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Morbidity and Mortality of a Cohort of Peruvian HIV-Infected Children 2003-2012

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Abstract

Background—Data on pediatric HIV in Peru is limited. The National Institute of Child Health (Instituto Nacional de Salud del Niño: INSN) cares for the most HIV-infected children under age 18 in the country. We describe the outcomes of children seen at INSN's HIV clinic over the 10 years when antiretroviral therapy (ART) and prevention of mother-to-child transmission (PMTCT) interventions became available in 2004.

Methods—We conducted a retrospective review of INSN HIV clinic patients between 2003–2012. De-identified data was collected and analyzed.

Results—A total of 280 children were included: 50.0% (140/280) were male, 80.0% (224/280) lived in metropolitan Lima. Perinatal transmission was the mode of HIV infection in 91.4% (256/280). Only 17% (32/191) of mothers were known to be HIV-infected at delivery; of these mothers, 41% (13/32) were receiving ART at delivery, 72% (23/32) delivered by Cesarean section, and 47% (15/32) of their infants received antiretroviral prophylaxis. Median age at HIV diagnosis for all children was 35.7 months (IQR 14.5–76.8 months), and 67% (143/213) had advanced disease (clinical stage C). After HIV diagnosis, the most frequent hospitalization discharge diagnoses were bacterial pneumonia, chronic malnutrition, diarrhea, anemia, and tuberculosis. Twenty-four patients (8.6%) died, at a median age of 77.4 months.

Conclusions—Most cases of pediatric HIV were acquired via perinatal transmission, few mothers were diagnosed before delivery, and among mothers with known HIV status, PMTCT was suboptimal even after national PMTCT policy was implemented. Most children were diagnosed with advanced disease. These findings underscore the need for improving early pediatric HIV diagnosis and treatment, as well as PMTCT strategies.

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Keywords

Pediatric HIV; Peru; morbidity and mortality

Introduction

In Peru, as in most of Latin America, the HIV epidemic is concentrated among men who have sex with men (MSM) and transgender women (TW).¹⁻³ However, there are other key populations living in Peru, including women and children. Perinatal transmission was the cause of 5.6% of all new HIV infections among children and adults in Peru from 1986-2012.⁴ According to Peru's Ministry of Health, from 1986 to 2012, there were 1,428 children under 15 years of age diagnosed with HIV, and in 2012, 586 children were receiving antiretroviral therapy (ART).⁴ However, it is estimated that Peru is home to between 1,900 to 6,900 HIV-infected children, the majority of whom are undiagnosed or not receiving ART.⁴

ART has been shown to decrease HIV-1 RNA viral load (VL), increase CD4+ lymphocyte counts, and decrease morbidity and mortality for HIV-infected children in both developed and low-resource countries.⁵⁻¹³ Early infant diagnosis and initiation of ART are essential in achieving these aims.¹⁴ In 2002, ART became available to some Peruvian children. In 2004, universal free access for ART and the national program for prevention of mother-to-child transmission (PMTCT) was initiated.¹⁵ These interventions resulted in a decline in the estimated MTCT rates,¹⁶ from 15-30% in 2004¹⁷ to 2-5% in 2012.^{1,18} However, no centralized program exists to follow HIV-exposed infants for recommended polymerase chain reaction (PCR) testing at 1, 3, and 6 months,¹⁹ and approximately two thirds have been lost during follow up HIV testing.^{1,2,18}

The Peruvian National Institute of Child Health in Lima (INSN or Instituto Nacional de Salud del Niño) is the country's pediatric referral center. As there are no newborn deliveries, all HIV-exposed or infected infants are referred to INSN from other health establishments. INSN's comprehensive multidisciplinary HIV clinic, La Estrategia, cares for the greatest number of HIV-infected children in Peru. The first 46 children to receive ART at INSN between 2002-2005 has been described, and most were older, in advanced stages of disease, and did not receive PMTCT interventions.²⁰ Starting in 2004, all children were initiated on a three-drug antiretroviral regimen per national guidelines: 2 nucleoside reverse transcriptase inhibitors (NRTI) and 1 protease inhibitor (PI), with lamivudine, zidovudine, and nelfinavir as the recommended regimen. Guidelines were updated in 2009 to recommend 2 NRTIs and 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) or PI (recommended regimen: lamivudine, zidovudine, and nevirapine or efavirenz).¹⁹ In 2008, HIV-1 genotype assays were made available by the National Institute of Health (INS).⁴ Since then, all children have genotype assays prior to ART initiation and change in ART regimen due to virologic failure.²¹ Any new or changed ART regimen is determined by the National Expert Committee of Pediatric HIV Physicians.

To date, a longitudinal review of outcomes of children living with HIV in Peru does not exist. Therefore, we aimed to describe the morbidity and mortality of children seen at

INSN's HIV clinic over the 10-year period during which ART became universally available countrywide and PMTCT interventions were initiated in Peru.

Methods

We conducted a retrospective review of the medical records of HIV-infected children younger than 18 years old seen at La Estrategia between January 1, 2003 and December 31, 2012. De-identified data was entered into EpiInfo (version 7.1, Atlanta, Georgia). Children's sociodemographic, HIV-related information and long-term treatment and care were collected, in addition to maternal perinatal information. Sociodemographic information included date of birth, sex, place of residence, primary caregiver (mother, father, other relative, institutional care), and socioeconomic status (SES). SES was determined by a hospital-standardized questionnaire regarding living situation and income and classified into five categories with three groupings: A/B/C (not in poverty), D (poverty), and E (extreme poverty), paralleling national quintiles.²² HIV-related information included mode of HIV transmission, age in months when diagnosed with HIV, Centers for Disease Control and Prevention (CDC) clinical stage at diagnosis (1994 guidelines),²³ date of ART initiation and initial ART regimen. HIV infection was established by enzyme-linked immunosorbent assay (ELISA) and Western Blot in children older than 18 months until 2006 when PCR became available at the central laboratory at INS. For children younger than 18 months after 2006, HIV infection was established by HIV DNA PCR at INS, with recommended testing for HIV-exposed infants occurring at 1, 3, and 6 months. The first positive HIV test was used as the date of HIV diagnosis. Children diagnosed with transfusion-associated HIV infection had a history of blood transfusion and both parents with negative HIV tests. Children with unknown route of transmission had parents with negative HIV tests and no known history of blood transfusions, sexual abuse, or other exposures. Long-term treatment and care information included weight, height, and body mass index (BMI), number of hospitalizations, length of hospitalizations, hospital discharge diagnoses, CD4+ lymphocyte counts, HIV VL, and ART regimens, including duration of each regimen, and reason for change. Maternal information for children who were perinatally HIV infected included maternal HIV status, and utilization of PMTCT services, all of which were determined from review of documentation in the child's medical record. Formula was provided to all known HIV-exposed and infected infants, and trimethoprim/sulfamethoxazole (TMP/SMX) prophylaxis was administered per national guidelines.¹⁹ All children were initiated on a three-drug antiretroviral regimen per national guidelines.¹⁹

Hospitalization discharge diagnoses were extracted from the discharge summary of each hospitalization. Clinical diagnosis of pneumonia was made without isolation of a particular bacteria or virus. Clinical diagnosis of *Mycobacterium tuberculosis* was made per national guidelines. Cause of death was determined by the death certificate in each deceased patient's chart or caregiver report if the patient died outside the hospital. No autopsies were done.

Absolute CD4+ lymphocyte counts were measured as frequently as every 3 months and VL every 6 months, all performed by the INS laboratory. CD4+ lymphocyte percentages were not available. VL lower limit of detection was 400 copies/mL until 2008 and less than 40 copies/mL after 2008. For data analysis, VL was converted to log₁₀. Virologic failure was

defined as detectable VL after 6 months on ART. Immunologic failure was defined as persistence of CD4+ lymphocyte count less than 200 cells/mm³ for children older than 5 years of age and less than 500 and 750 cells/mm³ for children ages 1-5, and younger than 1 year, respectively after 6 months on ART. In 2008, HIV-1 genotype assays were made available in Peru by the INS.⁴ Since that time, all children have genotype assays prior to ART initiation and prior to a change in ART regimen due to virologic failure.²¹ All new ART regimens are determined by the National Expert Committee of Pediatric HIV Physicians.

Patient records were excluded if they did not contain date of HIV diagnosis. Length of follow up was determined from date of HIV diagnosis to last documented clinic visit or end of study (December 31, 2012).

Data analysis

All the analyses were performed using SAS 9.4 (Cary, NC). Mann-Whitney test was used to analyze continuous variables, and Fisher's exact test was used to analyze categorical variables related to perinatal transmission separated into two groups by birth cohort: through 2004 and 2005-2012, prior to and after universal implementation of Peru's national HIV program. The Cochran-Armitage test was used to examine the time trend of categorical variables. Correlation coefficients were examined for associations among continuous variables. A univariate general linear model (GLM) examined the time trend (year of HIV diagnosis) with age at diagnosis, age at initiation of ART, and the time between diagnosis and initiation of ART.

Multivariate GLM was used to examine the association of covariates to outcome variables. The covariates considered are year of diagnosis, sex, mother as caregiver, residency in Lima, socioeconomic status (SES), CDC clinical stage (A, B vs. C), months to first ART failure, failure to thrive (FTT) and if maternal HIV status known at delivery, Cesarean section, maternal ART and infant HIV prophylaxis. Using these covariates as input variables, we determined the correlation to outcome variables, which were: CD4+ lymphocyte count at diagnosis and average hospitalizations/year. Overall survival analysis was done using a Cox proportional hazard (PH) model incorporating the following covariates: year of diagnosis, sex, mother as caregiver, residency in Lima, SES, CDC clinical stage (A, B vs. C), months to first ART failure, FTT, BMI and if maternal HIV status known at delivery, Cesarean section, maternal ART and infant HIV prophylaxis. For both the GLM and Cox PH models, the final model was obtained using a stepwise selection using a likelihood ratio test and by comparing Akaike information criteria.²⁴ P value < 0.05 was considered statistically significant and all the tests were 2-sided.

Ethics

The study was approved by the Institutional Review Boards at the University of California, Los Angeles and University of California, San Diego, and the Ethics Committee at the Instituto Nacional de Salud del Niño of Lima, Peru. All approvals were in place prior to the initiation of data collection.

Results

A total of 283 unique patient charts were reviewed: 3 were excluded with missing date of diagnosis. Children were born between August 1988 and May 2012; 50.0% (140/280) were male, 80.0% (224/280) lived in metropolitan Lima; a biological parent (mother or father) was the primary caregiver for 56.9% (152/267), relatives for 20.2% (54/267), and institutional care for 24.0% (64/267). Of the 206 children for whom there is documented SES, 99.0% (204/206) lived in poverty or extreme poverty (SES classes D and E) (Table 1). There were between 73 and 226 children in the cohort each year, increasing every year, with median 5.2 (2.9-9.4) person years contributed.

Mode of transmission, HIV diagnosis, clinical progression and treatment

Perinatal transmission was the mode of HIV infection in 91.4% (256/280). Among mothers for whom data was available, before 2005 only 5.4% (9/166) were known to be HIV-infected at delivery, compared to 25.6% (23/90) who delivered in 2005 or later when national PMTCT guidelines were in place ($p<0.05$). Of these mothers known to be HIV-infected at time of delivery, 52.2% (12/23) were on ART, 83.0% (18/23) had a Cesarean section, and 47.8% (11/23) of their infants received antiretroviral prophylaxis. This represented a significant improvement compared to children born prior to 2005 ($p<0.05$) (Table 1), however there was no progressive improvement observed in the number of women who were prenatally diagnosed after 2005.

Children were HIV-tested at INSN or the referring hospital because of their chronic symptoms, during pre-operative screening, or following diagnosis or death of a parent. There were variations in the age of HIV diagnosis by mode of transmission (Table 1). For all children, median age of diagnosis was 35.7 months (14.5-76.8), and 68.4% (143/209) had advanced disease (1994 CDC clinical stage C). Children infected via perinatal transmission were diagnosed at a median of 32.7 months (14.3-69.5), with only 20.3% diagnosed at younger than 12 months (52/256) with variations over time (Table 2).

At time of HIV diagnosis, median absolute CD4+ lymphocyte count was 275 cells/mm³ (87-591) and median VL was 5.3 log copies/mL (4.7-5.7) with no statistical difference between the study years. Of the 191 children with available medical history, 36% (68/191) had been hospitalized but not HIV tested prior to being diagnosed; of these, 51.5% (35/68) were hospitalized once and 36.8% (25/68) were hospitalized two to three times.

Median age at initiation of ART for all children was 59.0 months (23.7-106.2). For perinatally infected children born before and after 2005, the median age of ART initiation decreased from 81.7 (53.6-118.8) to 20.2 (9.6-34.9) months ($p<0.05$). The median number of months between HIV diagnosis and initiation of ART decreased for all children from 2003 (17.9, $n=15$) to 2012 (1.0, $n=19$) ($p<0.05$). Among the 122 children who had VL measured before and after starting ART, median VL prior to ART was 5.2 log copies/mL (4.8-5.7) and decreased on treatment with the median last recorded VL being 2.6 log copies/mL (1.6-3.9) ($p<0.05$).

Morbidity and mortality

There were 567 hospitalizations at INSN after HIV diagnosis among the 209 patients for which data was available. The median number of hospitalizations per patient was 2.0 (1.0-3.0). The most frequent diagnoses were bacterial pneumonia in 147/567 (26%), chronic malnutrition in 104/567 (18%), diarrhea in 80/567 (14%), anemia in 76/567 (13%), and tuberculosis in 34/567 (6%).

Older age at initiation of ART was associated with increased number of hospitalizations per year ($p < 0.01$). ART regimen was changed at least once for 48.9% (123/270), at a median of 32.7 months (10.1-54.5) after initiating ART with 26.0% (32/123) with two changes and 2.4% (3/123) with three changes. The most common reasons for the first ART change were: 81.8% (108/132) due to virologic failure, 16.7% (22/132) due to medication intolerance or toxicity, and 1.5% (2/132) due to immunologic failure.

Twenty-four patients (8.6%) died during the study period, at a median age of 77.4 months (36.7-98.7). Nineteen were HIV-infected via perinatal transmission and 5 via transfusion; 75.0% (18/24) lived in Lima. Seventeen (70.8%) of the children who died were born before 2005. Compared to children who died who were born in 2005 and after, they had older median age of HIV diagnosis at 27.6 months (12.2-78.8), statistically significant longer time between diagnosis and starting ART of 6.1 months (3.1-37.9), age at initiating ART of 69.0 months (20.9-94.7) and older age at death of 87.6 months (49.6-109.7). Children were initiated on the same ART regimens as the remainder of the cohort after 2004, per national guidelines. One child born after 2005 was never initiated on ART. The cumulative mortality rate was 1.5 deaths per 100-person-years, with an annual range of 0-5.8 deaths per 100-person-years in 2007. By mode of transmission, the mortality rate was as follows: 1.3 deaths per 100-person-years for perinatal infection and 5.2 per 100-person-years for transfusion. Pneumonia (organism not identified) was the most common cause of death in 13/24 (54%), followed by central nervous system (CNS) disease in 3/24 (12%), septic shock in 3/24 (12%) and cancer in 2/24 (8%) due to acute lymphoblastic leukemia and Ewing's sarcoma. Four children had unknown causes of death.

Malnutrition was associated with increased mortality. Of the 234 patients for whom anthropometric data was documented, those with malnutrition (weight -2 SD)²⁵ were 4.8 times more likely to die (95% CI 1.0-23.3, $p < 0.001$). The number of hospitalizations was also significantly associated with an increase in risk of mortality, with a hazard ratio of 3.3 (95% CI 2.3-4.9, $p < 0.001$) for each additional hospitalization/year in the cohort.

Discussion

Throughout 2003-2012, perinatal transmission continued to be the primary mode of HIV acquisition for pediatric patients at INSN; few mothers were diagnosed before delivery, and among mothers with known HIV status, PMTCT was suboptimal. Notably, only 3% (8/256) of the perinatally infected children were diagnosed per Peruvian national guidelines before 2 months of age.¹⁹ Most children were diagnosed with advanced disease and one third were hospitalized prior to diagnosis, representing missed opportunities for diagnosis and initiation of treatment. Other reasons for late diagnosis may include caregiver fear of discrimination

and health care providers that may not consider HIV given the concentrated epidemic in MSM and TW in Peru.

Although more than 95% of pregnant women in Peru access prenatal care,²⁶ and there has been an increase in HIV screening of pregnant women, up from 22.6% in 2000 to 79.9% in 2011,⁴ the mothers and their infants did not receive optimal PMTCT interventions. As HIV testing in the mothers occurred after the child was diagnosed, it is unknown if the transmission occurred during pregnancy, labor and delivery, or during breastfeeding. It is unknown how many HIV-exposed infants are HIV tested at 1, 3, and 6 months per national guidelines, and how many receive their results and are linked to care, as the loss to follow-up (LTFU) ratio of HIV-exposed infants is greater than 50%.¹

This gap in HIV testing of pregnant women and LTFU of HIV-exposed infants contributes to the persistence of new perinatally acquired pediatric HIV cases and the delayed diagnosis. As in other resource-limited countries, there are multiple other systemic barriers to optimal PMTCT interventions including: ensuring pregnant women and their healthcare providers receive the HIV test results so that pregnant women are started on ART; lack of access to the health records of pregnant and post-partum women across the different health establishments; and disjointed centers for follow up for HIV-exposed infants and their mothers. All these factors contribute to inadequate follow up of HIV-exposed infants, delivery of ART prophylaxis and proper infant HIV testing.²⁷ Delays in initiation of ART may be explained by time between date of test, receipt of positive test result, referral for treatment and start of ART at the referral center as well as LTFU after referral, not meeting treatment criteria, or requiring TB treatment. Improvements in PMTCT may result in early diagnosis and treatment of HIV-exposed and infected infants, and result in decreased morbidity and mortality of children.^{28,29}

Morbidity for HIV-infected children in Peru is similar to that seen in other resource-limited countries, with bacterial pneumonia as the most common cause of hospitalization.³⁰⁻³² While TMP-SMX prophylaxis was prescribed per national guidelines based on CD4+ lymphocyte count, pneumococcal conjugate vaccine (PCV) was not fully introduced into the national vaccine program until 2009 (PCV7 then PCV 10 in 2012).³³ Tuberculosis was also a common co-infection. As has been shown in other studies, diagnosis of pediatric tuberculosis, especially with HIV co-infection, is very challenging.^{34,35}

During this period when ART was available, mortality at INSN was 9% with a peak mortality rate of 5.78 deaths per 100-person-years in 2007 and an overall mortality rate of 1.5 deaths per 100-person-years. Compared to the mortality rates in other retrospective pediatric studies, it is similar to the rate in Nigeria (10%),³⁶ lower than Brazil (14%)³⁷ and higher than Malawi, Lesotho and Swaziland (4.5%).³⁸ Mortality was higher in children who were born before 2005 who were started on ART at older ages; however, they also died at older ages, possibly reflecting slower disease progression and survivor bias. It is possible that HIV-infected children in this cohort with a more rapid disease progression died undiagnosed, given diagnostic limitations of the country. As has been shown in prior studies, malnutrition and FTT was significantly associated with mortality.^{39,40} Children with transfusion-related HIV infection had higher mortality rates compared to those with

perinatal infection, possibly secondary to later age of diagnosis and ART initiation, though there is an unknown time between infection (transfusion exposure) and diagnosis.

Strengths of this study include the long retrospective time period, and the inclusive review of every patient that accessed care at INSN, representing the largest cohort of HIV-infected children in Peru. Limitations include its retrospective nature and the incomplete data in patient charts. For some patients, HIV was diagnosed at a different hospital and initial CD4+ lymphocyte counts and VL were not available. Mother-to-child transmission information was documented in the child's chart and based on caregiver recall. PMTCT interventions were unknown for many children whose caregiver was not their mother.

Conclusions

Most cases of pediatric HIV at INSN were acquired via perinatal transmission, few mothers were diagnosed before delivery, and among mothers with known HIV status, PMTCT delivery was suboptimal, despite improvements following implementation of national policy in 2004. Most children continued to be diagnosed with advanced disease and one third had been hospitalized prior to diagnosis. These findings highlight the need for improving PMTCT strategies and early pediatric HIV diagnosis and treatment.

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Table 2
Perinatal transmission: Age at HIV diagnosis by year of birth, N=256, National Institute of Child Health, Lima, Peru, January 2003 to December 2012

Year of birth	Median age at HIV diagnosis, months, (IQR)	HIV diagnosis prior to 12 months old, % (n)
All years	35.7 (14.5-76.8)	20.3 (52/256)
Prior to 2003	62.5 (31.3-92.0)	6.8 (10/133)
2003	30.7 (16.2-44.6)	23.5 (4/17)
2004	23.6 (11.8-48.2)	25.0 (4/16)
2005	20.5 (11.3-30.6)	28.6 (6/21)
2006	19.9 (7.1-34.3)	35 (7/20)
2007	16.0 (5.3-23.5)	36.4 (4/11)
2008	12.2 (4.9-30.3)	46.2 (6/13)
2009	8.0 (1.9-14.5)	58.3 (7/12)
2010	14.8 (12.2-18.3)	20.0 (2/10)
2011	15.9	0.0 (0/1)
2012	5.0 (4.0-6.0)	100 (2/2)