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Longitudinal anthropometric assessment of infants born to HIV-1-infected mothers, Belo Horizonte, Southeastern Brazil

Avaliação antropométrica longitudinal de lactentes nascidos de mães infectadas pelo HIV-1

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ABSTRACT

OBJECTIVE: To evaluate the growth parameters in infants who were born to HIV-1-infected mothers.

METHODS: The study was a longitudinal evaluation of the z-scores for the weight-for-age (WAZ), weight-for-length (WLZ) and length-for-age (LAZ) data collected from a cohort. A total of 97 non-infected and 33 HIV-infected infants born to HIV-1-infected mothers in Belo Horizonte, Southeastern Brazil, between 1995 and 2003 was studied. The average follow-up period for the infected and non-infected children was 15.8 months (variation: 6.8 to 18.0 months) and 14.3 months (variation: 6.3 to 18.6 months), respectively. A mixed-effects linear regression model was used and was fitted using a restricted maximum likelihood.

RESULTS: There was an observed decrease over time in the WAZ, LAZ and WLZ among the infected infants. At six months of age, the mean differences in the WAZ, LAZ and WLZ between the HIV-infected and non-infected infants were 1.02, 0.59, and 0.63 standard deviations, respectively. At 12 months, the mean differences in the WAZ, LAZ and WLZ between the HIV-infected and non-infected infants were 1.15, 1.01, and 0.87 standard deviations, respectively.

CONCLUSIONS: The precocious and increasing deterioration of the HIV-infected infants' anthropometric indicators demonstrates the importance of the early identification of HIV-infected infants who are at nutritional risk and the importance of the continuous assessment of nutritional interventions for these infants.

DESCRIPTORS: Infant. Body Weights and Measures. Growth and Development. HIV Infections. Infectious Disease Transmission, Vertical. Cohort Studies.

RESUMO

OBJETIVO: Avaliar os parâmetros de crescimento em lactentes nascidos de mães infectadas com o HIV-1.

MÉTODOS: Avaliação longitudinal dos z-escores peso-idade (PI), estatura-idade (EI), peso-estatura (PE) foi realizada em uma coorte. Foram estudados 97 lactentes não-infectados e 33 lactentes infectados nascidos de mães infectadas com o HIV-1 em Belo Horizonte, MG, de 1995 a 2003. O tempo mediano de seguimento para os lactentes infectados e não-infectados foi de 15,8 meses (variação: 6,8 a 18,0 meses) e 14,3 meses (variação: 6,3 a 18,6 meses), respectivamente. Utilizou-se o modelo de regressão linear de efeitos mistos ajustado por máxima verossimilhança restrita para construir as curvas de crescimento.

RESULTADOS: Os z-escores PI, EI e PE dos lactentes infectados com o HIV-1 apresentaram decréscimo. Aos seis meses, a diferença média nos z-escores PI, EI e PE entre lactentes infectados e não-infectados com o HIV era, respectivamente, 1,02, 0,59 e 0,63 desvios-padrão. Aos 12 meses, a diferença média nos z-escores PI, EI e PE entre lactentes infectados e não-infectados era, respectivamente, 1,15, 1,01 e 0,87 desvios-padrão.

CONCLUSÕES: O comprometimento precoce e crescente dos indicadores antropométricos de crianças infectadas com o HIV-1 mostra a importância de identificar precocemente crianças infectadas com o HIV que estão em risco nutricional e a necessidade de se avaliarem continuamente as intervenções nutricionais adotadas.

DESCRITORES: Lactente. Pesos e Medidas Corporais. Crescimento e Desenvolvimento. Infecções por HIV. Transmissão Vertical de Doença Infecciosa. Estudos de Coortes.

INTRODUCTION

The vertical (mother-to-child) transmission of HIV-1 is the major route for infection in children; 11,796 cases of pediatric acquired immunodeficiency syndrome (AIDS) have been reported in Brazil.[a] Initial studies on the transmission rate of HIV in this country reported a rate of 16% (95%CI: 13; 20).[19] After the introduction of antiretroviral therapy (ART) for the prevention of mother-to-child transmission of HIV-1 (PMTCT), a significant reduction in the transmission rate was observed. A multicenter study reported a transmission rate of 7.1% in 2001,[12] although lower rates have been reported in single-center studies conducted in Southeastern Brazil.[13,14,18]

The assessments of a child's weight at birth and of his or her growth are indicators of the child's nutritional status. Vertically HIV-infected children exhibit a similar weight and length at birth as non-infected children in developed countries,[17] but the differences between the infected and non-infected children begin to emerge during their first few months of life.[9,16,17] A cohort study that was conducted in Belo Horizonte, Southeastern Brazil, revealed that the decrease in growth in weight, but not in length, in HIV-infected children in Brazil was larger than that reported in a European cohort, which likely reflects background nutritional deficiencies and co-infections.[9]

The assessment of growth in HIV-infected children is important to determine the disease stage and prognosis, to assess the effectiveness and toxicity of antiretroviral therapies and to study the nutritional implications of the HIV infection.[5] Growth may be one of the most sensitive indicators of disease progression in children who are living with HIV/AIDS.[3] Even in children who are taking antiretroviral drugs, the absence of growth is a poor prognostic indicator. Weight gain is also an important indicator of the effectiveness of antiretroviral therapy.[21] Anthropometric methods are useful to monitor disease progression and to assess the response to treatment.

[a] Boletim Epidemiológico AIDST. Brasília: Ministério da Saúde. Programa Nacional de DST e AIDS; 2008[cited 2010 Feb 23];5(1). Available from: http://bvsms.saude.gov.br/bvs/periodicos/boletim_epidemiologico2008.pdf

Studies involving infants born to HIV-1-infected mothers may provide useful insights into the nutritional implications of the infection and may contribute to the development of intervention strategies for this segment of the population.

The objective of the present study was to evaluate the growth parameters of infants who were born to HIV-1-infected mothers.

METHODS

The present study included a single-center open cohort of children and began in June 1994. The data concerning the pregnancy, labor, and clinical and longitudinal laboratory evaluation of these infants were routinely collected. The Universidade Federal de Minas Gerais (UFMG) Maternal, Pediatric and Adolescent HIV Clinic is a referral center for the treatment and care of the HIV-infected population living in the Belo Horizonte metropolitan area and in other cities in the state of Minas Gerais (Southeastern Brazil). In the present study, the medical information was collected by pediatricians who specialized in immunology and infectious diseases using a standardized instrument. The time that elapsed between medical appointments varied according to each child's clinical conditions.

From 1995 to 2003, 300 HIV-infected children aged zero to 16 years were observed at the clinic. A total of 130 infants (33 infected and 97 uninfected) who were born to HIV-1-infected mothers and were admitted within the first three months of life were included in the analysis.

The average follow-up period for the infected and non-infected children was 15.8 months (variation: 6.8 to 18.0 months) and 14.3 months (variation: 6.3 to 18.6 months), respectively.

The determination of an HIV infection was based on the Brazilian National AIDS Program algorithm,[a] which considers the following as positive indicators: (a) the existence of two samples positive for HIV at two weeks of life according to a DNA–PCR (Amplicor®; Roche, Basel, Switzerland) or an RNA-PCR (NASBA®; Organon-Teknica, Boxtel, The Netherlands) method; (b) the persistence of HIV antibodies detected by an ELISA screening and a western blot at 18 months of age; or (c) the development, at any age, of a clinical condition compatible with AIDS according to the the 1994 Revised Classification System for Human Immunodeficiency Virus Infection in Children Less Than 13 Years of Age.[6] The following criteria were used to establish the absence of an HIV infection: (a)

two negative HIV DNA–PCR or RNA-PCR samples taken at ages two weeks to four months and four to six months; (b) two negative anti-HIV ELISA serum tests performed after six months of age, with a minimum interval of two months between the tests and (c) the absence of clinical conditions compatible with AIDS. All of the infants that were included in the present study were diagnosed with the infection or were confirmed to have an absence of HIV infection.

The protocol that was adopted by the UFMG Pediatric HIV Clinic to prevent the vertical transmission of HIV consists of antiretroviral use from the 14th week of pregnancy, intrapartum AZT, and postpartum oral AZT to the infant for the first six weeks of life.

The clinical and laboratory data (using standardized data forms) were coded and entered into a database.

The weight (in kilograms) and the length (in centimeters) of the non-infected infants and HIV-infected infants were measured by trained pediatricians during regular visits. The measurements were conducted according to standard procedures.[22] An electronic pediatric scale (Indústria Filizola S/A, São Paulo, Brasil) with a 125 g to 15 kg weighing capacity and a 5 g accuracy was used to weigh the children. Each child's body length was measured using a horizontal wooden stadiometer with the infant in the recumbent position. WHO Anthro software[c] (Version 2.02) was used to calculate the z-scores.

The non-infected children contributed 924 measurements to the weight-for-age z-scores, 906 measurements to the length-for-age z-scores and 906 measurements to the weight-for-length z-scores. Children living with HIV/AIDS contributed 372 measurements to the weight-for-age z-scores, 326 measurements to the length-for-age z-scores and 321 measurements to the weight-for-length z-scores.

The mean values of the weights and lengths of the infected and non-infected children, which were measured at the time of birth, were compared using a Student's t-test.[1] The distribution of the categorical variables, according to the two clinical groups, was evaluated using chi-squared and Fisher exact tests.[1] The level of significance was established at 5%. The HIV-infected children were classified according to the 1994 Centers for Disease Control and Prevention Classification for children under the age of 13.[6] Due to the unbalanced data set, the analysis was conducted using a mixed-effects linear model for z-scores. A restricted maximum likelihood was used to fit the models. The *xtmixed* function was used to determine

the estimates. The comparison of the models was based on the maximum likelihood ratio test. The effect of extra random terms was evaluated using the restricted maximum likelihood ratio test.[20]

The following covariates were included in the statistical analyses: exposure to prophylactic antiretroviral therapy regimens (1 = yes, 0 = no), gender (1 = male, 0 = female), clinical group (1 = HIV-infected, 0 = non-infected), and age (in months).

The statistical analyses were performed using Stata 9.0 software.

The present study was approved by the Ethical Review Board of UFMG (Process 075/2002).

RESULTS

The distribution by sex of the infected and non-infected infants was similar across the groups (p = 0.77). Males accounted for 45.4% and 54.6% of the infected and non-infected infants, respectively. All of the infants were born at full-term (gestational age ≥ 36 weeks).

The average age of the infants at the first medical appointment after birth differed between the infected and non-infected infants; the first medical appointment for the infected infants occurred at 1.6 months (variation: 0.06 to 3.5 months), and the first medical appointment for the non-infected infants occurred at 0.9 months (variation: 0.2 to 3.5 months) (p = 0.008).
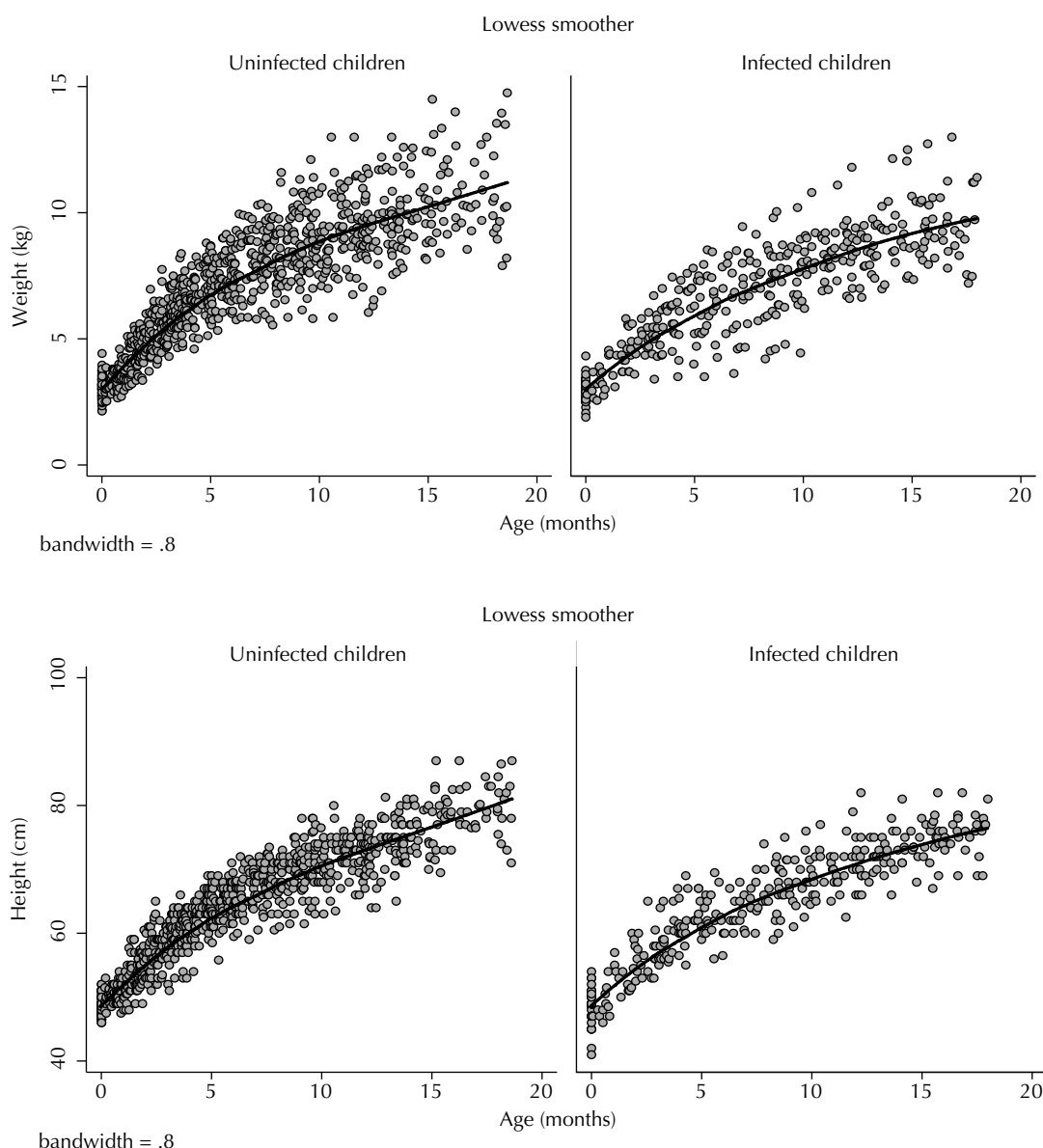
Figure 1. Observed weight and height by infection status. Belo Horizonte, Southeastern Brazil, 1995-2003.
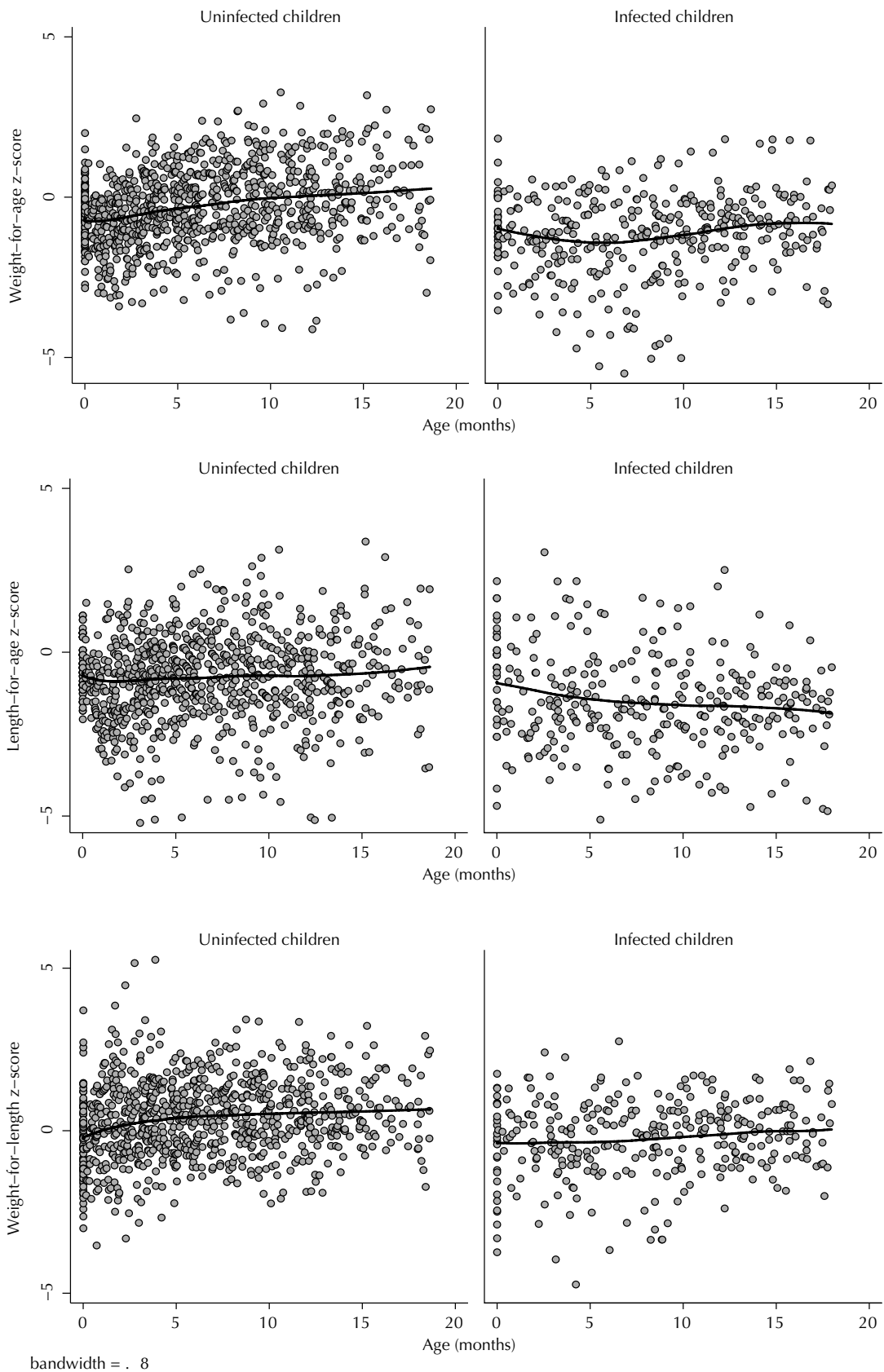
Figure 2. Observed weight-for-age, height-for-age and weight-for-length z-scores by infection status. Belo Horizonte, Southeastern Brazil, 1995-2003.

Among the infected infants, 77.4% (24/31) were asymptomatic, 16.1% (5/31) presented mild or moderate signs and symptoms of infection progression and 6.5% (2/31) presented an advanced infection progression at the first medical appointment. The clinical evaluation that was conducted at 12 months of age for 26 of the infected infants indicated that 26.9% of the children presented signs and symptoms of an advanced infection. Among the 30 infected infants for whom clinical information was available, three died, and six developed AIDS. No deaths occurred among the non-infected participants. The children's ages at the last medical appointment for the cases that ended in death were 6.8, 9.9 and 17.8 months all of these children presented signs and symptoms of advanced disease.

Exposure to antiretroviral therapy for PMTCT was reported by 95.8% of the non-transmitting mothers and by 66.7% of the transmitting mothers (p < 0.0005). Twenty-three of the 33 infected infants were exposed to antiretroviral therapy during the follow-up period; seven of the infants were not exposed to this therapy. In addition, no information about the presence of antiretroviral therapy was available for three of the participants.

Dual nucleoside analogue reverse transcriptase inhibitors (NRTI) were the initial regimen for eight of the subjects. The remaining 15 subjects were administered highly active antiretroviral therapy (HAART) as the initial therapy regimen. Twelve subjects were on a protease inhibitor (PI)-with the HAART regimen, and two were on a non-PI HAART regimen (two NRTI and one non-nucleoside analogue reverse transcriptase inhibitor). There were no changes in the initial antiretroviral therapy regimen over the course of the study.

No statistically significant differences in the weight (p = 0.15), length (p = 0.62), weight-for-age (p = 0.11), length-for-age (p = 0.68) and weight-for-length (p = 0.13) z-scores at birth were observed between the full-term infected and non-infected infants. The mean weight and length at birth were 3.1 (standard deviation – SD: 0.4 kg) and 48.7 (SD: 1.4 cm), respectively, for the non-infected infants and 3.0 (SD: 0.5 kg) and 48.6 (SD: 3.1 cm), respectively, for the infected infants. The weight-for-age, length-for-age and weight-for-length z-scores of the non-infected infants at birth were -0.52 (SD: 0.88), -0.44 (SD: 0.73), and -0.21 (SD: 1.21), respectively. The weight-for-age, length-for-age and weight-for-length z-scores of the infected infants were -0.83 (SD: 1.11), -0.56 (SD: 1.66) and -0.65 (SD: 1.55), respectively.

Figure 1 shows the height and weight measurements according to the HIV infection status, with the infected children growing more slowly than the uninfected children.

Figure 2 shows the weight-for-age, height-for-age and weight-for-length z-score measurements according to the HIV infection status, with the infected children growing more slowly than the uninfected children.

The variables clinical group (p < 0.0005), age (p < 0.0005) and exposure to antiretroviral therapy for PMTCT (p = 0.003) were significantly associated with the weight-for-age z-score in the univariate mixed-effects linear regression analysis. The final model (Table) shows a decrease in the weight-for-age z-score among the infected infants over time. The non-infected infants presented monthly average increases of 0.08 SD in their weight-for-age z-score. At six months, the

Lowess smoother
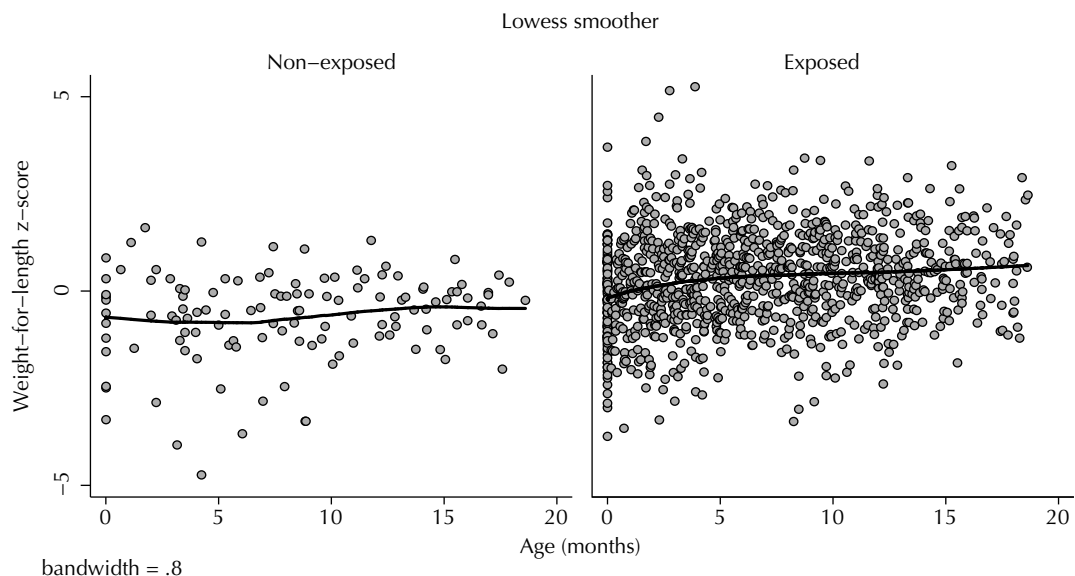
Figure 3. Observed weight-for-length z-scores by exposure to prophylactic treatment to prevent the vertical transmission of HIV. Belo Horizonte, Southeastern Brazil, 1995-2003.

average difference in the weight-for-age z-score was 1.02 SD between the infected and non-infected infants. At 12 months, the average difference in the weight-for-age z-score between the infected and non-infected infants was 1.5 SD.

In the univariate mixed-effects linear regression analysis, only the clinical group (p = 0.0004) was significantly associated with the length-for-age z-score. The age variable was included in the model to evaluate whether there was a longitudinal difference between the length-for-age z-scores of the infected and non-infected infants. The final model (Table) shows that the differences between the groups increased with age (p = 0.001). At six months, the average difference in the length-for-age z-score of the infected infants was 0.59 SD when compared to that of the non-infected infants. At 12 months, this difference increased to 1.01 SD.

In the univariate mixed-effects linear regression analysis, the variables clinical group, age and exposure to antiretroviral therapy for PMTCT were significantly associated with the weight-for-length z-score. The final model (Table) shows a decrease in the weight-for-length z-score among the infected infants over time (p=0.04). At six months, the average difference in the weight-for-length z-score between the infected and non-infected infants was 0.63 SD. At 12 months, the average difference in the weight-for-length z-scores of the infected and non-infected infants was 0.87 SD. The infants who were exposed to prophylactic treatment to prevent the vertical transmission of HIV were 0.75 SD heavier than those who were not.

Figure 3 shows the z-scores for the weight-for-length measurements by exposure to the prophylactic treatment intended to prevent the vertical transmission of HIV. The exposed children were heavier than the non-exposed children.

DISCUSSION

In the present study, no significant difference was observed between the HIV-infected and non-infected infants in terms of their weight and length at birth. Similar results have been reported in other studies.[9,17] The growth of the HIV-infected infants is affected by the disease, as shown in the differences between the weight-for-age, length-for-age and weight-for-length z-scores of this group when compared to those of the non-infected infants at six and 12 months.

The effect of intra-utero exposure to antiretrovirals on the growth pattern of HIV-uninfected infants is controversial. Many previous studies did not report differences between exposed and non-exposed infants.[7,8,11,15,17] However, one previous study reported a lower birth weight in exposed infants,[4] which was likely due to differences in the antiretroviral regimens.

Table. Final models for weight-for-age, length-for-age and weight-for-length z-scores of HIV-infected and uninfected infants. Belo Horizonte, Southeastern Brazil, 1995-2003.

Variable	Weight-for-age z-scores				Length-for-age z-scores				Weight-for-length z-scores			
	β	SD	95% CI	p	β	SD	95% CI	p	β	SD	95% CI	p
Intercept	-0.75	0.09	-0.93;-0.56	<0.0005	-0.86	0.10	-1.06;-0.65	<0.0005	-0.67	0.27	-1.19;-0.14	0.01
Clinical Group	-0.54	0.19	-0.91;-0.18	0.004	-0.17	0.21	-0.59;0.24	0.42	-0.39	0.20	-0.77;-0.0004	0.05
Age (months)	0.08	0.01	0.06;0.10	<0.0005	0.02	0.01	-0.009;0.03	0.06	0.06	0.009	0.04;0.08	<0.0005
ARTPMTCT									0.75	0.26	0.23;1.26	0.005
Interactions												
Clinical Group: age	-0.08	0.02	-0.12;-0.04	<0.0005	-0.07	0.02	-0.11;-0.03	0.001	-0.04	0.027	-0.07;-0.001	0.04
Random_effects												
Intercept	0.89	0.06	0.78;1.02		0.94	0.07	0.82;1.09		0.75	0.06	0.64;0.88	
Age	0.09	0.007	0.08;0.11		0.08	0.007	0.07;0.10		0.06	0.007	0.05;0.08	
Residues	0.50	0.01	0.48;0.53		0.75	0.02	0.72;0.78		0.84	0.02	0.81;0.89	
Measurements (n)	1.296				1.232				1.200			
Children (n)	130				130				128			

ARTPMTCT: Exposure to antiretroviral therapy for the prevention of mother-to-child transmission of HIV-1.

In the present study, the infants exposed to prophylactic treatment were heavier for their length than the children who were not exposed; this effect remained over time. The prophylactic treatment may reflect the patterns of health care and diet between the treated and non-treated mothers/infants.

A decrease over time was observed in the weight-for-age, length-for-age and weight-for-length z-scores of the infected infants. Similar results have been reported in a study conducted by Berhane et al[3] (1997) in a Uganda cohort. Growth impairment may be a consequence of the general debilitation caused by frequent opportunistic infections and the effects of these infections on the ingestion of food, nutrient absorption and energy expenditure. In addition, the literature suggests that viral replication is associated with growth impairment.[2,10]

The non-infected infants were evaluated at their first medical appointment after birth at a younger age than the infected infants. This finding may be explained by the fact that 95.8% of the mothers of the non-infected infants were followed up by the medical service of the HIV-specialized center, whereas only 66.7% of the mothers of the infected infants received this follow-up. The monitoring process that occurred throughout pregnancy may have caused these infants to be seen earlier by the team of pediatricians.

Because there were two types of individuals within the HIV-infected group (i.e., antiretroviral-therapy-treated and non-treated), various stages of the disease and differential treatments were present. Therefore, the diminished nutritional status observed amongst the HIV-infected infants may be a consequence of the progress of the disease in the treated and non-treated infants. In addition, the status may be associated with factors that were not evaluated in the present study (e.g., diminished ingestion of food, co-infections, side-effects of medication, resistance to antiretroviral therapy and adherence to treatment).

Because the infants of the Belo Horizonte cohort were regularly followed up in a specialized HIV referral center and many were born to mothers who underwent prenatal examination at the same institution, it is unlikely that these results were a consequence of selection bias. The choice of the comparison group (HIV-exposed but uninfected infants) appropriately controlled for many of the differences in the socioeconomic status and social backgrounds that may exist between the children of HIV-positive and HIV-negative mothers; however, this choice of controls is unable to separate the effects of HIV infection from social factors. Because information about food ingestion, socioeconomic data and clinical information were absent in the medical records, it was not possible to establish whether the diminished growth observed among HIV-infected children was caused by a reduced ingestion of food and nutrients, the side effects of medication, co-infections or the evolution of the disease. As is common in open cohort studies, the heterogeneity at the follow-up time points may represent a limitation of the present study. Several of the infants who were younger than 18 months when the analysis was performed were censored. Therefore, the reduced number of measurements at the end of the follow-up period for these infants may have compromised the growth model estimates.

The early and severe impacts of an HIV infection on growth parameters emphasizes the need for the identification of HIV-infected infants in the first weeks of life, followed by the implementation of nutritional interventions during care and treatment. Because of the close association of growth with immune function and the clinical progression for HIV-infected children, an understanding of the growth patterns of HIV-infected infants may represent an important tool for targeting infants for further assessment. Timely growth monitoring may be used to identify infants with suboptimal growth, to ensure the provision of appropriate care and treatment to these children and to help improve their clinical course and quality of life.

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