

Missed Opportunities for Perinatal HIV Prevention Among HIV-Exposed Infants Born 1996–2000, Pediatric Spectrum of HIV Disease Cohort

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ABSTRACT. *Objective.* Despite dramatic reductions in perinatal human immunodeficiency virus (HIV) transmission in the United States, obstacles to perinatal HIV prevention that include lack of prenatal care; failure to test pregnant women for HIV before delivery; and lack of prenatal, intrapartum, or neonatal antiretroviral (ARV) use remain. The objective of this study was to describe trends in perinatal HIV prevention methods, perinatal transmission rates, and the contribution of missed opportunities for perinatal HIV prevention to perinatal HIV infection.

Methods. We analyzed data obtained from infant medical records on 4755 HIV-exposed singleton deliveries in 1996–2000, from 6 US sites that participate in the Centers for Disease Control and Prevention's Pediatric Spectrum of HIV Disease Project. HIV-exposed deliveries refer to deliveries in which the mother was known to have HIV infection during the pregnancy.

Results. Of the 4287 women with data on prenatal care, 92% had prenatal care. From 1996 to 2000, among the 3925 women with prenatal care, 92% had an HIV test before delivery; the use of prenatal zidovudine (ZDV) alone decreased from 71% to 9%, and the use of prenatal ZDV with other ARVs increased from 6% to 70%. Complete data on maternal and neonatal ARVs were available for 3284 deliveries. Perinatal HIV transmission was 3% in 1651 deliveries with prenatal ZDV in combination with other ARVs, intrapartum ZDV, and neonatal ZDV; 6% in 1111 deliveries with prenatal, intrapartum, and neonatal ZDV alone; 8% in 152 deliveries with intrapartum and neonatal ZDV alone; 14% of 73 deliveries with neonatal ZDV only started within 24 hours of birth; and 20% in 297 deliveries with no prenatal, intrapartum, and neonatal ARVs. Complete data on prenatal events were available in 328 HIV-infected and 3258 HIV-uninfected infants. A total of 56% of mothers of HIV-infected infants had missed opportunities for perinatal HIV prevention versus 16% of mothers of HIV-uninfected infants. Forty-four percent of the infected infants were born to mothers who had prenatal care, a prenatal HIV diagnosis, and documented prenatal ARV therapy. Seventeen percent of women with reported illicit drug use had no prenatal

care versus 3% of women with no reported drug use. In a multivariate analysis, maternal illicit drug use was significantly associated with lack of prenatal care. In a multivariate analysis, year of infant birth and the combination of lack of maternal HIV testing before delivery and lack of prenatal antiretroviral therapies were significantly associated with perinatal HIV transmission.

Conclusions. Missed opportunities for perinatal HIV prevention contributed to more than half of the cases of HIV-infected infants. Prenatal care and HIV testing before delivery are major opportunities for perinatal HIV prevention. Illicit drug use was highly associated with lack of prenatal care, and lack of HIV testing before delivery was highly associated with perinatal HIV transmission. *Pediatrics* 2003;111:1186–1191; *perinatal HIV prevention, missed opportunities for perinatal HIV prevention, pediatric HIV infection.*

ABBREVIATIONS. HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; CDC, Centers for Disease Control and Prevention; ZDV, zidovudine; ARV, antiretroviral; PSD, Pediatric Spectrum of Disease; OR, odds ratio; CI, confidence interval; USPHS, US Public Health Service.

In the United States, the perinatal human immunodeficiency virus (HIV) epidemic began in 1977.¹ Cumulatively, as of June 2001, 8207 children with perinatal HIV infection have been reported with acquired immunodeficiency syndrome (AIDS) in the United States.² The Centers for Disease Control and Prevention (CDC) estimate that the number of births to HIV-infected women in the United States each year is between 6000 and 7000.^{3,4} In the early 1990s, before the availability of treatments to prevent perinatal HIV transmission, between 1000 and 2000 HIV-infected infants were born each year in the United States; in 2000, the estimated number of HIV-infected infants dropped to 280 to 370.⁴ The burden of HIV infection among children throughout the world is tremendous, with most cases occurring in the developing countries. The United Nations Program on HIV/AIDS and the World Health Organization estimate that in 2002, 800 000 children were newly infected with HIV, 3.2 million children were living with HIV infection, and 610 000 children died of AIDS.⁵

Prevention of perinatal HIV transmission is a major public health goal throughout the world.⁶ In 1994, the landmark AIDS Clinical Trials Group study 076 first demonstrated a 67% reduction in perinatal HIV transmission with the use of prenatal, intrapartum,

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and neonatal zidovudine (ZDV),⁷ which led to ZDV being recommended for perinatal HIV prevention.⁸ Since these recommendations were made, HIV-infected pregnant women in the developed world are being treated increasingly with ZDV in combination with other antiretroviral (ARV) agents. Perinatal HIV transmission rates are lower with the use of prenatal combination therapies compared with ZDV monotherapy.⁹ However, these treatments have been prohibitively costly for resource-poor countries, although the costs have been decreasing.¹⁰ In 1999, less costly short-course ARV therapy was demonstrated to be effective in reducing perinatal HIV transmission in several studies.^{11–16} Short-course therapies are also important in HIV-exposed deliveries in the United States when the maternal diagnosis is made close to the time of delivery.

In addition to recommendations for ARV therapies for perinatal HIV prevention, the American College of Obstetricians and Gynecologists issued recommendations in 1999 and 2000 that HIV-infected pregnant women be offered delivery by cesarean section at 38 weeks' gestation before rupture of membranes and onset of labor.^{17,18} In 2002, the Public Health Service Task Force recommended counseling regarding the benefit of scheduled cesarean section delivery for women with HIV-1 RNA levels >1000 copies/ml,¹⁹ a level that carries an increased risk of perinatal HIV transmission.^{20–22}

In the United States, federal funds are available for HIV treatments to prevent perinatal HIV transmission. Nevertheless, cases of perinatal HIV infection occur. The objectives of this analysis are to describe trends in perinatal HIV prevention methods and perinatal HIV transmission rates in the United States based on data from the Pediatric Spectrum of Disease (PSD) Project. We also describe the relative contribution of missed opportunities for perinatal HIV prevention to perinatal HIV transmission, based on the 1999 Institute of Medicine report on reducing the odds for perinatal HIV transmission.²³ We evaluate factors associated with lack of prenatal care among HIV-infected women and factors associated with perinatal HIV transmission.

METHODS

Study Population and Data Collection

The study population included HIV-exposed singleton births in 1996–2000 enrolled in the CDC-funded PSD project. HIV-exposed deliveries refer to deliveries in which the mother was known to have HIV infection during the pregnancy. PSD is an Institutional Review Board-approved longitudinal surveillance project in 6 US sites that was initiated in 1989. Detailed medical record data are collected on children exposed to HIV, both infected and uninfected. PSD is hospital based in 6 Texas cities; San Juan, Puerto Rico; New York City; and the District of Columbia and population-based in Los Angeles County and Massachusetts. HIV infection status is defined according to the CDC definition.²⁴ Medical records of HIV-uninfected or indeterminate children are reviewed until the children are 2 years of age if they remain in care at the site. Children who are lost to follow-up to the PSD project before determination of their HIV status remain categorized as indeterminate.

Data on maternal characteristics, obtained from the pediatric medical records, included race/ethnicity, prenatal care (any care beyond pregnancy testing), illicit drug use (including intravenous drugs, crack, and other street drugs), timing of maternal HIV

diagnosis, prenatal and intrapartum ARV use, and type of delivery (vaginal or cesarean section). Data on infant characteristics included source of medical insurance, neonatal ARV use, and infant HIV infection status. We used pediatric source of medical insurance as a proxy for maternal source of medical insurance.

Data Analysis

We analyzed trends in perinatal HIV prevention methods, perinatal HIV transmission rates, and missed opportunities for perinatal HIV prevention from 1996 to 2000 among singleton births. To describe perinatal HIV prevention methods, we excluded births without documentation of prenatal care.

We created a 3-step hierarchy to assess the relative contribution of missed opportunities for perinatal HIV prevention to perinatal HIV transmission (Fig 1).²³ Step 1 is the provision of prenatal care, step 2 is HIV testing during pregnancy and before delivery, and step 3 is prenatal ARV therapy followed by intrapartum and neonatal ARV prophylaxis. Prevention failures are infants who have HIV infection despite documentation of all 3 steps. We analyzed the relative contribution of the missed opportunities for perinatal HIV prevention to perinatal HIV transmission on the basis of the hierarchical evaluation. Deliveries with incomplete information on prenatal events, ie, the unknown groups, were excluded.

We used χ^2 analysis to evaluate the association between maternal illicit drug use and lack of prenatal care and to evaluate perinatal HIV transmission rates by maternal and neonatal ARV use. For transmission rates, odds ratios (ORs) were calculated on the basis of the comparison of infected and uninfected infants. In separate analyses, we used multiple logistic regression analyses to evaluate factors associated with lack of prenatal care and to evaluate factors associated with perinatal HIV transmission among the deliveries with prenatal care, controlling for differing rates among the PSD project sites.

RESULTS

From 1996–2000, 5159 HIV-exposed infants were enrolled in PSD. Among the enrolled infants, 4755 were singleton births (92%), 207 were multiple births (4%), and 197 were of unknown type (4%). Only the 4755 singleton births are included in the subsequent analyses.

The largest enrollments were from New York City ($n = 1386$ [29%]) and Texas ($n = 1339$ [28%]). Enrollments from the other sites were as follows: the District of Columbia, $n = 685$ (15%); Puerto Rico, $n = 480$ (10%); Los Angeles County, $n = 475$ (10%); and Massachusetts, $n = 390$ (8%). A total of 2839 (60%) of the mothers were black, 1458 (31%) were of Hispanic ethnicity, 358 (7%) were white, 16 (<1%) were Asian, and 3 (<1%) were Native American; for 81 (2%), race was unknown. Pediatric medical insurance was provided through Medicaid or other public funding in 3763 (79%) cases and through private insurance in 323 (7%) cases, 181 (4%) had no insurance, and insurance status was unknown for 488 (10%). Illicit drug use, including intravenous drugs, crack, and other street drugs, was reported for 1078 (23%) mothers. No illicit drug use was reported for 1398 (29%) mothers, and illicit drug use was unknown for 2279 (48%) mothers.

Among the 4755 deliveries, prenatal care increased from 79% in 1996 to 88% in 2000. Prenatal care was unknown for 10% of the deliveries. However, among the 4287 mothers with prenatal care data, 3925 (92%) had prenatal care and 362 (8%) had no prenatal care. Among the 4755 deliveries, cesarean section deliveries increased from 20% in 1996 to 25% in 1998, to 42% in 1999, and to 48% in 2000. Delivery type was unknown for 4% of the deliveries.

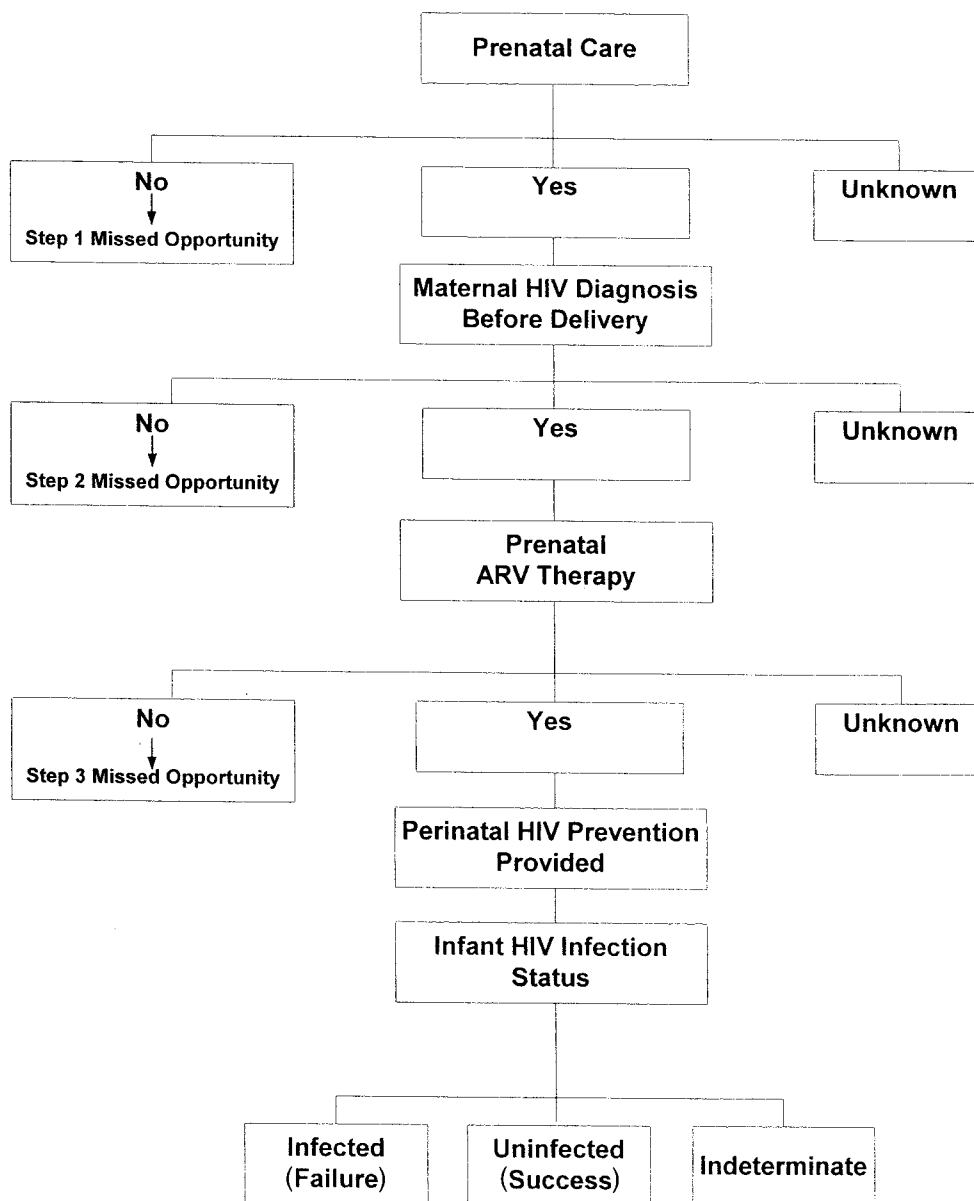


Fig 1. Hierarchical evaluation of perinatal HIV prevention methods. Based on the 1999 Institute of Medicine report on reducing the odds for perinatal HIV transmission.²³

HIV prevention methods were examined among the 3925 deliveries in which mothers were known to have received prenatal care. Among these women, the proportion who received a diagnosis of HIV before delivery rose from 90% in 1996 to 94% in 2000. Timing of maternal HIV diagnosis was unknown for 1% of these women. The proportion of women who were prescribed prenatal ARV therapy increased from 78% in 1996 to 87% in 2000. ARV use was unknown for 3% of these women. Prenatal ARV regimens that contained ZDV alone decreased from 71% in 1996 to 9% in 2000, and prenatal ARV regimens that contained ZDV in combination with other ARV therapies increased from 6% in 1996 to 70% in 2000. Overall, only 122 (3%) women received ARV regimens that did not contain ZDV. Neonatal ZDV use increased from 79% in 1996 to 92% in 2000 among the 4755 singleton deliveries. Neonatal ZDV use was unknown for 6% of infants.

Overall, 420 (9%) infants had HIV infection and 3670 (77%) did not have HIV infection. For 665 (14%), HIV status was indeterminate. Infant HIV infection status was examined by prenatal, intrapartum, and neonatal ARV use in 3284 infants for whom complete information on maternal and neonatal ARV regimens was available. Of the 1651 deliveries in which ZDV with other ARVs (other nucleoside analogues or protease inhibitors) was prescribed prenatally, along with intrapartum and neonatal ZDV, 3% of the infants had HIV infection. Of the 1111 deliveries in which ZDV was prescribed prenatally, intrapartum, and neonatally, 6% of the infants had HIV infection. Of the 152 deliveries with only intrapartum and neonatal ZDV, 8% of the infants had HIV infection. Of the 73 deliveries with neonatal ZDV prescribed neonatally within 24 hours of birth without prenatal and intrapartum ARVs, 14% of the infants had HIV infection. Of the 297 deliveries with no ARV treatment

at any time and in which the infants were first evaluated for HIV exposure within 2 months of birth, 20% of the infants had HIV infection.

We performed an analysis of the relative contribution of the missed opportunities for perinatal HIV prevention to perinatal HIV transmission on the basis of the hierarchical evaluation shown in Fig 1. Complete data on prenatal events were available for 4128 (87%) of the 4755 singleton deliveries. We identified at least 1 missed opportunity for prevention among 845 (20%) of the 4128 deliveries. Among the 845 deliveries with a missed opportunity, 22% of the infants were infected compared with 4% among the 3283 deliveries in which the recommended prenatal HIV prevention was provided. HIV-infected infants were significantly more likely than HIV-uninfected infants to be born to a mother with a missed opportunity (56% vs 16%, unadjusted OR: 6.45; 95% confidence interval [CI]: 5.05–8.23; Table 1). The most common missed opportunities among the mothers of infected infants were lack of prenatal care and lack of prenatal HIV diagnosis despite prenatal care. From 1996 to 2000, we did not observe a change in the proportion of missed opportunities among the mothers of HIV-infected infants. However, appropriate prenatal interventions did not prevent all perinatal HIV infections. Nearly half (44%) of the infected infants were born to mothers who had prenatal care, a prenatal HIV diagnosis, and documented prenatal ARV therapy.

We examined the proportion of HIV-infected women with prenatal care by report of illicit drug use, including intravenous drugs, crack, and other street drugs. Among 1078 women with a report of illicit drug use, 17% had no prenatal care compared with 3% among the 1398 women with a report of no illicit drug use (unadjusted OR: 6.76; 95% CI: 4.78–9.58). Among the 2279 women with unknown illicit drug use, 6% had no prenatal care. We performed a multivariate analysis to examine factors associated with lack of prenatal care among the 1997 women with data on illicit drug use and prenatal care (Table 2). Maternal illicit drug use was a significant factor associated with lack of prenatal care (OR: 7.97; 95% CI: 5.42–11.71). Black mothers were more likely to lack prenatal care compared with white mothers (OR: 2.12; 95% CI: 1.00–4.47). There were no significant associations with the year of infant birth or type of medical insurance.

We performed a multivariate analysis to examine factors associated with perinatal HIV transmission

among 3083 deliveries with prenatal care and known infant infection status (Table 3). The factor most highly associated with perinatal HIV transmission was the combination of lack of maternal HIV testing before delivery and lack of prenatal ARV therapies. Year of infant birth was associated with perinatal HIV transmission, with lower risk in each subsequent year compared with 1996. Maternal race/ethnicity, source of pediatric medical insurance, and mode of delivery had no statistically significant effect. A second analysis (results not shown) was based on 1776 deliveries with prenatal care and information on illicit drug use. In this model, the combination of lack of maternal HIV testing before delivery and lack of prenatal ARV therapies was also significantly associated with transmission. Maternal drug use had no statistically significant effect on transmission rate.

DISCUSSION

Today, perinatal HIV transmission can be prevented to a large extent.^{25,26} The key to prevention is to provide prenatal care and to diagnose HIV infection before delivery to offer the best medical interventions to prevent perinatal HIV transmission. Accordingly, in 1995, the US Public Health Service (USPHS) first issued guidelines for universal counseling and offering of voluntary HIV testing of pregnant women.²⁷ In 2001, the USPHS issued revised guidelines that recommended universal HIV testing of pregnant women.⁴ Our analysis demonstrated the success of these interventions in reducing perinatal HIV transmission. Perinatal HIV transmission rates were the lowest among infants who were born to mothers who received prenatal care, were offered HIV testing, were identified as HIV infected, and then received ZDV in combination with other ARV agents. We observed an increase in the proportion of deliveries by cesarean section delivery, most notably after 1998. In the multivariate analysis, type of delivery did not have an effect on HIV transmission, but the data are limited by the lack of information on reason for cesarean section delivery.

Despite these successes, missed opportunities for perinatal HIV prevention continue to occur. In the evaluation of missed opportunities, 20% of the deliveries had at least 1 missed opportunity. We observed 2 major missed opportunities to prevent perinatal HIV transmission. The first one relates to pregnant women's not receiving prenatal care. In this study, illicit drug use was highly associated with lack of

TABLE 1. Perinatal HIV Prevention Methods by Infant HIV Infection Status (Based on the Hierarchical Evaluation Shown in Fig 1), 4128 Infants Born 1996–2000*, PSD Project

	Infected (N = 328)	Uninfected (N = 3258)	Indeterminate (N = 542)
Missed opportunities for perinatal HIV prevention			
No prenatal care (step 1)	59 (18%)	250 (8%)	53 (10%)
Prenatal care but no HIV test before delivery (step 2)	94 (29%)	129 (4%)	30 (6%)
Prenatal care, HIV test before delivery, but no prenatal ARVs (step 3)	29 (9%)	149 (4%)	52 (9%)
<i>Any missed opportunity</i>	182 (56%)	528 (16%)	135 (25%)
Perinatal prevention provided			
Prenatal care, HIV test before delivery, and prenatal ARVs	146 (44%)	2,730 (84%)	407 (75%)

* Excludes 627 (13%) of 4755 infants who were born in the same period and have unknown data on any prenatal event.

TABLE 2. Logistic Regression Analysis of the Factors Associated With HIV-Infected Mothers not Receiving Prenatal Care Among 1997 Perinatally HIV-Exposed Deliveries, 1996–2000, PSD Project*

	AOR	95% CI
Year of infant birth		
1996	Referent	
1997	0.82	0.51–1.31
1998	0.96	0.60–1.54
1999	0.71	0.43–1.18
2000	0.64	0.38–1.09
Maternal race/ethnicity		
White	Referent	
Black	2.12†	1.00–4.47
Hispanic	1.47	0.64–3.37
Source of pediatric medical insurance		
Private	Referent	
Public	1.75	0.77–3.96
None	1.57	0.52–4.74
Maternal illicit drug use		
No	Referent	
Yes	7.97‡	5.42–11.71

AOR indicates adjusted odds ratio.

* Model was adjusted for PSD project sites.

† $P = .05$.

‡ $P < .0001$.

prenatal care. Other potential barriers to receiving prenatal care that we were not able to evaluate include language barriers among non-English-speaking immigrants and illegal immigrant status. The second missed opportunity relates to lack of HIV testing before delivery. Although the proportion of HIV-infected women who were tested for HIV before delivery is high, those who were not tested accounted for a large proportion of the missed opportunities among HIV-infected infants and this was a very significant factor in perinatal HIV transmission. These data support the USPHS guidelines that recommend universal HIV testing during pregnancy to prevent perinatal HIV infection.⁴

Failures of prevention (ie, HIV-infected infants born to mothers who received prenatal care, who were known to have HIV infection during pregnancy, and who were prescribed ARV therapies) are also an important concern and represented close to half of all infections in this population. As such, they require additional investigation to understand better the causes of failure such as poor adherence or resistant virus.

There are limitations to the interpretation of our data related to the chart review methods and to the fact that we reviewed only pediatric medical records, although they usually did include copies of the mothers' prenatal records. We did not have data on maternal immunologic, virologic, and clinical characteristics or on maternal adherence to ARV therapies. We used pediatric source of medical insurance as a proxy for the maternal source of medical insurance. Despite these limitations, PSD data also have a number of strengths, including that HIV-exposed infants in PSD are representative of the population of HIV-exposed infants in the United States and that they provide longitudinal prenatal and perinatal data.

PSD surveillance and epidemiologic data provide

TABLE 3. Logistic Regression Analysis of the Factors Associated With HIV Transmission Among 3083 HIV-Exposed Deliveries in 1996–2000 With Prenatal Care, PSD Project*

	AOR	95% CI
Year of infant birth		
1996	Referent	
1997	0.69	0.47–1.00
1998	0.61‡	0.41–0.92
1999	0.54§	0.35–0.85
2000	0.45§	0.27–0.76
Maternal race/ethnicity		
White	Referent	
Black	0.73	0.42–1.27
Hispanic	1.22	0.69–2.17
Others	0.79	0.19–3.20
Source of pediatric medical insurance		
Public	Referent	
Private	1.20	0.72–2.01
None	1.21	0.62–2.34
Prenatal interventions†		
None (no HIV testing and no prenatal ARVs)	Referent	
HIV testing but no prenatal ARVs	0.37	0.23–0.62
HIV testing and prenatal ZDV	0.13¶	0.09–0.19
HIV testing and prenatal ZDV with other ARVs	0.08¶	0.06–0.12
Delivery type		
Vaginal	Referent	
Cesarean	0.90	0.65–1.24

* Model was adjusted for PSD project sites.

† HIV testing refers to HIV testing before delivery

‡ $P = .02$.

§ $P = .003$ –.007.

|| $P = .0001$.

¶ $P < .0001$.

critical information that can help guide perinatal HIV prevention programs. These programs include outreach to at-risk pregnant women; case management; provider training, particularly on the importance of testing and diagnosing HIV infection during pregnancy; and state-of-art interventions to prevent perinatal HIV transmission. Furthermore, PSD data are critical for monitoring population-wide success of HIV perinatal prevention programs. These findings from PSD on missed opportunities and prophylaxis failures indicate that our most important public health challenge in eliminating new cases of perinatal HIV infections in the United States will be to ensure that barriers in obstetric settings are reduced so that all pregnant women are offered HIV screening prenatally or during labor and delivery for women whose HIV status is still unknown and that comprehensive interventions are then aggressively offered for both perinatal HIV prevention and the women's own health care.

ACKNOWLEDGMENTS

This work was supported in part by the following cooperative agreements: U64/CCU303310, U64/CCU206818, U64/CCU114918, U64/CCU603300, U64/CCU903273, and U64/CCU203312.

This study was presented in part at the 14th International AIDS Conference, July 2002, Barcelona, Spain.

Principal investigators, project coordinators, abstractors, data managers for the PSD project include the following. Centers for Disease Control and Prevention: Kenneth Dominguez, Mary Glenn Fowler, Alan Greenberg, Beverly Bohannon, and Thom Sukalac; Massachusetts: Ho-Wen Hsu, Joyce Cohen, Catherine

Reddington (University of Massachusetts Medical School, State Laboratory Institute), Barbara Stechenberg, Eileen Theroux, Maripat Toye (Baystate Medical Center, Springfield), Stephen Pelton, Anne Marie Regan, Sam Theodore (Boston Medical Center), Kenneth McIntosh, Catherine Kneut (Boston Children's Hospital), Katherine Luzuriaga, Dorothy Smith, Donna Picard (University of Massachusetts Medical School), H. Cody Meissner (New England Medical Center), Gerard Coste, Margaret Lynch (Cambridge Hospital), and Mark Pasternack (Massachusetts General Hospital); New York City: Vicki Peters, Kai-Li Liu, Polly Thomas, Chere Mapson, Annette Brooks, Myrna Beckles, Patricia Diggs, Stephanie Manning, Carol McFarlane, Karla McFarlane (New York City Health Department and Mental Hygiene), Arye Rubinstein (Albert Einstein Hospital), Saroj Bakshi (Bronx Lebanon Hospital), Edward Handelsman (Downstate University Hospital), Elaine Abrams (Harlem Hospital), Cathy Painter (Incarnation Children's Center), Andrew Wiznia (Jacobi Hospital), Ninad Desai (Kings County Medical Center), Nathan Litman (Montifiore Hospital), Joseph Stavola (New York Hospital), and Jacob Abadi (North Central Bronx Hospital); Washington, DC: Tamara Rakusan, Hans Spiegel, Andrew Bonwit, Vonterris Hagan-Temple, Waldo Perez (Children's National Medical Center), Sohail Rana, Renee Jenkins, Davene McCarthy-White, and Linda Hart (Howard University Hospital); Puerto Rico: Idith Ortiz, Juan Carlos Orengo, Aida Melendez, Myribel Santiago-Torres, Evelyn Rivera, Ruth Santos, Emily Maldonado (Puerto Rico Departamento de Salud), Eleanor Jimenez, Luis A. Martinez (San Juan City Hospital), Irma Febo, Lissette Lugo (University Pediatric Hospital), Wanda Figueroa, Odette Garcia (Bayamon Regional Hospital), Jose Vazquez Julia (Caguas Regional Hospital), Rosa Delgado, Orlando Quinceo, and Judith Gautier (Ponce Regional Hospital); Texas: Sharon Melville, Marcia Wolverton, Richard Yeager, Mary James (Texas Department of Health), Janet Squires, Janeen Graper (Children's Hospital, Dallas), Terence Doran, Rachel Davis, Mary Jane Varela (University of Texas, San Antonio), Gilberto Handel, Tony Millon (Texas Tech Medical Center, El Paso), Marilyn Doyle, Kathleen Paul (University of Texas, Houston), Mary Paul, Amy Leonard (Baylor College of Medicine, Houston), Janak Patel, Patti Forey (University of Texas Medical Branch, Galveston), and Saramistha Hauger (Children's Hospital of Austin); Los Angeles County: Toni Frederick, Laurene Mascola, Silvia Shin, Janielle Jackson-Alvarez, Priya Mukhopadhyay (Los Angeles County Department of Health), Yvonne Bryson (UCLA School of Medicine), Joseph Church (Children's Hospital of Los Angeles), Audra Devaikis (Memorial Miller Children's Hospital), Margaret Keller (Harbor-UCLA Medical Center), Deborah Lehman (Cedars-Sinai Medical Center), Andrea Kovacs (LAC+USC Maternal Child Clinic), Steve Taylor (Martin Luther King Jr/Drew Medical Center), and Victor Wong (Kaiser Permanente Southern California Group).

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