Growth in Virologically Suppressed HIV-Positive Children on Antiretroviral Therapy

Individual and Population-level References

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Background: Combination antiretroviral therapy (ART) suppresses viral replication in HIV-infected children. The growth of virologically suppressed children on ART has not been well documented. We aimed to develop dynamic reference curves for weight-for-age Z scores (WAZ) and height-for-age Z scores (HAZ).

Methods: Children aged <11 years at ART initiation with continuously undetectable viral loads (<400 copies/mL) treated at 7 South African ART programs with routine viral load monitoring were included. We used multilevel models to define trajectories of WAZ and HAZ up to 3 years and developed a web application to monitor trajectories in individual children.

Results: A total of 4876 children were followed for 7407 person-years. Analyses were stratified by baseline Z scores and age, which were the most important predictors of growth response. The youngest children showed the most pronounced increase in weight and height initially but catch-up growth stagnated after 1–2 years. Three years after starting ART, WAZ ranged from −2.2 [95% prediction interval (PrI), −5.6 to 0.8] in children with baseline age >5 years and Z score less than −3 to 0.0 (95% PrI, −2.7 to 2.4) in children with baseline age <2 years and WAZ greater than −1. For HAZ, the corresponding range was −2.3 (95% PrI, −4.9 to 0.3) in children with baseline age >5 years and Z score less than −3 to 0.3 (95% PrI, −3.1 to 3.4) in children with baseline age 2–5 years and HAZ greater than −1.

Conclusions: We have developed an online tool to calculate reference trajectories in fully suppressed children. The web application could help to define "optimal" growth response and identify children with treatment failure.

Key Words: HIV, antiretroviral therapy, growth

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Measuring a child's weight and height over time and comparing it with a reference is a simple way of assessing his or her growth and health. In HIV-infected children in settings with few resources, growth monitoring is used to identify children eligible for antiretroviral therapy (ART), and weight and height trajectories are often the only information on whether a child is responding to ART.[1–3]

Data on the association between growth and virologic response to ART are, however, conflicting.[4] Some studies showed that virologic control leads to improved growth, whereas no associations were found in others.[3,5] Studies from Malawi[6] and Uganda[7] reported that undernourished and stunted children often do not reach normal weight-for-age Z score (WAZ) and height-for-age Z score (HAZ) under ART. However, virologic response was not assessed in these studies, and the growth trajectories in African HIV-infected children with suppressed viral replication are not well defined. In contrast, children from Europe and the US, where regular viral load monitoring is used, reached normal values within 2 years of initiating therapy.[8]

African settings differ with regard to many factors related to growth: children generally start ART at an age of 5–6 years,[9] often with more advanced disease. Detrimental environmental factors such as coinfections, undernutrition and food insecurity are common.[10,11] Using data from the large pediatric International Epidemiological Databases to Evaluate AIDS (IeDEA) Southern Africa (IeDEA-SA) collaboration, we aimed to describe growth in children with consistently suppressed HIV viremia to derive reference standards of Z score trajectories and to make these available in a web application that displays expected growth up to 3 years on ART for individual children.

MATERIALS AND METHODS

International Epidemiological Databases to Evaluate AIDS

IeDEA-SA is a collaboration of 24 ART programs in 6 countries in Southern Africa (www.iedea-sa.org).[12] Data are collected at ART initiation (baseline) and follow-up visits using standardized instruments. All sites have ethical approval to collect data and

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participate in IeDEA-SA. In this study, we used the data merged up to January 1, 2014 and included 7 IeDEA-SA sites with at least 100 children that had started ART in South Africa, the only country within the IeDEA-SA collaboration where viral load was routinely monitored. Anthropometric measurements were generally scheduled to be done every 4–12 weeks. Viral loads were measured according to the South African guidelines as follows: semiannually before 2010 and then from 2010 to 2012 at 6 and 12 months after ART initiation and then yearly.

These primary sites include the Khayelitsha ART Program, McCord Hospital, Red Cross Children's Hospital, Hlabisa HIV Care and Treatment Program, Harriet Shezi Clinic, Rahima Moosa Mother and Child Hospital and Tygerberg Academic Hospital. An eighth site (Kheth'Impilo) which joined IeDEA only recently was used for model validation only.

Eligibility Criteria and Definitions

We included ART-naive children aged <11 years who initiated treatment with at least 3 antiretroviral drugs and had undetectable viral load measurements only during the first 3 years on ART (all viral load values <400 copies/mL). Children did not need to have 3 years of follow-up to be included in the analysis. We included children who died or transferred out during follow-up on ART. We excluded children without any anthropometric measurement after start of ART and 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 to age-adjusted and sex-adjusted Z scores using the World Health Organization (WHO) reference population 2007.[13] Underweight was defined as WAZ less than –2 and stunting as HAZ less than –2. We took weight and height measurements and CD4 cell counts closest to the starting date of ART (−6 months/+1 week) as baseline values. Immunodeficiency was defined as in the WHO case definitions of HIV.[14]

Statistical Analysis and Modeling

The analysis was conducted using data from all 7 primary sites. The WAZ and HAZ trajectories were analyzed using second order fractional polynomials.[15] The same approach was used in an earlier study in Malawi.[2] We used a model including all patients to determine which variables were most predictive of anthropometric trajectories and then stratified the analysis by these variables. In each stratum, the best fitting second order fractional polynomial was selected based on the deviance criterion.[15] Separate analyses were performed for the different strata. No interaction terms were included. We then extended the model to a Bayesian multilevel model[16] taking into account between-cohort and between-patient variabilities. The model fit was visually assessed by plotting the 95% prediction intervals (PrIs) and the observed trajectories for individual children. We assessed the model for overfitting by randomly splitting the data into a training data set (90% of patients) and a test data set (10% of patients). We performed the analysis on the training set and assessed how many measurements of the test dataset were within the 95% PrI.

We validated the model using data from the independent cohort (Kheth'Impilo) and checked how many measurements of the validation data were within the 95% PrI. We report all validation results after 1 and 3 years of follow-up.

Based on the predictive distribution of growth trajectories obtained from the training data set, a web application was developed. The joint predictive distribution of location and scale parameters was approximated by a normal inverse Gamma distribution and served as the prior distribution for the growth trajectories of a new child. Available anthropometric measurements were used to update the prior as new measurements become available. The growth trajectories for a given child were then predicted using this prior distribution and past Z scores (for more details see http://iedea-sa.org). All analyses were performed in R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria), Stata version 11 (StataCorp, College Station, TX), and WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge Institute of Public Health, Cambridge, UK).

RESULTS

Study Population and Baseline Characteristics

Of 12,476 children followed up in the 7 primary sites, 7130 (57.1%) children had continuously undetectable viral load, and 5423 had a weight and/or height measurement at the start of ART. Among these, 4876 were randomly selected for the training dataset and 547 for the test dataset (see Fig., Supplemental Digital Content 1, http://links.lww.com/INF/C206). The number of children included in analyses ranged from 74 children from Hlabisa in KwaZulu-Natal to 1944 children from the Harriet Shezi clinic in Soweto. The median age of the children was 3.7 years, and about half (2440 children, 50.0%) were female (Table 1). At baseline, most children (4871 children, 99.9%) had a weight measurement, and 3340 children (68.5%) had a height measurement. A substantial proportion of children with measurements were underweight (1805 children, 37.1%), stunted (1842, 55.1%) and had evidence of severe immunodeficiency at baseline (1831, 51.0%; Table 1).

In the first 3 years after starting ART, 217 (4.5%) children died, 241 (4.9%) were lost to follow-up, and 808 (16.6%) were transferred to another clinic. The median follow-up between ART initiation and the last available anthropometric measurement was 11 (interquartile range, 1–29; range, 0–36) months. During 5136 years of follow-up, 42,258 weight and 29,145 height measurements were recorded. A total of 3340 children had a baseline height available and were thus included in the analysis for HAZ. The children with baseline WAZ did not substantially differ from the children with baseline HAZ.

The validation dataset consisted of 480 children with available baseline weight or height from the Kheth'Impilo cohort. All children had baseline WAZ recorded, and 35 (7.3%) had baseline HAZ recorded. Children in the validation data were older, had lower baseline WAZ and HAZ, were in less severe WHO stages, were included more recently, were more likely on non-nucleoside reverse transcriptase inhibitor-based regimens and were less often lost to follow-up or transferred out than the children in the primary dataset.

Growth Trajectories for WAZ and HAZ

Baseline Z scores and age were the strongest predictors of growth response overall. Baseline viral load, CD4 and WHO stage were also associated with growth but with a small effect estimate. For the population projections, we, therefore, calculated separate growth curves for children with Z scores less than 3, −3 to less than −2, −2 to less than −1 or greater than −1 and age groups <2 years, 2 to <5 years and 5 to <11 years. The youngest children showed the most pronounced increase in weight and height initially, but in all children catch-up growth stagnated after the first 1 or 2 years. Figure 1 shows mean WAZ with 95% PrIs by baseline Z scores and age group up to 3 years after ART start. Three years after starting ART, WAZ ranged from −2.2 (95% PrI, −5.6 to 0.8) in children aged 5 years or older who started with a baseline Z score of less than −3 to 0.0 (95% PrI, −2.7 to 2.4) in children aged less than 2 years with a baseline WAZ -1 and above. For HAZ, the corresponding range was −2.3 (95% PrI,

TABLE 1. Characteristics of Children Starting ART

Characteristic		All Children, N = 4876	Weight-for-age Analysis, N = 4871	Height-for-age Analysis, N = 3340	Validation Data, N = 480
Site	Harriet Shezi, Soweto	1944	1942	1907	—
	Khayelitsha, Cape Town	980	979	128	—
	Red Cross, Cape Town	631	631	86	—
	Tygerberg, Cape Town	162	161	111	—
	McCord, Durban	689	689	683	—
	Hlabisa, KwaZulu-Natal	74	74	56	—
	Rahima Moosa, Johannesburg	396	395	369	—
	Khethimpilo, Cape Town	—	—	—	480
Age, median (IQR), years		3.7 (1.6–6.3)	3.7 (1.6–6.3)	4.1 (1.6–6.6)	5.6 (3.4–7.6)
Age group, n (%)	<2 yr	1679 (34.4)	1676 (34.4)	1143 (34.2)	81 (16.9)
	2–5 yr	1253 (25.7)	1251 (25.7)	818 (24.5)	113 (23.5)
	6–10 yr	1944 (39.9)	1944 (39.9)	1379 (41.3)	286 (59.6)
Sex, n (%)	Female	2440 (50)	2440 (50.1)	1669 (50)	248 (51.7)
Weight-for-age Z score, n (%)	< −3	946 (19.4)	946 (19.4)	748 (22.4)	261 (54.4)
	−3 to < −2	859 (17.6)	859 (17.6)	653 (19.6)	121 (25.2)
	−2 to < −1	1286 (26.4)	1286 (26.4)	883 (26.5)	59 (12.3)
	≥ −1	1780 (36.5)	1780 (36.5)	1051 (31.5)	39 (8.1)
Height-for-age Z score	< −3	917 (27.5)	914 (27.4)	917 (27.5)	21 (60)
	−3 to < −2	925 (27.7)	925 (27.7)	925 (27.7)	10 (28.6)
	−2 to < −1	815 (24.4)	814 (24.4)	815 (24.4)	2 (5.7)
	≥ −1	683 (20.4)	682 (20.4)	683 (20.4)	2 (5.7)
CD4 percentage	Missing data	1320	1320	698	319
	Median (IQR)	14.5 (9–21.1)	14.5 (9–21.1)	14.2 (8.8–21)	15 (10–21)
Immunodeficiency,† n (%)	Missing data	1288	1288	691	273
	Not significant	653 (18.2)	652 (18.2)	478 (18)	34 (16.4)
	Mild	454 (12.7)	454 (12.7)	336 (12.7)	25 (12.1)
	Advanced	650 (18.1)	649 (18.1)	479 (18.1)	49 (23.7)
	Severe	1831 (51)	1828 (51)	1356 (51.2)	99 (47.8)
WHO clinical stages, n (%)	Missing data	785	782	598	113
	Stage 1	287 (7)	287 (7)	126 (4.6)	33 (9)
	Stage 2	462 (11.3)	462 (11.3)	267 (9.7)	155 (42.2)
	Stage 3	2237 (54.7)	2235 (54.7)	1475 (53.8)	175 (47.7)
	Stage 4	1105 (27)	1105 (27)	874 (31.9)	4 (1.1)
Year of ART start, n (%)	1999–2004	315 (6.5)	315 (6.5)	274 (8.2)	0 (0)
	2005–2009	3269 (67)	3265 (67)	2328 (69.7)	240 (50)
	2010–2013	1292 (26.5)	1291 (26.5)	738 (22.1)	240 (50)
Type of regimen, n (%)	Non-nucleoside reverse transcriptase inhibitor-based	2762 (56.7)	2760 (56.8)	1945 (58.3)	341 (71)
	Protease inhibitor-based	2027 (41.6)	2024 (41.6)	1324 (39.7)	68 (14.2)
	Other/unknown	78 (1.6)	78 (1.6)	70 (2.1)	71 (14.8)
Outcome, n (%)‡	Death	217 (4.5)	216 (4.4)	163 (4.9)	8 (1.7)
	Loss to follow-up	241 (4.9)	241 (4.9)	85 (2.5)	0 (0)
	Transfer out	808 (16.6)	808 (16.6)	661 (19.8)	0 (0)

*No baseline weight or height available.
†WHO case definitions.[14]
‡Censored after 3 years.
IQR indicates interquartile range.

−4.9 to 0.3) in children aged 5 years or older who started with a baseline Z score of less than −3 to 0.3 (95% PrI, −3.1 to 3.4) in children aged 2–5 years with a baseline HAZ larger than −1 (Fig. 2).

Overall, the model fitted well in the test sample with 95% (93% during the first year) of observations included in the 95% PrI for WAZ. This percentage differed between subgroups. It was 89% (87% during the first year) for 0–2 year olds with baseline WAZ between −2 and −1 and 98% (97% during the first year) for 2–5 year olds with baseline WAZ less than −3. The model also fitted well for HAZ with 92% (91% during the first year) of observations in the PrI. This percentage was 76% (72% during the first year) for 0–2 year olds with baseline HAZ larger than −1 and 99% (97% during the first year) for 2–5 year olds with baseline HAZ between −2 and −3. In the independent validation sample, the model fitted well, with 92% (90% during the first year) of observations in the 95% PrI for WAZ. This percentage was 89% (87% during the first year) for 6–10 year olds with baseline WAZ larger than −1 and 96% (95% during the first year) for 2–5 year olds with baseline WAZ between −2 and −1. The validation sample only had data on HAZ for 35 patients with a total of 81% (81% during the first year) of observations in the 95% PrI.

Predictions for Individual Children–Web Interface

Figure 3 shows the output of the web application, which is available online (http://growthapp.iedea-sa.org). We also provide a step-by-step manual which is available online. The web application can be used to predict WAZ and HAZ trajectories by baseline age and Z score up to 3 years after starting ART. The example shows a hypothetical child aged between 2 and 5 years whose baseline WAZ was below −3 at ART initiation. The user entered either 1, 3 (the minimally required number for individual trajectories), 9 or 16 weight measurements (shown as black triangles in panels A, B, C and D of Fig. 3). The likely evolution of WAZ is then shown for up to 3 years after ART initiation. The predictions for a particular child are adjusted each time more values are entered. The expected range of values for an HIV-positive child with the same baseline age and

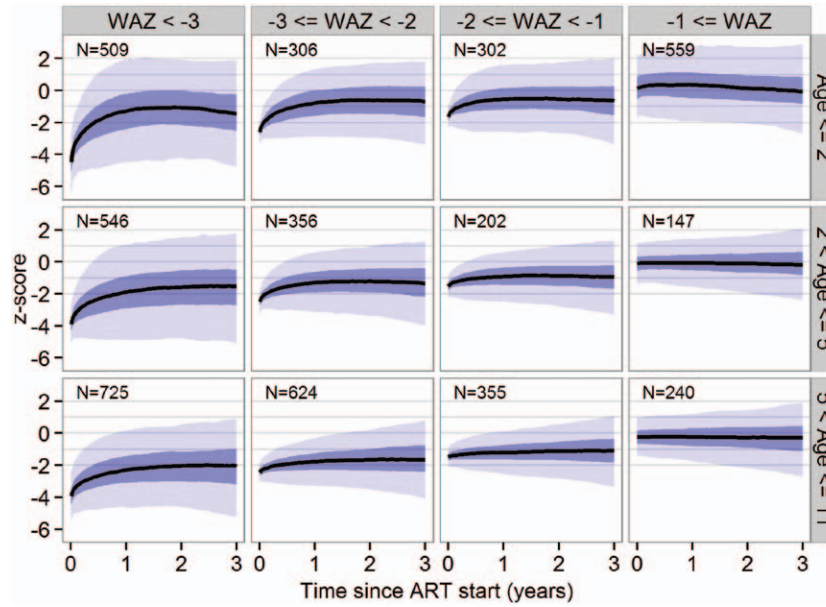

FIGURE 1. Weight-for-age Z scores trajectories by Z score and age at start of ART in children with consistently undetectable viral load. These curves represent population-level predictions and should not be used for individual treatment monitoring. The black lines are predicted response curves, the dark blue areas are 50% PrIs, and the light blue areas are 95% PrIs. A total of 4871 children from 7 clinics in South Africa were included.

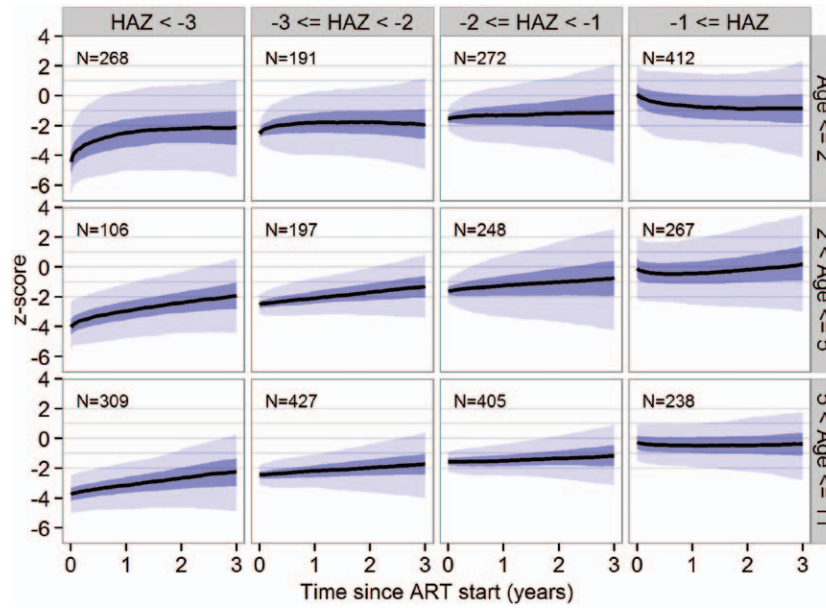

FIGURE 2. Height-for-age Z scores trajectories by Z score and age at start of ART in children with consistently undetectable viral load. These curves represent population-level predictions and should not be used for individual treatment monitoring. The black lines are predicted response curves, the dark blue areas are 50% PrIs, and the light blue areas are 95% PrIs. A total of 3340 children from 7 sites in South Africa were included.

WAZ categories and suppressed viral load values are shown as shaded areas.

DISCUSSION

Main Findings

We provide growth reference curves up to 3 years after starting ART both at the individual and at the population level. The reference was developed in children who never had detectable viral load. Therefore, it should have been closer to optimal than in children with detectable viral load. Although the population-level estimations may serve as a reference for children of a certain age and Z score at start of ART, the individual-level predictions take the history of previous measurements into account when making predictions. The individual-level predictions may, therefore, be more useful for children who deviate from the average and may be used as early warning indicators for treatment failure and comorbidities. The population-level predictions show that despite virologic suppression and initial catch-up growth, the median WAZ does not reach normal values. After about 1.5 years on ART, catch-up growth stops and, in particular, older children with low baseline Z scores catch-up very slowly. For HAZ, the increase is less pronounced but continuous over a longer period in the older age groups.

Comparisons with Other Studies

The overall pattern in weight and height gain is similar to the pattern given in a previous study within the IeDEA collaboration where data from sites with and without viral load monitoring were combined.[17] In both analyses, WAZ increased rapidly in the first year of ART but stagnated thereafter, whereas HAZ increased continuously over time. However, in contrast to the previous analysis where no difference between viral load and nonviral load sites was found, we now found that WAZ in virologically suppressed children seem

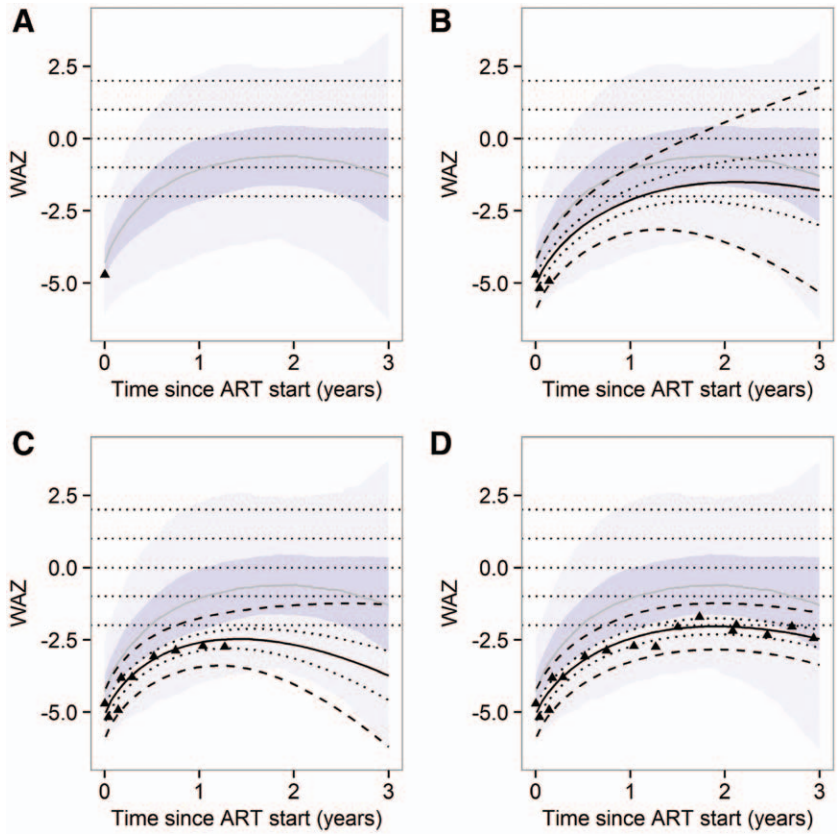

FIGURE 3. Illustration of the web-interface—example of individual predictions of weight for age growth trajectory. Predictions up to 3 years after start of ART can be made according to the characteristics of the child at start of ART and weight measurements thereafter. Predictions are based on predictive distributions from the Bayesian multilevel model. The example shows the actual measured values for 1 particular child with a baseline age of 2–5 years and a baseline WAZ less than −3. Observed values (dots) and PrIs (median, 50% and 95%) for that child are shown. The shaded area shows the PrIs for any child with the same baseline age and Z scores. The predictions for a particular child are adjusted each time more values are entered. A, Only the first weight measurement was available and population-level PrIs are shown. B, Three weight measurements were available and an individual-level prediction (black) is shown on top of the population-level predictions. C, Nine measurements were available. D, All measurements are shown. The PrIs for that particular child are based on the known values shown as dots. These predictions are implemented both for weight-for-age and height-for-age and can be accessed from the following webpage: http://growthapp.iedea-sa.org. The user can introduce his own values of interest and must then specify if the predictions are for a child from a cohort that was used to develop the model or if the child comes from an external cohort.

to be higher than in suppressed and nonsuppressed combined. For example, in children with a baseline WAZ of less than −3, estimated WAZ at 3 years ranged from −1.5 to −2.2 across age groups in our analysis compared with −2.1 across all ages in the previous analysis. For HAZ, no difference was found (ranging from −2 to −2.3 across age groups in our analysis compared with −2.3 previously). However, estimates between studies were not directly comparable because analyses were not stratified by age previously and loss to follow-up was lower (4.9% in our analysis versus 14.5% previously).

It remains unclear why catch-up growth in weight stops after about 1.5 years on therapy despite the continuous virologic suppression. In addition to unrecorded factors (eg, socioeconomic status, nutrition), chronic immune activation because of HIV or ART side effects may also play a role. A study in adults has shown that mitochondrial toxicity because of D4T may lead to weight loss in adults,[18] but to our knowledge, no data have been reported on children. In our study, the same downward trend in growth was apparent when children on D4T regimens were excluded from the analysis (data not shown). An analysis from rural Zambia found a similar growth pattern for both weight and height to ours. In the Zambian study, mean WAZ increased rapidly from −2.4 at ART initiation to −1.3 after 6 months and decreased slightly to −1.7 after 2 years. During the same time, mean HAZ increased almost linearly from −3.5 to −2.1. In contrast to us, other studies found a linear increase in WAZ during the first 2 years of ART in children older than 5 years[19] and in urban settings.[20]

Comparison with HIV-negative Children

Unfortunately, we were unable to compare our results with those from HIV-negative children from the same setting. One study from Kinshasa found lower WAZ in HIV-positive than in HIV-negative children: at 18 months, WAZ was −2.3 in HIV-positive compared with −1.3 in HIV-negative children—irrespective if the mother was HIV positive or not. For HAZ, the difference persisted but was only about half a Z score lower in HIV-positive versus HIV-negative children.[21] Similarly, in an Ugandan trial, HIV-infected children weighed less and were shorter during the whole 5 years of follow-up after birth.[22] In these studies, children were followed from birth and no distinction was made between those with and without virologic suppression.

Predictors of Growth Response

Many factors may influence growth, and simply having a continually suppressed viral load does not imply that normal growth will be achieved. Growth response has been shown to be better in younger children[23,24] and in children with low CD4 cell percentages and advanced stage of disease.[25,26] Other individual-level and site-level factors associated with poor growth but not recorded in our database, include coinfections (such as tuberculosis) and other comorbidities, low socioeconomic status and poor nutrition or food insecurity or the lack of food supplementation programs.[27,28]

Strengths and Limitations

The strengths of the analysis are that children from many sites and settings were included and that the characteristics of the children at start of ART are typical for the region. We used state of the art statistical analysis techniques and validated the prediction in an independent sample. Although viral load and nonviral load sites may differ with regard to many factors, our results may serve as a reference in sites where viral load monitoring is not available.

The study also has a number of limitations. Because the analysis was restricted to sites where viral load monitoring is available to assess virologic suppression, all included sites were in South Africa where the standard of care is higher than in other sites and the results may not necessarily be generalizable to other settings. Our selection criteria also restricted the available sample size and the follow-up duration; in particular, the number of children with height measurements was limited. Because of this limited sample size and because weight and height measurements were not always available at the same time point, an analysis of WHZ was not possible. Also children must have had at least 3 anthropometric measurements to make individual-level predictions of growth response. There was considerable loss to follow-up, which limited the precision of the population estimates during the third year. Although we included only virologically suppressed children, which indicates good adherence, adherence was not explicitly recorded and intermittent poor adherence including unmeasured viral failures are possible. Our results represent trajectories of children who remained in care. Children who were lost to follow-up, who transferred out or who died may have different growth responses. If sicker patients are more likely to get lost, our analysis overestimates growth response. We were unable to compare protease inhibitor-based regimen and non-nucleoside reverse transcriptase inhibitor-based regimen because the distribution of regimens was unbalanced across age groups. Finally, the model cannot predict the probability of viral failure.

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