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Mortality rate and Predictors in children under 15 years old who acquired HIV from mother to child transmission in Paraguay

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Abstract

We estimated mortality rate and predictors of death in children who acquired HIV from mother-to-child transmission in Paraguay. We conducted a cohort study among children <15 years of age at enrollment, in 2000–2014. We abstracted clinical data from medical records, and we obtained data from records and death certificates. We used the Cox model for the multivariable analysis of mortality predictors. A total of 302 subjects were included in the survey, 216 (71.6%) were younger than five years old, 148 (51.0%) male, and 214 (70.9%) from Asunción metropolitan area. There were 52 (17.2%) deaths, resulting in an overall mortality rate of 2.06 deaths/100 person-years. Those children with hemoglobin levels ≤9g/dL at baseline had a two-times higher hazard of death compared to those with levels >9g/dL (hazard-ratio: 2.27; 95%confidence interval,1.01–5.10). The mortality of HIV children in Paraguay is high, and anemia is associated with mortality. Improving prenatal screening to find cases earlier and improving pediatric follow-up are needed.

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All authors declare that they have no conflict of interest.

Compliance with Ethical Standards

The Ethics Committee of the Institute of Tropical Medicine in Paraguay approved this study. For this type of study formal consent is not required.

Abstract

Estimamos la tasa de mortalidad y los predictores de muerte en niños que contrajeron el VIH de la transmisión de madre a hijo en Paraguay. Se realizó un estudio de cohorte entre los niños <15 años de edad en la inscripción, en 2000–2014. Se extrajeron los datos clínicos de los registros médicos, y se obtuvieron datos de los registros y certificados de defunción. Se utilizó el modelo de Cox para el análisis multivariada de los predictores de mortalidad. Un total de 302 sujetos fueron incluidos en la encuesta, 216(71.6%) eran menores de cinco años, 148(51.0%) varones y 214(70.9%) del área metropolitana de Asunción. Hubo 52(17.2%) muertes, lo que resultó en una mortalidad general de 2.06 muertes/100 años-persona. Aquellos niños con niveles de hemoglobina ≤9g/dL en la línea de base tuvieron un riesgo de muerte dos veces mayor en comparación con aquellos con niveles ≥9g/dL (razón de riesgo:2,27; intervalo de confianza 95%,1.01–5.10). La mortalidad de los niños con VIH en Paraguay es alta y la anemia está asociada con la mortalidad. Se necesita mejorar la atención prenatal para detectar casos en forma más precoz y mejorar el seguimiento pediátrico.

Keywords

HIV; Child; Mortality; Paraguay; VIH; Niños; Mortalidad; Paraguay

INTRODUCTION

HIV remains a massive and ongoing public health problem despite the widespread introduction of antiretroviral therapy (ART) and impressive declines in incidence. In 2015 2.1 million [1.8 million – 2.4 million] people were newly infected with HIV worldwide, including 150,000 [110,000–190,000] infants [1]. The introduction of highly active antiretroviral therapy (ART) in 1996 has improved survival and quality of life among people living with HIV worldwide with implications for public health [2]. Early initiation of ART in infants reduces child mortality by up to 76% [3]. Without ART, 15% of HIV-infected infants die by 6 weeks, 50% by age of two years, and 80% by five years [4].

In Latin America, despite advances in the control of the HIV epidemic, trends in pediatric HIV survival and predictors of mortality have not been well characterized. In Brazil, cohort studies in children living with HIV infection, followed since diagnosis, were conducted in Belo Horizonte and Vitoria. They found cumulative mortality rates of 9.7%, and 15.0% by 15 years of age respectively [5,6]. In Buenos Aires, Argentina, the mortality rate has been reported to be 0.86 deaths per 100 person-years and overall mortality 3.4% [7]. Predictors of mortality in these studies were age <1 year at the time of diagnosis, having advanced clinical and immunological disease, CD4+ percentage <15% and HIV plasma viral load ≥100,000 copies/mL.

Data are quite limited on mortality among children with perinatally transmitted HIV infection for Latin American countries, and there are even fewer data in Paraguay. To date, there is not a sufficiently clear picture of trends in survival and risk factors for mortality to enable program planners to evaluate and implement strategies to reduce mortality in children living with HIV. Our goal in this study was to estimate mortality rate and predictors of

mortality in children who acquired HIV from mother to child transmission in Paraguay. The analysis of mortality in children with HIV in Paraguay is crucial, with implications for both individuals and public health. In addition to assessing the needs relating to patient care and the establishment of public policies, mortality attributable to HIV represents a key indicator to assess interventions aimed at prolonging life.

METHODS

Study design

We conducted a retrospective cohort study among persons living with HIV infection (PLWH) in Paraguay who were born from January 2000 to December 2014 and <15 years of age at enrollment, and who acquired HIV from mother to child transmission.

Study setting and historical context

Paraguay has a population of 6,854,536 million people distributed across 17 geographic regions and the capital city of Asunción [8]. The HIV epidemic in the country is concentrated in high-risk groups such as men who have sex with men, female commercial sex workers, people who inject drugs, and transgender individuals. Mathematical models suggest that around 17,500 people in Paraguay were living with HIV in 2015, with HIV prevalence of 0.4% among Paraguayans 15 years and older [9].

Study population and sampling

The study population comprised all children age <15 years who acquired HIV from mother to child diagnosed according to the Paraguayan National HIV Program's criteria (a plasma HIV-1 RNA level on PCR of >1000 copies/mL in children <18 months and a confirmed HIV antibody test in children ≥18 months of age) and who received care at one of the four clinics offering comprehensive HIV care, the Institute of Tropical Medicine, the Itagua National Hospital, the Ciudad del Este Regional Hospital, and the Encarnación Regional Hospital. These hospitals are distributed in the 4 main health regions of the country, they are located in urban areas, but they are responsible for providing care to people from urban and rural areas. They are the only ones with trained human resources for caring for and following children with HIV infection.

Data collection

We abstracted data from clinic records, using a standardized form that included demographic, diagnostic, clinical, and ART initiation data. We obtained date of death from clinic records and confirmed deaths using the national death certificate database from the Paraguay's Department of Statistics and Census. For children whose information about death was unknown, we used date of the last recorded visit to the clinics offering comprehensive HIV care as the date of censure. We abstracted the date and the values of CD4 cell counts (in cells/μL) and CD4 percentage in younger children and plasma HIV viral load (in copies/mL) from the initial medical evaluation from the Expert Information System of the National AIDS Program database. Children initiated ART per national guidelines, which were based on CDC recommendations: clinical stage B1 or C or severe immunosuppression per age specific CD4 before 2011 [10] and from 2011 onwards for any

child <12 months of age with confirmed HIV infection regardless of CD4 percentage or clinical stage.

Statistical Analyses

Our principal outcome variable was mortality, measured from date of birth. The follow up started at the moment of HIV diagnosis until age 15 for children that aged out. We used survival analysis techniques to estimate the incidence of death within 1 year, 5 years and 10 years of diagnosis. We examined the following characteristics as potentially associated with mortality: age, both as a continuous variable and categorized into three groups (<1, 1 to < 6 and 6 years or older); residence (metropolitan, which included Asunción and the Central Region, and other, including Alto Parana and Encarnación); stage of HIV infection based on age-specific CD4 cell count or percentage (Stage 1, Stage 2, Stage 3); diagnostic period, categorized into 3 groups: 2000–2004, 2005–2009, and 2010 to present; baseline hemoglobin levels, dichotomized as <9 and ≥9g/dL. We used Stata version 14.0 (Stata Corporation, College Station, Texas, USA) for data analysis

We used frequencies for categorical variables and median and interquartile ranges (IQRs) for continuous variables to summarize the general characteristics of the cohort. We used the Cox proportional hazard model for the multivariable analysis of predictors of mortality using the following covariates: age at diagnosis, residence, diagnostic period, baseline viral load, stage of infection, hemoglobin at admission, and age at ART initiation. The proportional assumptions for the Cox model were met in the analyses.

Ethical considerations

The Ethics Committee of the Institute of Tropical Medicine in Paraguay approved this study. The data collected from the charts were used exclusively for the purposes of this study. The patients' identity was kept confidential by use of surrogate participant identifiers.

RESULTS

A total of 302 children <15 years old who acquired HIV infection from mother-to-child transmission were included in this study. Of the study participants, 216 (71.5%) subjects were younger than five years of age, 129 (42.7%) had been diagnosed in 2010 or later and 131 (43.3%) from 2005 to 2009, 148 (51.0%) were male, and 214 (70.8%) were from Asunción. Clinically, 200 (66.2%) had a HIV viral load >100,000 copies/mL, and 241 (79.8%) had hemoglobin levels >9 g/dL (Table 1). Two hundred twenty-six (82.2%) initiated ART during the study period. Of these, 69 (27.7%) were younger than 18 months of age at the time of ART initiation.

We followed participants for 2,522.5 person-years. There were 52 deaths (17.2%, 95% confidence interval [CI], 13.1–21.9%), resulting in an overall mortality rate of 2.06 deaths per 100 person-years. In the first year there were 10 deaths (3.3%, 95% CI 1.5–6.0%), at 5 years 32 deaths (10.6%, 95% CI, 7.3–14.6%), and at 10 years 44 deaths (14.5%, 95% CI, 10.7– 19.1%). A total of 8.8% of the children were lost to follow-up. In the final Cox proportional hazards analysis, hemoglobin ≤9g/dL was found to be significantly associated with mortality (hazard ratio [HR] = 2.27; −95 CI%, 1.01–5.10). Lastly, the hazard ratio for

death for children diagnosed in the period ≥ 2010 was marginally reduced compared to those diagnosed before 2010 (HR=0.26, 95% CI, 0.07–0.88) (Table 2, Figs.1 and 2).

DISCUSSION

We found an overall mortality rate of 2.06 deaths per 100 person-years among children who had acquired HIV infection by mother-to-child transmission in Paraguay. Additionally the cumulative mortality at the end of the study period was 17.2%. The rate found was higher than that found in a cohort with 13 years of follow-up in a multicenter US study where the rate was 1.47 deaths per 100 person-years (95% CI, 1.31–1.65) [11]. Additionally the cumulative overall mortality at the end of the study period was higher than that found in the two Brazilian or the Argentine cohorts, which varied from 3.4 to 15.0% [5,6,7].

Badie et al. conducted a study of 1,495 HIV-infected children in Iran, including 259 (17.3%) who were lost to follow-up after their first visit, and 260 (17.4%) who were lost in the 6 months following the first visit [12]. In our study, 8.8% of the children were lost to follow-up. The reduced rate of loss to follow-up can be explained by the fact that the majority of Paraguayan children go to the National Reference Center for HIV-infected children in Asunción for CD4, viral load and dispensing of antiretroviral drugs. Consequently, there is a concentration of comprehensive care services for people with HIV and also centralized records that facilitated follow-up.

Risk factors for mortality that have been reported for children included high viral load and low CD4 percentage, which are markers of longer and more progressive infection. Mofenson et al., in a study of 254 children with HIV, found that the viral load greater than 100,000 copies/ml and the CD4 count below 15% were independent predictors with an increased risk of disease progression and death [13]. In general, children with HIV infection who acquire it through perinatal transmission have prolonged viremia [14]. Palumbo et al. found in a study that evaluated 556 HIV-infected children that there was a linear, age-dependent relationship between $\log_{10}$ plasma RNA and the relative risk of disease progression, which they interpreted as strongly supporting therapeutic efforts to achieve plasma levels of virus as low as possible in children [15]. We were unable to demonstrate a similar independent association between plasma viral load at baseline and death, but we may have had insufficient power to detect an effect. Alternatively, this may be due to difficulties in interpreting plasma viral load levels during the first year of life (in our cohort more than one- quarter were less than one year old at the time of diagnosis) because the values are high and have a lower predictive value of progression than in children older than 1 year old [15].

We found that baseline anemia was a strong predictor of mortality. This agrees with results from a Brazilian study, which found that anemia was strongly associated with mortality in HIV children (OR=6.73) [6]. Anemia is a common complication of HIV infection in pediatrics; while this is most likely anemia of chronic disease, it is nonetheless important to develop strategies for the nutritional assessment of children with HIV with an emphasis on the diagnosis and treatment of iron-deficiency and other nutritional anemias. In the present study, we found that children born from 2010 through 2014 were less likely to become diagnosed with HIV. Increased decentralization of health care for people living with HIV/

AIDS and improved access to antiretroviral therapy for children in Paraguay may contribute to this decrease in mortality between periods before 2010 and afterwards.

Our study has limitations. First, in Paraguay, it is estimated that 30% of births and deaths are not reported [16], so we may have under ascertained deaths. In order to reduce under ascertainment, we extracted data from death certificates that indicated the international certificate of death version 10 (ICD10) related to AIDS and cross referenced them with clinical records and the national ART database. Secondly, like all studies that abstract demographic and clinical data, there were missing data in our study. The overall sample size is moderate; however, the number of covariates in our model effectively reduces the sample size. Therefore, caution should be taken in the data interpretation of data. To reduce the inherent limitations of retrospective cohort designs using clinical records of children with HIV as a secondary source, we used a standardized data collection form.

Despite these limitations, we believe that our data accurately reflect mortality in HIV-infected children in Paraguay. As the world moves toward the goal of elimination of mother-to-child transmission [17], greater emphasis needs to be placed on diagnosing and treating HIV infection in pregnant women in Paraguay to prevent perinatal transmission, on screening infants born to HIV-infected mothers for HIV infection early in infancy, and on treating those who have become infected before they develop more advanced disease.

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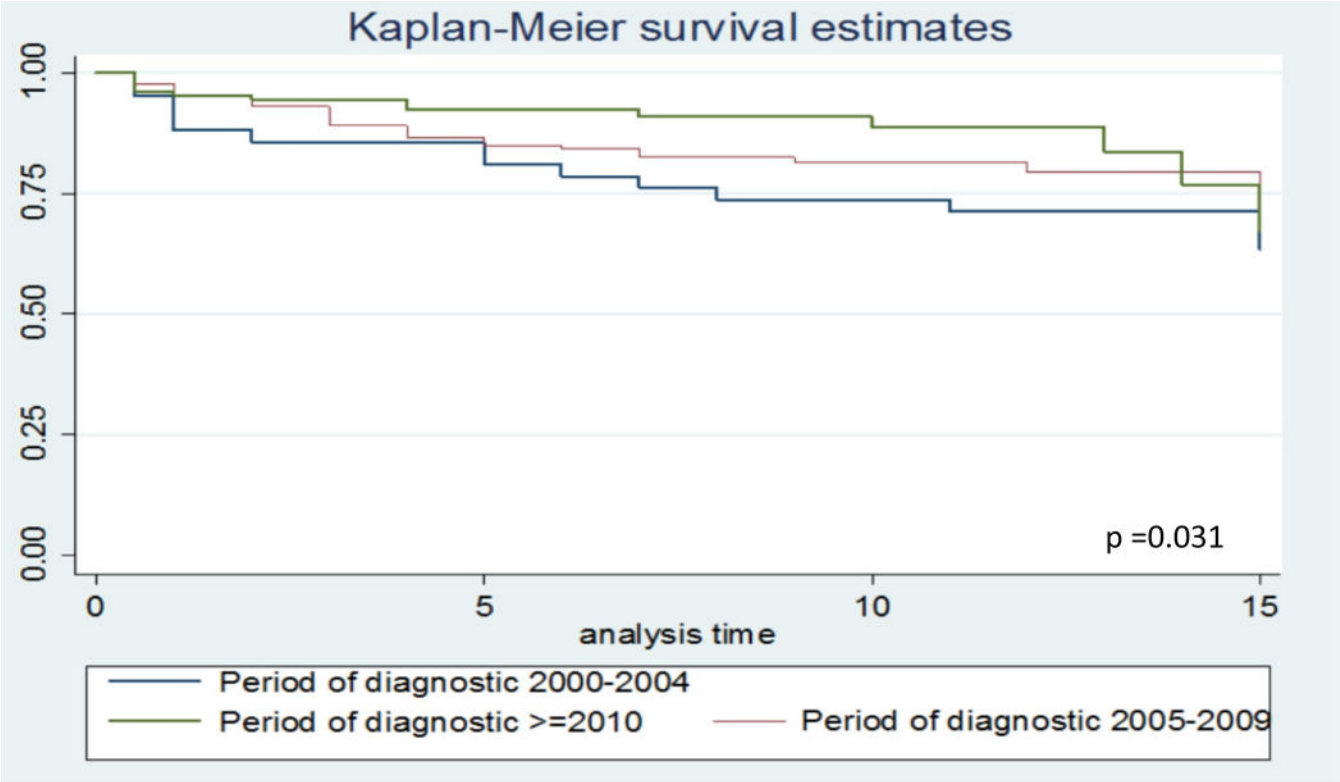

Figure 1:
Risk of mortality in children with HIV in Paraguay, stratified by period of diagnostic (2000–2004, 2005–2009, ≥2010).

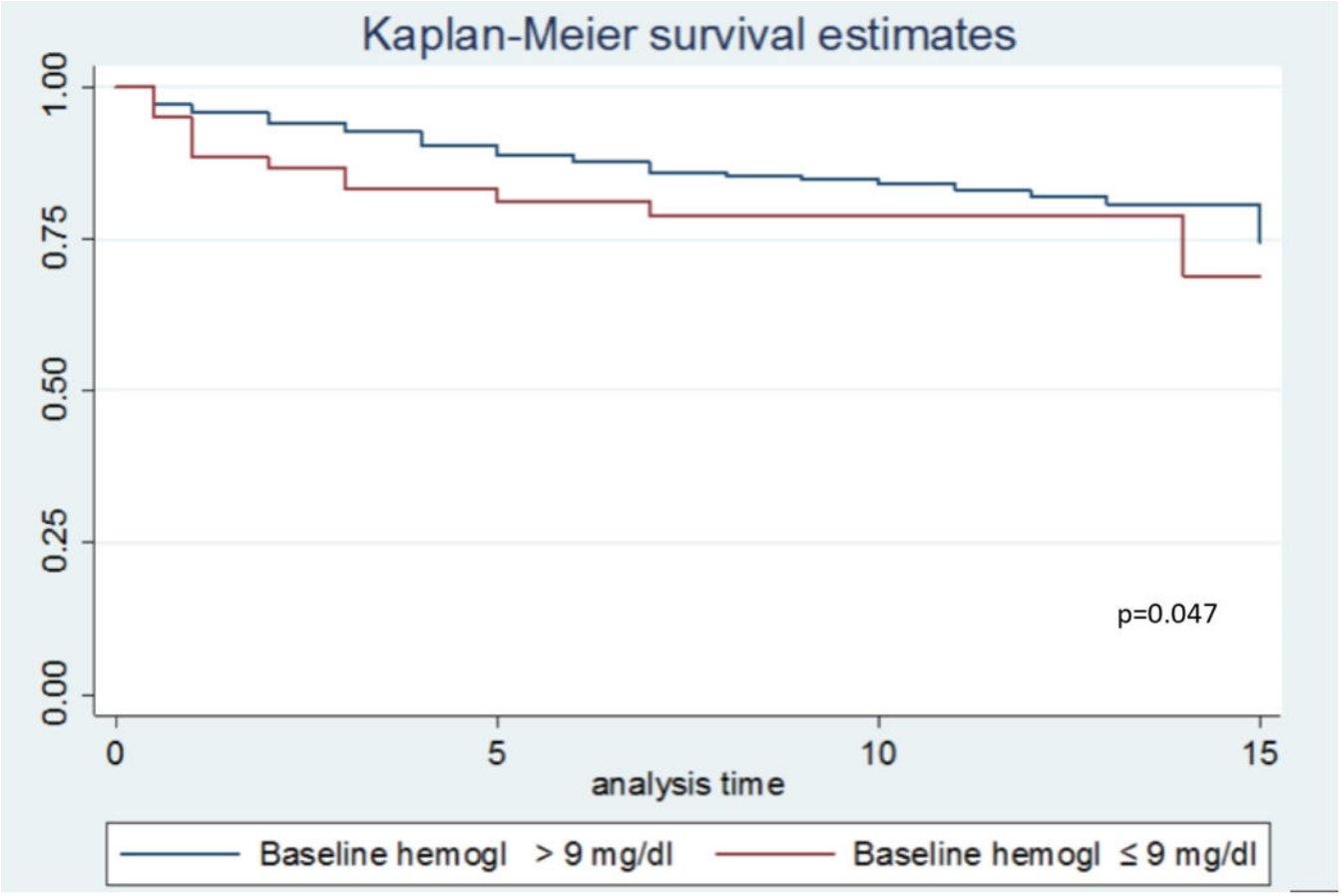

Figure 2:
Risk of mortality in children with HIV in Paraguay, stratified by baseline hemoglobin (>9 mg/dl, ≤9 mg/dl).

Table 1.

Baseline characteristics of children with HIV infection, Paraguay, 2000 – 2014 (N = 302)

Characteristics	n	%
Age of diagnosis, in years		
<1 year	71	23.6
1 a 5 years	145	48.0
>5 years	86	28.4
Period of diagnostic		
2000 – 2004	42	13.9
2005 – 2009	131	43.4
≥ 2010	129	42.7
Sex		
Male	148	51.0
Female	142	48.0
Home		
Metropolitan area	214	70.9
Another area	88	29.1
Baseline viral load, in copies ml		
≤ 100.000	102	33.7
>100000	200	66.3
Stage of infection		
Stage 1	109	39.7
Stage 2	71	25.8
Stage 3	95	34.5
Baseline Hemoglobin, in mg/dl		
> 9	241	79.8
≤9	61	20.2
Age of ART initiation, in months		
< 18 months	69	27.7
18 to 35 months	46	18.5
36 to 59 months	42	16.8
≥60 months.	92	36.0

*Another area: people living in other areas of the country (except the metropolitan area of Asuncion

Table 2.

Risk factors for mortality among HIV-infected children, Paraguay, 2000 – 2014. (N = 302)

Characteristics	n/N (%)	HR	95%CI [bivariate]	aHR	95%CI [multivariate]
Age of diagnosis, in years					
<1 year	71/302(23.51)	Ref		Ref	
1 a 5 years	145/302(48.01)	0.52	0.27 – 1.00	0.61	0.17–2.19
>5 years	86/302(28.48)	0.27	0.16 – 0.84	0.95	0.12–7.61
Period of diagnostic					
2000 – 2004	42/302(13.91)	Ref		Ref	
2005 – 2009	131/302(43.38)	0.65	0.33 – 1.28	0.51	0.20–1.33
≥ 2010	129/302(42.72)	0.47	0.22 – 1.02	0.26	0.07–0.88
Sex					
Male	148/290(51.03)	0.78	0.44 – 1.38	0.88	0.41–1.88
Female	142/ 290(48.97)	Ref		Ref	
Home					
Metropolitan area	214/302(70.86)	Ref		Ref	
Another area	88/302(29.14)	1.03	0.56 – 1,91	0.94	0.36–2.43
Baseline viral load, in copies ml					
≤ 100.000	102/302(33.77)	Ref		Ref	
>100000	200/302(66.23)	3.29	1.59–6.80	2.39	0.92–6.20
Stage of infection					
Stage 1	109/275(39.64)	Ref		Ref	
Stage 2	71/ 275(25.82)	0.36	0.15–0.85	1.40	0.57–3.45
Stage 3	95/275(34.55)	0.81	0.44–1.47	0.76	0.06–3.20
Baseline Hemoglobin, in mg/dl					
≤ 9	61/302(20.20)	1.44	0.77 – 2.70	2.27	1.01–5.10
> 9		Ref		Ref	
Age of ART initiation, in months					
< 18 months	69/249(27.71)	Ref.		Ref	
18 to 35 months	46/ 249(18.47)	1.10	0.41 – 0.97	1.50	0.41–5.50
36 to 59 months	42/249(16.87)	0.69	0.22 – 2.15	1.28	0.28–5.85
≥60 months.	92/ 249(36.95)	0.25	0.06 – 0.95	0.46	0.06–3.20

*Another area: people living in other areas of the country (except the metropolitan area of Asuncion