
abstract

BACKGROUND AND OBJECTIVE: Mother-to-child transmission of HIV can be prevented by prenatal and peripartum interventions. We sought to determine the prevalence of vertical HIV transmission in an urban cohort of HIV-exposed infants and describe cases of vertical HIV infection presenting during and after the neonatal period.

METHODS: This retrospective cohort study included HIV-exposed infants born between July 1, 2003, and June 30, 2012, who received care at an urban referral site.

RESULTS: There were 516 infants with HIV exposure known by the time of delivery; 9 of these infants (1.7%; 95% confidence interval: 0.8%–3.3%) were HIV infected. The HIV infection rate was 0.7% for those receiving prenatal antiretroviral (ARV) therapy and 9.3% for those receiving only intrapartum and/or postnatal ARV therapy. Among those diagnosed with HIV at delivery, 46% received no prenatal care.

CONCLUSIONS: Our data suggest that strategies to eliminate infant HIV infections ought to include ensuring better access to prenatal care, HIV testing, and ARV therapy initiation during pregnancy.

Without medical intervention, the risk of mother-to-child transmission (MTCT) of HIV is as high as 25% to nonbreastfed infants. A multipart strategy that includes maternal highly active antiretroviral therapy (HAART) and intrapartum and neonatal zidovudine prophylaxis can decrease the risk of MTCT to <2%.1 In the United States, the number of perinatally acquired HIV infections has decreased from an estimated 1500 cases in 1991 to <150 cases in 2004,2,3 despite an increase in the proportion of new HIV/AIDS cases among women of childbearing age4 and in the number of births to HIV-infected women.5

Recent studies have identified groups at risk for not receiving appropriate MTCT prophylaxis: women who do not receive prenatal care, women who receive prenatal care without HIV testing, and women who seroconvert during pregnancy after a negative test.6,8 The American College of Obstetrics and Gynecology and the Centers for Disease Control and Prevention (CDC) recommend routine, opt-out HIV testing of all pregnant women, a change from previous voluntary testing policies.9,10 The CDC also recommends repeat testing in the third trimester in several circumstances, including areas such as Philadelphia where HIV prevalence in pregnant women is >1 in 1000.8 However, provider surveys have reported challenges to uniform testing, such as inadequate reimbursement and insufficient time.11
Hospital medicine physicians often provide newborn care. As the admitting physician for a newborn infant, they are medically responsible for ascertaining the HIV status on all infants and therefore should be aware of the existing perinatal screening and pretreatment programs. In this role, hospital medicine physicians are also poised to ensure that systems are in place to test the mothers who had not received previous HIV testing and, after delivery, to ensure close follow-up with the postnatal treatment regimen. Our objectives were to determine the prevalence of vertical HIV transmission in an urban cohort of exposed infants, describe the use of HAART and prenatal care among their mothers, and describe cases of vertical HIV infection presenting during and after the neonatal period. In achieving these objectives, we hope to determine whether there are opportunities for hospital medicine physicians to improve perinatal HIV diagnosis.

METHODS
This retrospective cohort study included HIV-exposed infants born between July 1, 2003, and June 30, 2012, and who completed ≥1 outpatient visit at our clinic, an urban referral site for HIV-exposed and -infected children. There is 1 other referral site in our urban area. Exclusion criteria were international adoption and infant’s first HIV test at ≥18 months of age, if perinatal exposure could not be verified.

Standardized forms are used in the clinic to ensure consistent collection of data necessary for medical decision-making. A standardized data abstraction form facilitated collection of the following information from the medical record: timing of maternal HIV diagnosis, maternal and neonatal antiretroviral (ARV) medications, prenatal care, and infant HIV diagnosis. Infant HIV infection was determined by HIV qualitative RNA or DNA polymerase chain reaction testing per CDC guidelines. For the purposes of this study, we also considered infants with only 1 negative HIV polymerase chain reaction on record to be presumptively uninfected if it was performed after 2 weeks of age.

Categorical variables were described by using frequencies and percents. Risk of infection and binomial exact 95% confidence intervals were calculated overall and after stratifying by the mother’s or infant’s receipt of ARV medications. A linear test for trend was used to compare the perinatal HIV transmission rates among infants whose mothers received prenatal antiretroviral therapy, intrapartum and/or postnatal therapy only, or no therapy. A 2-tailed P value <0.05 was considered statistically significant. The Institutional Review Board of the Children’s Hospital of Philadelphia approved this study, with a waiver of informed consent.

RESULTS
Maternal HIV Diagnosis and Prenatal Care
The cohort comprised 516 mother-infant dyads (12 pairs of twins, 99 siblings total). Overall, 78.5% of mothers identified as black race and 11% as white race; 6.6% identified as Hispanic ethnicity. Most (90%) mothers received government insurance. There was no difference in analyses performed using all infants versus only the eldest sibling or first twin; thus we present results for the entire cohort. Information on the timing of maternal antiretroviral therapy initiation was available for 505 (98%) mother-infant dyads.

Maternal HIV infection was identified before pregnancy in 64.7% (n = 334) of cases, during pregnancy in 24.8% (n = 128), or at delivery. Thirty-three mothers (6.4%) did not receive any prenatal care. Mothers who did not receive any prenatal care accounted for 46% of all HIV diagnoses made at the time of delivery. Cesarean delivery was performed for 41% of infants. No mother was known to have breastfed her infant.

Neonatal HIV Diagnoses and Care
Nine infants in this cohort were infected with HIV. The prevalence of HIV infection varied by HIV prophylactic medications received (Table 1). The prevalence of perinatal transmission decreased with increasing degrees of prophylaxis (none, postnatal, prenatal) (P < .001; Table 1). Of the women without prenatal care, none reported taking prenatal ARV medications. Among women diagnosed before delivery, there was no difference in the proportion receiving prenatal by timing of maternal HIV diagnosis or by trimester of initiation of prenatal care.

There were 3 HIV-infected infants whose mothers had received prenatal antiretroviral therapy; 1 of these mothers was diagnosed in midpregnancy, and 2 were diagnosed in the month before delivery. All 3 mothers received HAART, but adherence was uncertain, and all 3 had high HIV RNA plasma levels (>100 000 copies/mL). For those mothers not receiving HAART during pregnancy, starting therapy during labor or right after delivery was associated with an HIV infection rate of 9.3% in their infants (Table 1).
Late Identification of Perinatal HIV Transmission

Fourteen additional infants not included in the foregoing cohort were born to mothers not known to be HIV-positive during pregnancy or at the time of birth. These infants were referred for clinic evaluation or hospital admission 1 week after delivery; 13 of those infants (12 mothers because this group included 2 siblings) were diagnosed with HIV infection. The infants were diagnosed at a mean of 14.7 months of age (range, 1 week–38 months). Maternal diagnosis (n = 3) and sibling diagnosis (n = 1) were the basis for initial HIV testing in 4 infants. HIV testing in the others was initiated due to clinical signs or symptoms: presumed candidal esophagitis (n = 2), *Pneumocystis jiroveci* pneumonia (n = 2), progressive encephalopathy (n = 2), extensive osteomyelitis (n = 1), lymphocytic interstitial pneumonitis (n = 1), and recurrent infections (n = 1). Five of the 13 infants with HIV were diagnosed with AIDS at presentation.

Four of the 12 mothers (of 5 infected infants) reported negative HIV tests during pregnancy, suggestive of primary HIV infection later in pregnancy. One mother and her partner reported negative HIV tests during 2 consecutive previous pregnancies. Without access to parental medical records, the results of previous testing could not be documented; however, both of those children were HIV infected.

**DISCUSSION**

This report emphasizes the importance of primary HIV testing during pregnancy and repeat HIV testing in the third trimester in areas of high seroprevalence. A quarter of mothers were first diagnosed during pregnancy. This finding not only confirms the need for routine testing during pregnancy but also indicates that many sexually active women are being screened for HIV outside of pregnancy care. These data also demonstrate that low rates of transmission can be achieved in nonresearch settings when ARV medications are started and did not account for maternal adherence to ARV therapy or plasma viral load, yet the effect of providing ARV medications was striking. The observed infant HIV prevalence was <1% when pregnant women received prenatal ARV medications. Our data suggest that strategies to eliminate infant HIV infections ought to include ensuring better access to prenatal care, mandatory prenatal or neonatal HIV testing, and antiretroviral therapy initiation during pregnancy.

In this study, 46% of women diagnosed at delivery reported no prenatal care. Providers should be aware that a diagnosis of HIV at delivery may be a warning sign that a family or caregiver may have increased difficulty completing the postnatal regimen or, more generally, interfacing with the healthcare system.

Our data highlight the importance of repeat HIV testing in the third trimester and the availability of rapid HIV tests on labor and delivery wards for women without third trimester test results available. We report that 4 mothers of 5 infants first diagnosed with HIV a significant time after delivery reported negative first-trimester HIV testing and no subsequent test. Our referral area includes parts of Pennsylvania, Delaware, and New Jersey; all of these states met CDC guidelines for repeat third trimester testing of all women as of 2004. Furthermore, 30% of late-identified infants in our cohort presented with AIDS. Earlier diagnosis, via repeat HIV testing, ideally during the third trimester or at delivery, could decrease the morbidity and mortality of neonatal HIV infection. Several successful policy models exist. States with “opt-out” models, where HIV tests are performed with other routine prenatal tests and without specific written consent, have prenatal HIV testing rates of ~90%. Additionally, maternal prenatal testing rates typically exceed 95% in states with mandatory newborn HIV screening. Hospital medicine physicians who practice in the newborn nursery have an opportunity to partner with those who provide obstetric care to ensure implementation of and adherence to protocols for maternal and newborn testing and treatment.

This study has several limitations. We relied on maternal self-report for information regarding prenatal care and previous ARV therapy. Reporting bias

<p>| TABLE 1 Receipt of Perinatal HIV Prophylaxis, Prenatal Care, and Infant Outcomes |
|-------------------------------|--------|------|-----------------|-----|</p>
<table>
<thead>
<tr>
<th>HIV Prophylaxis</th>
<th>Total</th>
<th>Infected</th>
<th>HIV Prevalence (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal ARV therapy</td>
<td>445</td>
<td>3</td>
<td>0.7 (0.1–2.0)</td>
</tr>
<tr>
<td>Intrapartum and/or postnatal</td>
<td>54</td>
<td>5</td>
<td>9.3 (3.1–20.3)</td>
</tr>
<tr>
<td>ARV therapy</td>
<td>6</td>
<td>1</td>
<td>16.7 (0.4–64.1)</td>
</tr>
<tr>
<td>No information on prenatal or perinatal ARV therapy</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Overall</td>
<td>516</td>
<td>9</td>
<td>1.7 (0.8–3.3)</td>
</tr>
</tbody>
</table>
on the part of mothers and physicians that favors health-positive behaviors could have led to overreporting on receipt of prenatal care or ARV medications. However, these biases would make engagement in care and ARV prophylaxis appear less effective at reducing vertical transmission. We were also limited by our status as a single referral center; thus, these findings may lack generalizability, although our incidence of overall HIV transmission risk is consistent with that reported elsewhere.¹

REFERENCES


5. Whitmore SK, Zhang X, Taylor AW. Estimated Number of Births to HIV+ Women in the US, 2006. Presented at the Conference on Retroviruses and Opportunistic Infections; February 8–11, 2009; Montreal, Canada.


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