International Journal of Gynecology and Obstetrics 122 (2013) 37–43

Contents lists available at SciVerse ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

CLINICAL ARTICLE

Trends in the management and outcome of HIV-1-infected women and their infants in the NISDI Perinatal and LILAC cohorts, 2002–2009☆

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ARTICLE INFO

Article history:
Received 30 August 2012
Received in revised form 14 December 2012
Accepted 17 December 2012

Keywords:
Antiretroviral
HIV-1
Latin America
Mother-to-child transmission
Prophylaxis
Treatment

ABSTRACT

Objective: To describe temporal management and outcome trends among HIV-1-infected pregnant women and their infants enrolled in the NISDI Perinatal and LILAC cohorts. *Methods:* A prospective cohort of 1548 HIV-1-infected pregnant women and their 1481 singleton live-born infants was analyzed. Participants were enrolled at 24 Latin American and Caribbean sites and followed-up for at least 6 months postpartum. Variables were compared by 2-year enrollment periods from September 27, 2002, to June 30, 2009, using logistic and linear regression modeling. *Results:* Antiretroviral (ARV) use during pregnancy remained high (99.0%). ARVs became increasingly used for treatment ($P < 0.001$). Regimens containing 2 nucleoside reverse transcriptase inhibitors plus a protease inhibitor became more common in later years ($P < 0.001$). The proportion of women with viral loads below 1000 copies/mL at hospital discharge after delivery (HD) increased over time ($P = 0.0031$). Median CD4 lymphocyte counts also rose at HD, from 441 cell/mm^3 to 515 cells/mm^3 ($P < 0.05$). Elective cesarean deliveries increased from 30.5% to 42.0% ($P = 0.018$). Most infants received ARV prophylaxis (99.7%). Few infants were breastfed (0.5%) or became infected with HIV-1 (1.2%). *Conclusion:* The results indicate that national HIV-1 treatment and transmission prevention policies are effective among patients with healthcare access in the region.

1. Introduction

Strategies that aim to prevent mother-to-child transmission (MTCT) of HIV-1 have been implemented in many regions worldwide, including Latin America and the Caribbean. These interventions include antiretroviral (ARV) prophylaxis, cesarean delivery before onset of labor and rupture of membranes, and total avoidance of breastfeeding [1–3]. International initiatives to ensure access to HIV-1 prevention and treatment programs, such as the US President's Emergency Plan for AIDS Relief and the Global Fund, have improved outcomes for women with HIV-1 and markedly reduced rates of MTCT, especially in low-income settings [4].

In 2002, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) began funding sites within 4 Latin American and Caribbean countries—Argentina, the Bahamas, Brazil, and Mexico—as part of the NICHD International Site Development Initiative (NISDI) Perinatal cohort study of HIV-1-infected women and their infants [5,6]. Sites in Jamaica and Peru were funded from 2005, and the NISDI Perinatal cohort completed enrollment in 2007. The following year, HIV-1-infected pregnant women and their HIV-1-exposed infants began enrollment into a revised protocol, the Longitudinal Study in Latin American Countries (LILAC). Sites in Argentina, Brazil,

☆ Manuscript presented in part at: XVIII International AIDS Conference; July 18–23, 2010; Vienna, Austria (abstract MOPE0244); and 15th International Workshop on HIV Observational Databases; March 24–26, 2011; Prague, Czech Republic (abstract 15_174). Members of the NISDI Perinatal/LILAC Study Group are listed in Supplementary Material S1.

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0020-7292/$ – see front matter © 2013 Published by Elsevier Ireland Ltd. on behalf of International Federation of Gynecology and Obstetrics.
http://dx.doi.org/10.1016/j.ijgo.2012.12.021

and Peru were funded for enrollment of participants into LILAC, which involved a longer duration of follow-up than that performed in the NISDI Perinatal protocol [6].

The aim of the present study was to describe changes in management and outcomes that occurred over time among HIV-1-infected women and their infants enrolled in the NISDI Perinatal and LILAC cohorts during the period 2002–2009.

2. Materials and methods

Data regarding HIV-1-infected women and their infants enrolled into the NISDI Perinatal or LILAC cohorts between September 27, 2002, and June 30, 2009, were analyzed. The present study was approved by the relevant institutional or ethics review boards at each of the 24 participating clinical sites, which were located in Argentina, the Bahamas, Brazil, Jamaica, Mexico, and Peru. In addition, approval was obtained from the review boards of the sponsoring institution (NICHD, Bethesda, USA) and the center responsible for data management (Westat, Rockville, USA). All participants provided written informed consent.

The enrollment and follow-up of the NISDI Perinatal and LILAC cohorts have been previously described [5,6]. Briefly, eligible women were enrolled at 8 weeks of pregnancy or later. Participants attended up to 3 prenatal visits, as well as study visits at delivery, at hospital discharge after delivery (HD), at 6–12 weeks after delivery, and at 6 months after delivery. Women enrolled in the LILAC protocol were then assessed every 6 months for up to 5 years after delivery. Infants were enrolled at birth; study visits were at 6–12 weeks and at 6 months of age. Infants enrolled in the LILAC protocol were then assessed at subsequent 6-month intervals for up to 5 years after birth. Infants diagnosed as HIV-1-infected were given the opportunity to enroll in a concurrent NICHD-funded protocol [7]. A medical history and physical examination were performed at each study visit. Laboratory evaluations, including CD4 lymphocyte count, HIV-1 viral load (VL), hematology, and biochemistry, were performed using blood samples collected at all study visits other than the maternal 6-month postpartum assessment.

Maternal eligibility criteria for the present study were enrollment in either the NISDI Perinatal or LILAC protocols with their first on-study pregnancy (data collected during subsequent pregnancies were excluded from the present analysis so that outcomes were assessed for only 1 pregnancy per woman). Inclusion criteria for infants were eligible mother, singleton, live birth, and availability of relevant data. Mode of delivery was categorized as elective cesarean delivery (before onset of labor and ruptured membranes), nonelective cesarean delivery after labor and/or after ruptured membranes, or vaginal delivery. Maternal ARV regimens were classified as follows: use of 1–2 nucleoside reverse transcriptase inhibitors (NRTIs); use of 2 NRTIs and 1 non-NRTI; use of 2 NRTIs and 1 protease inhibitor (PI); and use of any other regimen. Use of ARVs during pregnancy was categorized as "treatment" when these agents were used before pregnancy and/or after the 6–12 week visit. By contrast, ARV use during pregnancy was categorized as "prophylaxis" if these agents were started during pregnancy and discontinued by the 6–12 week visit. Clinical disease stage was categorized at each visit according to the Centers for Disease Control scheme [8]. In the present study, only maternal and infant variables that were assessed in both protocols up to 6 months after delivery were included in the analysis.

Births that completed fewer than 37 weeks of pregnancy were considered preterm. Infants weighing less than 2500 g at birth were categorized as having low birth weight. Diagnosis of infants as HIV-1-infected required any 2 of the following 4 test results: viral particles detected by cell culture; HIV-1 DNA detected by polymerase chain reaction assay; presence of neutralizable HIV-1 p24 antigen; or a VL of at least 10 000 copies/mL. These test results had to be recorded using separate specimens (i.e. from different blood-sampling events).

Data were analyzed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA). Temporal changes in management and outcomes were assessed by comparing data by period of maternal enrollment. This parameter was broken down into 2-year intervals: 2002–2003, 2004–2005, 2006–2007, and 2008–2009. Changes over time in categorical measures were analyzed using logistic regression modeling, with 2008–2009 serving as the reference period. Linear regression modeling was used for continuous-scaled measures. The Wald χ^2 test was used to test differences between periods; P values below 0.05 were considered statistically significant.

3. Results

Fig. 1 shows the derivation of the present study population. Of the 1630 pregnancies enrolled in the NISDI Perinatal or LILAC protocols, 1548 women with first-time, on-study pregnancies were included in the present analysis. The 82 subsequent pregnancies were excluded to avoid potential over-representation bias. A total of 1481 infants were eligible for inclusion in the present study. Follow-up throughout the 6-month period after delivery was completed by 1463 women (94.5%) and 1407 infants (95.0%). The median follow-up duration was 9 months for the women and 6 months for their infants.

During the follow-up period, 7 women and 9 infants died within 6 months of delivery. The causes of the 7 maternal death were AIDS with disseminated cryptococcosis and septicemia; HIV wasting syndrome with electrolyte abnormalities and metabolic acidosis; shock, disseminated tuberculosis, and AIDS; disseminated cancer (vulvar embryonal rhabdomyosarcoma) and AIDS; cardiac arrest related to respiratory failure caused by community-acquired severe pneumonia; septic shock; and severe dyspnea and hypotension, attributed to a pulmonary thromboembolism during the postpartum period. The causes of the 9 infant deaths were perinatal asphyxia and meconium aspiration; necrotizing enterocolitis, sepsis, and septic shock syndrome; bronchoaspiration of gastric contents resulting in respiratory insufficiency; pneumothorax in an extremely low birth weight infant, leading to respiratory failure and cardiopulmonary arrest; sudden death; respiratory distress owing to sepsis and pneumonia; bilateral bronchopneumonia; sepsis; and preterm birth at 27 weeks, with death occurring within 1 hour of birth.

The maternal characteristics are presented in Table 1. Enrollment by country varied substantially throughout the study period ($P < 0.001$); clinical sites in the Bahamas, Jamaica, Mexico, and Peru did not enroll participants during the years when they were not funded to participate in the NISDI Perinatal protocol. Maternal age at delivery, years of education, and gainful employment outside the home differed over time in the logistic model ($P = 0.0083$, $P < 0.001$, and $P < 0.001$, respectively). The diagnosis of HIV-1 infection during pregnancy also differed ($P = 0.0026$), with appreciably more women diagnosed during pregnancy in the period 2002–2003 than in 2008–2009 ($P = 0.0012$). Substance abuse differed significantly between enrollment periods ($P = 0.0134$). In particular, alcohol use during pregnancy differed significantly, with women enrolled in 2008–2009 more likely to use alcohol than women enrolled in the earlier years ($P < 0.001$). Differences were observed over time in clinical disease stage at enrollment, first CD4 lymphocyte count during pregnancy, and first VL measurement during pregnancy. Fewer women with class B and C disease enrolled in 2004–2005 and 2006–2007 than in 2008–2009 ($P = 0.0087$). Fewer women had a first CD4 lymphocyte count during pregnancy of 500 cells/mm^3 or higher in 2002–2003 and 2004–2005 than in 2008–2009 ($P = 0.002$). Finally, fewer women had a plasma VL below 1000 copies/mL in 2002–2003 and 2004–2005 than in 2008–2009 ($P < 0.001$). Similar changes were observed at HD and at the 6–12 weeks postpartum visit for the CD4 lymphocyte count and the plasma VL ($P < 0.005$ for all comparisons).

The median first CD4 lymphocyte count during pregnancy was higher among women enrolled in later time periods than among