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Human immunodeficiency virus infection, diarrheal disease and sociodemographic predictors of child growth

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Aim: To compare growth patterns between human immunodeficiency virus (HIV)-infected and -uninfected preschool children. To examine the associations between diarrheal and respiratory infections, sociodemographic factors and growth. *Methods:* A longitudinal study was conducted among 524 children who were 6–60 mo of age at recruitment. Information on sociodemographic characteristics was collected at baseline from the caregiver. Hemoglobin, malaria infection and HIV status of the children were assessed from a blood sample. Monthly height (length if $<$24 mo) and weight measurements were obtained, and clinical assessments carried out, during an average 12 mo follow-up period. Yearly increments in height and weight were compared by HIV status, incidence of diarrhea and respiratory infections, and levels of sociodemographic variables. *Results:* After adjusting for maternal education, anemia and vitamin A supplementation, HIV infection was related to 2.8 cm [95% confidence interval (95% CI) 0.6, 5.0] and 1.3 kg (95% CI 0.0, 2.5) lower yearly length and weight gains, respectively, in children who were between 6 and 11 mo old at baseline. Among children who were 12–23 mo old at recruitment, HIV infection was associated with 0.6 kg (95% CI 0.1, 1.0) less yearly weight gain. HIV infection was not related to linear or ponderal growth in children $\geq$24 mo old. Maternal illiteracy, severe child anemia and episodes of acute diarrhea were additional risk factors for growth delay in length.

Conclusion: HIV infection is associated with linear and ponderal growth retardation in children aged $<$24 mo. Additional predictors of linear growth retardation include preventable conditions such as poor maternal education, child anemia and diarrheal disease.

Key words: *diarrhea, growth, height, HIV, weight*

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Several causes of growth delay in the course of human immunodeficiency virus (HIV) infection have been identified in studies from industrialized countries (1). In sub-Saharan Africa, however, where the HIV epidemic is taking the highest toll and antiretroviral treatment is not widely available, longitudinal studies on the magnitude and causes of HIV-associated growth delay are limited. Results from some prospective studies suggest that postnatal growth retardation of HIV-infected African children starts early in life and affects both length-for-age and weight-for-age indicators (2–6). Follow-up beyond 2 y of age has been reported in only one study from Africa (2).

In the absence of antiretroviral therapy, poor growth patterns are predictive of increased infant mortality (5). Therefore, it is important to identify risk factors for growth retardation in the context of the HIV epidemic, in order to propose interventions that could decrease the burden of growth delay and the increased mortality risk associated with it. Using data from a vitamin A trial conducted in Dar es Salaam, Tanzania, this study compared the growth pattern of HIV-infected and -uninfected children who were 6–60 mo of age at recruitment, and were followed up monthly for 1 y. The study also examined whether sociodemographic conditions and the incidence of diarrheal and respiratory infections were related to the growth pattern of preschool children in this population.

Subjects and methods

Study population and design

Data for the present study were collected in the context of a clinical trial of vitamin A supplementation in Dar es Salaam, Tanzania. Details of the study design and

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population have been published previously (7, 8). In brief, 687 children 6–60 mo of age who were admitted to hospital with pneumonia were randomized to receive a dose of 200 000 IU vitamin A (100 000 if <12 mo) on 2 consecutive days, and third and fourth doses at 4 and 8 mo after discharge from hospital, respectively. At baseline, study personnel collected information from the caregivers on the children's feeding practices, history of immunizations and socioeconomic characteristics, which included parental age, level of education, occupation, quality of housing and water supply, and number and type of household possessions. A study physician conducted a complete clinical examination, and trained personnel obtained anthropometric measurements using standardized procedures. Height or recumbent length (if <24 mo) was measured to the nearest 0.1 cm using stadiometers or infant length boards. Weight was measured on calibrated beam balance scales to the nearest 0.1 kg. Mid-upper arm circumference (MUAC) was measured with a non-stretchable tape to the nearest 0.1 cm. Children were followed up for 1 y after discharge from the initial hospitalization. Follow-up was conducted through monthly visits to the study clinic and alternating biweekly visits to the child's home. At every monthly visit to the clinic a medical examination was carried out and anthropometric measurements were obtained. Morbidity surveillance for diarrhea and respiratory infections during the previous month was conducted during the follow-up visits using a pictorial diary. The child's respiratory rate was measured at each visit with a stopwatch. Diarrhea was defined according to the mother's perception of the number and characteristics of motions. An episode was considered finished when at least 3 d had elapsed without diarrhea. Acute diarrhea included all episodes that lasted for <14 d; episodes that lasted 14 d or more were categorized as persistent diarrhea. Dysentery included all episodes with mucus or blood, and all others were defined as watery diarrhea. Respiratory infection was defined as the occurrence of cough and fever or the occurrence of cough alone during the period and rapid respiratory rate on the home visit day.

Laboratory procedures

At baseline, a blood specimen was obtained from all children and from a subsample at 4 and 8 mo of follow-up. Hemoglobin, packed cell volume and red cell counts were determined by standard techniques. Malaria infection was assessed by thick and thin blood smears stained with Giemsa. The latest blood specimen available for each child was tested for HIV antibodies using enzyme-linked immunosorbent assay (Murex Biotech, Dartford, UK) and confirmed by Western blot (BioRad Laboratories, Hertfordshire, UK). The HIV status of children who were younger than 15 mo and had positive or indeterminate results was also tested using heat-denatured HIV-p24 antigen assays with confirmatory neutralization assays (DuPont, Wilmington, DE, USA). The p24 antigen assay has been found to have 98.7% sensitivity and 100% specificity for the diagnosis of HIV infection in infants, when compared against detection of HIV-1 DNA by polymerase chain reaction (9).

Data analyses

The study base comprised the group of children who had at least two anthropometric measurements available after 14 d of discharge from the hospital and for whom HIV status was known. The association between HIV status and two continuous endpoints, height and weight attained after 1 y of follow-up, was examined. The associations between these endpoints and other categorical exposure variables were also studied, including sociodemographic characteristics (maternal age, parity, level of education, occupation and marital status; number of household amenities, quality of water supply and presence of electricity at home), the child's gender, severe anemia (hemoglobin concentration $<70\ \mathrm{g\,l^{-1}}$), presence of malaria parasites in peripheral blood and low lymphocyte count (<25th percentile of the population-specific distribution: $4200\ \mathrm{mm^{-3}}$) at baseline, severity of pneumonia on admission to hospital (having either rapid respiratory rate, >60 breaths $\mathrm{min^{-1}}$; high fever, ≥39°C; or severe hypoxemia, defined as oxygen saturation <90%) and the estimated number of episodes per year of diarrhea or respiratory infection during follow-up (multiplying the total number of episodes by the number of follow-up days divided by 360). Analyses were conducted separately for baseline age groups 6–11, 12–23 and ≥24 mo.

Differences in attained height and weight between HIV-infected and -uninfected children were estimated from mixed effects models. In these models, the outcome variable was height or weight (*HEIGHT* in the equation below) of each child (*i*) at each point of follow-up (*j*), and predictors included HIV status as a binary exposure (*HIV*), age (*AGE*) of the child at the follow-up time when the outcome was assessed, and an interaction term between the exposure and the time terms (*HIV*AGE*). A model that incorporated a quadratic term for age yielded similar results as a linear model; therefore, the more parsimonious linear model was chosen:

$$HEIGHT_{ij} = (\beta_0 + b_{i_0}) + \beta_1 HIV_i + (\beta_2 + b_{i_1}) AGE_{ij} + \beta_3 HIV_i * AGE_{ij} + e_{ij}$$

Mixed models incorporate individual variability (random effects) and explanatory covariates (fixed effects), and do not require the same number of observations on each subject or that the measurements be at the same time intervals within or between individuals (10). Therefore, all available anthropometric measurements for every child were included in these models. The introduction of random effects accounts for within-person correlation of measurements in the estimation of the variances.

Adjusted differences in attained height or weight by HIV status were obtained from multivariate models in which the baseline characteristics that were significantly associated with growth in univariate analyses at $p < 0.10$, or whose distribution differed significantly by HIV status at baseline, were introduced as covariates. Only variables that remained significant at $p \leq 0.05$ or that were considered relevant from the mechanistic viewpoint were retained in the final multivariate models. Confidence intervals for the differences in attained height or weight by HIV infection and other covariates were calculated using robust estimators of the variance (10). Vitamin A supplementation had a positive effect on growth among HIV-infected infants in this population (8); therefore, all multivariate models were adjusted for regimen assignment (vitamin A vs placebo). Data were analyzed with Statistical Analyses System software (SAS Institute, Cary, NC, USA).

The protocol was approved by the Research and Publications Committee of Muhimbili University College of Health Sciences, the Research and Ethics Committee of Tanzania Food and Nutrition Center, and the Human Subjects Committee of the Harvard School of Public Health.

Results

Of 687 children recruited, 37 died in the hospital or within 14 d after discharge from the clinic and were excluded from growth analyses. Also excluded were children whose caregivers discharged them from the hospital and could not be traced ($n = 18$), moved out of the study area ($n = 25$) or moved within the city to an unknown address ($n = 33$). An additional 20 children did not have at least two measurements of height and weight available, and another 30 did not have a known HIV status. Therefore, 524 constituted the analysis cohort. There were no differences between this analysis cohort and the original group of 687 recruited children in terms of sociodemographic characteristics, hemoglobin concentration or prevalence of malaria.

Nine percent ($n = 47$) of children were HIV positive. The median duration of follow-up and number of anthropometric measurements per child were 351 d (25th–75th percentiles = 268–355) and 10 y^{-1} (25th–75th percentiles = 7–12), respectively, with 95% of children having three measurements or more. Thirty-four children died during follow-up. Sixteen of those deaths occurred among the 47 children infected with HIV, whereas 18 occurred in the group of 477 HIV-uninfected children. The number of measurements and length of follow-up were slightly lower among HIV-infected children owing to their higher mortality rate: 379 measurements (median per child = 9 measurements) during 11 854 d of follow-up (median per child = 317 d). Forty-six percent of the children were female, 42% were below 12 mo of age and 75% were below 24 mo. The majority of children had mothers who completed primary school (88%), were housewives (73%) and cohabited with a partner (82%). All children had been introduced to weaning foods at the time of recruitment. Some baseline characteristics differed between HIV-infected and -uninfected children (Table 1). HIV-infected children had a lower prevalence of malaria ($p = 0.06$) and their mothers were more likely to live without a partner ($p < 0.001$) than HIV-uninfected children. There were other non-statistically significant differences: HIV-infected children appeared to have a higher prevalence of stunting, severe anemia, lower lymphocytes count and severe pneumonia at admission to hospital than uninfected children.

Table 1. Characteristics of the study population according to the child's human immunodeficiency virus (HIV) status

Characteristic	HIV negative ($n = 477$)	HIV positive ($n = 47$)
Female gender	215 (45.1)	23 (48.9)
Child's age (mo)		
6–11	197 (41.3)	18 (38.3)
12–23	163 (34.2)	17 (36.2)
≥24	117 (24.5)	12 (25.5)
Stunted at baseline[a]	137 (29.6)	16 (35.6)
Wasted at baseline[a]	39 (8.4)	4 (8.9)
Low MUAC at baseline[b]	131 (27.5)	17 (37.0)
Severity of pneumonia at baseline[c]	168 (40.0)	20 (50.0)
Severe anemia (hemoglobin <70 g l^{-1})	96 (21.6)	11 (26.8)
Lymphocyte count <4200 mm^{-3}	109 (24.5)	14 (34.2)
Malaria parasites in blood film†	108 (25.8)	5 (12.5)
Mother is ≤20 y of age	66 (14.0)	8 (17.4)
Mother's parity		
1	142 (29.9)	15 (32.6)
2–5	293 (61.7)	26 (56.5)
≥6	40 (8.4)	5 (10.9)
Mother's level of education		
None/illiterate	60 (12.6)	3 (6.4)
Elementary	388 (81.3)	41 (87.2)
Secondary or higher	29 (6.1)	3 (6.4)
Mother works outside home	129 (27.1)	17 (36.2)
Mother lives with partner‡	399 (83.8)	27 (57.5)
Household has at least one amenity[d]	414 (87.0)	39 (83.0)
There is tap water in house or compound	215 (45.2)	24 (51.1)
There is electricity at home	261 (54.8)	21 (44.7)

Data are shown as n (%). Totals may not add up to 524 owing to missing values.

[a] Stunted children were below −2 Z-scores (NCHS /World Health Organization reference) in height-for-age. Wasted children were below −2 Z-scores in weight-for-height.

[b] Mid-upper arm circumference <25th percentile of the population age-specific distribution.

[c] Severe pneumonia was defined as having either rapid respiratory rate (>60 breaths min^{-1}), high fever (≥39°C) or severe hypoxemia (oxygen saturation <90%) on admission.

[d] From a list of five items: car, refrigerator, radio, bicycle and television.

† p for the difference in proportions between HIV(+) and HIV(−) = 0.06 (χ^2-test).

‡ $p < 0.001$ (χ^2-test).

HIV infection was associated with decreased length and weight gains after 1 y of follow-up among infants (Table 2). After adjusting for maternal education, severe anemia and vitamin A supplementation, HIV-infected children who were between 6 and 11 mo old at baseline grew an average 2.8 cm y^{-1} less than HIV-uninfected infants ($p = 0.01$), whereas HIV-infected children who were 12–24 mo old at baseline grew 1.3 cm y^{-1} less ($p = 0.08$). Weight gain was also lower among HIV-infected children; on average, 1.26 kg y^{-1} for infants ($p = 0.05$) and 0.59 kg y^{-1} for children 12–24 mo old ($p = 0.01$). HIV infection was not associated with growth retardation in length or weight among children who were ≥24 mo at baseline.

In addition to HIV infection, other predictors of growth included the level of maternal education and the presence of anemia at baseline. In children <12 mo of age, maternal illiteracy was related to an adjusted 2.0 cm y^{-1} (95% CI 0.9, 3.1, $p = 0.0002$) lower length gain, in comparison with children whose mothers had completed elementary school. Maternal education was not significantly related to growth among older children. Children < 12 mo at baseline who had severe anemia (hemoglobin < 70 g l^{-1}) grew 1.0 cm y^{-1} (95% CI 0.1, 2.0, $p = 0.04$) less than non-anemic children, after adjustment for HIV infection, maternal education and vitamin A supplementation. Non-statistically significant impairments in linear growth were observed in older children who were severely anemic (−0.9 cm y^{-1}, $p = 0.15$, and −0.4 cm y^{-1}, $p = 0.48$, for children 12–23 and ≥24 mo, respectively). Maternal parity was related to linear growth among children ≥24 mo; children with primiparous mothers grew 1.0 cm y^{-1} (95% CI 0.0, 2.0, $p = 0.05$) more than children born to multiparous women. After adjusting for maternal age, this association diminished to 0.9 cm y^{-1} ($p = 0.09$). Weight gain was not significantly associated with the level of maternal education or the presence of severe anemia. Neither linear nor ponderal growth was related to variables such as the severity of pneumonia on admission, malaria infection, the mother's marital status or other sociodemographic characteristics in this population.

Next, the association between the occurrence of diarrheal and respiratory episodes during follow-up and growth endpoints was examined. Seventy-four percent of the children had at least one episode of diarrhea during follow-up, with an overall incidence rate of 3.4 episodes per child per year. The incidence decreased with age: 4.2, 3.6 and 1.7 per child per year for the age groups 6–11, 12–23 and ≥24 mo, respectively. Infants who were <12 mo at baseline and had one or more episodes of diarrhea during follow-up grew, on average, 1.4 cm y^{-1} less than infants who did not have any episodes ($p = 0.08$), after adjusting for HIV infection, severe anemia and maternal education (Table 3). Acute diarrhea accounted for the majority of diarrheal episodes (94%, 96% and 97% for age groups 6–11, 12–23 and ≥24 mo, respectively). In children 6–11 mo of age, the incidence of one to two yearly episodes of acute diarrhea was related to an adjusted–2.0 cm (95% CI–3.8, −0.2, $p = 0.03$) difference in attained length after 1 y, compared with having no episodes. Having three to five episodes was related to an average 2.2 cm (95% CI 0.4, 3.9, $p = 0.02$) lower length increase, whereas the occurrence of more than five episodes was related to a non-statistically significant −1.4 cm difference (95% CI–3.1, 0.4, $p = 0.12$). There was no indication that the number of acute diarrheal episodes was linearly related to growth delay (p, test for trend = 0.41). No statistically significant associations were seen between diarrhea and growth in older age groups. The association between HIV infection and growth did not change after adjustment for diarrhea.

Dysentery appeared to be related to lower weight gain in children 12–23 mo of age; after adjusting for HIV infection, anemia and maternal education, the incidence of one or more episodes per year was related to a marginally significant lower weight gain of 0.32 kg y^{-1}, compared with having no episodes ($p = 0.06$). The incidence of respiratory infection episodes was not related to growth outcomes.

Table 2. Height (length) and weight gains after 1 y of follow-up, according to human immunodeficiency virus (HIV) status.

	Height (cm)				Weight (kg)			
Age at baseline (mo)	HIV(−) Mean ± SE[a]	HIV(+) Mean ± SE[a]	Unadjusted difference (95% CI)[a]	Adjusted difference (95% CI)[b]	HIV(−) Mean ± SE[a]	HIV(+) Mean ± SE[a]	Unadjusted difference (95% CI)[a]	Adjusted difference (95% CI)[b]
6–11	8.6 ± 0.2	6.3 ± 1.0	−2.3 (−4.4, −0.2)	−2.8 (−5.0, −0.6)	2.42 ± 0.08	1.16 ± 0.64	−1.26 (−2.52, 0.01)	−1.26 (−2.53, 0.02)
12–23	7.6 ± 0.3	6.4 ± 0.6	−1.2 (−2.6, 0.2)	−1.3 (−2.7, 0.1)	2.31 ± 0.08	1.76 ± 0.21	−0.55 (−0.98, −0.11)	−0.59 (−1.05, −0.12)
≥24	7.2 ± 0.3	7.4 ± 0.7	0.2 (−1.2, 1.7)	0.3 (−1.3, 1.8)[3]	2.17 ± 0.10	2.17 ± 0.25	0.00 (−0.52, 0.52)	−0.05 (−0.61, 0.51)[c]

[a] From a mixed effects linear regression model in which height or weight is the dependent variable and age, HIV status, and an interaction term between age and HIV are the predictors.

[b] From a multivariate mixed effects regression model with height or weight as the outcome variable and the following predictors: age, HIV status (one indicator variable), maternal level of education (two indicators), hemoglobin (Hb) <70 g l^{-1} (one indicator for Hb <70 and one indicator for missing) and vitamin A supplementation (one indicator); interaction terms for each indicator and age were also included.

[c] The multivariate model for the age group ≥24 mo included as covariates maternal education, hemoglobin <70 g l^{-1}, vitamin A supplementation and whether the mother is primiparous.

Table 3. Differences in estimated yearly length and weight gains attributable to ≥1 versus 0 episodes of infection

	Adjusted difference (95% CI) in attained length (cm y^{-1}) between children with ≥1 vs 0 episodes y^{-1} [a]			Adjusted difference (95% CI) in attained weight (kg y^{-1}) between children with ≥1 vs 0 episodes y^{-1} [a]		
	Age at baseline (mo)			Age at baseline (mo)		
Episode	6–11 (*n* = 215)	12–23 (*n* = 180)	≥24 (*n* = 129)	6–11 (*n* = 215)	12–23 (*n* = 180)	≥24 (*n* = 129)
Diarrhea (all)	−1.4 (−2.9, 0.2)	0.1 (−1.2, 1.3)	−0.2 (−1.2, 0.8)	0.07 (−0.41, 0.55)	0.01 (−0.44, 0.46)	−0.28 (−0.66, 0.10)
Acute diarrhea	−1.8 (−3.4, −0.1)	0.0 (−1.2, 1.2)	−0.2 (−1.2, 0.8)	−0.01 (−0.49, 0.48)	0.05 (−0.39, 0.49)	−0.29 (−0.67, 0.09)
Persistent diarrhea	0.0 (−1.1, 1.1)	0.5 (−0.9, 2.0)	−0.6 (−2.5, 1.3)	0.13 (−0.42, 0.68)	−0.16 (−0.70, 0.37)	0.37 (−0.26, 1.00)
Watery diarrhea	−0.6 (−1.6, 0.4)	0.1 (−0.9, 1.1)	−0.1 (−1.1, 0.9)	0.03 (−0.31, 0.37)	0.05 (−0.31, 0.40)	−0.32 (−0.68, 0.04)
Dysentery	−0.3 (−1.5, 0.9)	−1.0 (−2.3, 0.3)	−0.3 (−1.4, 0.8)	0.02 (−0.36, 0.39)	−0.32 (−0.64, 0.01)	0.05 (−0.32, 0.42)
Cough and fever	−0.3 (−1.4, 0.9)	−0.8 (−1.9, 0.4)	0.1 (−1.0, 1.2)	0.00 (−0.34, 0.33)	−0.02 (−0.37, 0.34)	−0.12 (−0.63, 0.39)

[a] From a mixed effects regression model for repeated measures with length or weight as the outcome variable and the following predictors: age (time), whether the child had at least one of the index episodes, human immunodeficiency virus status, maternal level of education (two indicators), hemoglobin (Hb) <70 g l^{-1} (one indicator for Hb <70 and one indicator for missing), assignment of the child to vitamin A or placebo (one indicator), and interaction terms between age and each of the other covariates' indicators.

Discussion

This study examined the association between HIV status and growth in a cohort of 524 Tanzanian children 6–60 mo of age who were followed for 1 y. After adjustment for potential confounding variables, HIV infection was related to large and significant impairments in linear and ponderal growth among children who were below 11 mo of age at the beginning of follow-up. HIV infection was also associated with low weight gain in children aged 12–23 mo.

These results are consistent with those from previous longitudinal studies in sub-Saharan Africa (Table 4) among children who were not receiving antiretroviral therapy. In all (2–6) but one (12) of these studies, HIV infection was related to large and significant linear and ponderal growth delays in children below 2 y of age. In these settings, growth retardation among HIV-infected versus -uninfected infants appeared early in life, between birth and 3 mo, and affected accrual of both length-for-age and weight-for-age. Weight-for-length growth was not affected in three (2, 4, 12) of the four studies that examined this indicator and, in the fourth one (6), it was significantly lower for HIV-infected children only after 12 mo of age. There were no differences in growth between children born to HIV-negative mothers and those born to HIV-positive mothers who did not become infected themselves (seroreverters).

One limitation of previous studies is that the timing of HIV infection is not considered in the estimation of the infection's effect on growth; instead, the comparison cohorts are defined in terms of each child's "final" HIV status. The preinfection growth pattern of children who become infected with HIV postnatally is therefore misclassified when analyzed as part of the HIV-infected exposure group. This misclassification may produce an underestimation of the actual effect of HIV on growth, particularly at early ages, and could partially explain why an effect of HIV on indicators such as weight-for-height is not observed, or it is observed only after an average age when most HIV transmission is expected to have occurred. However, if growth before infection is as poor as that after infection, early growth differences that are observed when comparing pooled pre- and post-infection growth with that of uninfected children may suggest that growth faltering could be a predictor of HIV infection.

This study shares similar limitations with previous studies, since an approximate date for HIV transmission was lacking. About one-third of mother-to-child transmission may occur through breastfeeding after 6 mo of age (13). Although the latest available blood samples were tested during follow-up for HIV, it is possible that some children who tested negative, especially the youngest at recruitment, may have become infected thereafter but were treated in the analyses as uninfected throughout the follow-up period. In this case, an association between HIV status and growth may be biased towards the null value, yet a significant growth effect for HIV infection was still observed. A second limitation is that only children who were at least 6 mo of age were recruited. Some children who were infected with HIV before this age may have died before becoming eligible for these analyses. If their deaths were preceded by growth impairment it is possible that the association between HIV and growth is actually of greater magnitude than observed in this study. Lastly, the study base comprises children who were admitted to the hospital with pneumonia. It is possible that HIV-infected children in this cohort were at a more advanced stage of HIV disease which predisposed them to the index episode of pneumonia, and whose growth pattern may have been more compromised than that of children at earlier stages, as shown in other settings (1, 14, 15). There was no information on the clinical and immunological stage of HIV disease. However, the episode of pneumonia may have affected the growth pattern of both HIV-uninfected and -infected children. The generalization of results to children who do not develop pneumonia may therefore be limited.

HIV infection was not related to growth retardation in children who were older than 2 y, in agreement with a study from Rwanda in which the growth pattern "stabilized" between 24 and 48 mo (2). It is unclear why HIV infection was not related to growth among children >24 mo in these studies. Growth delay in the course of HIV infection is a strong predictor of

Table 4. Longitudinal studies from sub-Saharan Africa that compared the postnatal growth pattern of human immunodeficiency virus (HIV)-infected versus HIV-uninfected children.

Author (ref.)	Place	Years	Sample sizes of comparison cohorts			Length of follow-up	Endpoints[b]	Associations found[c]	Variables adjusted for
			HIV(−)	Seroreverters[a]	HIV(+)				
Lepage (2)	Kigali, Rwanda	1988–93	207	140	46	Birth–48 mo	ΔH-A *Z*-score	H-A: ↓ in first 3 y of life	Cohorts matched for maternal age and parity
							ΔW-A *Z*-score	W-A: ↓ in first 3 y of life	
							ΔW-H *Z*-score	HC-A: ↓ in first 2 y of life	
							ΔHC-A *Z*-score	W-H: ↔	
Henderson (3)	Blantyre, Malawi	1989–90	686	270	92	Birth–24 mo	Δin mean growth curves: L-A, W-A	L-A: ↓ at 5 mo W-A: ↓ from birth	None
Berhane (5)	Kampala, Uganda	1990–92	124	251	84	Birth–25 mo	Δin mean growth curves: L-A, W-A	L-A: ↓ W-A: ↓	Cohorts matched for maternal age
Bailey (6)	Kinshasa, DRC	1989–90	256	190	68	Birth–20 mo	ΔL-A *Z*-score	L-A: ↓ by 3 mo until 18 mo	Mother's stature, serostatus, CD4 cell count, hemoglobin, SES, partner, WHO stage of disease; child's gender, adenopathy, CD4 count, diarrhea, fever
							ΔW-A *Z*-score	W-A: ↓ by 3 mo until 18 mo	
							ΔW-L *Z*-score	W-L: ↔ by 12 mo; ↓ thereafter	
							% stunting -$_s$	RR($_s$) = 2.1 (95% CI 1.3, 3.4)	
							% wasting -$_w$	RR($_w$) = 2.6 (95% CI 1.6, 4.0)	
							% underweight -$_u$	RR($_u$) = 2.8 (95% CI 1.6, 5.1)	
Bobat (4, 11)	Durban, South Africa	1990–93	–	93	48	Birth–26 mo (average)	ΔL-A *Z*-score	L-A: ↓ at 3, 6, 18 mo	None
							ΔW-A *Z*-score	W-A: ↓ at 3, 6, 9 mo	
							ΔW-L *Z*-score	W-L: ↔	
							Failure to thrive	RR = 4.5 (95% CI 2.6, 7.8) IRR = 4.1 (95% CI 2.1, 8.0)	
Sherry (12)	Nairobi, Kenya	1991–94	139	155	53	Birth–21 mo	ΔL-A *Z*-score ΔW-L *Z*-score	L-A: ↔ W-A: ↔	None

[a] Seroreverters are children born to HIV-positive mothers who did not become infected.
[b] L-A: length-for-age; H-A: height-for-age (children >2 y); W-L: weight-for-length; W-A: weight-for-age; HC-A: head circumference-for-age. In the studies reporting *Z*-scores as the endpoint, these were estimated using the NCHS /World Health Organization (WHO) growth reference. Failure to thrive was defined as weight and length below the 3rd percentile (of NCHS/WHO reference) on more than one occasion, or crossing percentile lines. Stunting is defined as an L-A *Z*-score <-2.0, wasting as a W-L *Z*-score <-2.0, and underweight as a W-A *Z*-score <-2.0.
[c] The direction of the arrow refers to the direction of the association with respect to HIV(+) children: ↓: statistically significantly lower in HIV(+) than in HIV(−) children; ↔: no difference between HIV(+) and HIV(−) children.
RR: risk (or hazard) ratio comparing HIV(+) with HIV(−) children; 95% CI: 95% confidence interval; IRR: incidence rate ratio.

mortality (5); therefore, it is possible that infants with the largest degree of growth retardation die before 2 y of age, and only the least sick children survive to become part of older cohorts.

Numerous causes of growth retardation in children infected with HIV have been identified in studies conducted in developed countries (1, 14–17). These include decreased protein and energy intake, increased utilization of nutrients and losses secondary to malabsorption, advanced stage of HIV disease as indicated by high viral load and low CD4-cell counts, exposure to antiretroviral treatment, alterations in the growth hormone axis and psychosocial factors. Much less evidence is available on the causes of growth retardation among HIV-infected African preschool children. Some studies suggest that the micronutrient status plays an important role. Low serum vitamin A and carotenoid concentrations have been related to decreased weight and height velocities in Ugandan infants (18), and vitamin A supplementation in this Tanzanian population resulted in rapid catch-up linear growth among HIV-infected infants who were <18 mo old (8).

Other possible causes of growth retardation among HIV-positive children include secondary infections. Diarrhea and respiratory infections are likely to have a more severe impact on the growth pattern of HIV-infected children than among uninfected children. Evidence to support this hypothesis, however, is lacking. In the longitudinal study from Rwanda (2), the authors report that growth retardation in weight- and height-for-age "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", but data were not presented. The incidence of acute diarrhea was related to large and significant linear growth delay in infants after adjusting for HIV infection; moreover, the effect of HIV status remained after adjustment for acute diarrhea. Because of low statistical power, a potential interaction between the combined effects of HIV and diarrheal infections on growth was not examined. The potential negative interaction between HIV and other highly prevalent infections on child growth and survival needs to be ascertained in future studies.

Some previous studies examined the short-term impact of diarrhea and respiratory infections on child growth, with varying results. Whereas in children >6 mo of age from Zimbabwe (19), rural Gambia (20) and the Philippines (21) the incidence of diarrhea during 1–3 mo of follow-up was related to lower length gains, no association was observed in other studies (22, 23). A short-term effect of diarrhea on weight gain has been more consistently observed across studies than one on height. Analyses over long-term intervals, such as the one presented here, have the advantage of reflecting the cumulative impact of morbidity and the extent of rapid catch-up growth after episodes of infection. In the present study, the occurrence of one or more episodes of diarrhea per year was associated with low length gain after an average 1 y of follow-up only among infants who were 6–11 mo of age at recruitment. The fact that the association was limited to the youngest children may be due, in part, to a significant decrease in the incidence of diarrhea among older children. A negative long-term impact of diarrhea on length gain has been found in other developing countries (24–26) and suggests that catch-up growth after episodes of infection may not be complete.

No association was found between the incidence of diarrhea overall and attained weight after 1 y; however, dysentery, a potentially severe form of diarrhea, appeared to be related to lower weight gains in children aged 12–23 mo. In a study from Brazil (24), episodes of diarrhea that were severe enough to require hospitalization were also associated with lower weight gains after 1 y of follow-up. In the present study, episodes of respiratory infection were not related to height or weight gains, in agreement with previous studies that examined this question over long periods of follow-up (24, 26, 27). One potential limitation of analyzing the association between the cumulative number of episodes of infection and attained growth over the same, long period is that there is room for reverse causality, i.e. poor growth within shorter periods may precede episodes of infection.

Other predictors of linear growth retardation among infants aged <12 mo in this population included severe anemia and low level of maternal education. Correcting anemia through iron supplementation has been shown to be effective in improving the growth pattern of children >12 mo of age (28), but not among younger anemic infants (29, 30). Causes of anemia other than dietary iron deficiency, such as malaria and possibly hookworm infection, may have a stronger influence on growth among weaned infants in settings where hygienic practices are poor. A higher level of maternal education may be related to improved feeding and hygienic habits, increased knowledge of preventive actions against infection and opportune use of health services.

In summary, HIV infection is associated with growth retardation in length and weight among infants 6–11 mo of age; it is also related to low weight gain in infants 12–23 mo, but not among older children. Prevention and early treatment of diarrheal infection and severe anemia, as well as investment in the formal education of women, could contribute towards alleviating the burden of growth retardation in settings with a high prevalence of HIV infection. Future studies should take into account the timing of HIV infection in the estimation of the effect of HIV on child growth.

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