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COHORT PROFILE

The NICHD International Site Development Initiative perinatal cohorts (2002–09)

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How did the study come about?

Efficacious and feasible interventions to prevent transmission of human immunodeficiency virus type 1 (HIV) from mother to child have been developed and implemented. As a result, there has been a dramatic reduction in mother-to-child transmission (MTCT) of this viral infection in many countries, including those in Latin America and the Caribbean. In addition, the medical management of HIV-infected women during pregnancy has evolved significantly. However, risks associated with such interventions and management also must be evaluated on an ongoing basis so that HIV-infected women can make informed decisions regarding their own health and that of their HIV-exposed children. Beginning in 2002, prospective follow-up of HIV-infected women and their children, with a particular focus on HIV-exposed but uninfected children, was initiated at multiple sites in Latin America and the Caribbean. This work was initiated because there was an expanding number of anti-retrovirals (ARVs) available for treatment of HIV, they were increasingly being used during pregnancy, and their association with pregnancy outcomes was unclear. Therefore, further study of pregnancy, neonatal and childhood outcomes, taking into account maternal use of ARVs and known risk factors for adverse outcomes, was imperative. In addition, although MTCT of HIV has been prevented to a large extent in many settings, follow-up of HIV-infected women and their infants allowed exploration of factors associated with HIV transmission in the few non-breastfeeding women who transmit despite receipt of ARVs and/or Caesarean section before labour and before ruptured membranes.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the data management and statistical center (Westat) developed and released a request for proposals (RFP) for Latin American and Caribbean sites in November 2000, soliciting potential investigators and sites in a systematic fashion through communication with regional and national public health and AIDS offices, professional organizations and universities. To be eligible to participate, sites were required to have prior experience in conducting clinical research studies, and the personnel and laboratory capabilities necessary to conduct observational studies. Availability of breastmilk alternatives, such as formula, ARV prophylaxis for the prevention of MTCT of HIV and ARV treatment for women also were required.

Neither ARVs nor alternatives to breastmilk were provided by the protocol, and initiation and management of ARV treatment or prophylaxis were decided by individual site investigators as per ARV availability,

clinical practice at the site and national guidelines. Sites were required to provide a subject retention plan, to demonstrate the ability to perform basic laboratory assays and the capability to perform flow cytometry and plasma HIV RNA concentration (viral load) assays either on site or through a laboratory routinely used by the site, and to have access to freezers for storage of repository samples. Given the selection criteria, centres chosen to participate in the study had either carried out research in the past or had sufficient infrastructure in place to carry out research. An external review committee made up of international experts in HIV infection reviewed proposals and made recommendations about site selection in 2001. Approximately half of the sites that submitted proposals were chosen. The data management and statistical centre subcontracted with 15 sites in four countries (Argentina, the Bahamas, Brazil and Mexico) to carry out the Perinatal protocol. During 2001 and 2002, NICHD and Westat staff and investigators from each site developed the study protocol. Subsequently, the NICHD institutional review board (IRB), the Westat IRB, separate in-country ethics committees and national review boards (where appropriate, e.g. Brazil) reviewed and approved the protocol. In 2006, two additional sites were added, one in Peru and one in Jamaica. Enrolment into the Perinatal protocol continued until 2007. In 2006, another RFP was issued and another external review committee reviewed proposals and made recommendations regarding site selection. In 2007, an additional two sites were selected to participate in a revised protocol entitled: The NICHD International Site Development Initiative (NISDI) Longitudinal Study in Latin American Countries (LILAC). There were seven sites that previously participated in the Perinatal protocol which did not continue participation in LILAC. During 2008 and 2009, a total of 12 sites in three countries (Argentina, Brazil and Peru) enrolled subjects into the LILAC protocol. The geographical locations of the sites participating in the Perinatal protocol and/or the LILAC Protocol from 2002 to 2009 are shown in Figure 1.

Who is in the study sample?

Enrolment into the Perinatal protocol occurred between 2002 and 2007. Eligibility criteria for enrolment into the Perinatal protocol included HIV infection in the pregnant woman and a gestational age of $\geqslant$8 weeks. Women could re-enroll into the perinatal protocol for subsequent pregnancies. Follow-up was completed in 2007. Enrolment into the LILAC protocol occurred between 2008 and 2009. Eligibility criteria for enrolment into the LILAC protocol included HIV infection in the pregnant woman and a gestational age of $\geqslant$22 weeks. Follow-up of the LILAC protocol participants is ongoing.

What does it cover?

The scientific objectives of both the perinatal and LILAC protocols were:

(i) to describe the characteristics of HIV-infected pregnant women and their HIV-exposed, uninfected children receiving care at participating clinical sites in Latin America, including the utilization of efficacious interventions related to decreasing the risk of MTCT (ARV prophylaxis, Caesarean section before labour and before rupture of membranes, complete avoidance of breastfeeding); the use of ARVs or other therapy for the woman's own health; and rates of MTCT of HIV; and

(ii) to characterize adverse events according to receipt of and exposure to ARVs (by HIV-infected women during pregnancy and postpartum and by their HIV-exposed but uninfected children *in utero* and during the first few weeks of life).

What has been measured?

For the perinatal and LILAC protocols, study visits for the HIV-infected women included medical histories, physical examinations and laboratory evaluations (including hematology, flow cytometry assays, viral loads and biochemical assays). Study visits for their children included medical histories, physical examinations, laboratory studies (flow cytometry, HIV diagnostic assays, haematology and biochemical assays) and assessments of growth and morbidity. Peripheral blood mononuclear cells and plasma were collected from all subjects (maternal and pediatric) and stored in a central repository for potential future studies.

How often have they been followed up?

Women in the Perinatal protocol were enrolled during pregnancy, at 8 weeks gestation or later (including at the time of presentation for delivery). They were followed during pregnancy, with up to three antepartum visits, at delivery and at hospital discharge, and at 6–12 weeks and 6 months postpartum. HIV-infected women who experienced pregnancy losses continued to be followed. In addition, HIV-infected women were eligible for re-enrolment with subsequent pregnancies during this study. Women in the LILAC protocol were enrolled during pregnancy at 22 weeks of gestation or later. They were followed during pregnancy with up to two antepartum visits, at delivery and hospital discharge, at 6–12 weeks and 6 months postpartum and then every 6 months thereafter up to 5 years postdelivery. HIV-infected pregnant women who experienced pregnancy losses also were followed according

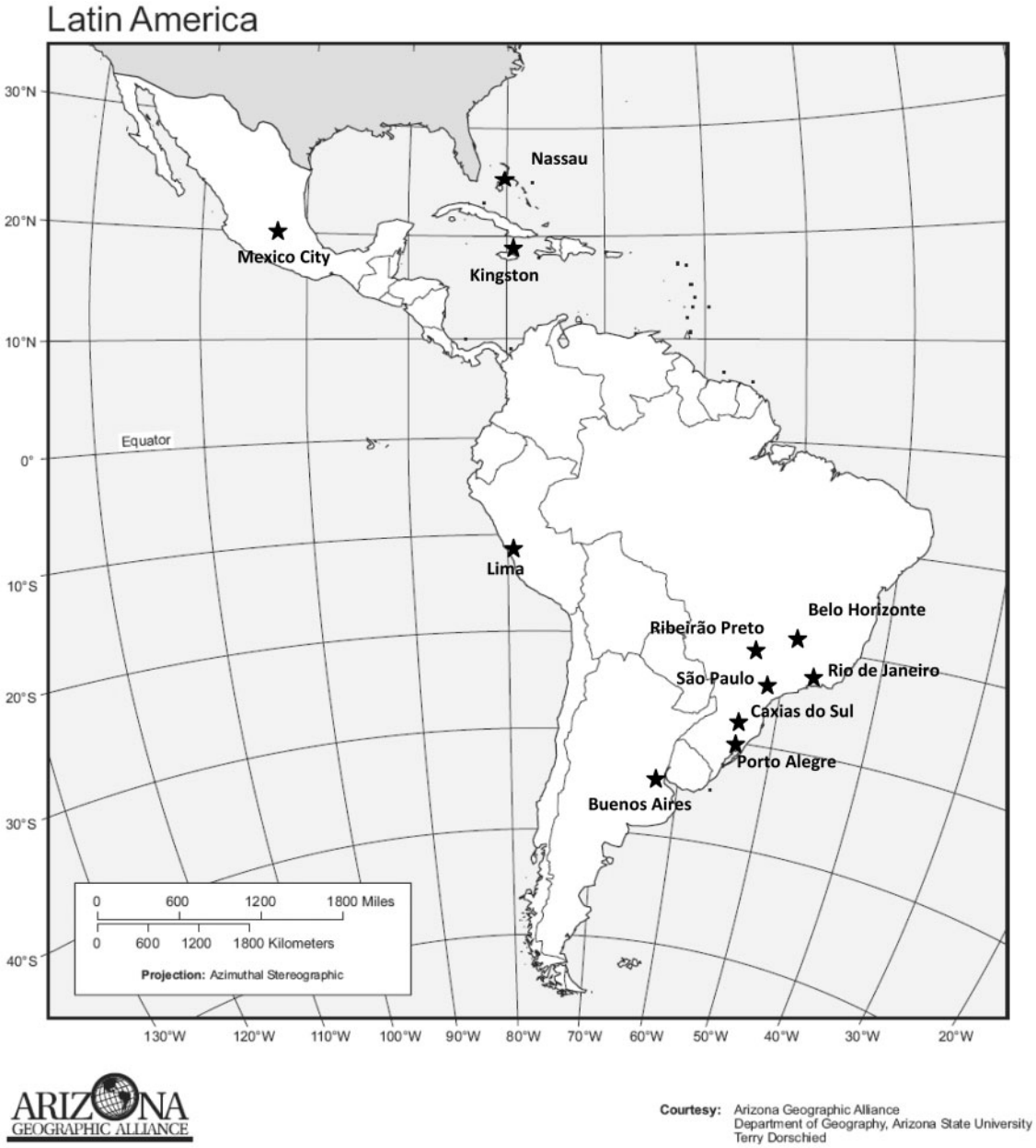

Figure 1 Map of location of clinical sites (Perinatal protocol and LILAC protocol)

to the regular evaluation schedule (i.e. at 6–12 weeks postpartum, 6 months postpartum and every 6 months thereafter, up to 5 years after delivery). Subjects with subsequent pregnancies were eligible to re-enroll in the study: however, their follow-up for the previous pregnancy was discontinued.

Children in the Perinatal protocol had study visits at birth, 6–12 weeks of age and at 6 months of age. There were two groups of children enrolled into the LILAC protocol: the dynamic cohort and the static cohort. Children enrolled in the dynamic cohort of the LILAC protocol followed the same visit schedule as the Perinatal protocol with the exception that, starting with the 6-month visit, they were followed on a semi-annual basis for up to 5 years. Children enrolled in the static cohort of the LILAC protocol were HIV-exposed, uninfected children between 6 months and 5 years of age who had available complete antenatal maternal ARV histories and documentation of maternal HIV infection before or during pregnancy or within 1 month postpartum. They also were followed on a semi-annual basis for up to 5 years. Children who became HIV-infected during the course of these protocols were discontinued from the study and offered enrolment into a concurrent NICHD-funded protocol for HIV-infected children, if

eligible and if the study was underway at the clinical site. Mothers of children who became HIV-infected continued their follow-up as originally planned. For women and children, study visits were allowed within a window of ±2 weeks for the 6–12 week visit, and ±2 months for every visit thereafter.

What was the attrition like?

Both protocols included follow-up of women and children through 6 months after delivery/birth. Thus, attrition during the first 6 months after delivery/birth was assessed. Of the 1548 women who enrolled into the perinatal and LILAC protocols and with their first on-study pregnancy, 739 (47.7%) returned for a second antenatal visit. A majority of the enrollees returned for their subsequent study visits through 6 months postpartum: 1444 (93.3%) returned for the delivery visit; 1528 (98.7%) provided hospital discharge (following delivery) information; 1496 (96.6%) returned at 6–12 weeks postpartum; and 1376 (88.9%) returned at 6 months postpartum. As of 31 December 2009, there were 372 (24.0%) women currently on study, 1114 (72.0%) who had completed study follow-up and 62 (4.0%) who had withdrawn from the study. Of the 62 maternal withdrawals, 8 (12.9%) died, 4 (6.5%) left due to job constraints, 5 (8.1%) emigrated from the study area, 5 (8.1%) withdrew their consent for participation, 3 (4.8%) left because they had transferred their clinical care to another hospital and 37 (59.7%) could not be located by the study staff. The median duration of maternal follow-up was 8 months, the mean duration was 8.2 months and the interquartile range was 6.5–9.9 months.

Of the 1508 live-born infants enrolled in the perinatal or LILAC protocols, 25 were part of multiple gestation births and two did not have data on-study. Retention on study through the 6-month study visit was assessed for 1481 singleton, live-born infants with data. Of these 1481 infants, 1477 (99.7%) had information at birth (3 were delivered at other hospital facilities, but returned for subsequent follow-up visits), 1446 (97.6%) returned at 6–12 weeks of age and 1328 (89.7%) returned for the 6-month study visit. As of 31 December 2009, 356 (24.0%) children were still on study, 1068 (72.1%) had completed study participation and 57 (3.98%) had withdrawn from the study. Of the 57 infant withdrawals, 11 (19.3%) died, 4 (7.0%) were HIV-infected, 2 (3.5%) had parents with job constraints, 6 (10.5%) had families who moved away from the study area, 5 (8.8%) had parents who withdrew consent for study participation, 2 (3.5%) had mothers who had transferred their clinical care to another facility and 27 (47.4%) could not be located. The median duration of infant on-study follow-up was 5.9 months, the mean duration was 5.7 months and the interquartile range was 4.6–6.4 months.

What has the study found?

As of 31 December 2009, 1548 pregnant women enrolled with their first on-study pregnancies (1174 from the Perinatal protocol and 374 from the LILAC protocol) (Figure 2). Characteristics of the 1548 women who enrolled with their first on-study pregnancy are presented in Table 1. Overall, most women enrolled in Brazil and Argentina. Most had 7–12 years of education (63.4%) and were unemployed. Approximately one-third of women reported any substance use during pregnancy, most commonly tobacco (24.8%) or alcohol (12.7%). Almost all participants (99%) reported at least some ARV use during pregnancy. Of those women who used ARVs during pregnancy, approximately half used ARVs for treatment of their own HIV infection and the other half used ARVs for transmission prophylaxis. The most common ARV regimen used for $\geqslant$28 days during the third trimester of pregnancy was the combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and one protease inhibitor (PI). For most women, the first viral load during pregnancy was $<$1000 copies/ml (58.4%), as was the last viral load before delivery (78.2%). The proportion of women with $CD4^+$ counts $\geqslant$500 cells/mm^3 increased from 35.4% (for the first $CD4^+$ count during pregnancy) to 41.9% (for the last $CD4^+$ count before delivery). Finally, most women had a CDC clinical classification of A, both at the first assessment during pregnancy (86.0%) and at the last assessment before delivery (85.9%).

A total of 1508 (97.6%) women had live-birth outcomes, 8 (0.5%) had spontaneous abortions, 29 (1.9%) had stillbirths and three had unknown pregnancy outcomes (Table 1). Of the 1508 live births (1139 from the perinatal and 369 from the LILAC protocol) (Figure 2), 1483 (98.3%) were singleton births and 25 (1.7%) were multiple gestations. Data were not available for two additional infants who were then excluded from analyses.

Thus, there was a total of 1481 unique mother–child pairs enrolled in the perinatal and LILAC protocols. (In addition, 100 static cohort children were enrolled into the LILAC protocol.)

Characteristics of the 1481 live-born singleton infants born to women enrolled in the perinatal or LILAC protocols are presented in Table 2. The proportion of infants born preterm ($<$37 completed weeks of gestation) was 9.7%, and 14.2% of infants had low birthweight ($<$2500 g). Almost all infants (99.7%) received one or more ARVs within 7 days of birth with most infants receiving zidovudine (ZDV) alone (97.0%). The next most common ARV regimen received within 7 days of birth was ZDV with nevirapine (2.8%), with a small proportion receiving other ARV regimens (0.2%). Only seven infants received breastmilk. An MTCT rate of 1% was observed in the cohort.

To date, 16 manuscripts have been published or are in press.[1–16] An additional two analyses have been

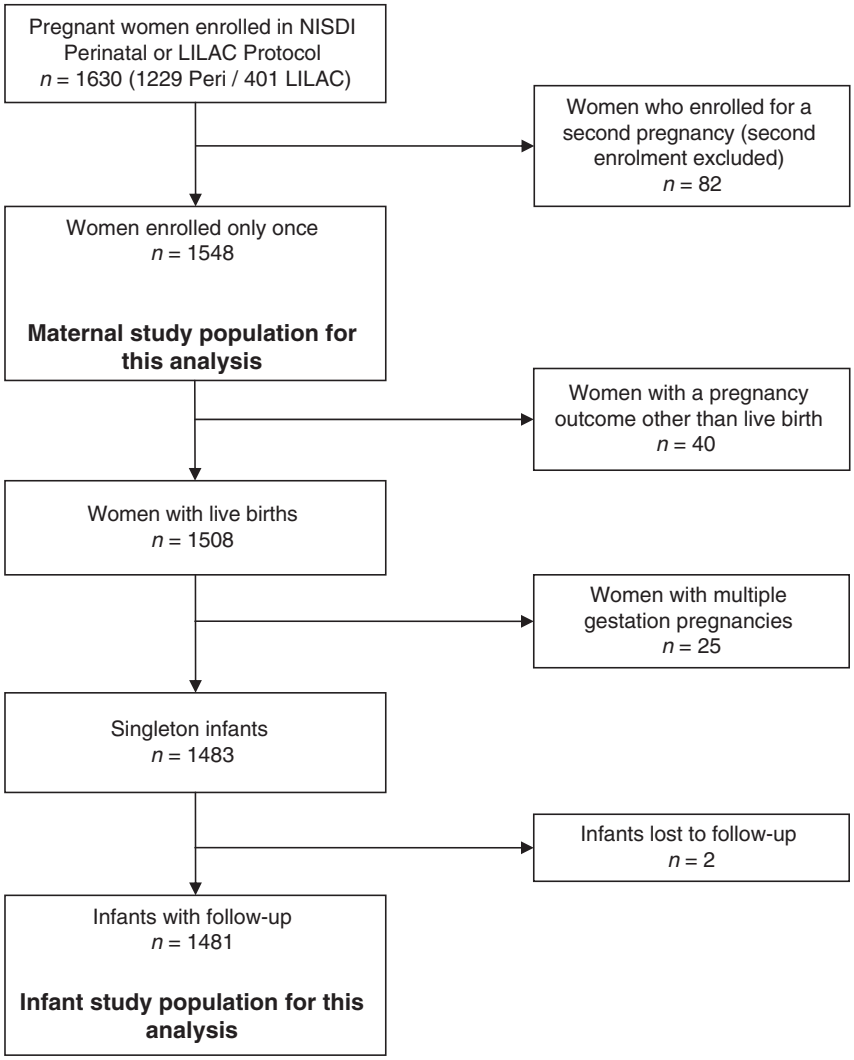

Figure 2 Derivation of the study populations for this analysis

presented or accepted for presentation as abstracts.[17,18] These analyses have addressed the management of, and changes over time in the management and outcomes of, HIV-infected pregnant women at Latin American and Caribbean sites.[6,18] Postpartum changes in plasma viremia and CD4 percent[14] and lopinavir/ritonavir standard and increased dosing in the third trimester[15] have been assessed. In addition, specific outcomes among HIV-infected women enrolled in the protocol have been evaluated (anti-retroviral resistance,[2,4,11] laboratory abnormalities[9] and postpartum morbidity[1]). Potential missed opportunities for prevention of MTCT of HIV have been evaluated,[7] as well as infant adverse outcomes related to maternal ARV use during pregnancy (low birth weight and preterm birth,[3] congenital anomalies[12]. Infectious disease morbidity[5] and specifically lower respiratory tract infections,[13] as well as hepatic enzyme and haematologic abnormalities,[8] among HIV-exposed but uninfected infants have been assessed. The association of body mass index of HIV-infected women and infant weight, body mass index, length and head circumference has been analysed.[10] Mode of delivery and neonatal respiratory morbidity has been assessed.[17] Finally, the knowledge and practice of pre-chewing/pre-warming by HIV-infected women has been evaluated.[16]

What are the main strengths?

The main strengths of this prospective cohort study include collection of data at specific intervals as called for by a common protocol, a centralized database and a central sample repository for future studies in this well-characterized cohort. There is ongoing data quality review by data management and statistical centre with data issues and discrepancies resolved by clinical sites. The dedicated site investigators are able and willing to propose and carry out individual secondary studies to answer specific scientific questions. These

Table 1 Characteristics of the maternal population ($n = 1548$)

Characteristics	*n* (%)
Country of enrolment	
Argentina	387 (25.0)
Bahamas	43 (2.8)
Brazil	967 (62.5)
Jamaica	37 (2.4)
Mexico	43 (2.8)
Peru	71 (4.6)
Maternal age at delivery (years)	
<20	89 (5.8)
20–29	830 (53.7)
>29	626 (40.5)
Missing	3
Maternal education (years)	
<7	484 (31.3)
7–12	981 (63.4)
>12	83 (5.4)
Gainful employment	
No	1145 (74.0)
Yes	403 (26.0)
Alcohol use during pregnancy	
No	1350 (87.3)
Yes	197 (12.7)
Missing	1
Tobacco use during pregnancy	
No	1163 (75.2)
Yes	384 (24.8)
Missing	1
Marijuana use during pregnancy	
No	1505 (97.3)
Yes	42 (2.7)
Missing	1
Cocaine/crack use during pregnancy	
No	1500 (97.0)
Yes	47 (3.0)
Missing	1
Heroin/opiate use during pregnancy	
No	1547 (100.0)
Yes	0 (0.0)
Missing	1
Any substance use during pregnancy	
No	1062 (68.6)
Yes	485 (31.4)
Missing	1
Any ARVs used during pregnancy	
No	15 (1.0)
Yes	1533 (99.0)
Reason for maternal ARV use during pregnancy	
Prevention of MTCT	738 (49.9)
Treatment	742 (50.1)
Missing	53
(No ARVs used during pregnancy)	15
Most complex maternal ARV regimen used ⩾28 days during third trimester of pregnancy	
2 NRTIs + 1 NNRTI	417 (27.2)
2 NRTIs + 1 PI	862 (56.2)
1–2 NRTIs	137 (8.9)
No ARVs ⩾28 days	76 (5.0)
Other	41 (2.7)
(No ARVs used during pregnancy)	15
First viral load during pregnancy (copies/ml)	
<1000	896 (58.4)
1000–9999	314 (20.5)
⩾10 000	324 (21.1)
Missing	14
Last viral load before delivery (copies/ml)	
<1000	1200 (78.2)
1000–9999	199 (13.0)
⩾10 000	135 (8.8)
Missing	14
First CD4 count during pregnancy (cells/mm^3)	
<200	216 (14.1)
200–499	773 (50.5)
⩾500	542 (35.4)
Missing	17
Last CD4 count before delivery (cells/mm^3)	
<200	185 (12.1)
200–499	705 (46.0)
⩾500	641 (41.9)
Missing	17
First CDC clinical classification during pregnancy	
A	1332 (86.0)
B	92 (5.9)
C	124 (8.0)
Last CDC clinical classification before delivery	
A	1329 (85.9)
B	94 (6.1)
C	125 (8.1)

(continued)

Table 1 Continued

Characteristics	*n* (%)
Mode of delivery	
Caesarean section before labour and before ruptured membranes	533 (34.4)
Caesarean section after labour and/or after ruptured membranes	383 (24.7)
Vaginal delivery	605 (39.1)
Missing	27 (1.8)
Pregnancy outcomes	
Spontaneous abortion	8 (0.5)
Live birth	1508 (97.6)
Still birth	29 (1.9)
Missing	3

proposals are evaluated for scientific merit, feasibility and resource utilization and only meritorious proposals move forward. In addition, there are opportunities for collaborations between investigators from different regions within Brazil and different countries. These collaborations have been supported by annual meetings with site investigators. Finally, there is the ability to collaborate with other perinatal and paediatric cohorts and to pool data when large data sets are necessary to answer important scientific questions in a timely manner.

What are the main weaknesses?

A weakness of the protocol is that it is heavily weighted towards Brazil and Argentina with limited participation of four other countries (the Bahamas, Jamaica, Mexico and Peru). Also, subjects may not be a representative sample of HIV-infected women and their children (Perinatal protocol and dynamic cohort of the LILAC protocol), or of HIV-exposed but uninfected children (static cohort of the LILAC protocol), at these sites or in these countries.

Can I get hold of the data? Where can I find out more?

Potential collaborators should contact the project manager at RoslynHennessey@westat.com. Requests to access data and/or samples will be reviewed for scientific merit, feasibility and resource utilization by the NISDI perinatal/LILAC executive committee, which consists of five site investigators, a representative of the data management and statistical center and the NICHD principal investigator.

Supplementary Data

Supplementary data are available at *IJE* online.

Table 2 Characteristics of the paediatric population ($n = 1481$)

Characteristics	*n* (%)
Gestational age at birth (weeks)	
<37	143 (9.7)
⩾37	1333 (90.3)
Missing	5
Birthweight (g)	
<2500	209 (14.2)
⩾2500	1267 (85.8)
Missing	5
Gender	
Female	718 (48.6)
Male	759 (51.4)
Missing	4
Receipt of ARVs within 7 days of birth	
No	5 (0.3)
Yes	1476 (99.7)
If receipt of ARVs within 7 days of birth, type of regimen	
ZDV alone	1432 (97.0)
ZDV with nevirapine	41 (2.8)
Other[a]	3 (0.2)
No ARVs within 7 days after birth	5
Received breastmilk	
No	1474 (99.5)
Yes	7 (0.5)
HIV-infection status	
Infected	15 (1.0)
Uninfected	1346 (92.3)
Indeterminate	98 (6.7)
Missing	22

[a]Two subjects received ZDV, lamivudine and nevirapine, one received ZDV, lamivudine and nelfinavir and one received lamivudine, nevirapine and ritonavir.

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Conflict of interest: None declared.

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