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Missed Opportunities for Prevention of Mother-to-Child Transmission of Human Immunodeficiency Virus

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PRÉCIS

Avoidable causes for mother-to-child human immunodeficiency virus (HIV) transmission included inadequate control of maternal viral load from poor medication adherence, short duration of therapy, and late maternal HIV diagnosis.

Abstract

OBJECTIVE: To identify missed opportunities for prevention of mother-to-child transmission of HIV.

METHODS: Data regarding HIV-infected children born between 2002–2009 to HIV-infected women enrolled in the US International Maternal Pediatric Adolescent AIDS Clinical Trials prospective cohort study (protocol P1025) were reviewed. The characteristics of the HIV-infected infants and their mothers, and the mothers' clinical management, are described.

RESULTS: Twelve cases of mother-to-child transmission of HIV occurred among 1857 live-born infants for a prevalence of 0.65/100 live births to HIV infected women (95% confidence interval

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*For a list of members of the DACS 637i-P1025 Team, see Appendix 1 online at <http://links.lww.com/xxx>.

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0.33 – 1.13). Four transmissions occurred in utero, three were peripartum transmissions, and the timing of transmission for five infants was unable to be determined. None were breastfed. Seven women had plasma viral loads >400 copies/mL near delivery. Six women had < 11 weeks of antiretroviral therapy during pregnancy; 3 of these women had premature deliveries. One woman received no antiretroviral therapy during pregnancy because she was diagnosed with HIV postpartum. Six had poor to moderate adherence to antiretroviral therapy. Four of the five mothers with viral loads >1000 copies/mL delivered preterm infants. There were 5 women who delivered by cesarean; Four were non-elective cesareans and only one was an elective cesarean for HIV prevention.

CONCLUSION: Despite access to high level care and follow-up, a small proportion of HIV-infected women transmitted the virus to their infants. This case series provides insight into factors contributing to HIV perinatal transmission and can inform the development of new strategies for prevention of mother-to-child transmission of HIV.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, <https://clinicaltrials.gov>, NCT00028145.

INTRODUCTION

The rate of mother-to-child transmission of human immunodeficiency virus type 1 (HIV) in the U.S. dramatically declined in recent years, due to widespread HIV testing of pregnant women and implementation of efficacious interventions to prevent mother-to-child transmission (1,2). The rate of mother-to-child transmission of HIV decreased from 22.6% among women not receiving antiretroviral therapy to 7.6% among women receiving zidovudine prophylaxis between 1991 and 1994, to 1–2% among women receiving combination antiretroviral regimens by 2000 (3,4,5).

Guidelines for pregnant women in the U.S. recommend routine HIV screening with the option to decline the test (6). HIV-infected pregnant women should receive highly active combination antiretroviral therapy during pregnancy and zidovudine during labor. (6, 7, 8). The goal of antiretroviral treatment for pregnant women is to completely suppress viral replication and provide pre-exposure prophylaxis to the fetus. All HIV-exposed infants should receive antiretroviral prophylaxis according to current recommendations (1, 9). Cesarean delivery before labor and before ruptured membranes is recommended at 38 weeks gestation if the plasma HIV RNA concentration is above 1000 copies/mL (10). In settings where safe breastfeeding alternatives are available, like the U.S., HIV-infected women should not breastfeed. (1, 9)

The objective of this study was to describe mother-to-child transmission of HIV among women and infants enrolled in a prospective cohort study in the U.S. International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) Protocol P1025, and to identify potential missed opportunities for prevention.

MATERIALS AND METHODS

P1025 was a prospective cohort study of HIV-infected women and their infants cared for at multiple clinical sites in the U.S. and Puerto Rico. The objectives of P1025 included evaluating the effectiveness and safety of interventions for the prevention of mother-to-child transmission and of antiretroviral therapy for maternal health. HIV-infected women receiving care at the participating clinical sites were eligible for participation if they were 14 years of age or older and pregnant with a gestational age of >8 weeks to less than two weeks postpartum (11). Enrollment began in October 2002. The study protocol and informed consent were reviewed and approved by the institutional review board at each study site.

Mothers and infants were followed for six months after delivery; prior to December 31, 2007, women and infants were followed to 12 months of age. Eligible women could enroll up to two weeks postpartum. Study visits were scheduled at entry, at 14–20 and >20–30 weeks of gestation, at >30 weeks gestation but prior to delivery, at delivery, at six weeks postpartum and at three and six months postpartum. Infant visits were scheduled at birth, two, four and six weeks of age and six months of age. During these visits, a history and physical exam was performed. Maternal adherence questionnaires were completed at each maternal visit during pregnancy. Laboratory studies including maternal viral loads, CD4 counts and infant diagnostic tests for HIV were abstracted from the chart. Maternal antiretroviral therapy and laboratory testing were determined by the site clinicians during routine clinical care and were not part of the study protocol.

Data collected on each mother-infant pair in which mother-to-child transmission of HIV occurred were compiled into case history reports to facilitate review. Diagnostic HIV test results for live born infants were reviewed by at least three pediatric HIV experts using an adaptation of the surveillance definition published by the Centers for Disease Control and Prevention (12, 13). Four diagnostic categories were defined: indeterminate, presumed uninfected, uninfected or infected. Infants of indeterminate infection status were lost to follow-up or did not have sufficient HIV tests to determine their status.

Study Population and Definitions for This Analysis

For the current study, live born infants born between October 2002 and December 31, 2009 with a determinate HIV status (infected or uninfected) and their mothers were included. The timing of transmission was categorized as presumed *in utero* or presumed intrapartum according to the definitions proposed by Bryson et al. (14). An infant was considered to have been infected *in utero* if a virologic test (HIV DNA PCR, HIV RNA PCR or HIV culture) was positive within 48 hours of life and subsequent tests were also positive. Infants were considered to have intrapartum HIV infection if diagnostic virologic test results were negative in the first 48 hours of life, but additional virologic testing after one week of life was positive. If an infant was born by cesarean section, the birth was categorized as elective or non-elective. An elective cesarean delivery was one performed before labor and before rupture of membranes. A non-elective cesarean delivery was one performed after onset of labor, after rupture of membranes or both. Cesarean deliveries were further classified according to indication: for interruption of HIV transmission or for obstetric reasons. Missed opportunities are defined as risk factors for mother-to-child transmission that are

preventable. An infant was considered preterm if born at <37 weeks of gestation. Low birth weight was defined as a birth weight of < 2500 grams. Parity was determined based on deliveries after 20 weeks of gestation. Reported adherence to antiretroviral therapy during pregnancy was designated as full (100%); moderate, reported adherence between 70% and 99%; or poor, reported adherence less than 70% during pregnancy.

Descriptive statistics were used to summarize the characteristics of mother-infant pairs. Because of the small number of cases with mother-to-child transmission, no statistical testing of differences in maternal characteristics by transmission was reported. The prevalence of mother-to-child transmission of HIV and the exact 95% confidence interval (CI) was estimated using Stata.

RESULTS

There were a total of 1961 live born infants during the study period. HIV infection status was indeterminate in 104 of these infants. Of 1857 infants with known HIV infection status, twelve infants were HIV-infected, yielding a transmission rate of 0.65/100 livebirths to HIV infected women (95% confidence interval: 0.33–1.13). None of these twelve infants were breastfed. Three of the infected infants were delivered between 2002 and 2004, two each in 2005, 2007 and 2008 and three in 2009. Table 1 compares the characteristics of 1845 mothers who delivered HIV uninfected infants with the 12 women who delivered HIV infected infants. A greater proportion of mothers delivering HIV infected infants had <4 weeks of antepartum antiretroviral therapy (17% vs. 2%) and a viral load > 400 copies/mL near delivery (58% vs. 31%). Characteristics of women delivering infected infants are shown in Tables 2 and 3. The median age was 23 years (range of 14 to 38 years) and only a minority were non-Hispanic, white women. Three of the women were primigravid and two had acquired HIV infection through mother-to-child transmission themselves. Six (50%) of the women were first diagnosed with HIV during pregnancy or within a few days postpartum. Eleven of the women sought prenatal care during the first or second trimester of pregnancy. Many of the women had relatively short courses of antiretroviral therapy during pregnancy (<11 weeks), two with less than 30 days and one with no antiretroviral therapy during pregnancy because the diagnosis of HIV infection was made postpartum. Shorter courses of antiretroviral therapy were in part related to the high rate of preterm births (50%) seen in this cohort. Of the six women delivering preterm infants, 4 were delivered by spontaneous vaginal delivery and 2 had cesarean deliveries. Five women had plasma viral loads near the time of delivery that were <400 copies/mL, two were between 500 and 1000 copies/mL, and five were > 1000 copies/mL. The median CD4+ count for all women delivering infected infants was 368 cells/mm³ (range 30 to 593 cells/mm³). Three of the women had severe immune suppression as defined by a CD4+ cell count <200 cells/mm³ or CD4+ percentage <14 and met criteria for CDC Category C (AIDS). Three of the seven mothers with adherence data reported poor adherence to medications. Five mothers reported exposure to tobacco, alcohol or both during pregnancy (Cases 2,7,8,11,12).

The characteristics of the deliveries and infected infants are summarized in Table 3. Seven infants were delivered by normal spontaneous vaginal delivery. Only one of the women had an elective cesarean delivery for purposes of preventing HIV. Of the six women with rupture

of membranes, five had membranes ruptured for greater than four hours. Zidovudine use during labor and delivery could be documented for ten of the women. Only one woman had no obvious increased risk for mother-to-child transmission (case 3).

The median gestational age at birth was 36.8 weeks (range 30.3 to 40 weeks). There were six (50%) preterm infants. All the infants were appropriate weight for gestational age. The median birth weight was 2683 grams (range 1670 to 3890 grams). Four of the infants (33.3%) were presumed infected *in utero*, three were presumed infected intrapartum (25%) and for five of the infants the timing of transmission could not be determined. All but one infant received zidovudine within 12 hours of birth. Table 4 compares the risk factors for mother-to-child transmission of HIV with the timing of infant infection. Common factors associated with presumed *in utero* transmission in this case series included late initiation of antiretroviral therapy (cases 5, 7, and 8) and poor adherence to antiretroviral therapy (cases 1, 7).

DISCUSSION

Overall, the rate of mother-to-child transmission of HIV in this cohort was very low (0.65%). The number of cases of mother-to-child transmission of HIV peaked in 1992 and subsequently declined, due in part to increased HIV testing and use of zidovudine prophylaxis (15). Four (33%) infected infants are presumed to have been infected *in utero*. This is comparable to the proportion of *in utero* HIV transmission reported in the literature (16). In this case series, 11 of 12 women have identified risk factors for mother-to-child transmission of HIV. Late initiation of and poor adherence to antiretroviral therapy, poor control of viral load, and duration of rupture of membranes of greater than 4 hours were the main factors identified as increasing risk of mother-to-child transmission. Women frequently had more than one missed opportunity.

Factors associated with mother-to-child transmission of HIV in the medical literature include high HIV viral load (>1000 copies/mL), rupture of membranes > 4 hours, low CD4 count, chorioamnionitis, instrumentation during delivery and preterm birth (17, 18, 19, 20).

Published reports regarding missed opportunities for prevention of mother-to-child transmission of HIV from Latin America and the Caribbean (21, 22) Europe (23) and the U.S. (24) found late initiation of prenatal antiretroviral therapy, poor control of viral load, late HIV diagnosis and lack of elective cesarean delivery as common factors resulting in mother-to-child transmission. These findings are similar in our case series. Failure in health care delivery systems and uptake also were factors in both a study from Georgia (24) and our study. Previous studies have shown an association between poor maternal health decisions, regarding cigarette smoking and an increased risk of perinatal HIV transmission (25, 26).

A key aspect in the prevention of mother-to-child transmission of HIV is control of maternal viral load near delivery. Viral load is a very strong predictor of the risk of HIV transmission. (17, 18, 27, 28) Five women in our study had viral loads greater than 1000 copies/mL near delivery. One of these was diagnosed with HIV post-partum following a preterm vaginal delivery. Three of these women had preterm labor; one delivered by normal spontaneous

vaginal delivery, and the other two had non-elective cesarean deliveries, one due to an obstetrical complication. Scheduled cesarean delivery at 38 weeks gestation is recommended for women with viral loads above 1000 as elective cesarean is effective in reducing mother-to-child transmission of HIV (29, 30). In this case series, 50% of mothers delivered preterm infants and 2/6 had a non-elective cesarean delivery.

Five women had rupture of membranes of four or more hours. The risk of mother-to-child transmission of HIV increases per unit increase in the duration of rupture of membranes (19) in women who receive zidovudine alone for prophylaxis. Two of these women had infants with presumed *in utero* transmission of HIV, but duration of rupture of membranes could have contributed to infection in the other three infants. Two women also had viral loads >1000 copies/mL around delivery and had preterm deliveries.

There was a high rate of preterm birth (50%) in this group when compared to the rate of 12.7% preterm births reported in the general U.S. population in 2005 (31). HIV transmission is associated with preterm birth. However, there is controversy whether *in utero* HIV acquisition predisposes to premature labor or whether preterm infants are more susceptible to HIV infection if exposed. (32, 33)

Limitations of this report include possible selection bias based on the unknown HIV status of 104 infants (5.3%) that could result if the limited laboratory data on these infants was due to mother-to-child transmission of HIV. In addition, this study was conducted at clinical sites which received funding for patient monitoring and follow-up; thus patient care at these site may have been more comprehensive than at other U.S. sites not included in the cohort. Data on the social context including income, housing stability, health insurance, and social support to further describe the prenatal experience of the women were unavailable. Strengths of this study include the prospective design, the standardized data collection and the varied locations of the participating sites.

The number of pregnancies in HIV-infected women are increasing in the U.S. due to antiretroviral therapy resulting in a longer and healthier life. We have the means in the U.S. to significantly reduce mother-to-child transmission of HIV. Women need to be educated about HIV and prevention of perinatal transmission, understand the importance of HIV testing and starting prenatal care early during pregnancy. It is critical that women have access to prenatal care and HIV testing and treatment. Services, such as case management, should be available to HIV infected women to enhance compliance with medical visits and adherence to antiretroviral treatment. Obstetrical providers should be aware of current national perinatal guidelines, test all pregnant women early during pregnancy and again later in pregnancy, monitor the viral load, consult with an HIV specialist as needed and plan the delivery appropriately (1,6). The obstetrician should also coordinate care with the pediatrician for optimal care and prophylaxis of the infant born to an HIV infected woman (6). Identification of missed opportunities can provide insight to improve existing strategies for prevention of mother-to-child transmission of HIV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Characteristics of HIV-infected pregnant women in the IMPAACT P1025 cohort, overall and by mother-to-child transmission (MTCT) of HIV.

Characteristic		All (N=1857)	No MTCT of HIV (N=1845)	MTCT of HIV (N=12)
Duration of antepartum ARV use (weeks)	< 4	44 (2%)	42 (2%)	2 (17%)
	4	1,801 (97%)	1,792 (97%)	9 (75%)
	None	12 (1%)	11 (1%)	1 (8%)
Age at conception (years)	19	186 (10%)	183 (10%)	3 (25%)
	20–30	1,116 (60%)	1,110 (60%)	6 (50%)
	> 30	555 (30%)	552 (30%)	3 (25%)
Maternal birth country	US and territories	1,367 (74%)	1,357 (74%)	10 (83%)
	Dominican Republic	51 (3%)	49 (3%)	2 (17%)
	Other	428 (23%)	428 (23%)	0 (0%)
	Unknown	11 (1%)	11 (1%)	0 (0%)
Viral load (copies/mL) near delivery ¹	< 400	1,102 (59%)	1,097 (59%)	5 (42%)
	400	583 (31%)	576 (31%)	7 (58%)
	Missing	172 (9%)	172 (9%)	0 (0%)
Gravidity	1	333 (18%)	330 (18%)	3 (25%)
	2–3	805 (43%)	798 (43%)	7 (58%)
	4	719 (39%)	717 (39%)	2 (17%)
Parity	0	576 (31%)	571 (31%)	5 (42%)
	1	513 (28%)	511 (28%)	2 (17%)
	2–3	590 (32%)	586 (32%)	4 (33%)
	4	178 (10%)	177 (10%)	1 (8%)
Race/ethnicity	Non-Hispanic white	177 (10%)	176 (10%)	1 (8%)
	Non-Hispanic black	1,043 (56%)	1,038 (56%)	5 (42%)
	Hispanic	591 (32%)	586 (32%)	5 (42%)
	Other	46 (2%)	45 (2%)	1 (8%)
Tobacco use during pregnancy	No	973 (52%)	968 (52%)	5 (42%)
	Yes	292 (16%)	290 (16%)	2 (17%)
	Unknown	592 (32%)	587 (32%)	5 (42%)
Alcohol use during pregnancy	No	1,129 (61%)	1,123 (61%)	6 (50%)
	Yes	476 (26%)	472 (26%)	4 (33%)
	Unknown	252 (14%)	250 (14%)	2 (17%)

¹ Closest to delivery is defined as within 35 days before delivery - 14 days after delivery; ARV: Antiretroviral therapy

Table 2.

Antepartum characteristics of the mothers

Case	Trimester of first prenatal visit	Timing of maternal diagnosis of HIV infection *	Time of entry into study protocol	Viral load closest to delivery (copies/mL)	CD4 count (cells/mm ³) / % near delivery	Antepartum ARV regimen ‡ (Length of use prior to delivery)	Adherence to ARV therapy during pregnancy §
1	Second	Before	3 rd TM ⁺	5012	479 / 20%	1 st and 2 nd TM+: ZDV, 3TC 3 rd TM: d4T, TDF, NVP (34 weeks)	Poor
2	First	Before	3 rd TM	14,200	432 / 31%	TDF, FTC, TPV, RTV, ENF On 3 years through delivery (39 weeks)	Full
3	Second	Before	3 rd TM	<80	373 / 24%	ZDV, 3TC, NFV On 3 years through delivery (39 weeks)	Full
4	Second	Before	2 nd TM	2130	218 / 17%	2 nd TM started ABC, 3TC, ZDV (15 days). ZDV, 3TC, NFV (8 weeks)	Poor
5	First	1 st TM+	Post-partum	793	364 / 30%	ABC, 3TC, FAMP, RTV started in 3 rd TM (7 weeks)	Unknown
6	Second	1 st TM	2 nd TM	<400	440 / 29%	ZDV, 3TC, LPV/RTV started in 2 nd TM, (10 weeks)	Unknown
7	Third	2 nd TM	Post-partum	<200	187 / 10%	ZDV, 3TC, LPV/RTV started in 2 nd TM, (3 weeks)	Poor
8	First	3 rd TM	Post-partum	848	30 / 3%	ZDV, 3TC, EFV (15 days)	Unknown
9	Second	After	Post-partum	8684	593 / 33%	None	Not applicable
10	Second	Before	Post-partum	180	447 / 34%	TDF, FTC, FAMP, RTV (10 weeks)	Moderate
11	Second	2 nd TM	3 rd TM	1944	266 / 22%	ZDV, 3TC, LPV/RTV (11 weeks)	Moderate
12	First	Before	2 nd TM	92	257 / 13%	ABC, ZDV, 3TC, LPV/RTV in 2 nd TM ABC, ZDV, 3TC, ATV, RTV in 3 rd TM. (22 weeks)	Moderate

* Before, before pregnancy; After, after delivery

⁺ TM indicates trimester

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* ARV, antiretroviral therapy; ABC, abacavir sulfate; d4T, stavudine; ZDV, zidovudine; 3TC, lamivudine ; FTC, emtricitabine; TDF, tenofovir; EFV, efavirenz; NVP, nevirapine; RTV, ritonavir; TPV, tipranavir; FAMP, fosamprenavir; NFV, nelfinavir; LPV, lopinavir; ATV, atazanavir and ENF, enfurvitide,.

§ Full indicates reported adherence during pregnancy of 100%; Moderate, reported adherence between 70% and 99%; Poor, reported adherence less than 70% during pregnancy.

Table 3.

Characteristics of HIV-infected infants and their mothers

Case [*]	Mode of delivery ^{**}	Duration of ruptured membranes ⁺	Intrapartum ARV regimen [‡]	Sex	Gestational age (weeks) at birth	Birth weight (grams)	Timing of initial positive HIV assay [§]	Infant ARV prophylaxis [‡]
1	NECS	5 h 10m ⁺	ZDV	Male	34.3	2265	Day 1	ZDV
2	NECS	0	Unknown	Female	38.6	3401	Day 49 (Neg Day 0)	ZDV
3	SVD	0	ZDV	Female	39.9	3385	Day 19 (Neg day 0)	ZDV
4	ECS-OB	0	ZDV	Male	30.3	1670	Day 53	ZDV
5	SVD	12 h	ZDV	Female	37.7	3300	Day 2	ZDV
6	SVD	10 h	ZDV	Female	34.0	2023	Day 25	ZDV
7	ECS-HIV	0	ZDV	Female	37.9	2767	Day 2	ZDV
8	NECS	1 m	ZDV + NVP	Male	39.3	3890	Day 1	ZDV, 3TC, NVP
9	SVD	0	None	Male	34.9	2600	Day 10	ZDV
10	SVD	4 h 14m	ZDV	Female	35.0	2470	Day 68	ZDV
11	SVD	20 h	ZDV	Female	35.9	2520	Day 49	ZDV
12	SVD	2 h 38 m	ZDV	Male	40	2880	Day 67 (neg. day 1)	ZDV

^{*} Cases are not presented in chronological order.

^{**} SVD, spontaneous vaginal delivery; NECS, cesarean section after onset of labor, after rupture of membranes or both

ECS-HIV, cesarean section BEFORE labor AND BEFORE ruptured membranes for the prevention of HIV infection

ECS-OB, cesarean section BEFORE labor AND BEFORE ruptured membranes for obstetrical indications

⁺ h = hours, m = minutes

[§] Days after delivery the infant first tested HIV positive with a diagnostic assay; day of any previous negative test is given in parentheses

[‡] ARV, antiretroviral therapy; ZDV, zidovudine; NVP, nevirapine; 3TC, lamivudine.

Table 4

Factors associated with mother-to-child transmission of HIV and the timing of transmission

Factors Associated with MTCT of HIV*	Timing of Transmission		
	<i>In Utero</i> (n=4)	Peripartum (n=3)	Unknown (n=5)
Short duration of ARV use during pregnancy (<4 weeks)	7, 8		
Viral load (copies/mL) >1000 at delivery	1	2	4, 9, 11
Late maternal diagnosis**	8+		9x
Duration of ruptured membranes (> 4 hours)	1,5		6, 10, 11
Adherence to antiretroviral therapy			
Full (100% adherence)		2,3	
Moderate (70%–99% adherence)		12	10,11
Poor (< 70% adherence)	1,7		4
Unknown	5,8		6

* Infant #3 had no identified risk factors for HIV transmission

** Maternal HIV diagnosis made in the third trimester+ or after delivery x