (21)          | 1.17 (0.82–1.67)                        |         |
| Alcohol intake during pregnancy    |                         |                  |   |         |
| No                                 | 256                     | 57 (22)          | 1.0                                     | 0.19    |
| Yes                                | 268                     | 47 (18)          | 0.79 (0.56–1.11)                        |         |
| Mean CD4+ level during pregnancy   |                         |                  |   |         |
| $\geq 29\%$                        | 252                     | 32 (13)          | 1.0                                     | <0.001  |
| <29%                               | 253                     | 69 (27)          | 2.15 (1.47–3.14)                        |         |
| Mean CD8+ level during pregnancy   |                         |                  |   |         |
| <50%                               | 253                     | 35 (14)          | 1.0                                     | <0.001  |
| $\geq 50\%$                        | 252                     | 66 (26)          | 1.89 (1.31–2.74)                        |         |
| Positive HIV-1 culture at delivery |                         |                  |   |         |
| No                                 | 117                     | 12 (10)          | 1.0                                     | 0.005   |
| Yes                                | 316                     | 69 (22)          | 2.13 (1.20–3.78)                        |         |
| Zidovudine use during pregnancy    |                         |                  |   |         |
| No                                 | 402                     | 82 (20)          | 1.0                                     | 0.70    |
| Yes                                | 119                     | 22 (18)          | 0.91 (0.59–1.38)                        |         |
| Maternal age at delivery (yr)      |                         |                  |   |         |
| <30                                | 335                     | 56 (17)          | 1.0                                     | 0.02    |
| $\geq 30$                          | 190                     | 48 (25)          | 1.51 (1.07–2.13)                        |         |

\*Includes placenta previa, abruptio placenta, hemorrhage during labor, use of fetal-scalp electrodes, and fetal-blood sampling.

†Includes episiotomy, infant skin breaks, and perineal, vaginal, and vulvar lacerations.

‡Before 37 weeks' gestation.

§Denotes use of heroin or other opiates, cocaine, methadone, or other injection drugs.

on zidovudine. Forty-eight women–infant pairs included in this analysis participated in AIDS Clinical Trials Group protocol 076: there was HIV-1 transmission in 2 of 23 pairs receiving zidovudine and in 9 of 25 receiving placebo.<sup>35</sup> When the women participating in that

study were excluded from the analysis, the results in Table 2 did not change substantially. The remaining 98 women treated with zidovudine during pregnancy received the drug for clinical indications at various dosages and for varying periods. Information on zidovudine use during pregnancy was collected retrospectively for the first four years of the study and did not include data on dosage, compliance, or the duration of treatment. These 98 women also had lower levels of CD4+ lymphocytes than all the women known not to use zidovudine, not including the participants in protocol 076; 21 percent had mean antenatal CD4+ levels below 14 percent, as compared with 4 percent of the women not receiving zidovudine, and 54 percent had levels between 14 and 28 percent, as compared with 41 percent among nonusers.

On the basis of previous research on the duration of ruptured membranes and perinatal transmission,<sup>13</sup> the cutoff points for the duration of ruptured membranes were chosen before the start of this analysis. To explore the relation between this variable and the risk of HIV-1 transmission further, a smoothed curve of the risk of transmission was created (Fig. 1). In this analysis, durations of ruptured membranes exceeding 48 hours were truncated to 48 hours. The curve shows that four hours is a reasonable cutoff point. About four hours after fetal membranes rupture, the risk of transmission increases rapidly and approximately doubles. Further increases in this risk, especially after 16 hours have passed, are less reliable, given the sparsity of events and the inherent limitations of the technique when it is applied to the "edges" of the distribution.

Table 3 shows the transmission rates broken down according to the duration of ruptured membranes and the mode of delivery. As noted, the effect of a shortened duration of ruptured membranes is independent of mode of delivery. Furthermore, after we controlled for the duration of ruptured membranes, the mode of delivery did not significantly alter the rate of transmission.

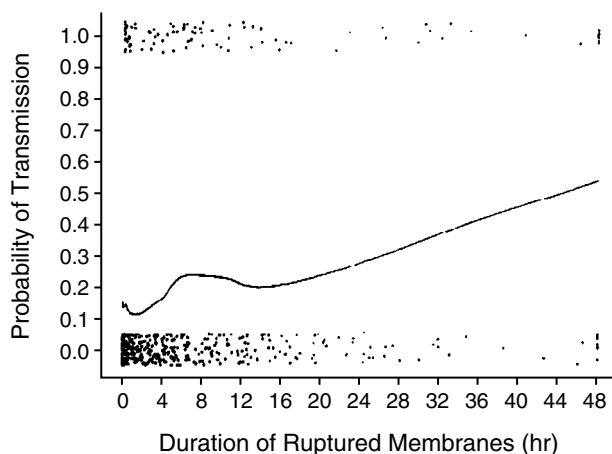


Figure 1. Probability of HIV-1 Transmission in Relation to the Duration of Ruptured Membranes.

The dots at the top represent women who transmitted HIV-1 to their infants, and those at the bottom women who did not transmit HIV-1. Data on women whose membranes were ruptured for more than 48 hours are shown at the 48-hour mark.

Table 3. Rates of Transmission of HIV-1 and Adjusted Relative Risks of Transmission According to Duration of Ruptured Membranes and Mode of Delivery.

| DURATION OF RUPTURE AND MODE OF DELIVERY | NO. STUDIED             | NO. INFECTED (%) |
|--|-------------------------|------------------|
| ≤4 Hr                                    |                         |                  |
| Cesarean                                 | 53                      | 8 (15)           |
| Vaginal                                  | 228                     | 31 (14)          |
| >4 Hr                                    |                         |                  |
| Cesarean                                 | 43                      | 12 (28)          |
| Vaginal                                  | 163                     | 40 (25)          |
| COMPARISON*                              | RELATIVE RISK (95% CI)† |                  |
| Duration of rupture >4 hr (vs. ≤4 hr)    | 1.81 (1.25–2.64)        |                  |
| Cesarean delivery (vs. vaginal)          | 1.13 (0.73–1.75)        |                  |

\*Each comparison is adjusted for the other variable in this table.

†CI denotes confidence interval.

When the covariates associated with mother-to-infant transmission in the univariate analysis ( $P < 0.10$ ) were considered in logistic-regression models, duration of ruptured membranes of more than four hours and three other variables — CD4+ cell levels below 29 percent, birth weight below 2500 g, and the use of hard drugs — were independently associated with HIV-1 transmission (Table 4). Performing analogous tests with stratified Mantel-Haenszel tests gave very similar results.

## DISCUSSION

This prospective study of perinatal HIV-1 transmission is unusual with regard to the large number of women for whom data on the duration of ruptured membranes and other obstetrical variables were available, together with CD4+ percentages and other major covariates of mother-to-infant transmission. Our findings indicate that the duration of ruptured membranes is an important determinant of HIV-1 transmission and suggest that this variable may at least partly explain the association of transmission with mode of delivery that has been observed in several previous studies.<sup>13-15,17</sup> Other variables found to be independently associated with the transmission of HIV-1 in our cohort were low CD4+ level, use of hard drugs during pregnancy, and low birth weight.

We found no significant association between mother-to-infant transmission of HIV-1 and variables associated with contamination of the birth canal by blood during labor or near the time of delivery. These variables included hemorrhage during labor, placenta previa or abruptio placenta, episiotomy, perineal or vaginal tears, the use of internal monitoring devices, and breaks in the infant's skin (Table 2). When each of these variables was analyzed separately, none were associated with an increased rate of transmission. This analysis, however, has limited power to detect increases by factors smaller than 1.75 in the risk of HIV-1 transmission due to exposure to blood. A study by Boyer et al.<sup>36</sup> using a considerably smaller sample did show an association between exposure to blood during labor or delivery and HIV-1 transmission. Our findings suggest that the duration of such exposure (or an associated factor) may

**Table 4. Logistic-Regression Analysis of Risk Factors for HIV-1 Transmission from Mother to Infant.**

| RISK FACTOR              | ODDS RATIO (95% CONFIDENCE INTERVAL)* | P VALUE |
|--------------------------|---------------------------------------|---------|
| Ruptured membranes >4 hr | 1.82 (1.10–3.00)                      | 0.02    |
| Mean CD4+ level <29%     | 2.82 (1.67–4.76)                      | <0.001  |
| Birth weight <2500 g     | 1.86 (1.03–3.34)                      | 0.04    |
| Hard-drug use            | 1.90 (1.14–3.16)                      | 0.01    |

\*For the increase in the odds of HIV-1 transmission associated with the presence or absence of the risk factor after adjustment for the other covariates used in the model.

be more important than the character or perhaps the amount of the maternal fluid (i.e., blood or another fluid in the birth canal) to which the infant is exposed.

Several studies have reported an association between low levels of CD4+ lymphocytes and increased HIV-1 transmission.<sup>1-7</sup> Although they reported different degrees of association between low maternal levels of CD4+ lymphocytes, severity of disease, and viral transmission, they all observed the same general relation. Despite the variations among these studies, the observation has consistently emerged that increasing severity of disease — by itself or as measured by the CD4+ count, admittedly an imprecise factor — is associated with increased mother-to-infant transmission. This observation is further corroborated by our findings.

Use of hard drugs during pregnancy was independently associated with an increased risk of HIV-1 transmission. Other studies have produced inconsistent findings concerning the relation of maternal drug use and mother-to-infant transmission.<sup>37-39</sup> None of these studies, however, evaluated the prevalence of maternal drug use in a standardized manner that included both self-reports and toxicologic testing of urine, as was done in this case. A more thorough analysis of these data has recently been published.<sup>40</sup>

We also found that low birth weight was independently associated with mother-to-infant transmission of HIV-1. Whereas most cohort studies have not found infected infants to have lower birth weights than uninfected infants,<sup>41</sup> three studies, two from the United States and one from Rwanda, have found such associations.<sup>42-45</sup> Although some have suggested that findings of this type may reflect an association of low birth weight with illicit-drug use or a more advanced stage of maternal disease,<sup>46</sup> in both our cohort and the New York City cohort studied by Abrams et al.<sup>43</sup> this association was independent of the maternal CD4+ lymphocyte level, the duration of ruptured membranes, and the use of hard drugs. This association could be related to transmission in utero in a proportion of cases, or to other confounding maternal factors, such as maternal infection with agents capable of causing growth retardation in utero and increased transmission of HIV-1.

Delivery more than four hours after the rupture of membranes nearly doubled the rate of mother-to-infant transmission of HIV-1. This relation was independent of the mode of delivery (Table 3). Recent studies support the concept that intrapartum transmission accounts for a substantial number of perinatally acquired HIV-1 infections and that exposure to infected cervico-

vaginal secretions is a probable mechanism of disease acquisition.<sup>17-20,47-51</sup> The strong association we observed between the duration of ruptured membranes and mother-to-infant transmission of HIV-1 supports these concepts.

In a perinatal study performed by St. Louis et al.<sup>1</sup> in Kinshasa, Zaire, no difference in HIV-1 transmission was detected when women who had ruptured membranes for more than 10 hours were compared with those who had such rupture for 10 hours or less. In a North American cohort examined by Burns et al.,<sup>2</sup> an increased transmission rate was observed among women with low CD4+ levels and premature rupture of membranes and among women with premature rupture of membranes during preterm delivery, regardless of the CD4+ level. A subsequent, more focused analysis of the same cohort documented an increased rate of transmission in women with low CD4+ levels and rupture of membranes for more than four hours.<sup>13</sup> A recent study by Dickover et al. of the relation between plasma levels of HIV-1 RNA and mother-to-infant transmission of HIV-1 found that the median duration of ruptured membranes was significantly longer among mothers who transmitted the virus than among those who did not ( $P=0.02$ ).<sup>52</sup>

Delivery by cesarean section may be associated with decreased exposure to cervicovaginal secretions, depending on the timing of delivery relative to the duration of ruptured membranes and labor. Studies of the effect of cesarean section on mother-to-infant transmission are inconclusive. Two meta-analyses of prospective studies of perinatal HIV-1 transmission found a protective effect among infants delivered by cesarean section as compared with those delivered vaginally.<sup>53,54</sup> However, inability to control for key covariates, such as CD4+ level, viral load, and the duration of ruptured membranes, makes it difficult to interpret these findings.<sup>55</sup>

The European Collaborative Study recently reported a lower rate of transmission of HIV-1 among infants delivered by cesarean section than among those delivered vaginally (11.7 percent vs. 17.6 percent).<sup>14</sup> We found no benefit of cesarean section. In the European Collaborative Study, however, 80 percent of cesarean sections were performed in women whose membranes were intact. By contrast, 45 percent of the women with cesarean sections in our study (Table 3) had ruptured membranes for more than four hours. The difference between the finding in the European Collaborative Study of a beneficial effect of cesarean section and our observation of no effect may be accounted for either by a shorter duration of ruptured membranes in their patients or by insufficient statistical power in our study to detect a small association.

Our data suggest that when the duration of ruptured membranes is limited to four hours or less, HIV-1 transmission is reduced from 18.7 percent (among all 487 women for whom the duration of membrane rupture was known) to 13.9 percent. This would result in five fewer cases of perinatal HIV-1 transmission per 100 deliveries, a reduction of 26 percent.

Translating this information into clinical practice will

be difficult. The current care of pregnant women infected with HIV-1 includes zidovudine therapy to reduce the perinatal transmission of HIV-1, given in accordance with the recommendation of the Public Health Service.<sup>56</sup> There is no evidence at present that transmission could be reduced further by combining the administration of zidovudine with a shortening of the duration of ruptured membranes. It remains unclear, however, whether zidovudine is equally effective in all cases, particularly when the woman receives prolonged therapy or may have evidence of resistance to zidovudine. In these cases and those in which zidovudine has not been used or cannot be used and in which the risk of transmission appears particularly high (that is, in women with low CD4+ counts, a high viral load, or both), consideration should be given to performing cesarean section if the duration of ruptured membranes appears likely to exceed four hours. However, no results of prospective trials comparing rates of perinatal HIV-1 transmission in patients delivered by cesarean section with those in patients delivered vaginally have been reported, although such a trial is under way in Europe (Semprini AE: personal communication). In addition, cesarean section may also be associated with an increased risk of infectious complications in severely immunocompromised HIV-1-infected women.<sup>57</sup> In such circumstances, the obstetrician and the patient considering cesarean section must balance the known risks of the procedure<sup>57,58</sup> against its probable but as yet unproved benefits in decreasing the transmission of HIV-1 to infants.

#### APPENDIX

In addition to the study authors, the participants in the Women and Infants Transmission Study included D. Mesthene (Brigham and Women's Hospital, Boston); J. Pitt and A. Higgins (Columbia-Presbyterian Hospital, New York); H. Mendez and G. Moroso (State University of New York, Brooklyn); C. Diaz and E. Pacheco-Acosta (University of Puerto Rico, San Juan); G. Alexander and K. Rich (University of Illinois at Chicago, Chicago); J. Lew (National Institute of Allergy and Infectious Diseases, Bethesda, Md.); A. Willoughby and J. Moye (National Institute of Child Health and Human Development, Bethesda, Md.); and S. McKinlay (New England Research Institute, Watertown, Mass.).

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