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Growth of human immunodeficiency type 1-infected and uninfected children: a prospective cohort study in Kigali, Rwanda, 1988 to 1993

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Objective. **To compare the anthropometric characteristics of children with and without HIV-1 infection.**

Methods. **In a prospective cohort study of 218 children born to HIV-1 seropositive mothers and 218 children born to HIV-1 seronegative mothers in Kigali, Rwanda, 3 groups were compared: infected children (n = 46); uninfected children born to seropositive mothers (n = 140); and uninfected children born to seronegative mothers (n = 207). Weight, height and head circumference were measured at birth, every 3 months during the first year of life and every 6 months thereafter. The weight-for-age, height-for-age, weight-for-height and head circumference-for-age mean z scores were calculated.**

Results. **The weight-for-age, height-for-age and head circumference-for-age mean z scores were lower among HIV-infected children than among uninfected ones at each time period. The reduction in the weight-for-age mean z score was the greatest between 12 and 36 months. The reduction in the height-for-age mean z score of HIV-infected children was persistently below 2 SD after 9 months of age. On the other hand the weight-for-height mean z score was not consistently lower in HIV-infected children when compared with uninfected ones. The anthropometric characteristics of uninfected children born to seropositive mothers were similar to those of children born to seronegative mothers.**

Conclusions. **In this study HIV-infected children were more frequently stunted (low height-for-age) than uninfected ones. Wasting (low weight-for-height) was not common among HIV-infected children.**

INTRODUCTION

Since the first descriptions of pediatric AIDS a decade ago,[1-3] a large body of information has accumulated on the mother to child transmission of HIV type 1, its natural history and the clinical expression of HIV infection in children.[4-11] However, few data are available on the anthropometric characteristics of HIV-infected children,[12-15] particularly in sub-Saharan Africa where the majority of pediatric AIDS cases occur.

From 1988 to 1994 a prospective cohort study on the perinatal transmission of HIV has been performed in Kigali, the capital of Rwanda.[16, 17] We report on the anthropometric findings collected during the first 4 years of life on children born to HIV-infected and uninfected mothers.

METHODS

Details about enrollment and follow-up procedures in the cohort have been described elsewhere.[16] Briefly 218 infants born to 215 HIV-seropositive mothers were enrolled at birth between November, 1988, and June, 1989, at the maternity ward of the Centre Hospitalier de Kigali. These children were matched with 218 children born to HIV-seronegative mothers of the same age and parity.

The children and their mothers were followed every 2 weeks during the first 2 years of follow-up and every

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4 weeks thereafter. They were either visited at home by a social worker or attended the outpatient clinic organized within the Mother and Child Health Clinic of the Centre Hospitalier de Kigali. In addition the children were systematically examined by a physician every 3 months during the first year of life and every 6 months thereafter. When necessary children were seen in the outpatient department or hospitalized in the Department of Pediatrics and treated free of charge. All the children were immunized during the first 15 months of life following the recommendations of the World Health Organization Expanded Programme of Immunization with one exception; a high dose Edmonston-Zagreb measles vaccine was given at 6 months of age in the place of the Schwarz vaccine at 9 months.[18] The physicians and social workers were blinded to the HIV infection status of the children to 18 months of age.

Definitions of pediatric HIV infection and classification of the children. Criteria used to define children born to seropositive mothers as infected with HIV, uninfected or with an indeterminate status were drawn from a Working Group Consensus on Mother-to-Child Transmission of HIV-1.[8] This classification takes into account the HIV antibody serostatus at 15 months of age and, when the child died before this age, the presence or absence of signs and symptoms possibly related to HIV infection. Death was defined as HIV-related either (1) in a child fulfilling the WHO clinical case definition of pediatric AIDS (in which severe and/or recurrent pulmonary infection was considered as a major sign in the place of chronic cough as a minor sign)[19, 20] or (2) in a child with at least one HIV-related sign/symptom when last seen and dying from severe infection or persistent diarrhea (≥14 days) beyond the first 4 weeks of life. The following signs and symptoms were regarded as HIV-related: persistent diarrhea; failure to thrive (< 80% weight for age); generalized lymphadenopathy (lymph nodes measuring at least 0.5 cm and present in two or more extrainguinal sites); oral candidiasis (beyond the neonatal period); severe or recurrent pneumonia; chronic parotitis and herpes zoster infection (shingles).

The children born to HIV-seropositive mothers were considered as HIV-infected (Group 1) (1) if they presented clinical manifestations of AIDS at any time during the follow-up, (2) if they were positive for HIV antibody at 15 months of age or (3) if they died before 15 months of age and their death was considered HIV-related. They were considered as HIV-uninfected or seroreverters (Group 2) if (1) they were negative for HIV antibody at 15 months or (2) if they died before that age, they were HIV-seronegative and their death was probably unrelated to HIV. Children born to HIV-seropositive mothers who were lost to follow-up before 15 months of age were considered uninfected when the HIV antibody test was negative at 9 months of age or beyond. In all other circumstances the HIV infection status of children born to HIV-seropositive women was considered indeterminate (Group 4).[8]

The children born to HIV-seronegative mothers (Group 3) were retested for HIV antibody every 3 months. Nine of them who became HIV seropositive before the age of 24 months[21] together with their mothers were excluded from the analysis after the presumed time of seroconversion.

Serologic methods. At delivery and at 3-month intervals thereafter, the child and mother's sera were tested for HIV-1 antibodies by a commercial enzyme-linked immunosorbent assay (EIA; Vironostika®; Organon Teknika, Boxtel, the Netherlands). Samples that tested positive were further confirmed by a commercial Western blot technique (Du Pont, Wilmington, DE) with the Centers for Disease Control criteria of interpretation.[22]

Anthropometric measurements. Weights, heights and head circumferences were obtained at birth and at 3-month intervals thereafter. Naked children were weighed on a mechanical scale (Seca®). Heights were obtained horizontally in a length-measuring box until 36 months of age and vertically thereafter.

Statistics. Weight-for-age (W-A), height-for-age (H-A), head circumference-for-age (HC-A) and weight-for-height (W-H) z scores were calculated with the data from the National Center for Health Statistics as references.[23, 24] The z score (or SD score) for W-A, for instance, is calculated by subtracting the median weight of the reference population at the child's age from the child's weight and dividing by the SD of the weight of the reference population at that age. Values are reported under Results as mean z score ± SD.

Analysis of variance was used for comparison between the groups. Each time the overall P value reached the chosen level of significance (0.05), two group comparisons (Group 1 *vs.* Group 2, Group 1 *vs.* Group 3 and Group 2 *vs.* Group 3) were performed and results were considered statistically significant at $P = 0.017$, using the Bonferroni correction for multiple comparisons and taking into account the sample size of each group compared.

RESULTS

Among the 218 children born to HIV-seropositive mothers, 46 were classified as HIV-infected (Group 1), 140 as uninfected (Group 2) and 32 as indeterminate for HIV infection (Group 4). Table 1 summarizes the number of children alive at each time of nutritional assessment, the number of children with anthropometric measurements performed and the number of children who died in the preceding period.

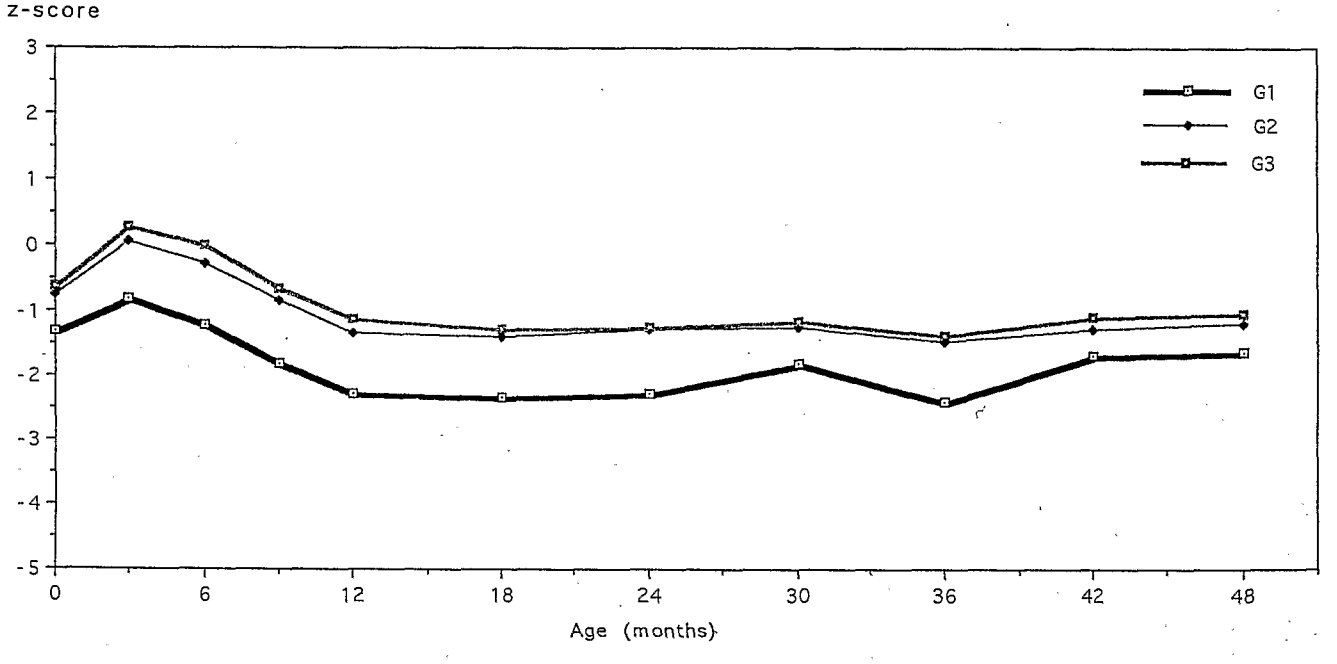
The W-A, H-A and HC-A mean z scores were lower

TABLE 1. Summary of the first 4 years of follow-up and of anthropometric measurements performed in children born to HIV-positive and -negative mothers, Kigali (Rwanda), 1989 to 1993

Age (mo)	Examined/Alive				Total	
	Group 1. HIV-1-infected children	Group 2. Uninfected children born to seropositive mothers	Group 3. Uninfected children born to seronegative mothers	Group 4. Indeterminate*	Examined/alive	Deaths in the preceding period
3	46/46 (100)†	140/140 (100)	207/207 (100)	21/21 (100)	414/414 (100)	15
6	41/42 (98)	140/140 (100)	196/204 (96)	16/18 (89)	393/404 (97)	6
9	37/39 (95)	140/140 (100)	186/201 (93)	3/11 (27)	366/391 (94)	5
12	33/33 (100)	137/139 (99)	182/199 (91)	0/8 (0)	352/379 (93)	10
18	22/25 (88)	126/137 (92)	164/195 (84)		312/357 (87)	9
24	18/22 (82)	117/130 (90)	156/189 (83)		291/341 (85)	5
30	16/18 (89)	112/127 (88)	157/184 (85)		285/329 (87)	3
36	13/15 (87)	101/112 (90)	146/170 (86)		260/297 (88)	1
42	13/14 (87)	96/112 (86)	134/158 (85)		243/284 (86)	1
48	10/14 (71)	93/107 (87)	132/148 (89)		235/269 (87)	1

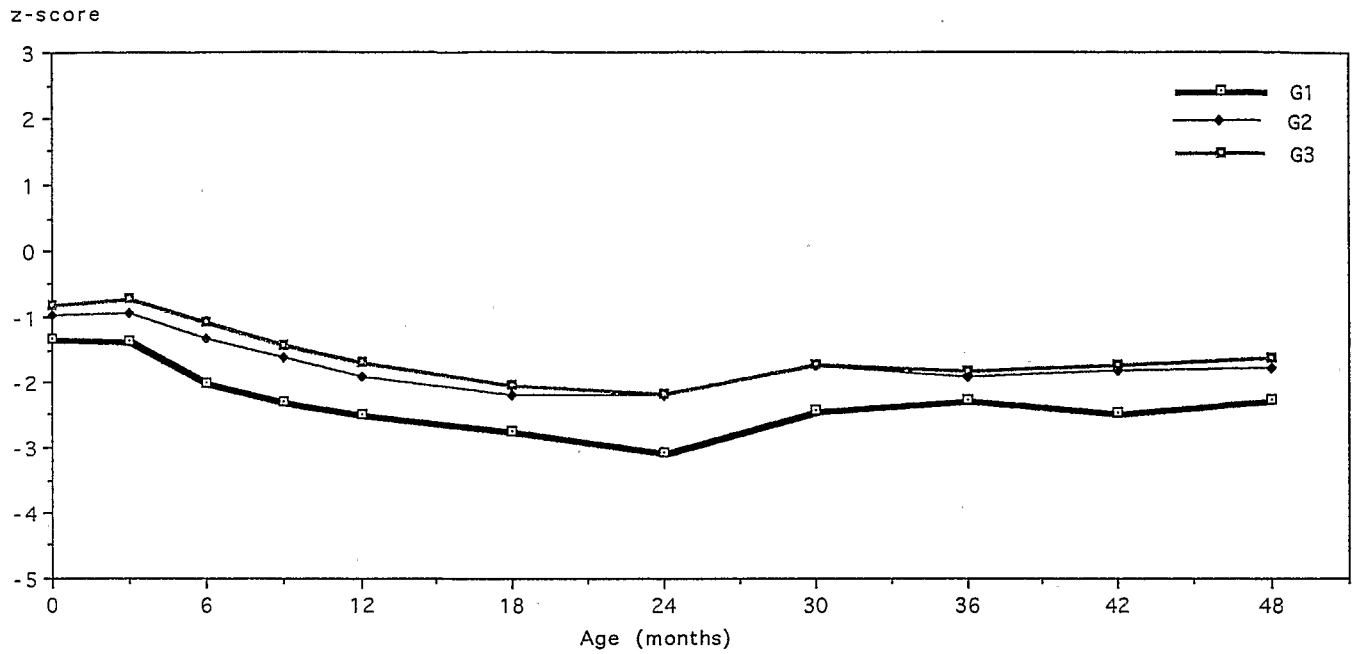
* See definitions under Methods.
† Numbers in parentheses, percent.

throughout the entire follow-up period among HIV-infected children than among uninfected ones (Figs. 1 to 3). The difference in the W-A and H-A mean *z* scores between Group 1 and Group 3 children was statistically significant ($P < 0.017$) during the first 3 years of life (except at 30 months of age for the W-A mean *z* score (Fig. 1) and except at 36 months of age for the H-A mean *z* score (Fig. 2)). The difference in the HC-A mean *z* scores between Group 1 and Group 3 children was statistically significant ($P < 0.017$) during the first 2 years of life (except at birth, 12 and 18 months of age (Fig. 3)). The reduction in the W-A mean *z* score was



p-value Age	0	3	6	9	12	18	24	30	36	42	48
G1 vs G2	0.003	10^{-5}	10^{-5}	10^{-5}	10^{-3}	10^{-3}	10^{-3}	0.05	10^{-3}	0.20	-
G1 vs G3	10^{-4}	10^{-8}	10^{-8}	10^{-7}	10^{-5}	10^{-3}	10^{-3}	0.02	10^{-3}	0.02	-
G2 vs G3	0.20	0.06	0.02	0.14	0.11	0.30	0.90	0.50	0.50	0.10	-
Overall	$< 10^{-3}$	10^{-3}	10^{-4}	$< 10^{-3}$	10^{-4}	10^{-4}	10^{-4}	0.03	10^{-3}	0.03	0.07

FIG. 1. Mean weight-for-age *z* score in HIV-1-infected and uninfected children, Kigali (Rwanda), 1989 to 1993. *G1*, HIV-infected children; *G2*, uninfected children born to seropositive mothers; *G3*, uninfected children born to seronegative mothers.



Age	0	3	6	9	12	18	24	30	36	42	48
p-value											
G1 vs G2	0.04	0.02	0.01	0.01	0.02	0.02	10^{-3}	0.01	-	0.05	-
G1 vs G3	$< 10^{-3}$	10^{-3}	10^{-5}	10^{-3}	0.01	0.01	10^{-3}	0.01	-	0.02	-
G2 vs G3	0.10	0.04	0.01	0.05	0.06	0.20	0.90	0.90	-	0.50	-
Overall	10^{-4}	10^{-3}	10^{-4}	10^{-4}	$< 10^{-3}$	0.006	0.002	0.02	0.28	0.04	0.13

FIG. 2. Mean height-for-age *z* score in HIV-1-infected and uninfected children, Kigali (Rwanda), 1989 to 1993. *G1*, HIV-infected children; *G2*, uninfected children born to seropositive mothers; *G3*, uninfected children born to seronegative mothers.

already noticeable at 3 months of age but was the greatest (below 2 SD) between 12 and 36 months of age (Fig. 1). The reduction in the H-A mean *z* score of HIV-infected children was also manifest at 3 months of age, with a decrease below 2 SD from 9 to 48 months of age (Fig. 2). Moreover the HC-A mean z score of HIV-infected children was below 1 SDSD from 18 to 36 months of age (Fig. 3).

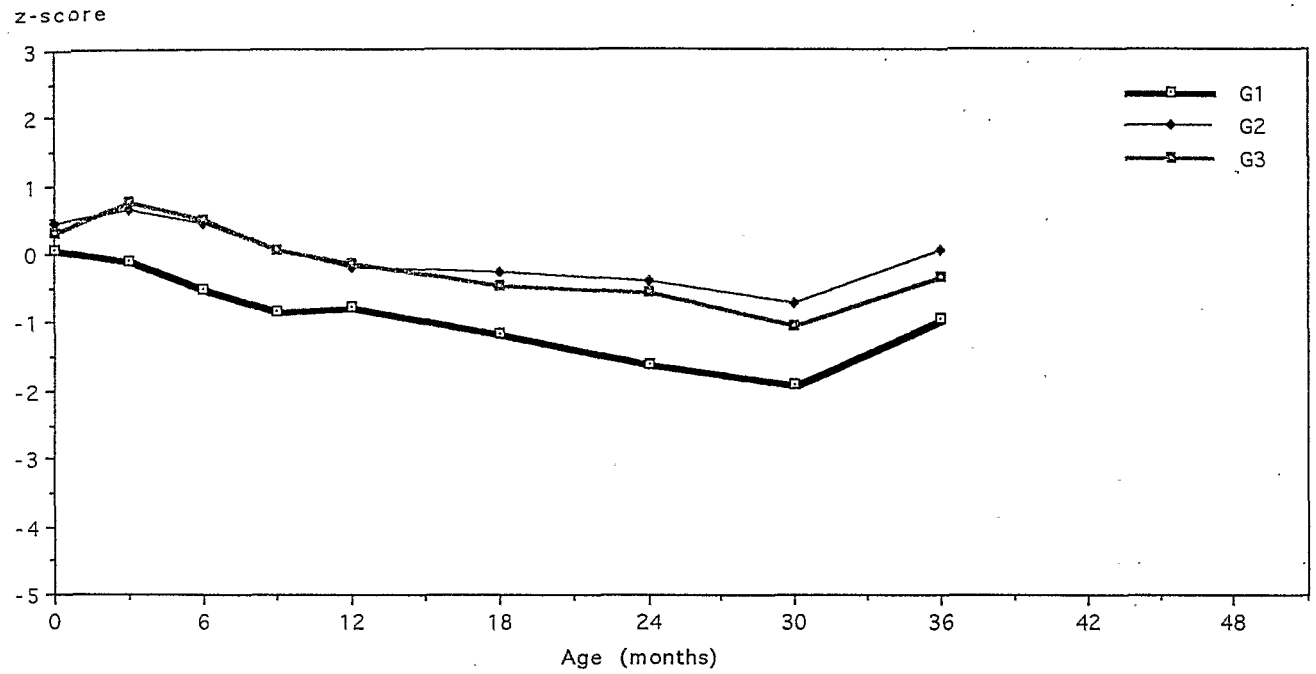
On the other hand the W-H mean *z* score was rarely lower in HIV-infected children than in uninfected ones, the difference being only statistically significant ($P < 0.017$ for Group 1 *vs.* Group 3) at ages 3, 6, 24 and 36 months (Fig. 4). The W-H mean *z* score of HIV-infected children was not frequently impaired according to international standards.

Although often low in comparison to international standards, the W-A, H-A and HC-A mean *z* scores of HIV-uninfected children born to seropositive (Group 2) and those born to seronegative mothers (Group 3) were comparable (Figs. 1 to 3). Indeed statistically significant differences for W-A, H-A and HC-A mean *z* scores ($P < 0.017$ for Group 2 *vs.* Group 3) were not observed during the first 48 months of life between these two groups except at 6 months of age for the H-A mean *z* score (Fig. 2).

Among the HIV-infected children who survived until 48 months of age, there was a decline of the W-A mean *z* score until 36 months of age (at 12 months, -1.53 ± 1.11; at 24 months, -1.90 ± 1.63; at 36 months, -2.31 ± 0.98) with a stabilization in the growth parameters thereafter. At 12 months of age the anthropometric characteristics of the HIV-1-infected children who survived this second year of life were better than those of infected children who died between 12 and 24 months: W-A mean *z* score of survivors ($n = 21$), -1.84 ± 1.42 *vs.* -3.05 ± 1.10 among those who died ($n = 12$) ($P = 0.009$); H-A mean *z* score of survivors, -2.12 ± 0.86 *vs.* -3.22 ± 1.85 among those who died ($P = 0.03$).

DISCUSSION

Studies from Africa[25, 26] have previously shown that the mean birth weight and the mean birth length of HIV-infected children was lower than among uninfected newborns of HIV-seronegative mothers. In the United States McKinney et al.[12] have retrospectively analyzed the growth of children born to seropositive

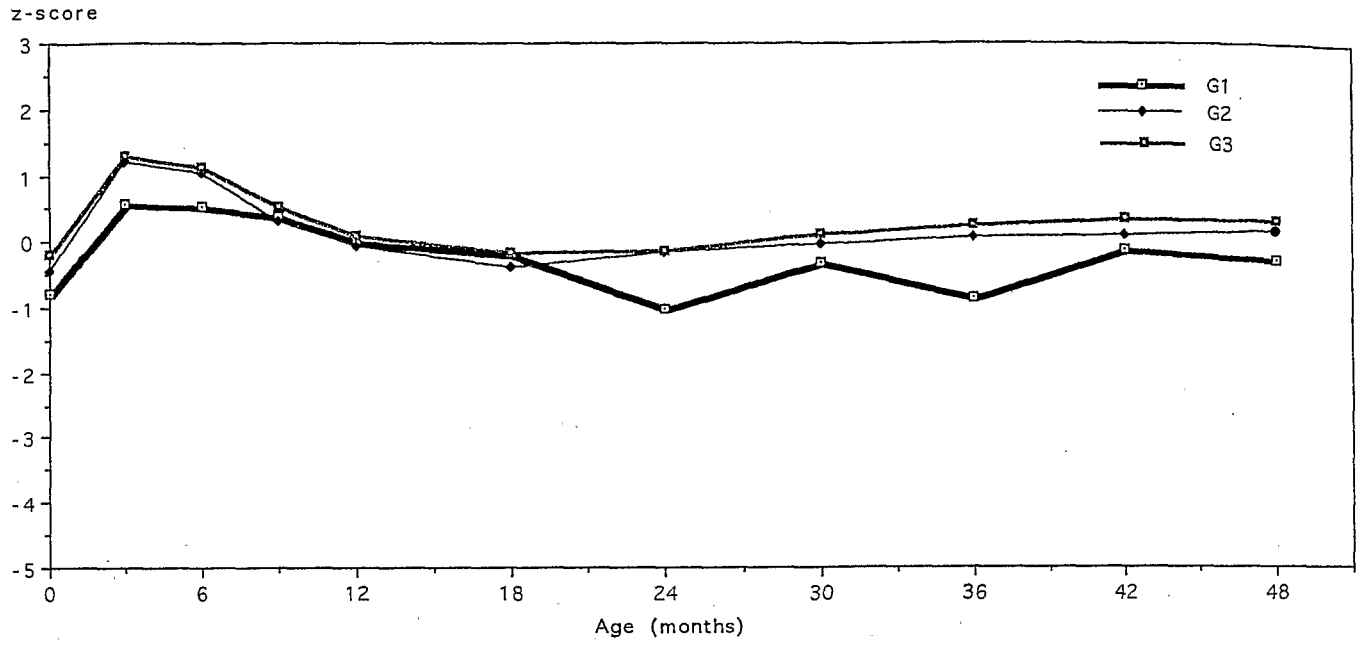


Age	0	3	6	9	12	18	24	30	36
p-value									
G1 vs G2	-	0.01	10^{-3}	0.01	-	0.01	0.01	0.01	-
G1 vs G3	-	10^{-3}	10^{-3}	0.01	-	0.05	0.01	0.05	-
G2 vs G3	-	0.34	0.81	0.99	-	0.30	0.50	0.10	-
Overall	0.26	0.003	$< 10^{-3}$	0.002	0.07	0.006	0.02	0.01	0.07

FIG. 3. Mean head circumference-for-age *z* score in HIV-1-infected and uninfected children, Kigali (Rwanda), 1989 to 1993. *G1*, HIV-infected children; *G2*, uninfected children born to seropositive mothers; *G3*, uninfected children born to seronegative mothers.

mothers and observed diminished stature and weight gain in HIV-infected children when they were compared to seroreverters. However, two-thirds of the HIV-infected children included in their study were referred for antiretroviral therapy after 3 months of age; therefore the design of this study was not optimal to evaluate the general impact of HIV on the nutritional status of young HIV-infected children. In the European Collaborative Study[15] HIV-infected children were shorter and weighed less than their uninfected counterparts. Although statistically significant, the difference between infected and uninfected children was small in this study.[15] Until now follow-up studies of anthropometric measurements of African HIV-infected children were lacking.

Our prospective cohort study of Rwandan children born to HIV-infected and uninfected mothers followed from birth until 48 months of age demonstrates an early, severe and sustained impairment in weight, height and head circumference gain among HIV-infected children when compared with uninfected ones of the same age, birth order and socioeconomic status. None of these African HIV-infected children received zidovudine. Indeed antiretroviral treatment has a positive impact on weight growth rates.[27] On the other hand the W-H mean *z* scores of HIV-infected children from this study were generally comparable to the figures obtained with uninfected ones or to international standards. The same findings were observed in North American children[12] as well as among perinatally HIV-1-infected school age children in Rwanda.[28] A cross-sectional study of malnourished children with an HIV-1 seroprevalence of 14% in Butare, Rwanda, also showed that seropositivity was found more frequently among children with low W-A and H-A than among those with low W-H.[29] The pathogenesis of malnutrition in HIV-1 infection is poorly understood and the respective roles of infections, endocrinologic dysfunctions and the possibility of an increased resting energy expenditure in infected patients remain to be delineated.[28, 30-32] In this study low W-A and low H-A occurred only in HIV-1-infected children with a history of severe and/or persistent infectious illnesses such as persistent diarrhea, chronic fever and pneumonia (data not shown), strongly suggesting that infections were an important cause of poorer growth in these infected



Age	0	3	6	9	12	18	24	30	36	42	48
p-value											
G1 vs G2	-	10^{-3}	0.02	-	-	-	0.01	-	0.01	-	-
G1 vs G3	-	10^{-3}	0.01	-	-	-	0.01	-	0.01	-	-
G2 vs G3	-	0.58	0.55	-	-	-	0.90	-	0.20	-	-
Overall	0.06	$< 10^{-3}$	0.02	0.50	0.50	0.27	0.004	0.20	0.003	0.15	0.27

FIGURE 4. Mean weight-for-height *z* score in HIV-1-infected and uninfected children, Kigali (Rwanda), 1989 to 1993. *G1*, HIV-infected children; *G2*, uninfected children born to seropositive mothers; *G3*, uninfected children born to seronegative mothers.

children. Larger numbers of HIV-1-infected children are needed to confirm the stabilization of the growth measurements observed between 24 and 48 months of age in this study. Moreover, more detailed nutritional studies should be undertaken to determine the mechanisms of malnutrition in these HIV-1-infected children.

Until 36 months of age the HC-A mean *z* scores of the HIV-1-infected children were lower than those of uninfected ones in this study. This is consistent with the demonstrated neurotropic characteristics of HIV-1.[33] HIV-infected children from this cohort have previously been shown to be more frequently developmentally delayed than HIV-uninfected children during the first 2 years of life, although no case of encephalopathy has been observed during this period.[34]

This study emphasizes the importance of the comparison groups of uninfected children of the same socioeconomic, obstetrical and genetic background for the interpretation of anthropometric indices and their evolution over time. In this study uninfected children born to seropositive mothers had the same W-A, H-A and HC-A mean *z* scores than those born to seronegative mothers. We have already shown that uninfected children born to seropositive mothers had the same neonatal characteristics and the same neurodevelopmental testing than those born to seronegative mothers.[25, 34] In contrast we have now demonstrated that these uninfected children are frequently thin and small in comparison to international standards.

In conclusion this study shows that Rwandan HIV-1-infected children ages 0 to 48 months old are frequently undernourished (low W-A) and stunted (low H-A), but not wasted (low W-H), compared with uninfected children. Uninfected children born to HIV-1-seropositive mothers and those born to seronegative mothers have the same anthropometric characteristics. Recent cross-sectional[35] and longitudinal[36] data from Zaire have shown that diarrhea was strongly associated with severe malnutrition and HIV-1 infection. Therefore it remains to be demonstrated whether early nutritional interventions in those children with stunting and low W-A have an impact on the survival of African HIV-1-infected children.

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This article is dedicated to the memory of Dr. Anatholie Bazubagira who was murdered in April, 1994, during the genocide in Rwanda.

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