Growth in HIV-infected children on long-term antiretroviral therapy

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ABSTRACT

Objectives: To describe growth in HIV-infected children on long-term antiretroviral therapy (ART) and to assess social, clinical, immunological and virological factors associated with suboptimal growth.

Methods: This observational cohort study included all HIV-infected children at an urban ART site in South Africa who were younger than 5 years at ART initiation and with more than 5 years of follow-up. Growth was assessed using weight-for-age Z-scores (WAZ), height-for-age Z-scores (HAZ) and body mass index (BMI)-for-age Z-scores (BAZ). Children were stratified according to pre-treatment anthropometry and age. Univariate and mixed linear analysis was used to determine associations between independent variables and weight and height outcomes.

Results: Majority of the 159 children presented with advanced clinical disease (90%) and immunosuppression (89%). Pre-treatment underweight, stunting and wasting occurred commonly (WAZ<-2= 50%, HAZ<-2= 73%, BAZ<-2= 19%). Weight and BMI improvement occurred during the initial 12 months, while height improved during the entire 5-year period. Height at study exit was significantly worse for children with growth impairment at ART initiation ($p<0.001$), whilst infants (<1 year) demonstrated superior improvement in terms of BMI ($p=0.04$). Tuberculosis was an independent risk factor for suboptimal weight ($p=0.01$) and height ($p=0.02$) improvement. Weight gain was additionally hindered by lack of electricity ($p=0.04$). Immune reconstitution and virological suppression were not associated with being underweight or stunted at study end point.

Conclusions: Malnutrition was a major clinical concern for this cohort of HIV-infected children. Early ART initiation, tuberculosis co-infection management and nutritional interventions are crucial to ensure optimal growth in HIV-infected children.

KEYWORDS

Children; HIV; Antiretroviral therapy; Growth; Tuberculosis

INTRODUCTION

Childhood HIV-infection has had a profound negative impact on paediatric morbidity and mortality in high-burden countries.[1] The South African antiretroviral therapy (ART) programme commenced in 2004 to improve outcomes for HIV-infected children, which is possible if therapy is initiated early.[2,3]

Suboptimal growth occurs commonly in HIV-infected children, with underlying mechanisms likely a combination of HIV itself, co-morbid diseases, decreased nutrient intake, malabsorption as well as neuroendocrine and psychosocial factors.[4,5] Several studies have shown a positive impact of ART on weight and, to a lesser extent, on height growth.[6-27] As opposed to studies from developed countries,[10,11,27] reports from developing countries have not shown normalization of growth parameters.[12-26] These studies, however, generally had relatively short follow-up periods of up to 2 years and were hampered by substantial loss-to-follow.

Kalafong Hospital is situated in the urban Gauteng Province in South Africa and hosts a large paediatric HIV treatment centre. The study aim was to describe growth in young HIV-infected children who were retained on the ART programme for at least 5 years and to study the clinical, virological, immunological and social factors associated with suboptimal growth.

METHODS

Patient selection and data collection

All HIV-infected children younger than 5 years at ART initiation at the Kalafong HIV-services, and who had ART follow-up data of at least 5 years, were included in this observational cohort study. The data, which was prospectively documented during clinical care and retrospectively analysed, included socio-demographic data, nutritional status at various time points, HIV disease severity, tuberculosis co-infection, CD4 counts/percentages and HIV viral loads (VL). Children with HIV-unrelated comorbid conditions known to influence childhood growth were excluded.

Standards of care and definitions

The children started ART between October 2003 and December 2006 according to the South African National HIV guidelines.[2] ART regimens for children below 3 years of age consisted of two nucleoside reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI), while in older children a non-nucleoside reverse transcriptase inhibitor (NNRTI) was prescribed instead of the PI. Diagnoses of tuberculosis were made clinically, assisted by microbiological and radiological services. A dedicated onsite social worker assisted with family matters, guardianship issues and applications for government grants.

Registered dieticians took anthropometrical measurements at routine follow-up visits. Weight was measured to the nearest 100g using an electronic scale. Height was measured with a stadiometer in standing children, while supine length was recorded in children who could not yet stand. The anthropometric data was adjusted for age and sex using World Health Organization (WHO) growth reference Z-scores.[28] Underweight was defined as weight-for-age Z-scores (WAZ) <-2, stunting as height-for-age Z-scores (HAZ) <-2 and wasting as body mass index(BMI)-for-age Z-scores (BAZ) <-2, while severe underweight, severe stunting and severe wasting were defined as Z-scores <-3. The height deficit, which is the difference between the individual's length/height and reference population norm (Z-score= 0), was also calculated. Vitamin supplementation was routinely given to all children. A standard operating procedure guided the dieticians in prescribing food supplementation to malnourished children after assessment of inadequate weight gain or the presence of

moderate to severe stunting (HAZ<-2), moderate to severe wasting (BAZ<-2) and chronic diarrhoea. Infants below 1 year of age received milk-based supplementation, while older children received a maize-based porridge. Children with chronic diarrhoea were given lactose-free or semi-elemental supplements. Sufficient weight gain or normalization of growth curves for 3 months were exit criteria for food supplementation.

WHO definitions were used for the classification of HIV clinical staging, immunosuppression and anaemia.[29-31] Immune reconstitution was defined as a normal CD4 category after 5 years of ART. Optimal virological response was defined as having a HIV VL of <400 copies/ml in >90% of samples, while suboptimal response and poor response meant that 50–90% or <50% of samples had HIV VLs of <400 copies/ml respectively (definitions by Guillén *et al).*[11]

Statistical analysis

Childhood growth was assessed using WAZ, HAZ and BAZ, with data censored after the 5 year cut-off. Baseline characteristics were summarized using means (continuous variables) and proportions (categorical variables). Comparisons between groups were done using the Chi-squared/Fischer Exact test for categorical variables and the two-sample Student t-tests for Gaussian distributed continuous data, and p-values of ≤0.05 indicate significance. Random-effects generalized least squares regression modelling, which can deal with panel data and missing data points, was employed to determine the association of independent variables with the outcomes (WAZ & HAZ). Included into the models were variables with univariate analysis p-values <0.1 or that were thought to significantly impact childhood growth, including ART duration (time-dependent variable), child-related factors (enrolment age, sex), socio-demographic factors (mother as caregiver, availability of electricity), co-morbidities (tuberculosis & anaemia at ART initiation) and HIV-disease control (HIV VL<400 copies/ml at 6 months of ART). Removal of an independent predictor was done if it was not significant. Interactions between age categories and ART duration were also considered.

The Ethics Review Committee, Faculty of Health Sciences, University of Pretoria, approved the study protocol.

RESULTS

Study population and baseline characteristics:

The study group included 167 HIV-infected children, eight of whom were excluded due to non-related comorbid conditions (cerebral palsy= 5; hemiplegia= 2; Down syndrome= 1), leaving 159 children for analysis. The median age at enrolment was 1.9 years [interquartile range 1.1; 3] and the male-to-female ratio 1.24:1 (Table 1). The mother was the primary caregiver in 104 cases (65.8%), and 13 children (8.2%) were residing in a children's home. The majority of children (87/140; 62.1%) came from small families (none/one sibling). In terms of housing, 71.4% of children were staying in a brick house, 83.2% had access to electricity and 81.5% had a fridge.

Hundred-and-forty-five children (90.2%) had advanced or severe disease on presentation (WHO Stages 3/4) and tuberculosis co-infection at ART initiation was diagnosed in 42.8% (68 children). The majority of children (n=119, 74.8%) started on PI-based regimens. The mean CD4% at ART initiation was 15.2%, mean absolute CD4 count was 657 cells/mm^3, and in terms of WHO CD4 categories, 144 (89.3%) had advanced or severe immunosuppression. After 5 years the CD4% had increased significantly to 31.8% (p<0.001), and complete immune reconstitution was achieved in 97.4% of children. HIV VLs at start of ART were high in all children (mean $VLlog_{10}$= 5.52). After 5 years the mean $VLlog_{10}$ was 1.15, with 102 children (64.2%) having an undetectable VL. Optimal VL control over time was reached in 35.2% of children, while another 44% achieved

suboptimal VL control and 20.8% had poor viral control. There was a documented treatment interruption in 9.4% of patients and nine children (5.7%) were switched to second-line ART during follow-up.

Weight:

Underweight at time of ART initiation was common. Mean WAZ at initiation was -2.21 ±1.77, with half (49.7%) of the cohort below WAZ<-2 (underweight= 20.8% plus severely underweight= 28.9%) (Figure 1). Weight improvement occurred primarily during the first year of ART, with minimal improvement thereafter. After 5 years 16.3% of children were still underweight and the mean WAZ was -0.94 ±0.97. Children within the normal weight category at ART initiation only recorded a small increase in WAZ (from -0.83 to -0.61), not reaching the population norm (Z-score= 0) (Figure 2A). Study participants who were underweight at study exit had more significant malnutrition at ART initiation than those with normal end weight (enrolment WAZ -3.6 ±1.3 vs -1.9 ±1.7; p<0.001). Severely underweight children had the most significant increase in weight (p<0.001), although there was no significant difference in weight at study exit for either underweight versus severe underweight children (p=0.3), with both groups having a significant lower WAZ than those children with normal initial weight (p<0.01) (Figure 2A).

Weight parameters were dependent on age at enrolment (Figure 2B): The two younger age groups had significantly worse initial WAZ scores than older children (<1 year: -2.63; 1-3 years: -2.39; 3-5 years: -1.47, p<0.001). Infants (<1 year) had the best improvement in weight during the initial 12 months (p=0.03 compared to children aged 1-3 years; p<0.001 compared to 3-5 years), followed by the 1-3 years group (p<0.001 compared to children aged 3-5 years). After 5 years WAZ was similar in all age groups, with a trend towards improved weight for infants (p=0.07).

Additional factors that were compared between children with and without underweight at ART initiation and study exit are depicted in Tables 2 & 3. Lack of electricity (p=0.002), tuberculosis (p=0.03) and anaemia (p=0.006) were associated with being severely underweight at start, while underweight after 5 years was associated with lack of electricity (p=0.03), lack of a fridge (p=0.03) and tuberculosis at ART initiation (p=0.03). There was no association with immune reconstitution (p=1.0) nor with virological suppression (p=0.79).

Mixed linear analysis was used to model factors affecting the rapid increase in WAZ during the initial 12 months (Table 4). Weight improved as children remained on ART (coefficient 0.16, p<0.001), with significant interactions observed between the age categories and ART duration (1-3 years: coefficient -0.04, p=0.03; 3-5 years: coefficient -0.12, p<0.001) due to better weight improvement in the younger age categories. Tuberculosis at ART initiation was found to be an independent risk factor for suboptimal weight (coefficient -0.50, p=0.01), while having access to electricity was protective (coefficient 0.53, p=0.04).

Height:

Stunting at time of ART initiation was even more prevalent than underweight, with a mean HAZ of -2.91±1.58 and height deficit of 9.0 ±5.2 cm. Almost two thirds (72.9%) of the cohort were below the HAZ<-2 cut-off (stunting= 26.4% plus severe stunting= 46.5%) (Figure 1). Of note, 43 of the 116 children (37.1%) with initial stunting were not underweight at enrolment. Maximum HAZ improvement occurred between 0 and 24 months of ART (+0.49 Z-score/year), while maximum improvement in height deficit was between 12 and 36 months (+1 cm/year). HAZ improved to -1.24 ±1.0 after 5 years, with still a clinically relevant height deficit of 6.7 ±5.5 cm and 20.2% of children remaining stunted. Both HAZ and height deficit were still improving during the last year of study (+0.07 Z-score/year and +0.3 cm/year).

All children with stunting at study endpoint (n=32) were stunted at enrolment (87.5% with severe stunting) and had significantly more growth impairment at ART initiation than those with normal end height (enrolment

HAZ -4.4 ±1.2 vs -2.5 ±1.4; p<0.001). Children with severe pre-treatment stunting did have the most improvement in HAZ (p<0.001 comparing severely stunted to stunted and normal groups), however, height at study exit was significantly worse for children with growth impairment at ART initiation (p<0.001 comparing severely stunted, stunted and normal groups) (Figure 2A).

HAZ at enrolment did not differ significantly between the three age groups (<1 year: -3.04; 1-3 years: -3.01; 3-5 years: -2.59, p>0.15), and the end HAZ was similar between the age groups (<1 year: -1.16; 1-3 years: -1.26; 3-5 years: -1.25, p>0.66) (Figure 2B). Severe stunting at ART initiation was significantly associated with tuberculosis (p=0.04) (Table 2), while stunting after 5 years was associated with being male (p=0.04), lack of electricity (p=0.03) and lack of a fridge (p=0.03). There was no association with immune reconstitution (p=0.58), nor with virological suppression (p=0.32) (Table 3).

HAZ displayed a steady increase and mixed linear models therefore included the entire period (Table 4). ART duration had a coefficient of 0.03 (p<0.001) and significant differences in the trajectories of HAZ were found by age group at ART initiation, with children older than 3 years experiencing significantly smaller HAZ increases per month compared to the younger age groups (p<0.001). Similar to findings in the weight model tuberculosis at ART initiation was found to be an independent risk factor for poor length growth (coefficient -0.38; p=0.02), while height was more affected in boys than girls (coefficient 0.31; borderline significance p=0.058).

BMI:

Wasting at ART initiation occurred in 18.8% of the cohort, including 7.5% of children with severe wasting (mean BAZ -0.46 ±1.78) (Figure 1). BAZ increased rapidly in the initial treatment phase and was highest at 12 months (0.93 ±1.12) due to delayed height improvement compared to the rapid initial weight gain. This resulted in 15.1% of the cohort being classified as overweight (BAZ>+2; ≤+3) and 3.8% as obese (BAZ>+3) after 12 months of ART. Thereafter BAZ declined over time and reached the population norm (Z-score= 0) at 42 months, reflecting continued height improvement. The mean BAZ after 5 years was -0.22 ±0.96, with 4.4% of children classified as wasted and 1.3% as overweight at study end point.

Children who were more wasted at start recorded more BAZ improvement (p<0.001 comparing severely wasted to wasted and normal groups) (Figure 2) resulting in the reversal of wasting for all groups. As a result, BAZ scores after 5 years were similar between the groups with or without initial wasting (p>0.3) (Figure 2B).

The degree of wasting was dependent on age at enrolment (Figure 2B): The two younger age groups had significantly worse initial BAZ scores than older children (<1 year: p<0.001; 1-3 years: p=0.002 when compared to 3-5 years). Reversal of wasting was best for infants (p=0.04 compared to 1-3 years; p<0.001 compared to 3-5 years), followed by the 1-3 years group (p=0.002 compared to 3-5 years). This resulted in significantly better final BAZ scores for children <1 year of age (p=0.04 compared with children >1 year).

DISCUSSION

In this study of South African HIV-infected children initiated on ART before 5 years of age, weight improved in the first 12 months and height improved much slower during the entire 5 year follow-up period. This resulted in the BMI rapidly increasing to above the zero Z-score during the first year of treatment, with this effect more pronounced in infants. This ART-related growth improvement is comparable to descriptions from other ART follow-up studies from India and Southern Africa.[15,22,24,26] At the end of the 5 year follow-up period stunting was the most important growth deficit observed in 20.2% of children, which is higher than published South

African malnutrition data in the age group 5 to 10 years in the year 2005 (13.9%).[32] Wasting, in contrary, occurred in only 4.4% of children at study exit, comparable to the overall prevalence of wasting in South Africa (5.2%).[32] Height Z-scores display an increasing standard deviation over time which, due to mathematical properties, result in spontaneous Z-score improvements. We therefore additionally studied the changes in the absolute height deficit, as previously suggested in literature, which was still improving at the end of the study.[33]

Growth curves of children were stratified according to pre-treatment anthropometry and age. The severity of pre-treatment malnutrition impacted on subsequent growth patterns similar to observations made in other African studies.[17,20,21,34]. Children who were wasted or stunted at ART initiation showed more absolute improvement in BMI and height respectively. Consequently, BAZ scores after 5 years were similar between groups with or without initial wasting. In contrary, stunted children remained shorter than their well-grown peers emphasizing the need of timely ART before the occurrence of irreversible stunting. Of note, one third of children with initial stunting were not underweight at enrolment underscoring the importance for weight and height measurements during routine clinical care.

Age at ART initiation impacted on growth improvement: Children older than 3 years experienced a lower weight and height increase compared to younger children and this resulted in better BMI outcome in infants, while height outcomes did not differ across age groups. Previous studies consistently describe improved weight outcomes for younger children,[16,18,21,22,24,26,35-38] possibly related to less severe gastrointestinal impairment and shorter duration of chronic immune activation.[39,40] Reports on the impact of age on height differ between studies, with improved height outcomes with younger age in some studies,[23,24,26,35] whilst others reported no difference[36] or worse height outcomes for younger children.[20,22] HIV-infected children are increasingly reaching adulthood due to the availability of ART, therefore studies to evaluate the impact of age at ART initiation on the timing and magnitude of the pubertal growth spurt and final adult height are needed.

The impact of clinical and sociodemographic characteristics on growth were further analysed by univariate and mixed linear analysis. Since wasting was not a clinically significant problem after 5 years of ART, BAZ was not included in this analysis. Tuberculosis at start of ART was common in our cohort and negatively affected the initial growth parameters. Moreover it was found to be an independent risk factor for impaired weight and length growth over time, resulting in 0.37 lower WAZ-scores and 0.38 lower HAZ-scores over time. This is an important new observation made by this study warranting further research. Several mechanisms can potentially cause tuberculosis-associated growth impairment, including impaired appetite, increased energy expenditure and chronic inflammation.[41,42] Increased pill burden, drug interactions and toxicities as well as the risk of immune reconstitution inflammatory syndrome can further impact on treatment outcomes.[43] Our results emphasize the need for tuberculosis prevention in HIV-infected children and early ART initiation before immunosuppression and tuberculosis co-infection occurs.

Poverty, for which the availability of electricity and fridge were used as proxies in this study, negatively affected growth. This is in line with the well described relationship between food insecurity and suboptimal childhood growth, as previously reported in paediatric ART studies.[44,45] The importance of nutrition in resource-constrained regions has been recognized and integrated into HIV care by WHO guidelines[46]. Nevertheless major gaps remain in the evidence regarding the types and optimal timing of nutritional supplementation in the ART era.[47] Our data suggest that the initial 12 months of ART is the window of opportunity for weight improvement and the reversal of wasting, while height deficits take years to resolve. Studies are needed to evaluate how food supplementation can optimize early weight gain and benefit stunted, but often overweight, children beyond the first year of treatment.

Studies in developing countries most commonly found an effect of immune response but not of virological suppression[9,16,48-50]. In our study none of the immunological and virological parameters that were examined had a significant effect on growth, but immunological failure was rare as staying in follow-up was an inclusion criteria. In contrary, a Spanish study, that included 5-year follow-up data, showed an effect of virological suppression but not of immunological control.[11] The importance of nutritional factors may possibly obscure the effect of virological suppression in areas where poverty is prevalent. Moreover the clinical effects of virological failure may be different in patients that are lost to care.

Study strengths include that we report on a large cohort of young HIV-infected children with the availability of robust clinical data and with length of follow-up exceeding that of the majority of prior African studies. The study gives insight into long-term growth of children who are retained on the ART programme, although the population selection process, with exclusion of children with adverse outcomes including death and lost-to-follow, potentially led to an underestimation of the prevalence of malnutrition among children on ART. Study limitations include the absence of an HIV-uninfected control group, as the lower attained anthropometry may reflect high rates of malnutrition in the underlying population irrespective of HIV. Data on specific nutritional interventions per individual were not available for analysis. Furthermore, patients from this hospital-based ART site may not be representative of the broader population of HIV-infected children, although at the time of study there was minimal paediatric ART initiation at local primary healthcare facilities. With South Africa now in the second decade of its ART programme, improved maternal health, increased breastfeeding rates as part of the prevention of mother-to-child transmission programme and focus on early paediatric ART initiation may impact on the future applicability of our study findings, highlighting the need for ongoing research.

CONCLUSIONS

Survival of HIV-infected children into adolescence and adulthood is now attainable due to ART availability, therefore optimization of early growth is of critical importance. Malnutrition, especially stunting, was prevalent in this South African cohort and directly related to growth outcomes, with ART positively impacting on growth but lack of height normalization despite long-term care retention. Poverty and tuberculosis co-infection had a more significant impact on growth than virological control. ART initiation is crucial before irreversible stunting, has occurred, while intervention studies on optimal nutritional support to attain growth normalization are urgently needed.

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Table 1: Socio-demographic and clinical characteristics of the cohort (n=159)

Socio-demographic information:		
Age at start of ART	Age in years (median; IQR)	1.9 [1.1;3.0]
Age in groups	Age group <1y	32/ 159 (20%)
	Age group 1-3y	87/ 159 (55%)
	Age group 3-5y	40/ 159 (25%)
Caregiver	Mother is primary caregiver	104/ 158 (66%)
	Living in children's home	13/ 159 (8%)
	Father involved in care	84/ 142 (59%)
Siblings	Number (median; IQR)	1 (0.3-2)
	Small family (no or one sibling)	87/ 140 (62%)
Housing	Brick house	100/ 140 (71%)
	Electricity available	119/ 143 (83%)
	Fridge available	110/ 135 (81%)
Maternal employment	Full-time	20/ 141 (14%)
	Temporary	37/ 141 (26%)
	Unemployed	54/ 141 (38%)
	Mother died	30/ 141 (21%)
Government grants	Child support grant	81/ 144 (56%)
	Other support grants	43/ 144 (30%)
	No grant	20/ 141 (14%)
HIV-related information at enrolment:		
Clinical staging (WHO)	Stage 1	4/ 159 (3%)
	Stage 2	10/ 159 (6%)
	Stage 3	46/ 159 (29%)
	Stage 4	99/ 159 (62%)
Co-morbid conditions	Tuberculosis at start of ART	68/ 159 (43%)
	Anaemia	89/ 132 (67%)
CD4 percentage/count	CD4% (mean; SD)	15.2% (8.4)
	Absolute CD4 count (mean; SD)	657 (468)
CD4 WHO categories*	Normal	8/ 159 (5%)
	Mild	9/ 159 (6%)
	Advanced	22/ 159 (14%)
	Severe	120/ 159 (75%)
HIV viral load (VL)	$VLlog_{10}$ (mean; SD)	5.52 (0.76)
VL categories	VL <4 log_{10}	5/ 159 (3%)
	VL 4 log_{10} to <5 log_{10}	30/ 159 (20%)
	VL 5 log_{10} to <6 log_{10}	72/ 159 (47%)
	VL ≥6 log_{10}	45/ 159 (30%)
ART information:		
PI regimen at ART initiation	d4T or AZT + 3TC + LPV/r	65/ 159 (41%)
	d4T or AZT + 3TC + RTV	54/ 159 (34%)
NNRTI regimen at ART initiation	d4T + 3TC + EFV	40/ 159 (25%)
ART adherence	Documented ART interruption	15 (9%)
	Switch to 2nd-line ART	9 (6%)
Immune response	CD4% after 5y (mean; SD)	31.8% (7.9)
	Absolute CD4 count (mean; SD)	1120 (496)
	Immune reconstitution	151/ 155 (97%)
Virological suppression**	Optimal	56/ 159 (35%)
	Suboptimal	70/ 159 (44%)
	Poor	33/ 159 (21%)
Tuberculosis during ART	None	66/ 159 (42%)
	One episode	83/ 159 (52%)
	≥ 1 episodes	10/ 159 (6%)

Abbreviations: ART= antiretroviral therapy; IQR= interquartile range; y= years; WHO= World Health Organization; d4T= stavudine; 3TC= lamivudine; LPV/r= boosted lopinavir; AZT= zidovudine; RTV= ritonavir; EFV= efavirenz; PI= protease inhibitor; NNRTI= non-nucleoside reverse transcriptase inhibitor

Definitions:

***CD4 classification (WHO)**:[30] **None:** >35% (age <12m); >25% (age 13-59m); >500/mm^3 (age >5y); **Mild:** 25-34% (age <12m); 20-24% (age 13-59m); 350-499/mm^3 (age >5y); **Advanced:** 20-24% (age <12m); 15-19% (age 13-59m); 200-349/mm^3 (age >5y); **Severe:** <20% (age <12m); <15% (age 13-59m); <200/mm^3 (age >5y)

****Virological suppression: Optimal:** HIV VL <400 copies/mL in >90% of samples; **Suboptimal**: HIV VL <400 copies/ml in 50–90% of samples; **Poor:** HIV VL<400 copies/ml in <50% of samples[11]

Table 2: Characteristics of children by weight-for-age and height-for-age Z-score at start of antiretroviral therapy

		Baseline weight-for-age			Baseline height-for-age		
		WAZ <-3 (n=46)	WAZ >-3 (n=113)	p value	HAZ <-3 (n=74)	HAZ >-3 (n=85)	p value
Socio-demographic information :							
Sex	Male sex	31 (67%)	57 (50%)	0.051	43 (58%)	45 (53%)	0.51
Caregiver	Mother is caregiver	30 (70%)	74 (73%)	0.73	45 (65%)	59 (78%)	0.1
Housing	Electricity available	28 (68%)	91 (89%)	**0.002**	53 (80%)	66 (86%)	0.39
	Fridge available	28 (72%)	82 (85%)	0.07	47 (80%)	63 (83%)	0.63
HIV-related information at enrolment:							
Co-morbid conditions	Tuberculosis at ART start	26 (57%)	42 (37%)	**0.03**	38 (51%)	30 (35%)	**0.04**
	Anaemia	33 (85%)	56 (60%)	**0.006**	40 (67%)	49 (68%)	0.87
CD4% & CD4 categories (WHO)*	CD4% (mean; SD)	16.2% (8.8)	14.8% (8.3)	0.33	15.2% (8.7)	15.3% (8.2)	0.92
	None	2 (4.5%)	5 (5%)	0.85	4 (5.5%)	3 (3.5%)	0.73
	Mild	2 (4.5%)	7 (6%)		4 (5.5%)	5 (6%)	
	Advanced	5 (11%)	17 (15%)		8 (11%)	14 (16.5%)	
	Severe	37 (80%)	83 (74%)		57 (78%)	63 (74%)	
HIV viral load (VL)	VL $\log_{10}$ (mean; SD)	5.7 (0.7)	5.5 (0.8)	0.13	5.7 (0.7)	5.5 (0.8)	0.53
	VL <4 $\log_{10}$	1 (2%)	4 (4%)	0.39	1 (1%)	4 (5%)	0.41
	VL 4 $\log_{10}$ to <5 $\log_{10}$	8 (19%)	22 (20%)		15 (22%)	15 (18%)	
	VL 5 $\log_{10}$ to <6 $\log_{10}$	17 (39.5%)	55 (50%)		29 (43%)	43 (51%)	
	VL ≥6 $\log_{10}$	17 (39.5%)	28 (26%)		23 (34%)	22 (26%)	

Data are n (%) unless otherwise specified. Percentages are not always calculable from table due to missing information.

Abbreviations: SD= standard deviation, WAZ= weight-for-age Z-score, HAZ= height-for-age Z-score, ART= antiretroviral therapy, WHO= World Health Organization.

***CD4 classification (WHO):**[30] **None:** >35% (age <12m); >25% (age 13-59m); >500/mm^3 (age >5y); **Mild:** 25-34% (age <12m); 20-24% (age 13-59m); 350-499 mm^3 (age >5y); **Advanced:** 20-24% (age <12m); 15-19% (age 13-59m); 200-349 mm^3 (age >5y); **Severe:** <20% (age <12m); <15% (age 13-59m); <200 mm^3 (age >5y)

Table 3: Characteristics of children by weight-for-age and height-for-age Z-score after 5 years of antiretroviral therapy

		Weight-for-age at end			Height-for-age at end		
		WAZ <-2 (n=26)	WAZ >-2 (n=133)	p value	HAZ <-2 (n=32)	HAZ >-2 (n=137)	p value
Socio-demographic information:							
Sex	Male sex	16 (62%)	72 (54%)	0.49	23 (72%)	65 (51%)	**0.04**
Caregiver	Mother is caregiver	18 (72%)	86 (72%)	0.97	23 (74%)	81 (71%)	0.73
Housing	Electricity available	15 (65%)	104 (87%)	**0.03**	20 (69%)	99 (87%)	**0.03**
	Fridge available	13 (62%)	97 (85%)	**0.03**	18 (67%)	92 (85%)	**0.03**
HIV-related information at enrolment:							
Co-morbid conditions	Tuberculosis at ART start	16 (62%)	52 (39%)	**0.03**	15 (47%)	53 (42%)	0.60
	Anaemia	14 (70%)	75 (67%)	0.79	21 (75%)	68 (65%)	0.34
CD4% & CD4 categories (WHO)*	CD4% (mean; SD)	17.3% (8.9)	14.8% (8.3)	0.18	15.9% (10.7)	15.1% (7.8)	0.64
	None	2 (8%)	5 (4%)	0.74	2 (7%)	5 (4%)	0.82
	Mild	2 (8%)	7 (5%)		1 (3%)	8 (6%)	
	Advanced	3 (12%)	19 (14%)		5 (16%)	17 (13%)	
	Severe	18 (72%)	102 (77%)		23 (74%)	97 (76%)	
HIV viral load (VL):	VL $\log_{10}$ (mean; SD)	5.4 (0.7)	5.5 (0.8)	0.38	5.6 (0.6)	5.5 (0.8)	0.34
	VL <4 $\log_{10}$	1 (4%)	4 (3%)	0.74	0 (0%)	5 (4%)	0.69
	VL 4 $\log_{10}$ to <5 $\log_{10}$	6 (25%)	24 (19%)		6 (19%)	24 (20%)	
	VL 5 $\log_{10}$ to <6 $\log_{10}$	12 (50%)	60 (47%)		16 (50%)	56 (47%)	
	VL ≥6 $\log_{10}$	5 (21%)	40 (31%)		10 (31%)	35 (29%)	
ART information:							
ART adherence and switches	Documented ART interruption	2 (8%)	13 (10%)	1.00	3 (9%)	12 (9%)	1.00
	Switch to 2nd-line ART	2 (8%)	7 (5%)	0.64	2 (6%)	7 (6%)	1.00
Immune response	CD4% after 5 yrs (mean; SD)	30.0% (6.7)	32.1% (8.1)	0.22	31.6% (8.2)	31.9% (7.8)	0.84
	Immune reconstitution	25 (100%)	126 (97%)	1.00	32 (100%)	119 (97%)	0.58
Viral suppression**	Undetectable VL at 60m	17 (65%)	85 (64%)	0.92	18 (56%)	84 (66%)	0.57
	Optimal VL success	8 (31%)	48 (36%)		8 (25%)	48 (38%)	
	Suboptimal VL success	13 (50%)	57 (43%)	0.79	15 (47%)	55 (43%)	0.32
	Poor VL success	5 (19%)	28 (21%)		9 (28%)	24 (19%)	

Data are n (%) unless otherwise specified. Percentages are not always calculable from table due to missing information.

Abbreviations: WAZ= weight-for-age Z-score, HAZ= height-for-age Z-score, ART= antiretroviral therapy, SD= standard deviation, WHO= World Health Organization; yrs= years

***CD4 classification (WHO):**[30] **None:** >35% (age <12m); >25% (age 13-59m); >500/mm^3 (age >5y); **Mild:** 25-34% (age <12m); 20-24% (age 13-59m); 350-499 mm^3 (age >5y); **Advanced:** 20-24% (age <12m); 15-19% (age 13-59m); 200-349 mm^3 (age >5y); **Severe:** <20% (age <12m); <15% (age 13-59m); <200 mm^3 (age >5y)

****Virological suppression: Optimal**: HIV VL <400 copies/ml in >90% of samples, **Suboptimal**: HIV VL <400 copies/ml in 50-90% of samples, **Poor**: HIV VL <400 copies in <50% of samples

Table 4: Mixed linear analysis to assess factors that significantly influenced growth in the cohort

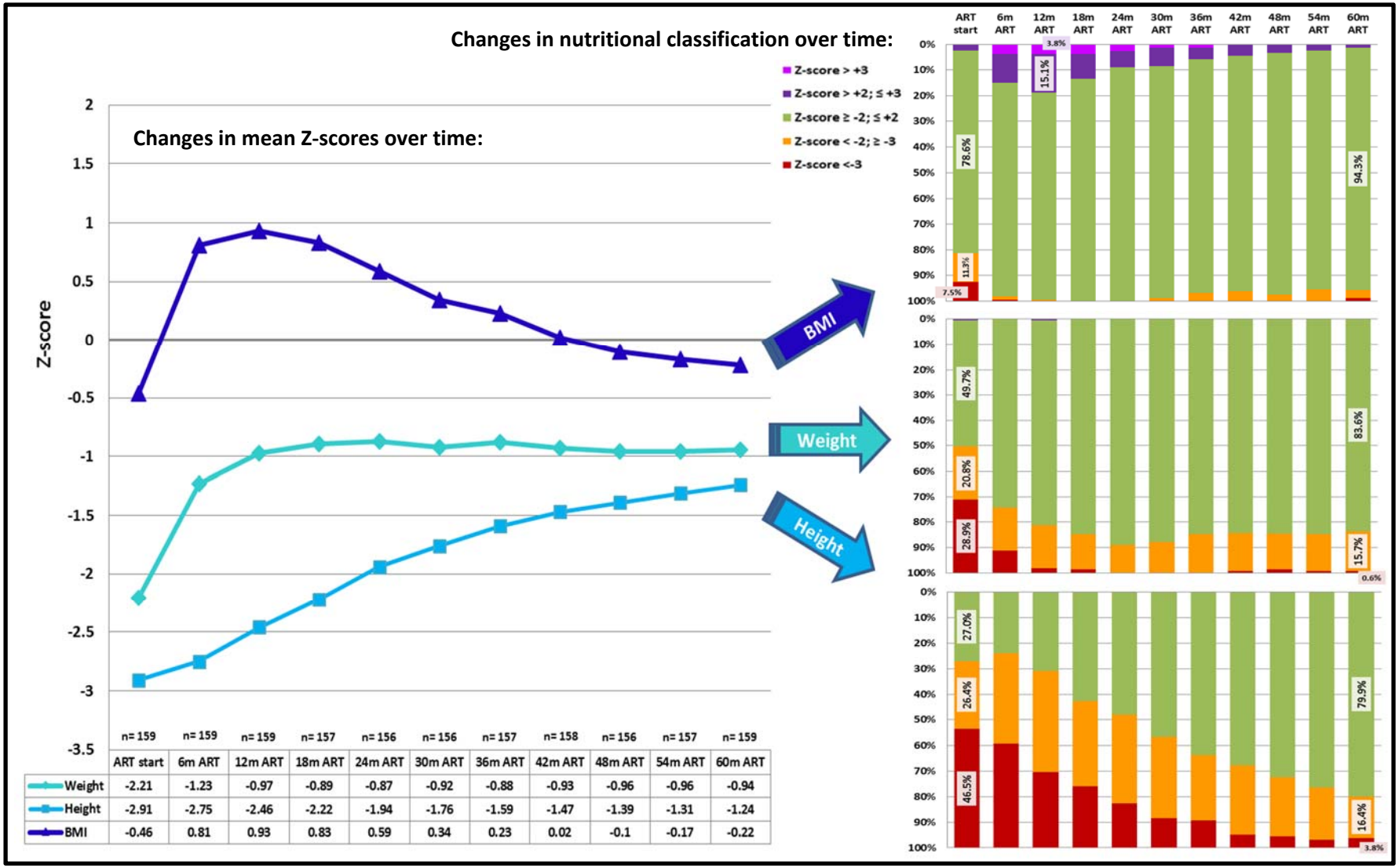
	Weight gain over time* (WAZ from start of ART to 12m)		Growth in length over time* (HAZ from start of ART to 5yrs)	
	Coefficient (SE)	**p-value**	**Coefficient (SE)**	**p-value**
ART duration	0.16 (0.18)	**<0.001**	0.03 (0.002)	**<0.001**
Age at enrolment:				
<1yr	Ref	Ref	Ref	Ref
1-3 yrs	0.19 (0.29)	0.51	-0.12 (0.22)	0.57
3-5 yrs	0.93 (0.33)	**0.005**** a)	0.44 (0.25)	0.08** b)
Interactions:				
Age <1yr # ART duration	Ref	Ref	Ref	Ref
Age 1-3yrs # ART duration	-0.04 (0.02)	**0.03**	0.0001 (0.002)	0.94
Age 3-5yrs # ART duration	-0.12 (0.02)	**<0.001**** c)	-0.009 (0.002)	**<0.001**** d)
Male sex	-----	---	-0.31 (0.16)	0.058
Electricity available	0.53 (0.26)	**0.04**	-----	---
Tuberculosis at ART initiation	-0.50 (0.19)	**0.01**	-0.38 (0.16)	**0.02**

***Included in WAZ and HAZ models:** ART duration (in months) as time-dependent variable, age at enrolment (<1yr/1-3yrs/3-5yrs), sex, mother is caregiver, availability of electricity, tuberculosis at ART initiation, anaemia at ART initiation and HIV VL<400 copies/ml at 6m ART. Only significant findings are shown.

****Additional p-values comparing groups 1-3 yrs vs 3-5 yrs:** a) p= 0.004; b) p= 0.005; c) p< 0.001; d) p< 0.001

Abbreviations: ART= antiretroviral therapy; WAZ= Weight-for-age Z-score; m=months; HAZ= height-for-age Z-score; yr= year; VL= HIV viral load; Ref= reference value

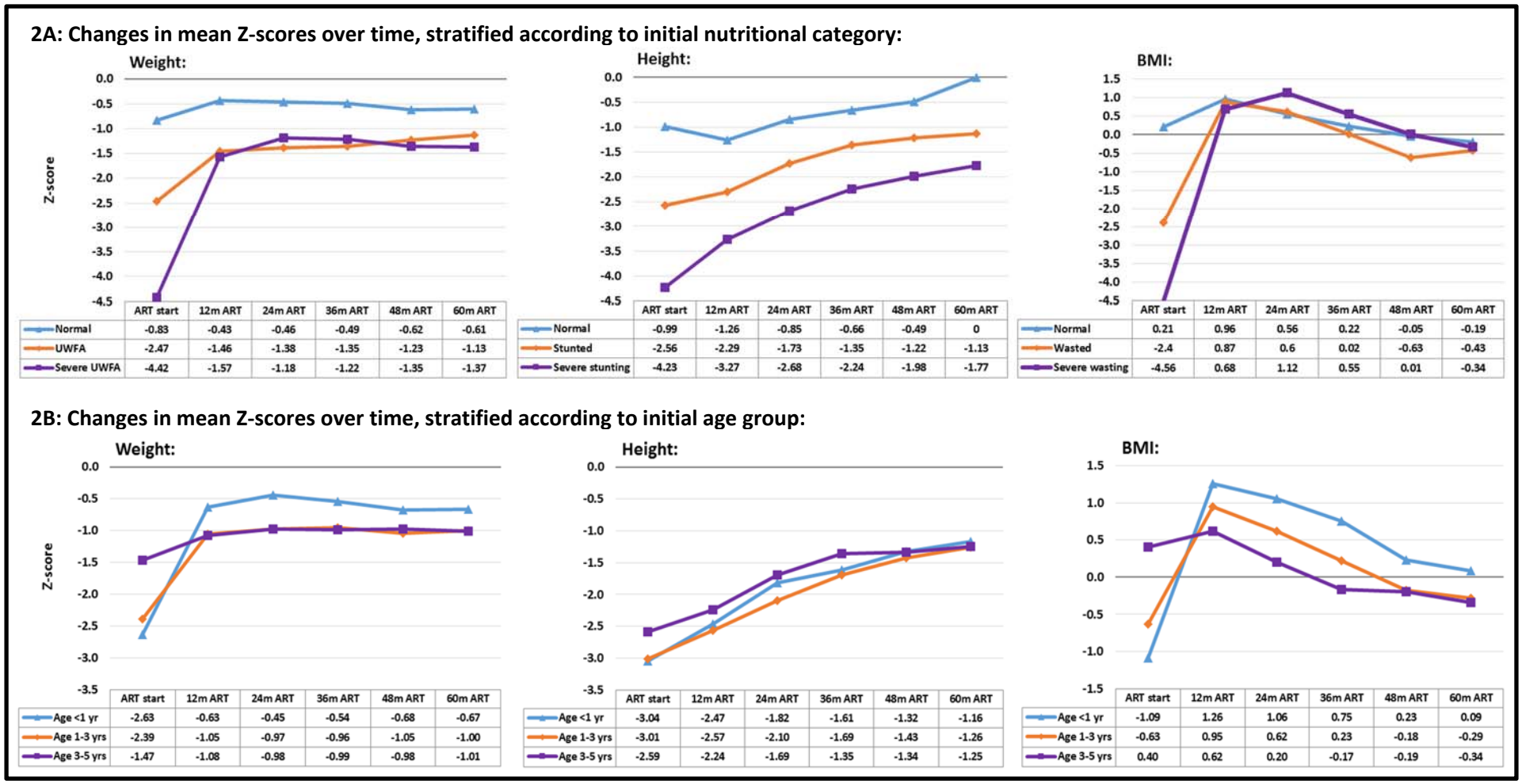
Figure 1: Growth of HIV-infected children on antiretroviral therapy over a 5 year period



	n= 159	n= 159	n= 159	n= 157	n= 156	n= 156	n= 157	n= 158	n= 156	n= 157	n= 159
	ART start	6m ART	12m ART	18m ART	24m ART	30m ART	36m ART	42m ART	48m ART	54m ART	60m ART
Weight	-2.21	-1.23	-0.97	-0.89	-0.87	-0.92	-0.88	-0.93	-0.96	-0.96	-0.94
Height	-2.91	-2.75	-2.46	-2.22	-1.94	-1.76	-1.59	-1.47	-1.39	-1.31	-1.24
BMI	-0.46	0.81	0.93	0.83	0.59	0.34	0.23	0.02	-0.1	-0.17	-0.22

Abbreviations: BMI= body mass index; ART= antiretroviral therapy; m=months

Figure 2: Growth of HIV-infected children on antiretroviral therapy, stratified according to initial nutritional category and age



Abbreviations: ART= antiretroviral therapy; yr= year; m= months; BMI= body mass index; UWFA= underweight-for-age