Growth among HIV-infected Children Receiving Antiretroviral Therapy in Dar es Salaam, Tanzania

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Summary

We assembled a prospective cohort of 3144 human immunodeficiency virus (HIV) infected children aged <15 years initiating antiretroviral therapy (ART) in Dar es Salaam, Tanzania. The prospective relationships of baseline covariates with growth were examined using linear regression models. ART led to improvement in mean weight-for-age (WAZ), height/length-for-age (HAZ) and weight-for-length or body mass index (WLZ/BMIZ) scores. However, normal HAZ values were not attained over an average follow-up of 17.2 months. After 6 months of ART, underweight ($P < 0.001$), low CD4 count or percent ($P = 0.001$), stavudine containing regimens ($P = 0.05$) and advanced WHO disease stage ($P < 0.001$) at ART initiation were associated with better WAZ scores. Age >5 years on the other hand was associated with less increase in WAZ score after 6 months of ART ($P < 0.001$). These findings suggest that although ART improved the growth of the HIV-infected children in Tanzania, adjunct nutritional interventions may be needed to ensure that the growth of these children is optimized to the greatest extent possible.

Introduction

Globally, there were an estimated 34 million people living with human immunodeficiency virus (HIV) in 2010 [1]. In the same period there were 2.7 million new HIV infections and 1.8 million HIV-related deaths [1]. Children account for an estimated 14% of all new HIV infections globally [2], and mother-to-child transmission is the primary mode of acquisition of HIV infection among pediatric patients worldwide [3, 4]. Sub-Saharan Africa (SSA) remains the region most heavily affected by HIV.

Tanzania faces a mature, generalized HIV epidemic. With a total population of around 40 million, the HIV prevalence for adults aged 15–49 in Tanzania stands at 5.7% in 2007/08 representing a slight decline in prevalence from 7% in 2003/04 [5]. By 2007, an estimated 1.4 million adults and children were living with HIV in Tanzania [6]. Among

children, approximately 140 000 children under the age of 15 years were living with HIV/AIDS in the same period [6].

Disturbance in growth is a common feature of children with HIV infection [7–10]. Apart from food insecurity, underlying HIV infection pathology and opportunistic infections can result in growth faltering by limiting food intake and increasing resting energy expenditure, among other mechanisms [7]. Poor growth may also be an indicator for treatment failure.

Despite the abundant literature on nutrition and growth in HIV-infected children [11–17], there is limited information on patterns and predictors of growth among pediatric patients receiving antiretroviral therapy (ART) particularly in SSA. Several previous studies were limited by their smaller sample sizes or shorter duration of follow-up [11–14, 17], and only a few studies examined growth response beyond 2 years of ART [15, 16]. Assessment of growth is key to monitoring disease progression [18, 19], and assessing response to treatment [7] particularly in resource-limited settings where laboratory measurements such as viral load and CD4 count may not be easily accessible.

The aim of this study was to describe the growth pattern and examine the predictors of growth among children receiving ART in Dar es Salaam, Tanzania. The Institutional Review Board of the Harvard School of Public Health approved the study.

Methods

Study design, setting and participants
We assembled a prospective cohort of HIV-infected children receiving ART at Management and Development for Health (MDH), a Tanzanian-based organization supporting high quality HIV/AIDS care and treatment services. Following enrollment, patients were evaluated at monthly clinic visits. At each visit, trained nurses measured patient's weight, height or length, and mid-upper arm circumference (MUAC) using standardized procedures. Patients also had a complete medical history in the preceding month taken and a detailed physical examination carried out by a physician, underwent nutrition and medication adherence counseling, and received ARV refills. Laboratory tests including complete blood count, liver function tests, and CD4+ cells percents and absolute counts were performed routinely every 4 months.

Patients were initiated on antiretroviral treatment according to the most recent National AIDS Control Program (NACP) ART initiation criteria at the time of initiation [20]. Accordingly, children were eligible for ART when presented with a World health Organization (WHO) clinical stage 4 or stage 3, irrespective of the absolute CD4+ cells count or percentage, or WHO stage 1 or stage 2 and severe immunodeficiency (CD4+ count <200 or CD4+ percent <15%). Standard ART in Tanzania was triple therapy consisting of 2 nucleoside reverse transcriptase inhibitors (NRTI) + 1 non-nucleoside reverse transcriptase inhibitors (NNRTI) or 2 NRTI + 1 protease inhibitor (PI) or 3 NRTI [21]. Standard first line regimens thus included zidovudine (AZT) + lamivudine (3TC) + nevirapine (NVP) for children under 3 years old; zidovudine (AZT) + lamivudine (3TC) + efavirenz (EFV) or nevirapine (NVP) for children 3 years old or more; abacavir (ABC) + lamivudine (3TC) + efavirenz (EFV) for children for children 3 years or more or nevirapine (NVP) for children under 3 years; stavudine (d4T) + lamivudine (3TC) + nevirapine (NVP). Standard first line regimens thus included zidovudine (AZT) + lamivudine (3TC) + nevirapine (NVP) for children under 3 years old; zidovudine (AZT) + lamivudine (3TC) + efavirenz (EFV) or nevirapine (NVP) for children 3 years old or more; abacavir (ABC) + lamivudine (3TC) + efavirenz (EFV) for children 3 years or more or nevirapine (NVP) for children under 3 years; stavudine (d4T) + lamivudine (3TC) + nevirapine (NVP). Stavudine was an alternative for AZT in cases of anemia (i.e. hemoglobin <7.5g/dl). To avoid drug interactions, efavirenz was substituted for nevirapine in patients receiving therapy (rifampin) for tuberculosis. ARVs were switched to second line as a result of toxicity or a lack of good clinical response to the regimen. The recommended second line regimens included the combination of didanosine (ddI) + ABC + ritonavir boosted lopinavir (LPV/r) or nelfinavir (NFV).

Statistical analysis
The outcomes for this study were the standardized anthropometric *z*-scores; weight-for-age (WAZ), height/length-for-age (HAZ) and weight-for-length or body mass index (BMIZ) scores. The *z*-scores were computed from the measurements of weight, height or length, and child age in months and sex using the 2006 World health Organization (WHO) Child Growth reference standards [21]. A child was considered to be underweight, stunted or wasted when WAZ, HAZ or WLZ/BMIZ score, respectively, was below –2 of the reference population. Using the WHO guidelines, children up to 5 years of age were classified as having low MUAC if they had MUAC <11.5 cm. However, for children older than 5 years, a cut-off of 16.4 cm (10th percentile) was adopted from NHANES (National Health and Nutritional examination Survey) 2003–06 conducted by Centers for Disease Control (CDC) and National Centre for Health Statistics (NCHS) for children older than 5 years.

We first described growth pattern by plotting the mean *Z*-scores over time. Associations between baseline covariates and the change in *Z*-scores after

6 months of ART, point at which the growth patterns stabilize, were then examined using linear regression with the change as a continuous variable. Variables were included in the multivariate models if they were significantly associated with the outcomes in univariate analyses ($P < 0.20$) or if they were believed to be mechanistically relevant. The missing indicators method was used for covariates with more than 1% of missing data. Adjusted differences in WAZ, HAZ, WLZ/BMIZ and their corresponding 95% confidence intervals (CI) were constructed. The criterion for significance for all analyses was a P-value significant at level of $\alpha = 0.05$. All P-values were two tailed.

All statistical analyses were performed with the statistical software package SAS (version 9.2, SAS Institute Inc., Cary, NC).

Results

A total of 3180 children <15 years were initiated on ART between October 2004 and December 2010. Thirty six out of these children had invalid or missing information on age and were excluded from the analyses. The remaining sample of 3144 children contributed a median of 17.2 months of follow-up (interquartile range [IQR], 4.6–31.4 months). At ART initiation, 51% were 5 years old or younger, and 50% were girls. The prevalence of underweight was 40% while 30% of the children were wasted, 52% had stunting and 39% had low MUAC. All the children were initiated on the recommended first line ARVs regimens. The rest of the general characteristics of the study population are shown in Table 1.

The mean WAZ, HAZ and BMIZ Z-scores and their 95% CI during the period of follow-up are shown in Fig. 1. Administration of ART on average led to an increase in mean Z-scores. However, there was a plateau in growth after 6 months of ART. The age-stratified mean WAZ Z-scores pattern over time are shown in Fig. 2. Administration of ART on average led to an increase in mean WAZ scores with greater effect among children below 2 years of age ($P < 0.001$) even though they started worse off. However, there was less increase in WAZ scores for children over 5 years of age. Similarly, ART led to improvement in mean HAZ and WLZ/BMIZ scores with greater effect on younger children ($P < 0.001$). However, only WAZ and WLZ/BMIZ scores reached or approached normal values. Normal HAZ scores on the other hand, were not attained over an average follow-up of 17.2 months.

Table 2 shows the factors associated with change in mean WAZ scores after 6 months of ART initiation. After 6 months of ART, underweight (mean change, 0.78 (95% CI: 0.67, 0.88; $P < 0.001$), low CD4 count or percent (mean change, 0.29 (95% CI: 0.18, 0.41; $P < 0.001$), stavudine containing regimens (mean change, 0.12 (95% CI: 0.001, 0.24; $P = 0.05$), anemia

TABLE 1

Demographic and clinical characteristics of 3144 HIV-infected children at the time of ART initiation in Dar es Salaam, Tanzania (2004–10)

Characteristic	No. of patients (%[a])
Age (years)	
0–2	927 (29)
>2–5	687 (22)
>5	1530 (49)
Sex	
Male	1562 (50)
Female	1582 (50)
Year of ART initiation	
2004–05	204 (6)
2006	222 (7)
2007	617 (20)
2008	841 (27)
2009	736 (23)
2010	524 (17)
Underweight (WAZ < –2 SD)	
Yes	1270 (40)
No	1147 (36)
Missing	727 (23)
Wasting (WLZ < –2 SD if ≤2 years; BMIZ < –2 SD if >2 years)	
Yes	946 (30)
No	1968 (63)
Missing	230 (7)
Stunting (HAZ < –2 SD)	
Yes	1639 (52)
No	1298 (41)
Missing	207 (7)
Low MUAC (11.5 cm if ≤ 5 years; 16.4 if >5 years)[b]	
Yes	1222 (39)
No	1880 (60)
Missing	42 (1)
Hemoglobin level (g/dl)	
>11	403 (13)
8.5–11	1281 (41)
<8.5	502 (16)
Missing	958 (30)
Severe immune suppression (CD4 + T-cells <15% if ≤5 years; <200 cells/μl if >5 years)[c]	
Yes	1035 (33)
No	1162 (37)
Missing	947 (30)
WHO disease stage	
I	266 (8)
II	479 (15)
III	1538 (49)
IV	224 (7)
Missing	637 (20)
Past history of TB	
Yes	612 (19)
No	2472 (79)
Missing	60 (2)

(continued)

TABLE 1
Continued

Characteristic	No. of patients (%[a])
Opportunistic infections[d]	
Yes	360 (11)
No	2772 (88)
Missing	12 (0.4)
Use of cotrimoxazole	
Yes	1580 (50)
No	1390 (44)
Missing	174 (6)
ARV regimen	
Contains stavudine	761 (24)
No stavudine	1287 (41)
Missing	1096 (35)
ARV regimen	
Contains efavirenz	356 (11)
No efavirenz	1692 (54)
Missing	1096 (35)
District of residence	
Ilala	1372 (44)
Kinondoni	888 (28)
Temeke	824 (26)
Missing	60 (2)

[a]Percents may not add up to 100 because of rounding.
[b]There are no established MUAC cut-offs for children >5 years. The 16.4 cm reference (10th percentile) was adopted from NHANES 2003–06 conducted by CDC, NCHS (McDowell, MA).
[c]Adopted from CDC. Guidelines for Preventing Opportunistic Infections Among HIV-Infected Persons – 2002. MMWR 14 June 2002 (CDC).
[d]Patient currently having at least one or more of the following: herpes zoster, fungal infection, oral candidiasis, oral hairy leukoplakia, recurrent severe bacterial infection, pneumocystis jirovecii pneumonia, toxoplasmosis, cryptosporidiosis with diarrhea, cryptococcal meningitis, extrapulmonary TB, lymphoma, kaposis sarcoma and HIV encephalopathy.

(mean change, 0.17 (95% CI: 0.02, 0.31; $P = 0.02$) and advanced WHO disease ($P < 0.001$) at ART initiation were associated with better WAZ scores change. Age >5 years on the other hand was associated with poorer WAZ score change after 6 months of ART (mean change, –0.30 (95% CI: –0.43, –0.17; <0.001).

Similarly, wasting, low CD4 count or percent, stavudine containing regimens and advanced WHO disease stage at ART initiation were associated with better WLZ/BMIZ Z-scores while age >5 years and cotrimoxazole use ($P = 0.02$) were associated with less increase in Z-scores. Stunting and age >2 years at ART initiation were associated with better HAZ scores after 6 months of ART (Table 3). Similarly, wasting, low CD4 count or percent, stavudine containing regimens, and advanced WHO disease stage at ART initiation were associated with better

WLZ/BMIZ Z scores while age >5 years and cotrimoxazole use ($P = 0.02$) were associated with less increase in Z-scores (Table 4).

Discussion

The results of our study indicate that child anthropometric Z-score profiles improved after ART initiation, however, only WAZ, and WLZ or BMIZ scores reached or approached normal values. HAZ scores did not reach the normal values even after 6 years of follow-up. The growth effect was on average greater in younger than older children even though the younger children always started worse off.

Undernutrition at ART initiation as defined by underweight, stunting and wasting was consistently associated with better Z-scores change after 6 months of ART. Our results concur and extend data from previous studies done in Africa and beyond [15, 22–24]. Nachman *et al.* [22] in their study of children up to 17 years of age and who had received ART for at least 16 weeks reported that children with weight below the 50th percentile for age and gender exhibited relatively more improvement than did those with weights above the 50th percentile. In a study from Zambia, children who were underweight at ART initiation experienced a greater increase in WAZ in the first 6 months of ART [23]. Similarly, Gsponer *et al.* [15] found that lower baseline WAZ, HAZ and WLZ were the most important determinants of faster catch-up growth on ART. In our study, normal HAZ score were not achieved despite long duration of treatment. Similar findings have been reported in other studies [15, 24]. However, our results contrast the findings from a study in the USA where normal HAZ were reached after 2 years of ART, though the baseline Z-scores were much higher in these children [22].

Advanced HIV disease stage was associated with better WAZ scores change in our study. Similar to our findings, a study from Southern Africa also reported that advanced stage of the disease was predictive of faster catch-up growth in WAZ [15]. In another study, Diniz *et al.* [25] reported a greater weight and height catch-up after starting HAART in patients with clinically advanced disease at baseline.

We found that a low CD4+ T-cells count or percent were significantly associated with better WAZ scores change after 6 months of ART in this population. A study comparing factors associated with initial growth, CD4 and viral load responses to ART in HIV-infected children in Kampala, Uganda and the UK/Ireland found that children with low pre-ART CD4% had poorer immune responses in Kampala compared with those in the UK/Ireland [26].

Anemia at ART initiation was associated with better WAZ scores change after 6 months of ART in this study. Similarly, in a study by McGrath *et al.* [27], low baseline hemoglobin (<9 g/dl) was
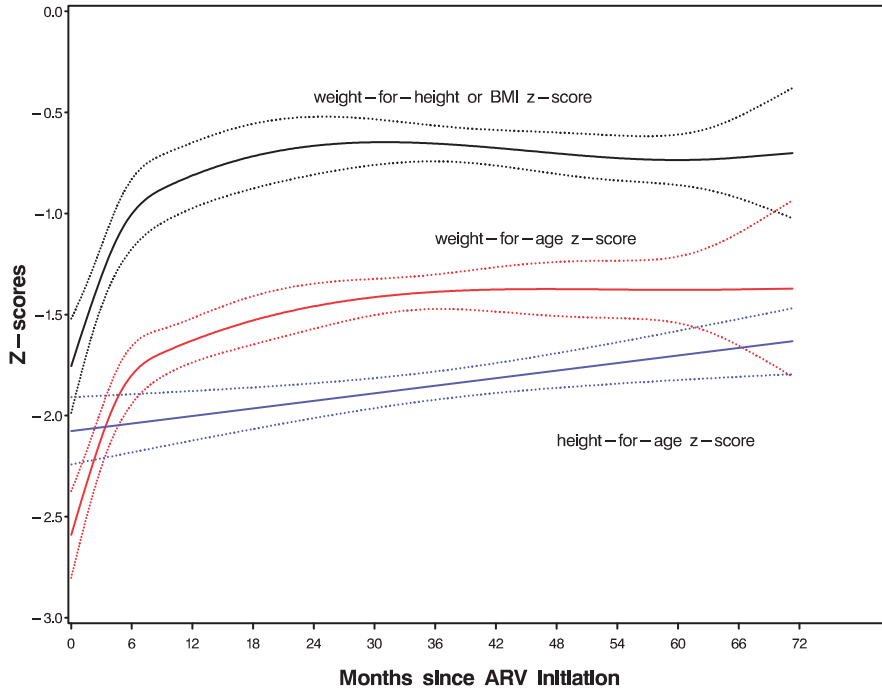
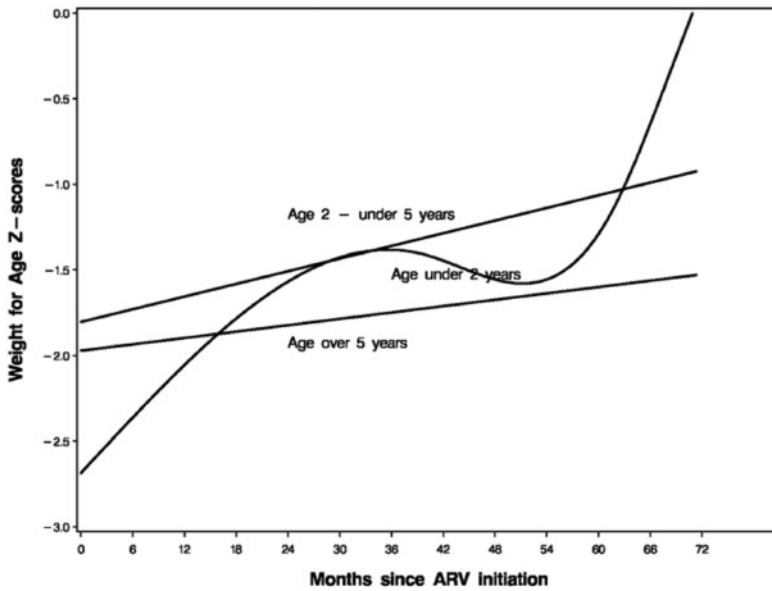FIG. 1. Mean WAZ, HAZ and BMIZ *Z*-scores and 95% CI with time.

FIG. 2. Age-stratified mean WAZ *Z*-score pattern over time.

TABLE 2
Predictors of WAZ score change after 6 months of ART[a]

Predictor	Number	Univariate	P	Number	Multivariate[b]	P
Disease stage	1694/3144		<0.001	1694/3144		<0.001
I		Reference			Reference	
II		0.07 (−0.09, 0.23)			0.13 (−0.04, 0.30)	
III		0.30 (0.17, 0.42)			0.22 (0.08, 0.37)	
IV		0.69 (0.39, 1.00)			0.45 (0.16, 0.74)	
ARV regimen	1694/3144		0.02	1694/3144		0.05
No stavudine		Reference			Reference	
Contains stavudine		0.15 (0.02, 0.28)			0.12 (0.001, 0.24)	
ARV regimen	1694/3144		0.78	1694/3144		0.89
No efavirenz		Reference			Reference	
Contains efavirenz		−0.02 (−0.19, 0.14)			0.01 (−0.15, 0.17)	
Anemia, g/dl[c]	1694/3144		0.001	1694/3144		0.02
No		Reference			Reference	
Yes		0.27 (0.11, 0.44)			0.17 (0.02, 0.31)	
Age, years	1694/3144		0.001	1694/3144		<0.001
0–2		Reference			Reference	
>2–5		−0.01 (−0.15, 0.14)			−0.07 (−0.21, 0.06)	
>5		−0.22 (−0.36, −0.09)			−0.30 (−0.43, −0.17)	
Use of cotrimoxazole	1694/3144		0.77	1694/3144		0.37
No		Reference			Reference	
Yes		0.02 (−0.09, 0.12)			−0.05 (−0.15, 0.06)	
Opportunistic infections[d]	1694/3144		0.07	1694/3144		0.41
No		Reference			Reference	
Yes		0.16 (−0.01, 0.33)			0.07 (−0.09, 0.23)	
Pulmonary TB	1694/3144		0.21	1694/3144		0.70
No		Reference			Reference	
Yes		0.08 (−0.04, 0.20)			0.02 (−0.10, 0.15)	
Severe immune suppression (CD4+ T-cells < 15% if ≤5 years; <200 cells/μl if >5 years)[e]	1694/3144		<0.001	1694/3144		<0.001
No		Reference			Reference	
Yes		0.37 (0.25, 0.50)			0.29 (0.18, 0.41)	
Underweight at ART initiation (WAZ <−2 SD)	1694/3144		<0.001	1694/3144		<0.001
No		Reference			Reference	
Yes		0.82 (0.73, 0.92)			0.78 (0.67, 0.88)	

[a]Linear regression models.
[b]Adjusted for factors indicated in the table plus gender, district of residence and calendar year.
[c]Hemoglobin: <11 g/dl (age < 5 years); <11.5 g/dl (age 5–11 years); <12 g/dl (age 12–14 years).
[d]Patient having at least one or more of the following: herpes zoster, fungal infection, oral candidiasis, oral hairy leukoplakia, recurrent severe bacterial infection, pneumocystis jirovecii pneumonia, toxoplasmosis, cryptosporidiosis with diarrhea, cryptococcal meningitis, extrapulmonary TB, lymphoma, kaposis sarcoma, HIV encephalopathy.
[e]Adopted from CDC. Guidelines for Preventing Opportunistic Infections Among HIV-Infected Persons – 2002. MMWR 14 June 2002 (CDC).

TABLE 3
Predictors of HAZ score change after 6 months of ART[a]

Predictor	Number	Univariate	P	Number	Multivariate[b]	P
Disease stage	2133/3144		<0.001	2133/3144		0.05
I		Reference			Reference	
II		0.17 (0.04, 0.29)			0.11 (−0.03, 0.26)	
III		0.13 (0.03, 0.23)			0.04 (−0.09, 0.16)	
IV		0.31 (0.15, 0.48)			0.16 (−0.03, 0.34)	
ARV regimen	2133/3144		0.84	2133/3144		0.25
No stavudine		Reference			Reference	
Contains stavudine		0.01 (−0.10, 0.08)			−0.06 (−0.15, 0.04)	
ARV regimen	2133/3144		0.39	2133/3144		0.11
No efavirenz		Reference			Reference	
Contains efavirenz		−0.05 (−0.15, 0.06)			−0.09 (−0.20, 0.02)	
Anemia, g/dl[c]	2133/3144		0.37	2133/3144		0.23
No		Reference			Reference	
Yes		−0.06 (−0.19, 0.07)			−0.08 (−0.21, 0.05)	
Age, years	2133/3144		0.02	2133/3144		0.01
0–2		Reference			Reference	
>2–5		0.46 (0.33, 0.59)			0.38 (0.25, 0.51)	
>5		0.18 (0.07, 0.29)			0.18 (0.06, 0.30)	
Use of cotrimoxazole	2133/3144		0.55	2133/3144		0.54
No		Reference			Reference	
Yes		−0.02 (−0.11, 0.06)			−0.03 (−0.11, 0.06)	
Opportunistic infections[d]	2133/3144		0.77	2133/3144		0.85
No		Reference			Reference	
Yes		−0.02 (−0.14, 0.10)			−0.01 (−0.14, 0.11)	
Pulmonary TB	2133/3144		0.12	2133/3144		0.58
No		Reference			Reference	
Yes		0.07 (−0.02, 0.16)			0.03 (−0.07, 0.13)	
Severe immune suppression (CD4+ T-cells < 15% if ≤5 years; <200 cells/µl if >5 years)[e]	2133/3144		0.13	2133/3144		0.52
No		Reference			Reference	
Yes		0.07 (−0.02, 0.16)			−0.03 (−0.11, 0.06)	
Stunting at ART initiation (HAZ <−2 SD)	2133/3144		<0.001	2133/3144		<0.001
No		Reference			Reference	
Yes		0.44 (0.36, 0.52)			0.42 (0.34, 0.50)	

[a]Linear regression models.
[b]Adjusted for factors indicated in the table plus gender, district of residence and calendar year.
[c]Hemoglobin: < 11 g/dl (age <5 years); <11.5 g/dl (age 5–11 years); <12 g/dl (age 12–14 years).
[d]Patient having at least one or more of the following: herpes zoster, fungal infection, oral candidiasis, oral hairy leukoplakia, recurrent severe bacterial infection, pneumocystis jirovecii pneumonia, toxoplasmosis, cryptosporidiosis with diarrhea, cryptococcal meningitis, extrapulmonary TB, lymphoma, kaposis sarcoma and HIV encephalopathy.
[e]Adopted from CDC. Guidelines for Preventing Opportunistic Infections Among HIV-Infected Persons – 2002. MMWR 14 June 2002 (CDC).

TABLE 4
Predictors of WLZ or BMIZ score change after 6 months of ART[a]

Predictor	Number	Univariate	P	Number	Multivariate[b]	P
Disease stage	2084/3144		<0.001	2084/3144		<0.001
I		Reference			Reference	
II		0.004 (−0.20, 0.21)			0.13 (−0.08, 0.34)	
III		0.27 (0.11, 0.43)			0.27 (0.09, 0.46)	
IV		0.91 (0.57, 1.25)			0.49 (0.16, 0.81)	
ARV regimen	2084/3144		0.01	2084/3144		0.001
No stavudine		Reference			Reference	
Contains stavudine		0.22 (0.06, 0.37)			0.25 (0.11, 0.40)	
ARV regimen	2084/3144		0.24	2084/3144		0.52
No efavirenz		Reference			Reference	
Contains efavirenz		0.12 (−0.08, 0.32)			0.06 (−0.13, 0.25)	
Anemia, g/dl[c]	2084/3144		0.001	2084/3144		0.001
No		Reference			Reference	
Yes		0.40 (0.16, 0.64)			0.37 (0.14, 0.59)	
Age, years	2084/3144		<0.001	2084/3144		<0.001
0–2		Reference			Reference	
>2–5		−0.26 (−0.47, −0.04)			−0.06 (−0.26, 0.14)	
>5		−0.31 (−0.49, −0.14)			−0.33 (−0.50, −0.16)	
Use of cotrimoxazole	2084/3144		0.29	2084/3144		0.02
No		Reference			Reference	
Yes		−0.07 (−0.21, 0.06)			−0.15 (−0.28, −0.02)	
Opportunistic infections[d]	2084/3144		0.05	2084/3144		0.79
No		Reference			Reference	
Yes		0.21 (0, 0.42)			−0.03 (−0.17, 0.22)	
Pulmonary TB	2084/3144		0.62	2084/3144		0.34
No		Reference			Reference	
Yes		0.04 (−0.12, 0.21)			−0.08 (−0.24, 0.08)	
Severe immune suppression (CD4+ T-cells < 15% if ≤5 years; <200 cells/μl if >5 years)[e]	2084/3144		<0.001	2084/3144		0.004
No		Reference			Reference	
Yes		0.36 (0.21, 0.50)			0.20 (0.07, 0.34)	
Wasting at ART initiation (WLZ or BMIZ <−2 SD)	2084/3144		<0.001	2084/3144		<0.001
No		Reference			Reference	
Yes		1.52 (1.38, 1.66)			1.49 (1.34, 1.63)	

[a]Linear regression models.
[b]Adjusted for factors indicated in the table plus gender, district of residence and calendar year.
[c]Hemoglobin: <11 g/dl (age < 5 years); < 11.5 g/dl (age 5–11 years); <12 g/dl (age 12–14 years).
[d]Patient having at least one or more of the following: herpes zoster, fungal infection, oral candidiasis, oral hairy leukoplakia, recurrent severe bacterial infection, pneumocystis jirovecii pneumonia, toxoplasmosis, cryptosporidiosis with diarrhea, cryptococcal meningitis, extrapulmonary TB, lymphoma, kaposis sarcoma and HIV encephalopathy.
[e]Adopted from CDC. Guidelines for Preventing Opportunistic Infections Among HIV-Infected Persons – 2002. MMWR 14 June 2002 (CDC).

associated with more rapid improvements in WLZ. In the latter study, however, low baseline hemoglobin was not associated WAZ changes [27].

Older children (age >5 years) showed poorer WAZ score change after 6 months of ART compared with younger children in our study. A study by Nachman et al. [22] reported a similar trend. In their trial, subjects <2 years of age though entered the study with the worst height growth; they exhibited faster improvement during the 48 weeks than did older children [22]. Younger age at ART initiation was a predictor of greater weight and height gain in a study in Brazil [25]. Similar findings have been described for weight gain [14, 23, 27, 28]. Better growth outcomes among younger children could be related to the duration of infection. Younger children may have less severe gastrointestinal impairment due to a shorter duration of HIV infection therefore better nutrients absorption after viral suppression by ART [27, 29]. The longer duration of HIV infection in older children may further require more time to reverse the damage implying a more prolonged metabolic cost [27]. Patients who received stavudine containing regimens at ART initiation had better WAZ scores change after 6 months of ART. This effect of stavudine could be mediated through body fat redistribution, a side effect of stavudine and a few other antiretroviral drugs [30, 31]. There was no association between WAZ score change in after 6 months of ART and receiving efavirenz containing regimens at ART initiation. Recent studies have demonstrated that efavirenz may contribute as a side effect, to adipose tissue alterations in patients receiving ART as well [31–33].

There was no association between cotrimoxazole use and WAZ score change after 6 months of ART in this study. A study in Zambia found that, children taking cotrimoxazole had significantly slower decreases in WAZ and HAZ than did children taking placebo [34]. However, the children in the latter study were not on ART. Cotrimoxazole is a broadspectrum antibiotic that has been found to reduce morbidity and mortality among HIV-infected children when taken daily as prophylaxis [35, 36].

Patients with opportunistic infections may have limited food intake and increased energy expenditure leading to poor growth. However, in this study, opportunistic infections and pulmonary TB at the time of ART initiation were not associated with growth outcomes after 6 months of ART in this population.

The current study has a couple of limitations; first, the timing of HIV infection was not known, and residual confounding by this and other unrecorded measures of disease stage was difficult to exclude; second, duration on ART was not long enough and future studies should assess this in a longer duration on ART. Furthermore, deaths and lost to follow-up could be potential sources of bias in our findings; the estimated cumulative mortality rates were 4.8%, 7.3% and 8.5% at 3, 12 and 60 months, respectively, while the cumulative lost to follow-up rates at 3, 12 and 60 months after ART initiation were, respectively, 10.6%, 21.1% and 58.2%. However, there was no difference in the results comparing models weighted for deaths and lost to follow-up using inverse probability weights and unweighted models. The major strength of our study is that its population consisted of a wide age range, belonged to diverse socioeconomic levels. We suggest that our results are generalizable to the population of HIV-infected children receiving ART in Tanzania as well as in other resource-limited countries.

In conclusion, ART led to improvement in mean WAZ, HAZ and WLZ or BMIZ scores. However, there was no catch-up growth on HAZ for all the children over the duration of follow-up. These findings suggest that although ART improved the growth of the HIV-infected children in Tanzania, nutritional interventions and other therapeutic strategies may be needed to ensure that the growth of these children is optimized to the greatest extent possible.

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