Birth order, delivery route, and concordance in the transmission of human immunodeficiency virus type 1 from mothers to twins

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Background: We evaluated data from prospectively identified twins to understand better the mechanisms and covariates of mother-to-infant transmission of human immunodeficiency virus (HIV).

Methods: Using data obtained from an international collaboration and multivariate quasilikelihood modeling, we assessed concordance, birth order, route of delivery, and other factors for HIV infection in 115 prospectively studied twin pairs born to HIV-infected women. Actuarial methods were used to evaluate overall survival and survival free of acquired immunodeficiency syndrome for HIV-infected twins.

Results: Infection with HIV occurred in 35% of vaginally delivered firstborn (A) twins, 16% of cesarean-delivered A twins, 15% of vaginally delivered secondborn (B) twins, and 8% of cesarean-delivered B twins. In a multivariate model, the adjusted odds ratios for HIV infection were 11.8 (confidence interval: 3.1 to 45.3) for concordance of infection with the co-twin, 2.8 (confidence interval: 1.6 to 5.0) for A versus B twins, and 2.7 (confidence interval: 1.1 to 6.6) for vaginally delivered versus cesarean-delivered twins. Among A twins, 52% (lower confidence limit: 6%) of the transmission risk was related to vaginal delivery. Comparing vaginally delivered A twins (infants most exposed to vaginal mucus and blood) to cesarean-delivered B twins (infants least exposed), 76% (lower confidence limit: 48%) of the transmission risk was related to vaginal exposure. Infected B twins had slightly reduced Quetelet indexes and more rapid development of illnesses related to acquired immunodeficiency syndrome.

Conclusions: These results indicate that HIV infection of B twins occurs predominantly in utero, whereas infection of A twins (and, by implication, singletons) occurs predominantly intrapartum. We propose that intrapartum transmission is responsible for the majority of pediatric HIV infections and that reducing exposure to HIV in the birth canal may reduce transmission of the virus from mother to infant. (J Pediatr 1995;126:625-32)

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In industrialized countries, the overall transmission rate of human immunodeficiency virus type 1 from mother to child is currently estimated to be approximately 15% to 25%.\textsuperscript{1-6} Risk of transmission is higher with more advanced disease in the mother, whether ascertained by the duration of HIV infection, clinical status, or degree of immunodeficiency.\textsuperscript{5,7} The roles of maternal humoral and cellular immunity in protecting against transmission are not yet clear.\textsuperscript{8} Transmission probably occurs both in utero and intrapartum, but clinical and molecular virologic studies of mothers and children have not yet clarified the mechanisms or proportions of transmission by each route.\textsuperscript{9-12}

In a previously published study of twin pairs born to 66 mothers who were infected with HIV-1,\textsuperscript{13} we found that HIV-1 infection was more common in firstborn than in second-born twins. We suggested that a substantial proportion of transmission occurred during labor or delivery and that contact with the birth canal may be particularly important in the transmission process. We have now collected information on 148 sets of twins with known infection status. The three primary goals of the current study were to confirm our initial findings, to evaluate intrauterine and intrapartum factors that may affect the risk of HIV-1 transmission among the subset of sets of twins that came to medical attention through prospective follow-up of infants born to HIV-1–infected mothers, and to compare the progression of HIV-1–related disease in firstborn and second-born HIV-1–infected twins.

\begin{table}
\centering
\begin{tabular}{|l|}
\hline
AIDS & Acquired immunodeficiency syndrome \tabularnewline
CI & Confidence interval \tabularnewline
HIV & Human immunodeficiency virus \tabularnewline
HIV-1 & Human immunodeficiency virus type 1 \tabularnewline
\hline
\end{tabular}
\end{table}

\section*{METHODS}

Data for the International Registry of HIV-Exposed Twins were abstracted from clinical records and submitted on standardized forms by collaborators, mainly pediatricians, obstetricians, infectious disease specialists, and nurse practitioners, in 14 countries. Follow-up forms were sent to all participants to update information about the infection status of twins, to obtain additional details related to birth conditions, and to enroll new sets of twins. For most sets, zygosity was assessed by clinical criteria (including gender, placentaion, and physical appearance). Firstborn twins were designated as A twins, second-born twins as B twins. HIV-1 status (infected, uninfected, or indeterminate) included clinical and laboratory criteria as previously report ed.\textsuperscript{13}

The risk of infection in the twin pairs was assessed by quasilielihood modeling.\textsuperscript{14} This approach estimated the marginal probability of infection for each twin from predictors with adjusted odds ratios (and 95% confidence intervals) rather than relative risks, thereby allowing for the within-twin correlation of infection. Similar results (not presented) were obtained with the McNemar test for the matched twin pairs and with log-linear models of each twin’s risk adjusted for the co-twin’s infection status. Twin sets with mixed deliveries (that is, the A twin delivered vaginally, the B twin by cesarean section) were excluded when the effect of route of delivery on the risk of HIV-1 infection was evaluated. To assess effects of continuous covariates, specifically birth weight (in grams), birth length (in centimeters), Quetelet index (weight/length\textsuperscript{2}), and head circumference (in centimeters), we performed logistic regression with HIV-1 infection in one twin as the outcome, with and without adjustment for the co-twin’s infection status.\textsuperscript{15} As in the previous study,\textsuperscript{13} co-twins were considered to have equal birth weights if their weights did not differ by more than 10%. To compare concordance of infection for monozygous and dizygous pairs, the kappa (κ) coefficient ± one standard error was used.\textsuperscript{16} The proportions of maternal acquired immunodeficiency syndrome by continent and of vaginal deliveries by AIDS status were compared by the chi-square test.

The proportions of transmission that could be attributed to (1) method of delivery and (2) exposure to birth canal products were estimated as the fractions of exposed twins who were infected, minus the fractions of nonexposed twins who were infected, divided by the fractions of exposed twins who were infected.\textsuperscript{17} Among the A twins, the attributable proportion from vaginal delivery was obtained by comparing the infected fraction delivered vaginally with the infected fraction delivered by cesarean section. We also calculated a proportion attributable to birth-canal exposure by comparing vaginally delivered A twins (the infants most exposed to birth canal products) and cesarean-delivered B twins (the infants least exposed to birth canal products). The lower 95% confidence limits for the attributable proportions were determined by the percentile method applied to 5000 paramedic bootstrap replications.\textsuperscript{18} One-tailed estimates were justified because we focused on the minimal proportions of infection that could be prevented by avoiding the exposure. Kaplan-Meier actuarial survival curves were compared by log-rank tests.

\section*{RESULTS}

Data from 203 sets of twins and two sets of triplets born to HIV-1–infected women had been recorded in the Registry by Dec. 1, 1993. Complete data on HIV-1 infection status were available for 148 sets, including 115 sets of twins.
ascertained by the collaborators prospectively (by follow-up of infants born to HIV-infected mothers), 28 sets ascertained by clinical signs or symptoms of HIV-1 infection in one or both twins, and five sets with uncertain modes of ascertainment. Both sets of triplets were excluded from the analysis of HIV-1 risk factors, one set because of uncertain HIV-1 infection status and the other because infection status was not ascertained prospectively. The 115 prospectively ascertained sets were predominately from North America (63%) and Europe (23%) but included 16 sets (14%) from Africa and one from Australia. These 115 sets include 32 sets that were previously reported.13

**Major risk factors.** The crude prevalence of HIV-1 infection among 115 prospectively followed twin sets (230 infants) was 20%—26% for A twins and 13% for B twins (Table). In 80% of the sets, both twins had similar infection status (neither infected 70%, both infected 10%). Concordance of infection status was 83% in monozygotic and 77% in dizygotic twin pairs. Thus the kappa coefficients were not significantly higher in monozygotic ($\kappa = 0.52 \pm 0.19$) than in dizygotic twins ($\kappa = 0.32 \pm 0.12$). Adjusted for concordance within pairs, the odds ratio of HIV-1 infection for A twins compared with B twins was 2.4 (CI: 1.4 to 4.0). Excluding sets of twins previously reported,13 the A twins were still significantly more likely to become infected than B twins (odds ratio: 2.9; CI: 1.3 to 6.6).

Vaginal delivery was associated with an approximately twofold greater risk of transmission than cesarean delivery:

<table>
<thead>
<tr>
<th>Total No. of sets</th>
<th>No. of sets by HIV-1 infection status</th>
<th>% HIV-1 infected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neither infected</td>
<td>Both infected</td>
</tr>
<tr>
<td>All sets</td>
<td>115</td>
<td>81</td>
</tr>
<tr>
<td>Delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both vaginal</td>
<td>65</td>
<td>41</td>
</tr>
<tr>
<td>Both cesarean</td>
<td>38</td>
<td>30</td>
</tr>
<tr>
<td>Zygosity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monozygotic</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Dizygotic</td>
<td>73</td>
<td>49</td>
</tr>
<tr>
<td>Birth weight concordance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twin A heavier</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>Same (±10%)</td>
<td>55</td>
<td>39</td>
</tr>
<tr>
<td>Twin A lighter</td>
<td>28</td>
<td>17</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;34</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>34-37</td>
<td>55</td>
<td>39</td>
</tr>
<tr>
<td>&gt;37</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td>Mother's race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>72</td>
<td>51</td>
</tr>
<tr>
<td>White</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Mother's route of infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous drug abuse</td>
<td>57</td>
<td>45</td>
</tr>
<tr>
<td>Sexual/other</td>
<td>53</td>
<td>36</td>
</tr>
<tr>
<td>Mother with AIDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>No</td>
<td>54</td>
<td>42</td>
</tr>
<tr>
<td>HIV infected sibling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>No</td>
<td>57</td>
<td>39</td>
</tr>
<tr>
<td>Continent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>72</td>
<td>54</td>
</tr>
<tr>
<td>Europe</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>Africa</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Breast fed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Neither</td>
<td>63</td>
<td>45</td>
</tr>
</tbody>
</table>

*Numbers may not sum to 115 due to missing values.
35% of A twins delivered vaginally compared with 16% of A twins delivered by cesarean section; for B twins, 15% were infected with vaginal delivery and 8% with cesarean delivery (Fig. 1). By quasilikelihood modeling, the adjusted odds ratios of infection were 11.8 (CI: 3.1 to 45.3) for concordance, 2.8 (CI: 1.6 to 5.0) for first birth, and 2.7 (CI: 1.1 to 6.6) for vaginal delivery.

**Attributable proportions.** We estimated the proportion of infection attributable to route of delivery and the proportion attributable to birth canal exposure. For these analyses we excluded the African twins, all of whom were born vaginally. Among A twins, 52% of HIV-1 transmission was related to vaginal delivery (lower confidence limit, 6%). When A twins delivered vaginally were compared with B twins delivered by cesarean section, 76% of the transmission risk was related to vaginal exposure (lower confidence limit, 48%).

**Secondary risk factors.** Transmission of HIV-1 was 31% in Africa, 18% in North America, and 15% in Europe (Table); the differences were not statistically significant. All twins from Africa were delivered vaginally and were breast fed. By comparison, 56% of non-African twins were vaginally delivered, and only 3% were breast fed. In addition, the prevalence of AIDS was 38% in African and 10% in non-African mothers (p = 0.16). Thus it was not possible to dissect the risks associated with geography, breast-feeding, and AIDS illness. Despite universal breast-feeding and a higher prevalence of maternal AIDS, the excess risk of HIV-1 infection for A twins (44%) compared with B twins (19%) was evident in the African sets (adjusted odds ratio, 3.4; CI, 0.8 to 14.0).

Transmission of HIV-1 also appeared to be more frequent when the mother had AIDS, and the rate of infection was twice as high for A twins as for B twins whether or not AIDS had developed in the mother (Table). Mothers with AIDS were more likely than mothers without AIDS to deliver vaginally (91% vs 50%; p = 0.01). In a four-variable quasilikelihood model including concordance and birth order, odds ratios of HIV-1 transmission were 3.7 (CI, 0.9 to 13.4) for vaginal delivery and 1.4 (CI, 0.4 to 5.0) for mothers with AIDS.

In three of the twin sets, only one infant was reported to have been breast fed and infected with HIV-1. In a fourth set, scalp electrodes were used only on the A twin, who also became infected. Excluding these four sets and two others with uncertain breast-feeding histories, the odds ratios for HIV-1 infection were 2.2 (CI, 1.0 to 4.9) for first birth, 2.4 (CI, 0.6 to 9.3) for vaginal delivery, 1.4 (CI, 0.4 to 5.4) for mothers with AIDS, and 11.1 (CI, 1.7 to 71.3) for concordance in the 53 non-African sets with complete data.

**Other factors.** In univariate analyses, HIV-1 infection of the B twin, but not of the A twin, was associated with longer body length (odds ratio, 1.04 per cm; CI, 1.01 to 1.07 per cm), lower Quetelet index (odds ratio, 14.3 per gm/cm²; CI, 1.8 to 112.7 per gm/cm²), and larger head circumference (odds ratio, 1.0 per cm; CI, 1.0 to 1.1 per cm). However, these associations were not significant in models that included concordance of infection with the A twin.

In 50 of the 105 sets with adequate data, birth weights differed between co-twins by at least 10% (Table). In multivariate quasilikelihood models, difference in birth weight was not associated with HIV-1 infection (p >0.1) and did not reduce the associations of HIV-1 infection with the co-twin’s HIV-1 status (odds ratio, 23.8), first birth (odds ratio, 2.9), or vaginal delivery (odds ratio, 2.6).

Risk of HIV-1 did not appear to be associated with gestational age, zygosity, having an older sibling with HIV-1 infection, or mother’s source of HIV-1 infection (Table). The male/female sex ratio was 1:1, and there was no evidence of a sex difference in risk of HIV-1 infection or of an interaction between sex and birth order (data not shown).

**Survival analysis.** Including all 148 sets that had complete HIV-1 infection data, 84 children were infected, including 54 A twins, 27 B twins, and one set of triplets. Including the first two triplets as twins, information on survival was available for 52 A twins and 27 B twins, and on the incidence of AIDS for 51 A twins and 26 B twins. The median duration of follow-up for the group was 25 months (mean, 35 months) and was similar for A twins and B twins. Of the 52 infected A twins, 16 (31%) have died, compared with seven (26%) of the 27 infected B twins. The 3-year actuarial survival rate was 69% for A twins and 75% for B twins.
(p = 0.94). Twenty-seven (53%) of the 51 A twins and 19 (73%) of the 26 B twins have AIDS. Median actuarial AIDS-free survival time was 42 months for A twins and 17 months for B twins (p = 0.54; Fig. 2).

**DISCUSSION**

Twins born to HIV-infected women provide a unique perspective on the epidemiology and natural history of HIV-1 infection and AIDS. Infection with HIV-1 was concordant in 80% of our 115 prospectively followed twin pairs, a level similar to that previously reported for 18 twin sets not included in this Registry. With such high concordance, which presumably reflects the mother’s level of infectiousness during the twin pregnancy and at the time of delivery, the strongest risk factor for an infant in our study was infection of the co-twin. Among the 20% of HIV-discordant twin sets, the A twin was more likely to be infected than the B twin, even among newly ascertained twin sets, which confirms our previous results.

In both univariate and multivariate analysis, there was a significant, twofold lower risk of HIV-1 infection with cesarean delivery. With the acknowledgment that the Registry approach is an observational study and not a clinical trial, the magnitude of the effect of cesarean delivery, as well as the lack of attenuation after adjustment for birth order, concordance with the co-twin, maternal AIDS, and birth weights, all argue that the protective effect of cesarean delivery is real and clinically meaningful. We had hoped to evaluate the indications for cesarean delivery and the duration of rupture of membranes, but the available data were too sparse. We suggest that twin pregnancies represent high-risk obstetric conditions in which cesarean deliveries are more often elective and more likely to occur before or sooner after the rupture of membranes than for singletons, thus reducing the risk of ascending infections. No randomized clinical trial to reduce perinatal transmission of HIV-1 with elective cesarean delivery before or shortly after rupture of membranes has been reported. However, some reduction in risk with cesarean delivery has been found in most observational studies of singletons, an effect that was statistically significant in a recent metaanalysis.

Mother-to-infant transmission of HIV-1 can occur dur-
ing gestation, during labor or delivery, or even after delivery if the child is breast fed. Dunn et al., showed that the incidence of HIV-1 infection was 14% higher for infants who were breast fed by an HIV-infected mother than for those fed only by bottle. All 16 of the African twin sets had been breast fed, and a large proportion of them were born to mothers with AIDS. Both breast-feeding and maternal AIDS may contribute to higher perinatal HIV-1 infection rates in African. However, we suspect that a higher frequency of vaginal delivery or ascending infection also contributes, because African A twins, like their non-African counterparts, were at substantially higher risk than B twins.

The Registry has several limitations, particularly a lack of specimens and primary laboratory data. For example, we found no difference in HIV-1 concordance by zygosity, but few of our same-sex twin sets had laboratory studies performed to support clinical impressions of identity. Likewise, we could not categorize mothers by laboratory measures of viremia, antigenemia, or immunodeficiency. However, mothers with AIDS were more likely to transmit HIV-1, as noted in singleton births. In our study, nearly all mothers with AIDS had a vaginal delivery. More important, among the larger number of mothers who did not have AIDS, the risk for A twins was twofold higher than for B twins, a finding that points to a significant rate of intrapartum transmission among women who did not have overt disease.

The mechanisms of intrapartum HIV-1 infection remain unclear. Three hypotheses can be suggested. First, infection might occur with mixing of maternal and fetal blood during the contractions. This hypothesis seems unlikely because B twins are exposed to uterine contractions for a longer period and should be at higher risk than A twins.

Second, breaks in the skin could become contaminated by infected maternal blood or secretions. Fetal scalp monitoring does cause a wound, and this procedure was associated with higher HIV-1 transmission in at least some European centers. In this model, ready access to the A twin’s but not the B twin’s scalp would lead to a higher risk for the A twin. However, scalp electrodes and other traumatic procedures were reported so rarely to the Registry that they could not account for the observed effect of birth order. They also would not have occurred in deliveries to African women, among whom the birth order effect was apparent.

Third, the infant might be infected through mucus membranes or by swallowing maternal blood or secretions before or during passage through the birth canal. Episiotomy and tears of the cervix or vagina introduce blood into the birth canal, and some centers in the European Collaborative Study had higher transmission rates with episiotomy or with traumatic or complicated vaginal deliveries. The Registry had no specific information about episiotomy or intrapartum instrumentation, but cell-free and cell-associated HIV-1 can be detected in the genital secretions of 12% to 50% of HIV-infected women even in the absence of gross blood. One study suggested that genital shedding of HIV-1 is significantly higher in pregnant women than in nonpregnant women. Comparing the frequency of HIV-1 detection in umbilical cord blood with other sites, particularly the neonate’s gastric fluid, could shed further light on this model.

Even though the mechanisms of transmission are unclear, the increased risk of infection for A twins supports the hypothesis that most HIV-1 perinatal infections occur around the time of delivery. Vaginally delivered A twins have the greatest exposure to birth-canal products, because they pass through infectious mucus and blood, and because they are in the birth canal longer than B twins. In a cesarean delivery, the A twin usually is the one presenting at the cervical os and thus has ready exposure to ascending infections. Therefore the A twins have birth experiences and, not surprisingly, rates of infection that are similar to those of singletons.

The birth experiences of B twins differ from those of A twins. Although vaginally delivered B twins are exposed to the birth canal, the duration of exposure usually is relatively short. In addition, the A twin will have dilated and, to some extent, mechanically cleansed the canal. We found that infected B twins tended to be smaller than uninfected B twins. This suggests that some growth retardation with in utero infection may occur but would be difficult to detect in A twins and singletons, among whom most infections probably occur in the intrapartum period. Cesarean section–delivered B twins never enter the birth canal and have only remote exposure to blood and mucus that ascends into the uterus. Except for their exposure to blood during cesarean delivery, B twins have a relatively minimal exposure that might be close to the baseline rate of HIV-1 infection in utero. We used this baseline rate of in utero transmission to estimate that at least half of mother-to-infant transmissions of HIV-1 occurred by exposure to the birth canal. This frequency corroborates studies of the prevalence of HIV-1 infection that can be detected during the first few days of life.

We conclude that three factors were strongly associated with HIV-1 infection of twins: HIV-1 status of the co-twin, birth order, and vaginal delivery. These results are consistent with the hypothesis that exposure to HIV-1–contaminated blood and mucus in the birth canal accounts for the majority of subsequent infection in infants. Although we
base this conclusion on a study of twins, it likely applies to both single and multiple births.

Our data indicate that elective cesarean section may be a useful method of avoiding exposure to HIV-1 in the birth canal. However, cesarean delivery may not be as effective as zidovudine in reducing mother-to-infant transmission. We found that the mother-to-infant HIV-1 transmission rate may be halved with cesarean delivery, whereas zidovudine reduced the rate by two thirds. Unfortunately, in many developing countries that have a high prevalence of HIV-1 among pregnant women, zidovudine is not available and cesarean delivery cannot be a routine intervention. To investigate a potential alternative, we have initiated a clinical trial of vaginal cleansing during labor, using a soap that neutralizes HIV-1 in vitro, to reduce infants’ birth-canal exposure to HIV-1 and other infections. If such a simple, sustainable intervention proves to be safe and effective, it could be used to reduce HIV-1 perinatal transmission everywhere.

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