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Growth in HIV-Infected Children Receiving Antiretroviral Therapy at a Pediatric Infectious Diseases Clinic in Uganda

MARK M. KABUE, Dr.P.H.,[1] ADEODATA KEKITIINWA, M.D.,[2] ALBERT MAGANDA, B.Stat.,[2] JAN M. RISSER, Ph.D.,[3] WENYAW CHAN, Ph.D.,[3] and MARK W. KLINE, M.D.[4]

ABSTRACT

Antiretroviral therapy (ART) improves growth and survival of HIV-infected individuals. We designed a retrospective cohort study to assess clinical factors associated with growth in HIV-infected children on ART in Uganda between July 2003 and March 2006. Height and weight measurements taken pre- and post-ART initiation for at least 6 months were age- and gender-standardized to CDC 2000 reference. We analyzed medical records of 749 children receiving ART. Descriptive and logistic regression analyses were conducted to identify covariates associated with risk of either stunting or being underweight. Longitudinal regression analysis with a mixed model using autoregressive covariance structure was used to compare change in height and weight before and after initiation of ART. The mean age of the study population at first visit was 7.5 years. Mean height-for-age, weight-for-age, and weight-for-height percentiles at first visit were 8.6, 7.7, and 7.9, respectively. At last visit mean height-for-age, weight-for-age, and weight-for-height percentiles were 8.6, 13.3, and 13.8, respectively. Baseline weight-for-age *z* score of 1 or more was protective against stunting (odds ratio [OR] 0.25, confidence interval [CI] 0.18–0.35) while baseline height-for-age *z* score of 1 or more was protective against becoming underweight (OR 0.75, CI 0.63–0.88). Children in World Health Organization (WHO) stages II, III, and IV at baseline were 1.5 times more likely to become underweight (OR 1.51, CI 1.07–2.14). Initiation of ART resulted in improvement in mean standardized weight-for-age *z* score and weight-for-age percentiles ($p < 0.001$). Weight-for-age percentile and *z* score improved significantly after initiation of ART. This pediatric population gained weight more rapidly than height after initiation of ART.

INTRODUCTION

HIV INFECTION adversely affects growth of children. Prior to antiretroviral therapy (ART) in Africa, studies in HIV-infected children from Uganda, Malawi, South Africa, and Rwanda have demonstrated that perinatally acquired HIV infection is associated with poor growth outcome marked by high mortality, stunting, and wasting.[1–4] Comparative studies

[1]Baylor College of Medicine, Abbott Fund Children's Clinical Centre of Excellence, Malawi.
[2]Baylor College of Medicine International Pediatric AIDS Initiative Mulago Pediatric Infectious Diseases Clinic, Kampala, Uganda.
[3]The University of Texas School of Public Health, Houston, Texas.
[4]Baylor College of Medicine International Pediatric AIDS Initiative, Texas Children's Hospital, Houston, Texas.

Table 1. Weight, Height, Viral Load, and CD4$^+$ Changes in Children Receiving Antiretroviral Therapy

Reference, study location	*Type of study*	*Sample size*	*Changes in weight and height z scores, VL & CD4$^+$ cell counts*	p *value*	*Duration of follow-up*
Verwell (2002)[8] United States	Prospective cohort	24	A trend toward a significantly increased *z* score change after initiation of ART compared with *z* score change before ART for both height and weight.	0.052 (weight) 0.056 (height)	96 weeks
Newell (2003)[9] 11 European countries	Prospective cohort	1587	The *z* scores for height and weight gain improved in children on combination therapy regardless of their clinical classification.		10 years (1987–1997)
Kline (2004)[10] Romania	Prospective cohort	173	+284 cells/μL increase	< 0.001	67 weeks (2002–2003)
		542	Median growth velocity: 25th–50th percentile		
Viani (2004)[11] United States	Historical cohort	129	VL decrease from 4.53 $\log_{10}$ to 3.27 $\log_{10}$ copies/mL.	< 0.001	6 years (1994–2001)
			Increase in CD4$^+$ cell percentage from 22.5% to 31.2%.	< 0.01	
Nachman (2005)[12] United States	Prospective cohort	192	Mean weight *z* score increase from -0.57 to -0.16		96 weeks

VL, viral load; CD4$^+$, CD4 cells per microliter of blood; ART, antiretroviral therapy.

of HIV-infected with non-HIV–infected children have demonstrated that HIV-infected children have lower mean *z* scores at each period with deficits in weight occurring earlier in life than deficit in height or length.[3] *z* scores are calculated through the conversion of raw weight and height measurements from the study population compared to age- and gender-matched sample from a standard population.[5]

With the introduction of protease inhibitor and non-nucleoside analogue combination therapy in 1996, highly active antiretroviral therapy (HAART) has been shown to be effective in suppressing viral replication, and decreased HIV-1 associated mortality and morbidity while promoting growth.[6,7] Studies conducted in HIV-infected children and adolescents receiving ART have demonstrated that ART improves weight and height, and reduces mortality and morbidity as summarized in Table 1.[8–12] When ART is initiated early in eligible HIV-infected children, clear benefits on weight and height gain can be expected.[13] In the absence of timely initiation of ART, HIV-infected children may end up being stunted, underweight, or both. The World Health Organization in 2006[14] published new growth standards that differ considerably from the previously recommended National Center for Health Statistics (NCHS)/WHO international reference particularly in infancy. The new WHO standards will result in estimates of stunting being higher throughout childhood, but prevalence of overweight will be greater and vary by age, gender, and nutritional status particularly in developing countries.[14]

Growth retardation at crucial developmental stages in children impacts their overall mental and physical development. Approximately 43% of children (230 million) in developing countries are stunted.[15] Data from Uganda indicate that growth deficiencies are present among the children in the general population;

according to the United Nations Children's Fund (UNICEF)[16] the prevalence of moderate to severe stunting in children younger than 5 years of age in Uganda is 39% while the prevalence of moderate to severe underweight is 23%. Although mass vitamin A supplementation for all children has been proposed and implemented in countries like Uganda, its effectiveness in reducing morbidity and promoting growth has not been demonstrated in HIV-infected children. A clinical trial[17] in Uganda reported that vitamin A supplementation did not have significant effect in reducing the prevalence of fever, ear discharge, and bloody stools in children. Pediatric HIV infection may result in children being underweight, stunted, or wasted despite having good nutrition and a normally functioning endocrine system.[18–20] Some possible explanations for the poor growth in HIV-infected children include acute infection episodes, inadequate dietary intake, gastrointestinal malabsorption, increased energy utilization for HIV replication, and psychosocial problems.[18–20]

In an attempt to identify clinical predictors of HIV disease progression in children, a group of researchers used Pediatric AIDS Clinical Trials Group data (PACTG 300)[21] to assess the usefulness of physical examination to predict HIV disease progression with an aim of applying the technique in resource-poor settings especially in Africa, where routine laboratory monitoring for all patients is not feasible. The clinical model used treatment regimen, age, and height velocity. The researchers concluded that the clinical model performed similarly to using laboratory HIV viral load measurements and recommended that the model be validated using data from resource-poor settings. We designed a study to describe changes in weight and height in HIV-infected children receiving ART at Mulago Pediatric Infectious Disease Clinic (PIDC) using outpatient clinical data collected during routine clinic visits. The specific objectives were: (1) to compute and compare, age- and gender-standardized weight and height measurements before and after initiation of ART in a pediatric population on ART at Mulago PIDC between July 2003 and March 2006 and (2) to assess factors associated with changes in weight and height in this HIV-infected pediatric population.

MATERIALS AND METHODS

This was a retrospective cohort study that used secondary data from Mulago PIDC, in Uganda. The study population consisted of 1041 patients who attended the Mulago PIDC between July 2003 and March 2006 who had a minimum of two clinic visits. A subset of 749 children and adolescent Ugandan children receiving ART who had at least 6 months of follow-up was identified after thorough data cleaning after the study was approved by both Mulago Hospital (Uganda) and Baylor College of Medicine Institutional Review Board. Viral load and CD4 cell count data were not available. The variables investigated in this study were: age, gender, weight, height, and HIV disease stage (WHO clinical staging).

Height and weight measurements were first converted to age- and gender-standardized values with United States as the reference population, using Epi Info 2000 (Centers for Diseases Control and Prevention [CDC], Atlanta, GA).[22] Growth was analyzed primarily in terms of height-for-age-and-gender *z* scores (HAZ), and weight-for-age-and-gender *z* scores (WAZ). Weight-for-height *z* scores (WHZ), body mass index *z* scores (BMIZ), and height and weight percentiles were also generated during the age and gender standardization process. Stunting was ascertained when a patient was below the fifth height-for-age percentile compared to a reference population during any clinic visit. On the other hand, underweight was ascertained when a patient was below the fifth BMI percentile compared to a reference population. A majority of the study children were aged 2–19 years (82.3%), and it was decided to use BMI percentile to define underweight.

Logistic regression analysis was carried out to identify covariates associated with risk of stunting and being underweight. Longitudinal regression analysis using mixed model with autoregressive covariance structure was used to compare trends of height and weight before and after initiation of ART. The model containing two lines intersecting at the time of initiation of ART allows two slopes, one before and the other after initiation of ART. The two slopes were used to examine weight and height

Table 2. Description of the Study Population

Parameter	n *(%)*
Age (n = 749)	
0–2 years	105 (14.0)
> 2–8 years	321 (42.8)
> 8–13 years	199 (26.6)
> 13 years	124 (16.6)
Gender (n = 749)	
Male	384 (51.3)
Female	365 (48.7)
WHO HIV disease staging (n = 399)	
I—Asymptomatic	46 (11.5)
II—Early HIV disease	109 (27.3)
III—Chronic HIV associated infections	201 (50.4)
IV—Recurrent severe bacterial infections	43 (10.8)

changes before and after initiation of ART. Stata software version 9.0 (StataCorp, College Station, TX) was the principal statistical package used for data analyses. p value and 95% confidence interval were used to determine levels of significance. A p value of < 0.05 was considered statistically significant.

RESULTS

The mean age of the study population who had at least 6 months of follow-up (n = 749) at first visit was 7.5 years (standard deviation [SD] = 4.7), all aged younger than 20 years. There were approximately equal numbers of males and females, and half of the children were in WHO stage III (Table 2). The mean pre-ART follow-up time was 4 months while mean follow-up time on ART was 6 months. Mean height-for-age, weight-for-age, and weight-for-height percentiles at first visit were 8.6, 7.7, and 7.9, respectively. At last visit, mean height-for-age, weight-for-age, and weight-for-height percentiles were 8.6, 13.3, and 13.8, respectively. With respect to the z scores, mean height-for-age, weight-for-age, and weight-for-height z scores at first visit were -2.7, -3.2, and -1.5, respectively. At last visit mean height-for-age, weight-for-age, and weight-for-height z scores were -2.4, -2.1, and -0.2 respectively (Table 3). There was statistically significant improvement in height-for-age z score, weight-for-age z score, and body mass index z score, from first to last visit ($p < 0.05$).

Logistic regression on the changes in weight and height percentiles before after initiation of ART showed that before initiation of ART, height-for-age percentiles were on a downward trend ($p < 0.05$) but this trend reversed after initiation of ART ($p < 0.05$). Weight-for-age percentiles increased only slightly before initiation of ART but improved rapidly after

Table 3. Changes in Age, Height, Weight, Percentiles, and z Scores from First to Last Visit

Growth indicator	*At first visit*	*At last visit*	p *value*
Age (years): n = 749			
Mean, SD (Range)	7.5, SD = 4.7 (0.1–19.3)	8.6, SD = 4.8, (0.6–19.9)	< 0.001
Height-for-age z Score: n = 749			
Mean, SD (Range)	−2.7, SD = 1.8 (−11.2 to 4.5)	−2.4, SD = 1.5 (−10.2 to 3.8)	0.002
Weight-for-age z Score: n = 749			
Mean, SD (Range)	−3.2, SD = 2.5 (−25.4 to 2.0)	−2.1, SD = 1.9 (−20.6 to 2.5)	< 0.001
Weight-for-height z Score: n = 399			
Mean, SD (Range)	−1.5, SD = 1.9 (−11.9 to 3.7)	−0.2, SD = 1.4 (−6.8 to 2.6)	< 0.001
Height-for-age percentile: n = 749			
Mean, SD (Range)	8.6, SD = 19.0 (0 to 100.00)	8.6, SD = 17.3 (0–100.00)	0.856
Weight-for-age percentile: n = 749			
Mean, SD (Range)	7.7, SD = 17.7 (0 to 97.9)	13.3, SD = 20.6 (0–99.3)	< 0.001
Weight-for-height percentile: n = 399	7.9, SD = 18.2 (0–97.9)	13.8, SD = 20.9 (0–94.00)	< 0.001

SD, standard deviation.

TABLE 4. UNIVARIATE AND MULTIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH STUNTING AND UNDERWEIGHT

Stunting Predictor variable (n = 399)	*Univariate odds ratio (95% CI)*	p *value*	*Multivariate odds ratio*[a] *(95% CI)*	p *value*
Baseline age	1.09 (0.91–1.31)	0.333	0.85 (0.60–1.21)	0.364
Gender	1.21 (0.86–1.70)	0.254	0.61 (0.33–1.14)	0.122
Baseline WAZ	0.26 (0.21–0.33)	< 0.001	0.25 (0.18–0.35)	< 0.001
Baseline WHO Stage	2.13 (1.60–2.84)	< 0.001	1.23 (0.83–1.80)	0.299
Underweight Predictor variable (n = 399)	*Univariate odds ratio (95% CI)*	p *value*	*Multivariate odds ratio (95% CI)*	p *value*
Baseline age	1.92 (1.59–2.32)	0.001	2.42 (1.81–3.25)	< 0.001
Gender	1.17 (0.83–1.63)	0.368	1.14 (0.68–1.91)	0.618
Baseline HAZ	0.77 (0.70–0.85)	< 0.001	0.75 (0.63–0.88)	0.001
Baseline WHO Stage	1.52 (1.12–2.05)	0.007	1.51 (1.07–2.14)	0.019

[a]Each variable adjusted for others in the multivariate analysis.

CI, confidence interval; WAZ, weight-for-age-and-gender *z* scores; WHO, World Health Organization; HAZ, height-for-age-and-gender *z* scores.

initiation of ART ($p < 0.05$). Table 4 shows that after adjusting for age and gender in multivariate logistic regression analysis, baseline weight-for-age *z* score of 1 or more was protective against stunting (OR 0.25, CI 0.18–0.35) while baseline height-for-age *z* score of 1 or more was protective against becoming underweight (OR 0.75, CI 0.63–0.88). Children in WHO stages II, III, and IV at baseline were 1.5 times more likely to become underweight (OR 1.51, CI 1.07–2.14).

Changes in height-for-age and weight-for-age tracked for a period of 24 months from the first visit. Improvement in height-for-age *z* score was statistically significant in all patients who had at least 6 months follow-up and again at 12 months follow-up ($n = 749$, $p = 0.007$; $n = 392$, $p = 0.002$), respectively. Weight-for-age *z* score improvement were statistically significant at 6 months, 12 months, and 18 months follow-up ($n = 749$, $p < 0.001$; $n = 392$, $p < 0.001$ and $n = 151$, $p < 0.001$), respectively.

DISCUSSION

Access to pediatric ART treatment is still limited to approximately 8% of the eligible children (43,700) receiving ART in Uganda. The national ART program was still in the early stages and data on side effects to antiretrovirals necessitating treatment failure were few. At the time this study was undertaken, over 98%, of the few children who received antiretrovirals in 2003 were still on their first regimen. In case of treatment failure on the first regimen, patients were switched to another ART regimen but administration of antiretrovirals was not stopped. Less than 5% of the enrolled children were on second-line regimen in Uganda in 2006.

The goal of administering ART to HIV-infected children is prolonging life and ensuring that HIV-infected children achieve sustained growth and development.[13] Growth is an important outcome that is assessed in any pediatric HIV care and treatment program as it may be marker of a program's effectiveness. The low height and weight percentiles reported in this study may be partly attributed to the fact that the referent population (United States) is markedly different from the Ugandan population with respect to nutritional status. A majority of the *z* scores in many patients were in the negative (minus), suggesting a downward shift for the general Ugandan population compared to the United States population.[22]

When the impact of administering ART on change in height was examined, it became ev-

ident that administration of ART was of great benefit in this pediatric population because it resulted in the reversal of a downward trend in both height-for-age *z* score and height percentile to positive values ($p < 0.001$). With regard to weight and administration of ART, both weight-for-age *z* score and weight-for-age percentiles improved significantly implying that administration of ART to these children resulted in greater improvement in weight than height. Our findings are consistent with other studies that have reported improvement of both weight and height in HIV infected children[12,13] after initiation of ART. Differences in the referent population (United States) and Ugandan populations may be responsible for the large standard deviations observed in this study. According to WHO, with accurate age assessment and anthropometric measurements, the standard deviation of the observed height-for-age, weight-for-age, and weight-for-height *z* scores should range from 0.85 to 1.3.[23] Furthermore, the study population was in a way selected (HIV-positive children and attending Mulago PIDC), and therefore different from the referent population. Adherence to ART in this population can be presumed to have been good since 86% of the patients were reported to have been 100% adherent to all three ART medications. However, adherence was not appropriately measured and documented in our study population and thus the percent level of adherence could not be calculated.

This study had several strengths. We used a cohort design, which provides a higher level of evidence of the relationship between explanatory and outcome variables compared to cross-sectional and case-control designs. Another strength of this study is the use of numerous weight and height measurements before and after initiation of ART during clinic visits in the analysis, which provided a good estimate of the true changes in weight and height values analyzed. On the contrary, the manner in which weight and height measurements were obtained and documented may have been a possible weakness in this study given that nearly one third of patient visits were deleted in the data cleaning phase mainly due to either missing or wrong height and weight values. One possible explanation for missing and wrong entries may be differential implementation of the weight and height measurement protocol by the clinic staff that carried out the measurements during each clinic visit. Data entry errors may also have occurred because data were first captured on paper during clinic visits and then entered into the respective electronic medical record for each clinic visit. Finally, viral load and CD4 cell measurements that are valuable resources for monitoring response to administration of ART were not available for analysis in this study. In conclusion, administration of ART was of great benefit to the children in this study population. Stunting was a common feature in HIV infected children at Mulago PIDC in Uganda, and remained so after ART initiation. However, this pediatric population on ART Mulago PIDC gained weight more rapidly upon initiation of ART. We recommend closer monitoring of weight and height measurements at Mulago PIDC to ensure high-quality data especially in settings in which routine laboratory monitoring is not feasible.

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Address reprint requests to:
Mark M. Kabue, Dr.P.H.
Kamuzu Central Hospital
Baylor College of Medicine
Children's Clinical Centre of Excellence
Private Bag B-397
Lilongwe
Malawi

E-mail: mkabue@bcm.edu