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Missed opportunities for prevention of mother-to-child transmission of HIV-1 in the NISDI Perinatal and LILAC cohorts

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Conflict of interest

The authors have no conflicts of interest.

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Abstract

Objective—To evaluate cases of mother-to-child transmission of HIV-1 at multiple sites in Latin America and the Caribbean in terms of missed opportunities for prevention.

Methods—Pregnant women infected with HIV-1 were eligible for inclusion if they were enrolled in either the NISDI Perinatal or LILAC protocols by October 20, 2009, and had delivered a live infant with known HIV-1 infection status after March 1, 2006.

Results—Of 711 eligible mothers, 10 delivered infants infected with HIV-1. The transmission rate was 1.4% (95% CI, 0.7–2.6). Timing of transmission was in utero or intrapartum (n=5), intrapartum (n=2), intrapartum or early postnatal (n=1), and unknown (n=2). Possible missed opportunities for prevention included poor control of maternal viral load during pregnancy; late initiation of antiretrovirals during pregnancy; lack of cesarean delivery before labor and before rupture of membranes; late diagnosis of HIV-1 infection; lack of intrapartum antiretrovirals; and incomplete avoidance of breastfeeding.

Conclusion—Early knowledge of HIV-1 infection status (ideally before or in early pregnancy) would aid timely initiation of antiretroviral treatment and strategies designed to prevent mother-to-child transmission. Use of antiretrovirals must be appropriately monitored in terms of adherence and drug resistance. If feasible, breastfeeding should be completely avoided.

Keywords

HIV-1; Mother-to-child transmission; Prevention

1. Introduction

Efficacious interventions to prevent mother-to-child transmission (MTCT) of HIV-1 have been developed and implemented worldwide, and the global elimination of MTCT of HIV-1 is now envisioned. However, cases of MTCT of HIV-1 continue to occur, even in areas where effective interventions to prevent such transmission are available.

The National Institute of Child Health and Human Development (NICHD) International Site Development Initiative (NISDI) Perinatal and LILAC (Longitudinal Study in Latin American Countries) protocols aimed to study MTCT of HIV-1 at multiple sites in Latin America and the Caribbean [1]. Previously, data from the NISDI Perinatal cohort were evaluated regarding missed opportunities to prevent MTCT of HIV-1 among HIV-1-infected women and their children between 2002 and 2006 [2].

The aim of the present study was to evaluate more recent cases of MTCT of HIV-1 in the NISDI Perinatal and LILAC cohorts (i.e. 2006–2009) in terms of possible missed opportunities for preventing MTCT of HIV-1.

2. Materials and methods

The NISDI Perinatal and LILAC cohorts have been described in detail previously [1]. The enrollment period for the Perinatal protocol was September 27, 2002, to April 17, 2007, while the enrollment period for the LILAC protocol was June 18, 2008, to October 20, 2009. Briefly, women infected with HIV-1 were enrolled at sites in Argentina, The Bahamas, Brazil, Jamaica, Mexico, and Peru during the eighth week of pregnancy or later.

As part of the eligibility criteria for clinical sites to participate in the NISDI protocols, and as part of each participating country's guidelines for prevention of HIV-1 MTCT [3–5], HIV-1-infected women receiving care at these sites had to have access to antiretrovirals for treatment or prophylaxis, and antiretroviral prophylaxis had to be available for all infants. In addition, cesarean delivery before labor and before ruptured membranes (ECD) for prevention of MTCT of HIV-1 had to be available for women receiving clinical care at these sites, and infant formula had to be provided for all infants of HIV-1-infected women receiving care at the study sites.

Enrolled women had up to 3 prepartum study visits. Subsequent study visits were scheduled at delivery, hospital discharge after delivery, 6–12 weeks postpartum, and 6 months postpartum. Women enrolled in the LILAC protocol had additional study visits at 12 months postpartum and every 6 months thereafter up to 5 years after delivery. Infants enrolled in the Perinatal protocol had study visits scheduled at birth, at 6–12 weeks after delivery, and at 6 months of age. Infants enrolled in the LILAC protocol who were not infected with HIV-1 had additional study visits at 12 months of age and at 6-month intervals thereafter up to 5 years after birth. Infants found to be HIV-1-infected discontinued LILAC study follow-up upon confirmation of HIV-1 infection status, and were offered enrollment into a NISDI protocol for HIV-1-infected children.

At each study visit, a medical history was obtained and a physical examination was performed. Laboratory evaluations, including flow cytometry, viral load (VL), hematology, and biochemistry, were performed on samples collected at most study visits. However, laboratory studies were not conducted at the 6 month postnatal visit for women enrolled in the Perinatal protocol. Although adherence data were not collected as part of the original Perinatal protocol, maternal and infant adherence data were collected by maternal interview as part of the LILAC protocol. Both protocols were approved by the ethical review board at each clinical site where participants were enrolled, as well as institutional review boards at the sponsoring institution (NICHD) and at the data management center (Westat) [1].

Eligibility criteria for the present analysis were enrollment of the mother in either protocol by October 20, 2009, and delivery of a live infant with known HIV-1 infection status after March 1, 2006, who was either followed to the 6-month visit or discontinued from the study before this visit. Mode of delivery was categorized as ECD; cesarean delivery after labor and/or after ruptured membranes (non-ECD); or vaginal delivery. Use of antiretroviral agents during pregnancy was categorized as "treatment" if these drugs were used before pregnancy and/or continued after the 6–12 week study visit. Use of antiretrovirals during pregnancy was categorized as "prophylaxis" if these drugs were initiated during pregnancy

but were not continued after the 6–12 week visit. The participants' clinical disease stage was categorized at each study visit according to the Centers for Disease Control and Prevention classification system [6].

Preterm births were defined as those before 37 completed weeks of gestation. Low birth weight infants weighed less than 2500 g at birth. Classification of infants as HIV-1-infected required any 2 of the following test results from blood samples obtained through separate venipuncture events: positive for HIV-1 by viral culture; positive for HIV-1 by a DNA polymerase chain reaction (PCR) assay; positive for HIV-1 by neutralizable HIV-1 p24 antigen assay; or an HIV-1 VL of at least 10 000 copies/mL. Diagnostic HIV-1 testing of infants was performed at each of the first 3 study visits. In the absence of breastfeeding, the timing of MTCT of HIV-1 was categorized according to the definitions of Magder et al. [7]. An infant with a first positive HIV-1 assay at or before 7 days of age was classified as having in utero infection. Intrapartum infection was defined as a negative HIV-1 assay at or before 7 days of age, with the first positive assay after 7 days of age. If breastfeeding occurred, and the child met the criteria for intrapartum infection, then the timing of infection was categorized as "intrapartum or postnatal."

The last prepartum plasma sample (for women) and the first plasma sample after birth (for infants) were accessed for HIV-1 genotyping if the VL was above 20 copies/mL at the study visit and the volume of plasma was at least 1.2 mL. In some cases, if no other appropriate samples were available, a sample with an unknown VL was accessed. Genotyping of the viral protease and reverse transcriptase genes was performed at Quest Diagnostics, Baltimore, USA. HIV-1 RNA was extracted on a MagNA Pure instrument (Roche, Basel, Switzerland) from 0.5 mL of plasma. RNA was reverse-transcribed and amplified using nested PCR to produce a 1497-base-pair fragment spanning the entire protease gene (codons 1–99) and the first 400 codons of the reverse transcriptase gene. The amplicon was sequenced bidirectionally on a 3730XL sequencing instrument (Applied Biosystems, Foster City, CA, USA) and the sequence data were assembled and compared with the Los Alamos wild-type subtype B reference sequence. Resistance mutations were identified and resistance predictions performed using an in-house algorithm based on published data.

Data were analyzed using SAS version 9.1 (SAS Institute, Cary, NC, USA). Descriptive statistics were used to characterize the infants and their mothers. An exact 95% confidence interval (CI) was calculated for the rate of MTCT of HIV-1 in the study population.

3. Results

Between March 1, 2006, and June 30, 2009, 824 HIV-1-infected women were enrolled in the present study; 821 had a pregnancy outcome by October 20, 2009. In all, 779 women delivered live born infants, and a total of 711 infants were either followed to the 6-month visit or were discontinued from the study before this visit with known HIV-1 infection status. Of the 711 infants studied, 10 were found to be infected with HIV-1. The transmission rate was 1.4% (95% CI, 0.7–2.6). These 10 infants were born in Brazil (n=5), Peru (n=4), and Argentina (n=1). Most mothers (n=9) acquired HIV-1 through heterosexual contact, while the mode of infection was unknown for the remaining 1 mother.

All women used antiretroviral agents during pregnancy, and all except 1 received intrapartum antiretrovirals. Just 1 woman delivered vaginally; the indication for cesarean delivery for the remaining 9 women was prevention of MTCT of HIV-1. Only 1 of the 10 mothers experienced lacerations during delivery. None of the infants had fetal scalp electrodes placed, and none experienced lacerations during delivery. All 10 infants received antiretroviral prophylaxis initiated on the day of birth. Only 1 infant received any breast milk. Additional characteristics of the 10 HIV-1-infected infants and their mothers are shown in Tables 1 and 2, respectively.

The timing of acquisition of HIV-1 infection was presumed to be either in utero or intrapartum for 5 infants; intrapartum for 2 infants; either intrapartum or early postnatal for 1 infant; and unknown for 2 infants. Missed opportunities for prevention of MTCT of HIV-1 are summarized in Table 3. Of 5 infants with presumed in utero or intrapartum acquisition of HIV-1 infection, Case 1 was considered a missed opportunity for prevention of MTCT because of the late diagnosis of maternal HIV-1 infection and initiation of antiretrovirals during pregnancy (at 31 and 34 weeks of gestation, respectively), leading to a short duration of antiretroviral use during pregnancy (3.9 weeks). Case 2 was considered a missed opportunity because of poor control of maternal VL (>100 000 copies/mL) and lack of ECD. Case 3 was associated with poor control of maternal VL during pregnancy (>100 000 copies/mL) in a woman with self-reported non-adherence and lack of intrapartum use of antiretroviral agents. Case 4 was considered a missed opportunity for transmission prevention owing to late diagnosis of HIV-1 infection (at 35 weeks of gestation) and late initiation of antiretrovirals during pregnancy (at 36 weeks of gestation), resulting in a short duration of antiretroviral use during pregnancy (1.4 weeks). Furthermore, ECD was lacking in Case 4. Case 5 was considered a missed opportunity because of poor control of maternal VL (46 673 copies/mL at hospital discharge following delivery) and because of lack of ECD.

Of the 2 infants with presumed intrapartum acquisition of HIV-1 infection, Case 6 was considered a missed opportunity because of the late initiation of antiretrovirals (at 36 weeks of gestation), resulting in a short duration of antiretroviral use during pregnancy (1.3 weeks), and poor control of maternal VL (>1000 copies/mL during pregnancy and at hospital discharge after delivery). Case 7 was considered a missed opportunity because of the late diagnosis of HIV-1 infection (at 30 weeks of gestation) and late initiation of antiretrovirals during pregnancy (31 weeks of gestation). The duration of use of antiretrovirals during pregnancy for this case was 9.3 weeks.

Case 8 acquired infection either during the intrapartum period or postnatally (through exposure to breast milk). This case was considered a possible missed opportunity because of incomplete avoidance of breastfeeding (if transmission occurred postnatally).

Finally, the timing of HIV-1 infection was unknown for 2 infants because diagnostic test results were unavailable at birth and the first HIV-1 testing was not performed until 6–12 weeks of age. Case 9 was born following an unknown type of cesarean delivery. Case 10 was considered a missed opportunity because of poor control of maternal VL (>1000 copies/mL).

4. Discussion

In the present case series, 10 HIV-1-infected infants were identified among 711 infants born to women with HIV-1 who enrolled in the NISDI Perinatal and LILAC cohorts between March 1, 2006, and June 30, 2009. Possible missed opportunities to prevent MTCT of HIV-1 were identified for each of these 10 infants. Poor control of maternal VL during pregnancy was the most common missed opportunity (50.0% of cases), with late initiation of antiretrovirals during pregnancy and lack of ECD occurring in 40.0% of cases. Late diagnosis of HIV-1 infection occurred in 30.0% of cases. Finally, lack of intrapartum use of antiretrovirals and incomplete avoidance of breastfeeding each occurred in 10.0% of cases.

The results of the present study are consistent with previous studies of MTCT of HIV-1 conducted over the past 8 years in Europe [8,9], the USA [10,11], Africa [12], and Latin America and the Caribbean [2,13]. These studies identified various missed opportunities for prevention of infection, which included late or no HIV-1 testing [10–12]; late or no initiation of prenatal care or maternal antiretrovirals [2,8,10,11]; limited or no use of maternal antiretroviral regimens [2,9,11,13]; poor control of maternal VL during pregnancy [2]; and lack of ECD [2,11].

Treatment of the mother's HIV-1 infection and interventions to prevent MTCT cannot be initiated or utilized until maternal infection is diagnosed. In the present case series, of the 6 cases of MTCT with maternal HIV-1 infection diagnosed during the index pregnancy, 3 were diagnosed during the third trimester (at 30, 31, and 35 weeks of gestation). With each of these late diagnoses of maternal HIV-1 infection, there was late initiation of maternal antiretroviral regimens (at 31, 34, and 36 weeks of gestation). Use of antiretroviral drugs is recommended for all pregnant women infected with HIV-1, whether as treatment or prophylaxis [14]. A longer duration of antiretroviral use during pregnancy is associated with a reduced risk of MTCT [15]. Of the 10 mother–infant pairs in the present case series, 4 women had late initiation of antiretrovirals (3 related to late diagnosis of HIV-1 infection). For 3 of these 4 women, the duration of antiretroviral use before delivery was less than 4 weeks (range 1.3–3.9 weeks).

Poor control of maternal VL during pregnancy occurred in 5 of the 10 cases identified in the present study. Reasons for poor control of maternal VL during pregnancy include poor adherence, with or without antiretroviral drug resistance. Irrespective of whether a specific etiology for poor control of maternal VL is ascertained, it must be remembered that simply prescribing antiretrovirals to a patient infected with HIV-1 does not guarantee effectiveness of any given regimen. A patient's response to antiretroviral drugs should be monitored by assessing the plasma VL at 2–4 week intervals after initiation of therapy, and then every 1–2 months thereafter until the virus is undetectable in plasma. Once VL becomes undetectable, it should be monitored every 3–4 months. Plasma VL data at 34–36 weeks of gestation are useful for making decisions about mode of delivery (i.e. whether ECD should be performed) [16]. Finally, lack of intrapartum use of antiretrovirals, lack of ECD, and incomplete avoidance of breastfeeding represented possible missed opportunities for prevention in some cases identified in the present study.

In summary, a low rate of MTCT of HIV-1 was observed among women and their infants enrolled in the NISDI Perinatal and LILAC cohorts over a 3 year period. The efficacy of antiretroviral treatment for HIV-1 and of interventions to prevent MTCT has been definitively demonstrated, and the observed transmission rate would be expected to be substantially higher without treatment and prevention. However, the lack of complete elimination of MTCT among the mother–infant pairs seems to have been preventable using currently available interventions. Several issues must be addressed to reach the goal of eliminating MTCT of HIV-1. First, HIV-1 testing must be made widely available, such that pregnancy does not occur in the setting of unknown HIV-1 infection status. Early diagnosis of HIV-1 infection status (before pregnancy, or else early in pregnancy) would allow for timely initiation of antiretroviral treatment and strategies to prevent MTCT. Second, the use of antiretrovirals must be appropriately monitored by, for example, regular clinical and laboratory assessments, including evaluation of adherence to antiretrovirals and antiretroviral resistance testing. Adequate virologic response to antiretrovirals cannot be assumed, and changes in antiretroviral regimens must be anticipated. It is recommended that women with detectable or unknown VL undergo ECD before labor and before ruptured membranes. Third, complete avoidance of breastfeeding is recommended where feasible. Fourth, each woman's understanding of the rationale for such recommendations should also be confirmed.

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Table 1

Characteristics of HIV-1-infected infants (n=10)

Characteristic	Case									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Age at first positive HIV-1 diagnostic test, d	3	3	4	7	3	161	69	49	39	87
HIV-1 diagnostic test results [a]	3 (positive)	3 (3 760 000)	4 (760)	7 (1183)	3 (2922)	4 (<400)	4 (<400)	4 (<400)	39 (466 000)	87 (750 000)
	38 (positive)	52 (14 500)	60 (>750 000)	54 (650 998)	46 (382 916)	161 (314 760)	69 (602 555)	49 (580 000)	242 (720 000)	213 (395 712)
			79 (positive)	69 (597 242)	74 (1 571 690)	187 (710 104)	188 (123 694)	59 (123 089)	Not tested	Not tested
Estimated timing of MTCT of HIV-1	In utero	In utero	In utero	In utero	In utero	Intrapartum	Intrapartum	Intrapartum or postnatal	Unknown	Unknown
Birth weight, g	2600	2400	3100	2900	3000	2900	3500	3200	2900	3800
Pediatric estimate of gestational age at delivery, wk	36	38	39	39	41	38	38	38	38	40
Antiretroviral prophylaxis regimen	Zidovudine	Zidovudine + lamivudin e + lopinavir/ ritonavir	Zidovudine	Zidovudine	Zidovudine	Zidovudine	Zidovudine	Zidovudine	Zidovudine	Zidovudine
Exposure to breast milk	No	No	No	No	No	No	No	Yes [b]	No	No
Resistance testing:										
Study visit	Enrollment	Data not available	6–12 wk	6–12 wk	6–12 wk	Data not available	6–12 wk	6–12 wk	6–12 wk	6 mo
HIV-1 subtype	B	---	B	F1	B	---	B	B	C	B
Drug resistance	None	---	None	None	None	---	None	None	None	Efavirenz; nevirapine

Abbreviation: MTCT, mother-to-child transmission.

[a] Values are given as age in days at HIV-1 testing (test result). HIV-1 diagnostic test results refer to DNA polymerase chain reaction assay (positive or negative) and viral load (copies/mL).

[b] Case 8 was exposed to breast milk on 1 occasion at approximately 2 weeks of age.

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Table 2

Characteristics of mothers who transmitted HIV-1 to their children (n=10)

Characteristic	Mothers									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
HIV-1 infection first diagnosed (wk)	During pregnancy (31)	During pregnancy (2)	Before index pregnancy	During pregnancy (35)	Before index pregnancy	Before index pregnancy	During pregnancy (30)	During pregnancy (27)	During pregnancy (25)	Before index pregnancy
Timing of first ultrasonographic examination, wk	34	19	12	17	8	20	36	21	30	23
Gestational age at enrollment, wk	35	27	30	36	24	28	40	29	32	25
Use of any antiretrovirals at enrollment	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Overall adherence to antiretrovirals, %										
At enrollment	100.0	Not collected as part of protocol	0.0	NA	100.0 [a]	Not collected as part of protocol	Not collected as part of protocol	100.0	Not collected as part of protocol	Not collected as part of protocol
At hospital discharge	100.0	---	NA	83.3	100.0	---	---	NA	---	---
CDC clinical classification at enrollment	A	A	C	A	A	A	A	A	A	A
Viral load at enrollment, copies/mL	180	137 000	103 172	54 214	56	16 489	<400	1130	<400	5886
CD4+ count at enrollment, cells/mm^3	390	230	511	597	283	515	397	439	74	374
Obstetric estimate of gestational age at initiation of antiretrovirals, wk	34	18	17	36	8	36	31	28	28	23
Duration of antiretroviral use during pregnancy, wk	3.9	19.6	21.6	1.4	32.7	1.3	9.3	10.1	7.7	15.0
Prepartum antiretroviral regimen	Zidovudine + lamivudine + nelfinavir	Zidovudine + lamivudine + nelfinavir	Zidovudine + lamivudine + nelfinavir	Zidovudine + lamivudine + lopinavir/ritonavir	Zidovudine + lamivudine + lopinavir/ritonavir	Zidovudine	Stavudine + lamivudine + nevirapine	Zidovudine + lamivudine + lopinavir/ritonavir	Zidovudine + lamivudine + nelfinavir	Stavudine + lamivudine + lopinavir/ritonavir

Characteristic	Mothers									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Intrapartum antiretroviral regimen	Prepartum regimen + IV zidovudine	Prepartum regimen + IV zidovudine	None	Prepartum regimen + IV zidovudine	Prepartum regimen + IV zidovudine	Oral zidovudine	Prepartum regimen	IV zidovudine	Prepartum regimen + IV zidovudine	Prepartum regimen
Mode of delivery	ECD	NECD	ECD	NECD	Vaginal	ECD	ECD	ECD	Unknown type of CD	ECD
Duration of ruptured membranes, min	3	0	0	0	10	0	0	0	0	0
Laceration	No	No	No	No	Yes	No	No	No	No	No
Time between delivery and hospital discharge, d	2	2	3	11	2	3	3	3	2	3
Antiretroviral use at hospital discharge	No	Yes	No	Yes	Yes	No	Yes	No	No	Yes
CDC clinical classification at hospital discharge	A	A	C	A	A	A	A	A	A	A
Viral load at hospital discharge, copies/mL	50	107 000	1090	<400	46 673	7267	<400	<400	Not tested	7411
CD4+ count at hospital discharge, cells/mm^3	289	235	631	696	175	639	430	576	Not tested	369
Resistance testing:										
Study visit	Data not available	2nd prepartum visit	Enrollment	Enrollment	Data not available	2nd prepartum visit	Data not available	Data not available	Data not available	Enrollment
HIV-1 subtype	---	C	B	F1	---	B	---	---	---	B
Drug resistance	---	None	None	None	---	None	---	---	---	None

Abbreviations: CD, cesarean delivery; CDC, Centers for Disease Control and Prevention; ECD, cesarean delivery before labor and before ruptured membranes; IV, intravenous; NA, not applicable; NECD, cesarean delivery after labor and/or ruptured membranes.

[a]Adherence was 91.7% at the second prenatal visit.

Table 3

Missed opportunities for prevention of mother-to-child transmission of HIV-1

Case	Presumed timing of transmission	Reason categorized as missed opportunity
1	In utero or intrapartum	Late diagnosis of maternal HIV-1 infection Late initiation of maternal antiretrovirals
2	In utero or intrapartum	Poor control of maternal VL during pregnancy Lack of ECD
3	In utero or intrapartum	Poor control of maternal VL during pregnancy Lack of intrapartum antiretrovirals
4	In utero or intrapartum	Late diagnosis of maternal HIV-1 infection Late initiation of maternal antiretrovirals Lack of ECD
5	In utero or intrapartum	Poor control of maternal VL during pregnancy Lack of ECD
6	Intrapartum	Late initiation of maternal antiretrovirals Poor control of maternal VL during pregnancy
7	Intrapartum	Late diagnosis of maternal HIV-1 infection Late initiation of maternal antiretrovirals
8	Intrapartum or early postnatal	Lack of complete avoidance of breastfeeding (if early postnatal transmission)
9	Unknown	Possible lack of ECD
10	Unknown	Poor control of maternal VL during pregnancy

Abbreviations: ECD, cesarean delivery before labor and before ruptured membranes; VL, viral load.