Variability of Growth in Children Starting Antiretroviral Treatment in Southern Africa

WHAT'S KNOWN ON THIS SUBJECT: HIV-infected children on antiretroviral therapy in low-income settings show initial catch-up in weight and height growth during the first years of treatment, but long-term outcomes remain unknown.

WHAT THIS STUDY ADDS: We demonstrate that even after 3 years on antiretroviral therapy, normal values were not reached. Although catch-up growth in weight stagnated after the first year, catch-up growth in height was slower but continued over the whole period.

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abstract

BACKGROUND: Poor growth is an indication for antiretroviral therapy (ART) and a criterion for treatment failure. We examined variability in growth response to ART in 12 programs in Malawi, Zambia, Zimbabwe, Mozambique, and South Africa.

METHODS: Treatment naïve children aged <10 years were included. We calculated weight for age z scores (WAZs), height for age z scores (HAZs), and weight for height z scores (WHZs) up to 3 years after starting ART, by using the World Health Organization standards. Multilevel regression models were used.

RESULTS: A total of 17 990 children (range, 238–8975) were followed for 36 181 person-years. At ART initiation, most children were underweight (50%) and stunted (66%). Lower baseline WAZ, HAZ, and WHZ were the most important determinants of faster catch-up growth on ART. WAZ and WHZ increased rapidly in the first year and stagnated or reversed thereafter, whereas HAZ increased continuously over time. Three years after starting ART, WAZ ranged from −2.80 (95% confidence interval [CI]: −3.66 to −2.02) to −1.98 (95% CI: −2.41 to −1.48) in children with a baseline z score < −3 and from −0.79 (95% CI: −1.62 to 0.02) to 0.05 (95% CI: −0.42 to 0.51) in children with a baseline WAZ ≥ −1. For HAZ, the corresponding range was −2.33 (95% CI: −2.62 to −2.02) to −1.27 (95% CI: −1.58 to −1.00) for baseline HAZ < −3 and −0.24 (95% CI: −0.56 to 0.15) to 0.84 (95% CI: 0.53 to 1.16) for HAZ ≥ −1.

CONCLUSIONS: Despite a sustained growth response and catch-up growth in children with advanced HIV disease treated with ART, normal weights and heights are not achieved over 3 years of ART. *Pediatrics* 2012;130:e966–e977

Growth retardation is common among HIV-infected children in general and in particular in low income settings.[1–3] Reasons for growth retardation are multifactorial and include genetic and environmental factors such as poor nutrition, low socioeconomic status, and infection by different pathogens.[4,5] All of these factors are interrelated and may decrease immunity and lead to malabsorption of food and to endocrine dysfunction.[6] Growth monitoring identifies HIV-infected children eligible for antiretroviral therapy (ART) and is useful to assess response to therapy,[1,7] and it is particularly important in many settings in sub-Saharan Africa with limited access to CD4 count and viral load monitoring to assess treatment failure.

Although most studies from sub-Saharan Africa described positive short-term responses of weight and height,[8–10] results were not consistent and only few studies revealed growth response beyond 2 years on ART[11–13]; several studies revealed no improvements in height[9,13,14] or stagnation after a short time period,[15] whereas others revealed continuous improvements.[1,12,16–18] Similarly, most studies revealed marked improvements in weight gain after ART start,[1,12,16,19] but some studies revealed no improvements.[11,20] The short follow-up duration, wide age range (including many older children starting ART as they approach puberty), and the variability in access to virologic monitoring could explain some of the differences and also be a reason that, in general, values similar to those of HIV-uninfected children were not reached in resource-limited settings.

The aim of this study is to describe growth responses up to 3 years after ART initiation, to describe variability of growth response between different cohorts, and to examine associations between patient and site characteristics with growth response in Southern Africa.

METHODS

Study Population

The International Epidemiological Databases to Evaluate AIDS, Southern Africa (IeDEA-SA) collaboration includes 24 programs in 6 southern African countries (www.iedea-sa.org). Data are collected at each site as part of routine monitoring at baseline (ART initiation) and each follow-up visit, by using standardized definitions. Data from the different sites are transferred to data centers at the Universities of Cape Town, South Africa, or Bern, Switzerland, in a standardized format and merged at regular intervals. All IeDEA-SA sites with at least 100 children on ART were included.

ART-naïve children who initiated treatment with at least 3 antiretroviral drugs at age <10 years were included. We excluded children who were transferred from another site. A child was considered lost to follow-up if the time between the last visit and the closing date of the cohort was longer than 6 months. Weight and height measurements were converted into age- and gender-adjusted z scores by using the latest World Health Organization (WHO) growth standards from 2007.[21] Underweight was defined as weight for age z score (WAZ) < -2, stunting as height for age z score (HAZ) < -2, and wasting as weight for height z score (WHZ) < -2. For WHZ, the analysis was limited to children aged 2 to 5 years because WHO reference values were only available for this age group. We took weight and height measurements and CD4 cell counts closest to the starting date of ART (-6 months/+1 week) as baseline values.

Statistical Analysis

We used a multilevel model to account for the hierarchical structure of the data (ie, repeated anthropometric measurements within a child

and children belonging to different cohorts). To model the nonlinear increase of the anthropometric measurements on ART over time most accurately, we used a second order fractional polynomial transformation of time[22] as described previously.[1] All available weight and height measurements from ART initiation up to 3 years afterward were included in the analysis, provided the child had a baseline and at least 1 weight or height measurement after the start of ART. The adjusted model included the following variables at ART initiation: gender; age (<2, 2–4, and 5–10 years); WAZ, HAZ, and WHZ (< -3, ≥ -3 to < -2, ≥ -2 to < -1, and ≥ -1); WHO clinical stage (1 or 2, 3, and 4); degree of immunodeficiency ("severe," "advanced," "mild," and "asymptomatic" according to WHO criteria[23]); type of ART regimen (nonnucleoside reverse transcriptase inhibitor [NNRTI]-based, protease inhibitor [PI]-based, other, and unknown); and time period of ART start (1997–2005, 2005–2006, 2006–2007, and 2008–2010). We also included interactions between time and all baseline variables because it can be expected that growth response varies by baseline variables. The model was fitted by using a fully probabilistic approach (see Appendix). The model fit was visually assessed by plotting the predicted median with 95% prediction intervals and the observed trajectories for individual children and by the deviance information criterion. Missing values of stage of disease, degree of immunodeficiency, and type of regimen were imputed. We used multinomial regression models with stage of disease, degree of immunodeficiency, and type of regimen as outcome and age, gender, year of starting ART, and baseline z score at start of ART as predictors. Missing data were imputed by randomly sampling from the predictive multinomial distribution. Crude and adjusted estimates of z scores

were shown over time and by treatment site. In addition, we created 1000 z-score trajectories based on the adjusted model and calculated the percentages of children in each z-score category over time. We performed 2 additional analyses: a complete case analysis without multiple imputation and an analysis where we included only children who were followed for at least 3 years. A particular risk factor was defined as being associated with faster catch-up growth if it was associated with higher z scores at 1 year after initiating ART. All analyses were done in R-2.11.1 (The R Development Core Team, University of Vienna, Vienna, Austria), Stata version 11 (Stata Corp, College Station, TX), and WinBUGS 1.4.3 (Lunn et al 2010). In all sites, institutional review boards approved the participation in IeDEA-SA.

RESULTS

Study Population and Baseline Characteristics

A total of 17 990 children from 12 programs in Malawi, Zambia, Zimbabwe, Mozambique, and South Africa were included and followed for 36 181 person-years from date of ART initiation. Table 1 shows the characteristics of the sites and gives more details on anthropometric measurements and food supplementation. In the first 3 years after ART start, 1183 children died (rate 3.3 per 100 person-years), 2611 were lost to follow-up (7.2 per 100 person-years), and 878 were transferred out of care in the particular sites (2.4 per 100 person-years).

Table 2 shows the characteristics of the children at ART initiation by treatment site. One-third of children were aged ≤ 2 years, and 37.8% were 5 years or older. Most children were underweight (49.7%) and stunted (66.1%). The median number of measurements after start of ART was 6 (interquartile range [IQR]: 2–13) for weight and 4 (IQR:

1–10) for height. The 17 990 children included in the analysis contributed 154 775 weight measurements and 123 006 height measurements. A total of 11 015 children had a baseline height available and were thus included in the analysis for HAZ, and 4155 children were aged 2 to 5 years and had a baseline weight and height available and were thus included in the analysis for WHZ.

Weight for Age

Three years after starting ART, WAZ across sites ranged from -2.80 (95% confidence interval [CI]: -3.66 to -2.02) to -1.98 (95% CI: -2.41 to -1.48) in children who started with a baseline z score of < -3 and from -0.79 (95% CI: -1.62 to 0.02) to 0.05 (95% CI: -0.42 to 0.51) in children with a baseline WAZ ≥ -1 (Supplemental Fig 5). Catch-up growth was fastest in the first year and was particularly pronounced in the 2 tertiary sites (numbers 6 and 7). No difference was apparent between sites that do or do not measure viral load routinely. Figure 1 shows the results from the adjusted analyses. Estimated z scores per cohort are shown for a "typical child" (ie, a girl aged 5 years or older, who started ART after 2007 with an NNRTI-based regimen, was in WHO stage 3, and was severely immunodeficient). Adjustment for baseline differences reduced the heterogeneity of WAZ across sites, and in particular growth response in the tertiary sites became more similar to other sites. Lower baseline z scores, younger age, advanced stage of the disease, more advanced immunodeficiency, and a PI-based regimen were predictive of faster catch-up growth in WAZ, and there was a 3-way interaction between type of regimen, baseline z score, and age ($P <$ .001). This means that the effect of the type of regimen was not only different in each baseline z-score category but also in each age group within each z-score category. No effect was seen for the year of ART start and gender.

Height for Age

Figure 2 and Supplemental Fig 6 show adjusted and crude analyses for height for age. Three years after starting ART, HAZ across sites ranged from -2.33 (95% CI: -2.62 to -2.02) to -1.27 (95% CI: -1.58 to -1.00) in children who started with a baseline z score of < -3 and from -0.24 (95% CI: -0.56 to 0.15) to 0.84 (95% CI: 0.53 to 1.16) in children with a baseline HAZ ≥ -1. As for WAZ, pooled estimates remained below zero for all but the highest baseline z-score group. For growth in height, the pattern is, however, different in several ways; catch-up growth is slower in the first year of ART, but it is continuous during the whole 3-year time period for all children who start ART with HAZ baseline values < -1. Heterogeneity between sites was smaller than for WAZ, and again no difference between viral load sites and nonviral load sites was apparent. For HAZ, the predictors for growth response were similar as for WAZ with the exception of age where the youngest children showed the slowest growth response, and stage of disease and degree of immunodeficiency were not associated with height growth response.

Weight for Height

Supplemental Figs 7 and 8 show crude and adjusted analyses for WHZ. Three years after starting ART, WHZ ranged from -4.03 (95% CI: -5.44 to -2.60) to -2.36 (95% CI: -3.52 to -1.13) in children who started with a baseline z score of < -3 and from -0.66 (95% CI: -1.43 to 0.12) to 1.01 (95% CI: 0.42 to 1.60) in children with a baseline WHZ ≥ -1. Catch-up growth in WHZ was fast in the first year of ART so that normal values were reached already within 1 year irrespective of the starting value. As weight gain stagnated after the first year on ART while HAZ continued to increase, WHZ decreased again after the first year. As for WAZ, heterogeneity

TABLE 1 Characteristics of Treatment Programs Providing ART to Children in Southern Africa

	Harriet Shezi	Khayelitsha	McCord	Hlabisa	Rahima Moosa	Red Cross	Tygerberg	Light-house	CIDRZ-MOH	Pediatric Day	Newlands Clinic	SMART-ZIM
Country (City/Province)	South Africa (Soweto)	South Africa (Cape Town)	South Africa (Durban)	South Africa (Kwa Zulu-Natal)	South Africa (Johannesburg)	South Africa (Cape Town)	South Africa (Cape Town)	Malawi (Lilongwe)	Zambia (Lusaka)	Mozambique (Maputo)	Zimbabwe (Harare)	Zimbabwe (Masvingo)
Level of care	All levels	Primary	Secondary	Primary/secondary	All levels	Tertiary	Tertiary	All levels	Primary	All levels	Secondary	Primary/secondary
Main reasons for entry of patients in cohort	From hospital wards, referral from other medical facilities, and TB program	VCT, spontaneous referral	Spontaneous referral, other family members attending the clinic	VCT, referral from other sites	From hospital wards, tuberculosis program, orphans program	Hospitalized children with severe OIs or with advanced HIV infection	Referral from other medical facilities, from clinical research center	VCT, spontaneous referral	Referral from VCT and OPD	From hospital wards, referral from other medical facilities	Referral from other sites	VCT, referral from other medical facilities
Routine viral load monitoring	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No
Second-line therapy available	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Weight												
Weighting scale												
Children < 2 y												
Digital	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No
Mechanical	No	No	No	No	No	No	No	Yes	No	Yes	Yes	Yes
Children ≥ 2 y												
Digital	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Mechanical	Yes	Yes	No	No	No	No	No	No	No	Yes	Yes	Yes
Standardized approach for clothes[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Regular calibration	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	No
Height												
Children < 2 y measured while lying on back?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wall-mounted growth chart	Yes	Yes	Yes	No	No	Yes	No	No	Yes	No	Yes	Yes
Standardized approach for shoes?[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

across sites was substantial, and adjusting for differences in baseline variables reduced the heterogeneity only slightly. Lower baseline z scores, male gender, and severe immunodeficiency were predictive for faster catch-up growth in WHZ. No clear effect was seen for the year of ART start and type of regimen.

Figure 3 shows the overall pooled estimates across the sites for WAZ, HAZ, and WHZ. The results from the complete case and for the multiple imputation were similar, whereas children who were followed during the whole time period had a slightly better growth response (Supplemental Table 3). For children who were followed for 3 years, the proportion of children in different z-score categories over time is shown in Fig 4. Although over 60% reached WAZ > −1, 46% reached HAZ > −1. For WHZ, this proportion increased rapidly to 90% within 1 year but decreased again later to over 50%.

DISCUSSION

This collaborative analysis of ~18 000 children in 12 ART programs revealed that although WAZ and WHZ improved during the first years of ART, there was a reversed trend from year 2 onwards. Although catch-up growth in weight was faster initially, catch-up growth in height was more constant and continued over the whole 3-year time period. Only children with baseline WAZ and HAZ > −1 approached normal values within 3 years irrespective of age. In multivariable analyses, lower baseline WAZ, HAZ, and WHZ were the most important determinants of faster catch-up growth on ART. The use of a PI-based regimen was associated with faster catch-up growth in weight and height, whereas other variables were associated only with growth in WAZ (younger age, advanced stage of the disease) or in height (old age) or not at all (gender, year of ART start).

Few studies have directly compared weight and height growth by calculating WHZ[24] or BMI[2,25–27] and data are therefore limited. Because children were underweight and stunted and catch-up growth in the first year of ART was particularly fast for WAZ, the degree of wasting was only moderate and normalized rapidly within 1 year. Although the consistent increase in HAZ over 3 years is reassuring, the reasons for the increase in the proportion of children who are underweight or wasted after 2 years on ART need to be studied further.

Our findings differ substantially from growth patterns in high-income settings; in our study, normal values of WAZ and HAZ were not reached despite observing growth over an extended period of time. In contrast, in a study of ART-naïve children in the United States, normal WAZ and HAZ were reached after 1 and 2 years of ART, respectively,[2] but baseline z scores were much higher. A study comparing children from Uganda and the United Kingdom and Ireland[15] revealed that the median change in HAZ after 12 months on ART was smaller in Uganda with differences being attributed to lower baseline levels in Ugandan children. In a European study including nonnaïve children,[25] it took 5 years to reach normal WAZ, and HAZ did not reach normal values.

We found that the baseline z scores were the most important predictors of growth response. However, although the more severely underweight children showed a more rapid catch-up growth on ART, they did not reach the same weight as children who started with higher values. The association between age and growth response was smaller and less consistent across studies; we and others found that young age is associated with a more rapid catch-up growth in weight but not height,[24] whereas other studies revealed associations with weight and height.[2,28,29] It has been speculated that

TABLE 2 Characteristics of Children Starting ART

Characteristic	Study Site											
	1	2	3	4	5	6	7	8	9	10	11	12
Patients, n (% of total children)	1987 (11.1)	615 (3.4)	345 (1.9)	951 (5.3)	975 (5.4)	829 (4.6)	1047 (5.8)	486 (2.7)	8975 (49.9)	1048 (5.8)	494 (2.8)	238 (1.3)
Age, median (IQR), y	4.0 (1.7–6.7)	3.2 (1.6–5.4)	5.3 (2.4–7.2)	4.1 (1.7–6.8)	3.3 (1.2–6.1)	1.3 (0.5–3.6)	1.5 (0.6–4.3)	5.7 (3.4–7.9)	3.6 (1.6–6.8)	3.0 (1.5–5.4)	6.4 (3.4–8.4)	5.3 (1.7–8.1)
Age group, n (%), y												
<2	580 (29.2)	200 (32.5)	70 (20.3)	286 (30.1)	364 (37.3)	518 (62.5)	599 (57.2)	37 (7.6)	2873 (32.0)	367 (35.0)	59 (11.9)	69 (11.9)
2–5	593 (29.8)	230 (37.4)	92 (26.7)	265 (27.9)	273 (28.0)	156 (18.8)	215 (20.5)	166 (34.2)	2644 (29.5)	374 (35.7)	126 (25.5)	126 (25.5)
5–10	814 (41.0)	185 (30.1)	183 (53.0)	400 (42.1)	338 (34.7)	155 (18.7)	233 (22.3)	283 (58.2)	3458 (38.5)	307 (29.3)	309 (62.6)	309 (62.6)
Gender												
Girl, n (%)	979 (49.3)	290 (47.2)	159 (46.1)	477 (50.2)	484 (49.6)	401 (48.4)	519 (49.6)	243 (50.0)	4442 (49.5)	503 (48.0)	254 (51.4)	123 (51.7)
WAZ												
Median (IQR)	−1.91 (−3.07 to −1.01)	−1.00 (−1.92 to −0.13)	−1.41 (−2.42 to −0.63)	−1.25 (−2.34 to −0.39)	−1.92 (−3.07 to −0.95)	−2.51 (−3.87 to −1.37)	−1.82 (−3.44 to −0.67)	−1.70 (−3.0 to −0.72)	−2.20 (−3.42 to −1.13)	−1.57 (−2.63 to −0.74)	−1.78 (−2.79 to −0.96)	−1.84 (−3.14 to −0.98)
Underweight, n (%)	883/1844 (47.9)	104/443 (23.5)	39/124 (31.5)	279/869 (32.1)	328/674 (48.7)	487/807 (60.4)	291/620 (46.9)	97/225 (43.1)	4679/8553 (54.7)	370/977 (37.9)	187/423 (44.2)	93/198 (47.0)
HAZ												
Median (IQR)	−2.55 (−3.50 to −1.63)	−2.32 (−3.03 to −1.60)	−1.75 (−2.99 to −0.97)	−1.90 (−2.69 to −0.32)	−2.35 (−3.42 to −1.23)	−2.61 (−3.65 to −1.68)	−2.29 (−3.44 to −1.16)	−2.58 (−3.55 to −1.00)	−2.84 (−4.07 to −1.69)	−2.80 (−3.80 to −1.64)	−2.39 (−3.50 to −1.59)	NA
Stunted, n (%)	1216/1828 (66.5)	69/118 (58.5)	35/77 (45.5)	28/62 (45.2)	388/665 (58.4)	491/753 (65.2)	321/578 (55.5)	37/60 (61.7)	3810/5532 (68.9)	626/921 (68.0)	262/421 (62.2)	NA
WHZ												
Median (IQR)	0.10 (−3.49 to 2.23)	0.80 (−0.78 to 2.65)	0.46 (−3.33 to 3.06)	−3.36 (−5.51 to 2.32)	0.03 (−3.97 to 2.29)	−0.14 (−4.54 to 3.16)	0.32 (−3.14 to 3.47)	0.87 (−2.72 to 3.13)	−0.34 (−4.95 to −3.18)	0.71 (−3.41 to 3.63)	0.10 (−2.98 to 2.43)	NA
Wasted, n (%)	53/581 (9.1)	0/96 (0)	3/43 (7.0)	(5/8) (62.5)	34/245 (13.9)	21/148 (14.2)	14/169 (8.2)	8/77 (10.4)	483/2305 (21.0)	34/369 (9.2)	5/114 (4.4)	NA
CD4 cell percentage												
n	1787	389	164	798	663	802	805	276	5710	711	16	20
Median (IQR)	11.4 (7.0–16.0)	14.0 (10.0–20.0)	9.4 (5–14.2)	14.0 (7.0–16.0)	12.2 (7.1–18.2)	12.4 (7.7–19.5)	16.7 (11.0–24.0)	11.5 (7.6–15.4)	14.4 (9.7–20.6)	13.2 (9.2–17.7)	12.0 (10.3–16.0)	17.0 (11.8–25.5)
Immunodeficiency												
No. of observations	1784	413	185	799	661	802	826	297	6311	709	272	85
Not significant, n (%)	221 (12.4)	63 (15.3)	14 (7.6)	116 (14.5)	82 (12.4)	67 (8.4)	135 (16.3)	56 (18.9)	1076 (17.1)	91 (12.8)	39 (14.3)	3 (3.5)
Mild, n (%)	173 (9.7)	44 (10.7)	18 (9.7)	100 (12.5)	54 (8.2)	65 (8.1)	98 (11.9)	45 (15.2)	802 (12.7)	71 (10.0)	43 (15.8)	9 (10.6)
Advanced, n (%)	293 (16.4)	57 (13.8)	34 (18.4)	152 (19.0)	100 (15.1)	115 (14.3)	128 (15.5)	55 (18.5)	1330 (21.1)	107 (15.1)	69 (25.4)	24 (28.2)
Severe, n (%)	1097 (61.5)	249 (60.3)	119 (64.3)	431 (53.9)	425 (64.3)	555 (69.2)	465 (56.3)	141 (47.5)	3103 (49.2)	440 (62.1)	121 (44.5)	49 (57.7)
WHO clinical stages												
3 and 4, n/total (%)	867/1371 (63.2)	453/615 (73.7)	NA	702/863 (81.3)	283/352 (80.4)	714/810 (88.2)	738/827 (89.2)	419/436 (96.1)	5957/8669 (68.7%)	735/934 (78.7%)	40/48 (83.3)	200/238 (84.0)
Type of regimen, n (%)												
NNRTI-based	1054 (53.0)	377 (61.3)	254 (73.6)	604 (63.5)	488 (50.1)	358 (43.2)	318 (30.4)	486 (100)	8451 (94.2)	92 (8.8)	487 (98.6)	238 (100)
PI-based	640 (32.2)	233 (37.9)	81 (23.5)	347 (36.5)	386 (39.6)	451 (54.4)	610 (58.3)	0 (0)	4 (0.04)	10 (1.0)	5 (1.0)	0 (0)
Other/unknown	293 (14.8)	5 (0.8)	10 (2.9)	0 (0)	101 (10.4)	20 (2.4)	119 (11.4)	0 (0)	520 (5.8)	946 (90.3)	2 (0.4)	0 (0)
Outcome, n (%)[b]												
Death	74 (3.7)	14 (2.3)	15 (4.4)	39 (4.1)	25 (2.6)	116 (14.0)	82 (7.8)	21 (4.3)	749 (8.4)	9 (0.9)	27 (5.5)	12 (5.0)
Loss to follow-up	4 (0.2)	20 (3.3)	8 (2.8)	23 (2.4)	101 (10.4)	41 (5.0)	74 (7.3)	63 (14.2)	2233 (27.4)	27 (2.6)	0 (0)	17 (7.2)
Transfer-out	13 (0.7)	0 (0)	23 (6.7)	32 (3.4)	52 (5.3)	375 (45.2)	259 (24.7)	107 (22.0)	0 (0)	13 (1.2)	0 (0)	4 (1.7)
Follow-up time, median (IQR), y[b]	3.0 (3.0–3.0)	3.0 (3.0–3.0)	1.4 (0.5–2.2)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	1.3 (0.6–3)	2.5 (0.9–3)	1.2 (0.4–2.5)	1.4 (0.5–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)

HAZ, height for age z score; NA, not available; WAZ, weight for age z score; WHZ, weight for height z score.
a Only available for children aged 2 to 5 years.
b Censored after 3 y.
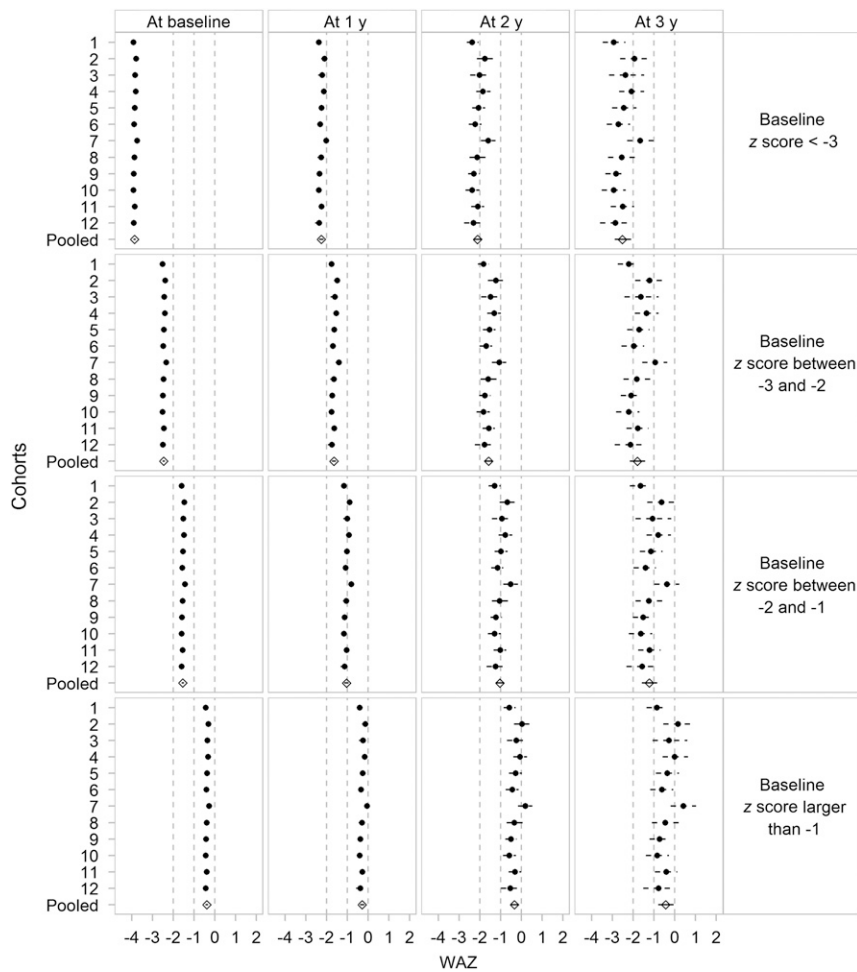
FIGURE 1
WAZs by baseline z score at ART start and 1, 2, and 3 years afterward in 12 treatment programs of IeDEA-SA (adjusted analysis). Medians and IQRs are shown together with an overall pooled estimate. Missing values at start of ART were imputed by multiple imputation.

younger children experience less intestinal damage and are therefore better able to absorb micronutrients, and that the shorter duration with chronic immune activation is associated with lower metabolic costs.[30,31] Alternatively, younger children may have faster normal growth and different growth regulation.[32]

The finding that growth response was better for children on PI-based regimens is topical in the light of the recently presented P1060 clinical trial.[33] This trial comparing lopinavir/ritonavir (LPV/r) versus nevirapine as first-line regimen for non-nevirapine exposed infants and young children revealed better virological and combined virological/mortality outcomes in children

on LPV/r. There was, however, a trend toward worse growth in the LPV/r group. Although our results indicate that growth response may be superior with a PI-based regimen including LPV/r, this association was modified by both age and baseline WAZ. There may be unmeasured confounders, which favor the use of 1 versus the other regimen, and prevention of mother to child transmission exposure is poorly documented in the current IeDEA-SA database.

Despite the large variability of sites, these sites may not necessarily reflect the situation of the region as a whole; all except 2 sites were located in urban areas and cohorts from South Africa predominated. However, this is one of

the largest pooled analyses of children on ART ever published and from one of the regions most heavily affected by the HIV epidemic. Results should therefore be applicable to many other children on ART. A strength of our study is the relative large number of young children. By limiting the analysis to children aged <10 years, we excluded the growth spurt during adolescence.

Although we were able to present results up to 3 years on ART, the median follow-up time was shorter. Due to the rapid scale up of ART, the majority of children started ART only recently and mortality and loss to follow-up were substantial. The growth response in these children may well differ from the response in children who remained in
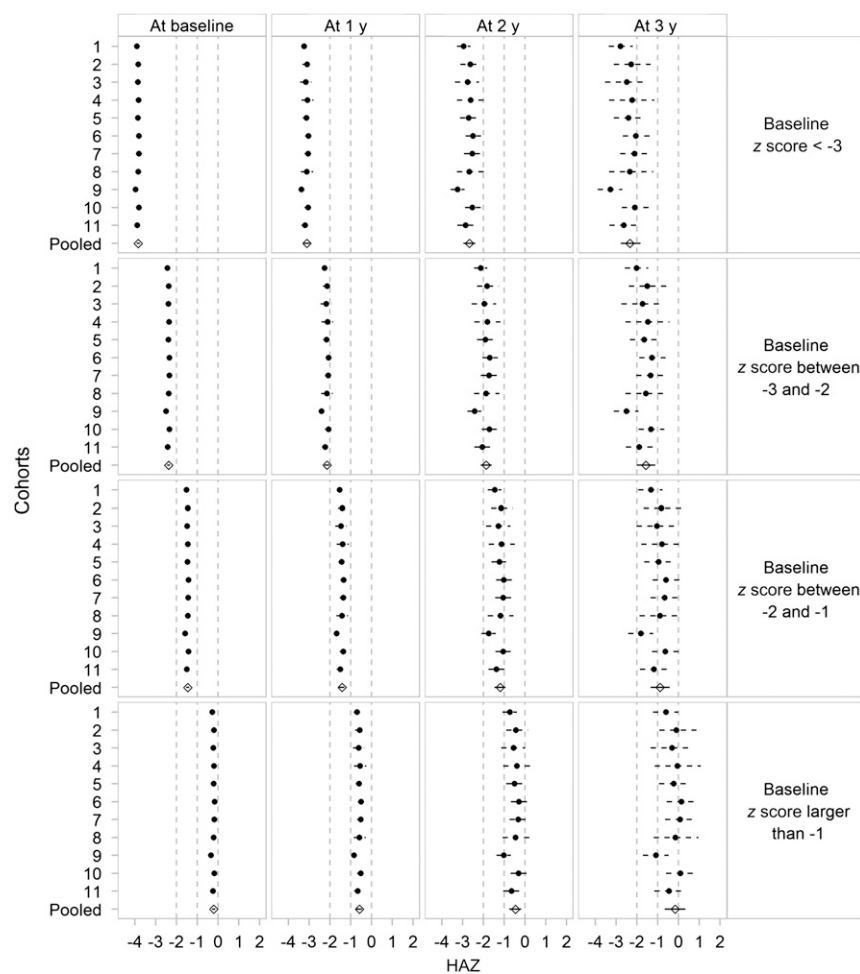
FIGURE 2
HAZs by baseline z score at ART start and 1, 2, and 3 years afterward in 11 treatment programs of IeDEA-SA (adjusted analysis). Medians and IQRs are shown together with an overall pooled estimate. Missing values at start of ART were imputed by multiple imputation. Cohort 12 is missing because no data about heights are collected.

care. Many studies have revealed that mortality is high among patients lost to follow-up,[34,35] and they may have stopped taking ART. If sicker patients are more likely to get lost, our analysis overestimates growth response. When we repeated the analysis with children remaining in care during the whole time period, z scores were in general similar or slightly higher. Therefore, loss to follow-up may not have distorted results to an important degree.

Many factors that could influence growth response were not recorded, which may explain why adjusting for the recorded baseline variables reduced heterogeneity only moderately; we had no individual level data on nutrition and

food supplementation, nor on socio-economic status, tuberculosis treatment, hemoglobin, birth weight, or adherence to therapy. The presence or absence of peripheral edema was not recorded and therefore a nutritional assessment based on WHO definitions was not possible. The provision of food supplementation that may have affected growth trajectories and measurements for shoes and clothes were only standardized within but not between sites. Children with lower z scores may have received food supplements and may therefore have had a better growth response. Because we did an intention-to-treat analysis, we ignored treatment interruptions.

Further, stage of disease does not fully capture the severity of different coinfections. Similarly, the proportion of missing data was relatively high. Results were, however, similar if missing values were completed by multiple imputation and in the complete case analysis. Other limitations are that no standardized measurements of weight and heights were done, and finally that no comparisons to HIV-negative children were possible for the different sites.

CONCLUSIONS

This study demonstrated that although weight and height increased rapidly on
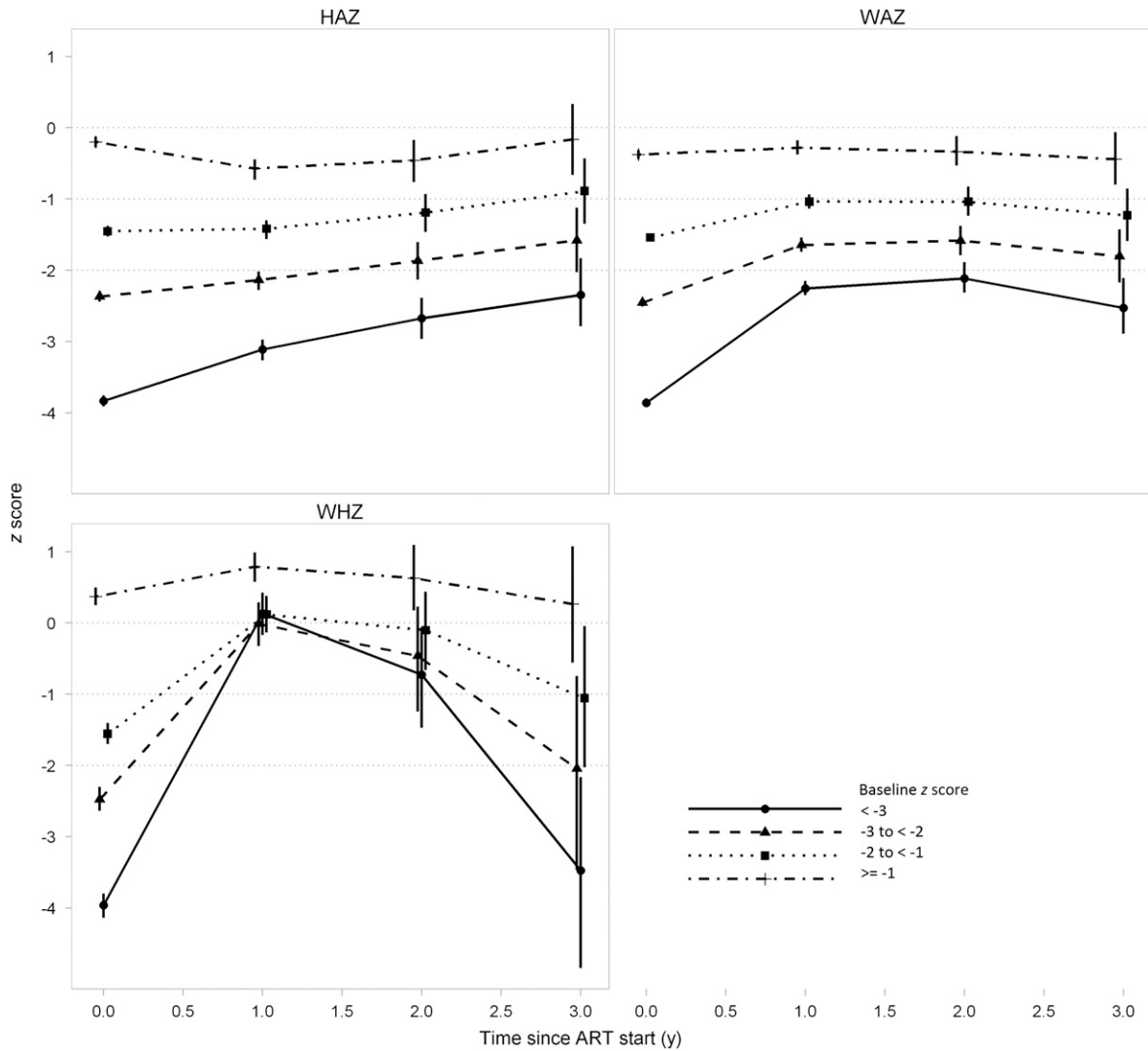
FIGURE 3

WAZs, HAZs, and WHZs by baseline *z* score at ART start and 1, 2, and 3 years afterward. Pooled adjusted estimates of treatment programs of IeDEA Southern Africa. Medians and IQRs are shown.

ART and was particularly pronounced for weight in the first year of ART, neither weight nor height values normalized during 3 years of ART. There is an urgent need to better understand the reasons for the large variability in growth response across sites and to better document individual level and site level characteristics that influence response to therapy.

APPENDIX: FULL PROBABILITY MODEL

Let Y_{jk} (*t*) denote the anthropometric measure be it WAZ, HAZ, or WHZ for

child $j = 1,...,N$ at time $t = 1,...,T$ with time in years in cohort $k = 1,...,K$. The model can be written as

The error term ε represents the measurement error for each child, and in the final model is a centered Student's

$$Y_{ijk} = \alpha_{jk} + \beta_{jk} \cdot t_i + \gamma_{jk} \cdot t_i \cdot \log(t_i) + \varepsilon_{ijk}, \quad \varepsilon_{ijk} \sim N(0, \sigma^2)$$

$$\alpha_{jk} = X_\alpha \alpha_k + \eta_{jk}, \quad \eta_{jk} \sim N(0, \tau_\alpha^2)$$
$$\beta_{jk} = X_\beta \beta_k + \zeta_{jk}, \quad \zeta_{jk} \sim N(0, \tau_\beta^2)$$
$$\gamma_{jk} = X_\gamma \gamma_k + \xi_{jk}, \quad \xi_{jk} \sim N(0, \tau_\gamma^2)$$

$$\alpha_k = Z_\alpha \alpha_0 + \eta_k, \quad \eta_k \sim N(0, \nu_\alpha^2)$$
$$\beta_k = Z_\beta \beta_0 + \zeta_k, \quad \zeta_k \sim N(0, \nu_\beta^2)$$
$$\gamma_k = Z_\gamma \gamma_0 + \xi_k, \quad \xi_k \sim N(0, \nu_\gamma^2)$$
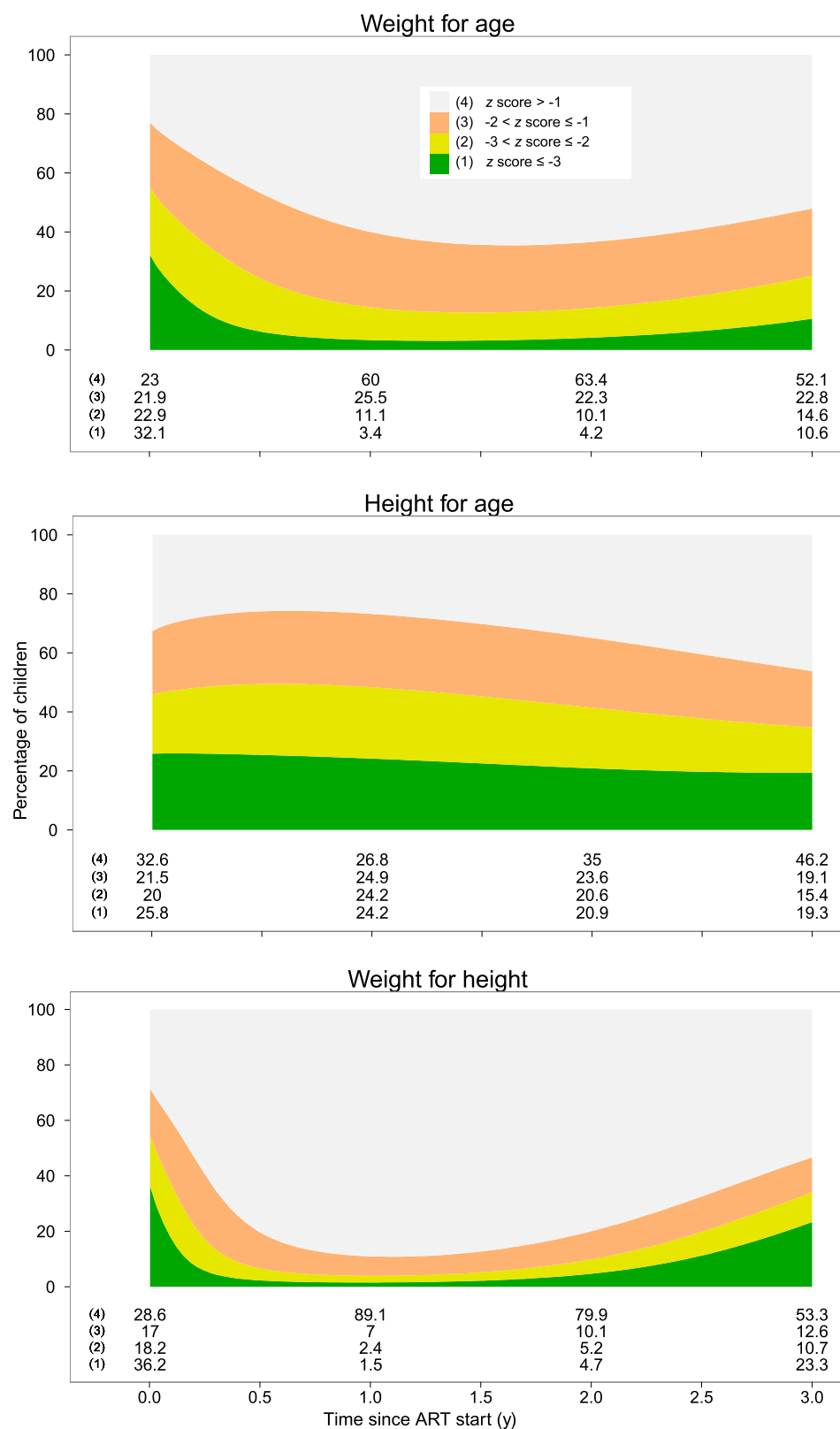
FIGURE 4
Percentage of children in different *z*-score categories over time.

t test distribution with 3 degrees of freedom and scale parameter σ^2. The children level random effects distributions are centered Student's t test distributions as well with 3 degrees of freedom and scale parameters τ_α^2, τ_β^2, and τ_γ^2. The cohort level random effects distributions are centered Student's t test distributions with 3 degrees of freedom and scale parameters υ_α^2, υ_β^2, and υ_γ^2. Student's t test distributions were preferred because these heavy tailed distributions yield robust estimates and outperform the model with normal distribution in terms of the deviance information criterion.

The prior distributions for α_0, β_0, and γ_0 are centered normal with SD = 5. For the other α, β, and γ parameters, the priors are centered normal with SD = 10.

The prior distributions for all scale parameters are inverse γ distributions with shape and rate parameters equal to 1 and 0.01, respectively.

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