Published in final edited form as:

AIDS. 2011 January 28; 25(3): 345–355. doi:10.1097/QAD.0b013e32834171db.

Younger age at HAART initiation is associated with more rapid growth reconstitution

Christine J. McGrath^a, Michael H. Chung^{a,b,d}, Barbra A. Richardson^{c,e}, Sarah Benki-Nugent^b, Danson Warui^f, and Grace C. John-Stewart^{a,b,d}

^aDepartment of Epidemiology, University of Washington, Seattle, Washington, USA

^bDepartment of Medicine, University of Washington, Seattle, Washington, USA

^cDepartment of Biostatistics, University of Washington, Seattle, Washington, USA

^dDepartment of Global Health, University of Washington, Seattle, Washington, USA

^eDivision of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

^fCoptic Hospital, Nairobi, Kenya

Abstract

Objectives—Patterns of growth following highly active antiretroviral therapy (HAART) administration among children are not well defined. The objective of this study was to determine rates and predictors of growth reconstitution among children on HAART.

Methods—A study was conducted among HIV-1-infected children initiating HAART at an HIV treatment clinic in Kenya. Kaplan–Meier survival curves and Cox proportional hazards regression models compared catch-up growth (Z -score = 0) at 12 months post-HAART. Multivariate linear mixed-effects models determined rates and predictors of growth following HAART.

Results—One hundred and seventy-three HIV-1-infected children initiated HAART with a median age of 4.7 years [interquartile range (IQR) 2.4, 7.0]. At baseline, children below 3 years had lower weight-for-age (WAZ) and weight-for-height (WHZ) Z -scores than children 3–5 and 6–10 years (WAZ: $P = 0.03$; WHZ: $P = 0.006$). Adjusting for baseline growth, children below 3 years were two to three-fold more likely to attain population age-norms (Z -score = 0) than 6–10 years (WAZ: $P = 0.055$; WHZ: $P = 0.005$) at 12 months post-HAART. After adjustment, children below 3 years had higher increases in WAZ and WHZ following HAART than 6–10 years (WAZ: $P = 0.006$; WHZ: $P = 0.005$). Children at WHO stage at least 3 at baseline experienced more rapid WHZ reconstitution ($P = 0.002$). Food supplementation while on HAART was associated with increased monthly gains in weight indices (WAZ: $P = 0.001$; WHZ: $P = 0.005$), and multivitamins were associated with greater increases in height ($P < 0.01$).

© 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins

Correspondence to Christine J. McGrath, HMC, Box 359909, 325 Ninth Avenue, Seattle, WA 98104, USA. Tel: +1 206 543 4278; fax: +1 206 543 4818; mcgrathc@u.washington.edu.

Author's contributions

C.J.M. contributed to the design of the study, analysis of the data, and drafted manuscript. M.H.C. contributed to the design of the study and reviewed manuscript. B.A.R. contributed to the analysis of data and reviewed manuscript. S.B.-N. contributed to the design of the study and reviewed manuscript. D.W. contributed to implementation of the study and reviewed manuscript. G.J.-S. contributed to the implementation and design of the study, analysis of data and drafted manuscript. All the authors have read and approved the text as submitted to *AIDS*.

Conclusion—Following HAART initiation, younger children had more rapid catch-up to the population-average weight of their peers than older children, demonstrating growth benefit of earlier HAART. In addition to HAART, food supplementation and multivitamins may also accelerate growth reconstitution.

Keywords

growth; HAART; HIV; nutritional supplementation; pediatrics; sub-Saharan Africa

Background

Worldwide, more than 2.5 million children are infected with human immunodeficiency virus (HIV-1), nearly 90% of whom are living in sub-Saharan Africa [1,2]. A common feature of HIV-1 infection in children is growth failure [3–5]. HIV-1-infected infants tend to have substantially lower weight and height compared to HIV-1-uninfected children of similar age [4,6]. In Africa, many HIV-1-infected children also lack adequate nutrition. Malnourished HIV-1-infected children struggle to meet metabolic demands of growth and development, and poor nutrient status weakens the immune system and decreases the likelihood of survival [7,8]. Growth faltering has been reported in up to 50% of untreated HIV-1-infected children in resource-limited settings.

Highly active antiretroviral therapy (HAART) suppresses viral replication and results in immune recovery and growth reconstitution in HIV-1-infected children. Although HAART improves growth in pediatric HIV-1, the pattern and determinants of growth reconstitution following HAART are not well defined. In the US, HIV-1-infected children generally achieve normal weight-for-age *Z*-scores (WAZ) within a year of HAART initiation and experience improvement in height-for-age *Z*-scores (HAZ) by 2 years [6,9]. In Africa, baseline WAZ and HAZ in untreated HIV-1-infected children are substantially lower (typically with *Z*-scores <−2 which is <2nd percentile) than reported in US/European cohorts (*Z*-scores >−0.5, or >30th percentile) [10–14].

Whereas HAART may improve growth by decreasing metabolic expenditures and improving nutrient absorption, side-effects of HAART could adversely affect growth [15]. Moreover, benefits of HAART on subsequent catch-up growth may vary based on age at initiation, severity of disease, and HIV-1 viral load [6,16–19]. Few studies have focused on growth reconstitution following HAART among children with undernutrition. Although it is plausible that malnutrition may alter the effectiveness of HAART, marked improvements in growth have been shown following HAART in Africa [10,11]. In pediatric HIV-1 treatment programs in Africa, empiric food supplementation is widespread [20] despite limited evidence that it provides additional benefit to HAART in growth reconstitution.

It is important to define rate and determinants of catch-up growth following HAART in order to maximize long-term growth in children and to provide accurate estimates for anticipated growth reconstitution for clinicians and parents. We determined rates and predictors of growth reconstitution in a large pediatric HIV-1 treatment program in Nairobi, Kenya.

Methods

Study population and sample

Data are from HIV-1-infected children enrolled at the Coptic Hope Centers for Infectious Diseases in Nairobi, Kenya who initiated HAART between January 2004 and March 2008. Clinic protocols have been described elsewhere [21]. Children were included in the analysis

if they were antiretroviral-naïve at clinic enrollment, below 10 years of age, and eligible to initiate HAART per Kenyan national guidelines. Specifically, children were eligible to initiate HAART if World Health Organization (WHO) clinical stage above 2 or CD4 cell counts/percents were below age-related WHO criteria if in an earlier WHO clinical stage of disease [22]. The University of Washington Institutional Review Board and Kenyatta National Hospital Ethical Review Committee approved the use of clinic data for this study.

Data collection

At enrollment, information was collected from caregivers on sociodemographic and clinical characteristics. Physical examination was conducted, including measurement of weight and height or recumbent length if below 24 months of age. Follow-up visits occurred at least every 3 months, at which time information on weight, height, morbidity, nutritional supplementation, and clinical data were collected. CD4 cell counts were assessed at enrollment and every 6 months thereafter. *Z*-scores were used to standardize anthropometric measurements. The *Z*-score quantifies how many standard deviations (SDs) a child's anthropometric value is from the mean (*Z*-score = 0, or 50th percentile) value of a child of the same age and sex in a reference population. The 2006 WHO reference population [23] was used to calculate WAZ, HAZ and weight-for-height (WHZ) *Z*-scores.

Data analyses

For analyses the cohort was divided into three age groups (<3, 3–5, 6–10 years) at HAART initiation. Comparisons between age at HAART initiation and baseline characteristics were made using the Pearson χ^2 test for categorical variables and the Kruskal–Wallis test for continuous variables. WAZ, HAZ and WHZ profiles were plotted based on age group at HAART initiation.

Kaplan–Meier survival curves and Cox proportional hazards regression models were used to compare time to catch-up growth to at least the population mean (*Z*-score = 0) by age at 12 months post-HAART initiation. Logistic regression was used to assess the relationship between cohort characteristics and growth failure (*Z*-score <−2) prior to HAART. Linear mixed-effects models with random intercepts and slopes for time were constructed to assess the rate of change in growth in HIV-1-infected children after HAART initiation and to determine predictors of growth reconstitution. The trajectory of growth was measured by the change in WAZ, HAZ, and WHZ, after adjusting for baseline WAZ, HAZ or WHZ, covariates significantly associated with growth in univariate analyses or those associated with growth based on *a priori* assumptions. Time-independent baseline characteristics, time-varying covariates (food supplements and multivitamins), and a time-dependent variable (months on HAART) were examined for their effect on growth following HAART.

Secondary analyses were conducted to assess the effect of nutritional supplementation on growth following HAART. Statistical analyses were conducted using SPSS 18 (Chicago, Illinois, USA) and STATA 11.0 (College Station, Texas, USA).

Results

Cohort characteristics

Between January 2004 and March 2008, 173 HIV-1-infected children initiated HAART (Table 1). At enrollment, the median age was 4.7 years [interquartile range (IQR) 2.4, 7.0], 42% of children were classified as WHO clinical stage 3 or 4, and 62% of children had CD4 cell counts below normal for age. Median baseline WAZ, HAZ, and WHZ were all below average and nearly half (48%) of children were underweight (WAZ <−2), 48% were stunted (HAZ <−2), and 25% wasted (WHZ <−2).

Median WAZ and WHZ at baseline were significantly lower among children below 3 years followed by children 6–10 and 3–5 years (WAZ: -2.2 vs. -2.1 vs. -1.5 , $P = 0.03$; WHZ: -1.6 vs. -1.0 vs. -0.6 , $P = 0.006$, respectively). At HAART initiation, there were no statistically significant differences in median HAZ or CD4 cell count by age.

The median time to HAART initiation was 37 days (IQR 25, 64) and median follow-up time was 19 months (IQR 9, 28). During follow-up, 12 (7%) children died and 7 (4%) were lost. There were no significant differences in rates of death or loss to follow-up based on age group at HAART initiation ($P > 0.70$ for each).

Correlates of growth failure (Z-score < -2) at baseline prior to HAART

WHO stage 3 or 4 was associated with 3.19 higher odds of being underweight (WAZ < -2) at baseline [odds ratio (OR) 3.19, 95% confidence interval (CI) 1.68, 6.05; $P < 0.01$] (Table 2). Children 3–5 years were 74% less likely to be wasted (WHZ < -2) at baseline than those 6–10 years (OR 0.26, 95% CI 0.09, 0.77; $P = 0.02$).

Changes in weight-for-age Z-score following HAART

Low WAZ or being underweight (WAZ < -2) indicates protein-energy malnutrition and/or weight loss. The ability to rapidly gain weight and reach the population average (50th percentile) constitutes catch-up growth in weight. At baseline, 92% of children below 3 years, 84% of 3–5-year-olds and 93% of 6–10-year-olds were below the population average for WAZ ($P = 0.19$). Following 12 months of HAART, 34% of children below 3 years reached the population average (WAZ = 0) compared to only 21% of children 3–5 and 21% of those 6–10 years (Fig. 1a). The predicted median time to reach the population average (WAZ = 0) following HAART initiation was 28.5 months. Among children below 3 years, the anticipated median time to reach the population norm was 20.2 months, compared to 33.6 months for children 3–5 years, and 34 months for children 6–10 years at HAART. Using Cox regression to examine the effect of age on catch-up growth, children below 3 years were more likely to achieve the population norm at 12 months post-HAART compared to children 6–10 years, even after adjusting for baseline WAZ (hazard ratio 2.26, 95% CI 0.98, 5.19; $P = 0.055$).

Overall, the rate of WAZ change was 0.05 SD/month (95% CI 0.03, 0.06; $P < 0.001$). Univariate predictors of change in WAZ are shown in Table 3. WHO stage 3 or 4 and low baseline hemoglobin (< 9 g/dl) were associated with more rapid improvements in WAZ ($P = 0.05$ and $P = 0.001$, respectively). Children below 3 years had a greater rate of change in WAZ compared to 6–10 years ($P = 0.001$) (Fig. 2a). Receipt of food supplements was associated with greater gains in WAZ ($P = 0.001$).

After adjusting for other predictors of WAZ change (baseline WAZ, WHO stage and hemoglobin), only age remained significantly associated with rate of growth reconstitution (Table 4, model 1). The average monthly rate of change in WAZ was 0.05 SD ($P = 0.001$) in children below 3 years, 0.02 SD ($P = 0.08$) in 3–5-year-olds, and 0.004 SD ($P = 0.78$) in 6–10-year-olds. In multivariate analysis assessing the impact of nutritional supplements, age and receipt of food supplements were independently associated with a higher rate of increase in monthly WAZ following HAART (Table 4, model 2).

Changes in weight-for-height Z-score following HAART

Low WHZ or wasting (WHZ < -2) indicates a reduction in body fat and muscle, consistent with acute malnutrition. Prior to HAART, 73% of children below 3 years, 69% of 3–5-year-olds, and 68% of children 6–10 years were below the population average for WHZ ($P = 0.83$). Eighty-seven percent of children 3–5 years and 70% below 3 years reached the

population average (WHZ = 0) by 12 months, compared to 36% of children 6–10 years (Fig. 1b). Following HAART initiation, the median time to population average WHZ was 5.8 months (95% CI 3.5, 7.9). Median time to population norm WHZ was 2.7 months (95% CI 1.3, 6.2) in children 3–5 years and 5.9 months (95% CI 3.2, 10.5) for those below 3 years at HAART. The predicted median time to reaching the population average in children 6–10 years was 16.6 months. Adjusting for baseline WHZ, the rate of reaching the population average WHZ at 12 months was significantly greater in younger (<3 or 3–5 years old) compared to older children (6–10 years) (<3 years: hazard ratio 2.86, 95% CI 1.37, 5.93, $P=0.005$; 3–5 years: hazard ratio 3.86, 95% CI 1.92, 7.76, $P<0.001$). However, there was no significant difference between children 3–5 years compared to below 3-year-olds (hazard ratio 1.35, 95% CI 0.81, 2.24, $P=0.24$).

Overall, the rate of WHZ change was 0.06 SD/month (95% CI 0.04, 0.08, $P<0.001$). WHO stage 3 or 4 and hemoglobin (<9 g/dl) were associated with greater improvements in monthly WHZ ($P<0.001$ and $P=0.001$, respectively) (Table 3). Additionally, children below 3 years experienced a greater rate of change in monthly WHZ compared to children 6–10 years old ($P=0.005$) (Fig. 2b). Children receiving food supplements experienced greater monthly gains in WHZ ($P=0.007$). Multivitamins were not associated with a change in WHZ following HAART.

In multivariate analysis, younger age (<3 years), WHO stage 3 or 4, and hemoglobin (<9 g/dl) remained independently associated with greater improvements in WHZ ($P=0.01$, $P=0.003$, and 0.05, respectively) (Table 4, model 1). The monthly change in WHZ was 0.06 SD ($P<0.001$) in children below 3 years, 0.004 SD ($P=0.76$) in 3–5 years, and 0.006 SD ($P=0.73$) in 6–10 years. In secondary analyses, the rate of increase in WHZ remained significantly higher in children receiving food supplements compared to children not receiving supplements ($P=0.005$) (Table 4, model 2).

Changes in height-for-age Z-score following HAART

Low HAZ or stunting (HAZ <−2) indicates a reduced rate of linear growth and represents chronic malnutrition and infections since early childhood or even prebirth. Catch-up growth in height includes rapid gain in height to the population average or 50th percentile. Almost all children had a HAZ below the population norm at baseline (<3 years: 92%; 3–5 years: 95%; 6–10 years: 93%; $P=0.81$). By 12 months following HAART, 19% of children below 3 years reached the population average for HAZ (HAZ = 0) compared to 11% of children aged 3–5 years and 6% 6–10 years (Fig. 1c). The anticipated median time to population average (HAZ = 0) was 62.6 months. Median time to reach the population norm HAZ was predicted to be 35.9 months among children below 3 years, and more than 64 months for older children (3–5 and 6–10 years). The rate of reaching average HAZ by 12 months did not differ significantly based on age at HAART initiation.

The rate of HAZ change was 0.03 SD/month (95% CI 0.02, 0.04; $P<0.001$) (Fig. 2c). Multivitamin use was univariately associated with greater improvements in HAZ ($P=0.008$) (Table 3), and this association remained after adjustment ($P=0.009$) (Table 4, model 1). After adjusting for multivitamins, and baseline HAZ and WHO stage, the average monthly rate of change in HAZ was 0.01 SD ($P=0.31$) in children below 3 years, 0.02 SD ($P=0.04$) in 3–5 years, and 0.02 ($P=0.08$) in 6–10 years.

In multivariate analyses assessing the role of nutritional supplements, children reporting multivitamin use had a 0.01 SD/month ($P=0.003$) greater increase in HAZ than children not taking multivitamins (Table 4, model 2). Food supplements, age, and WHO stage were not associated with a significantly different change in HAZ.

Changes in CD4 cell count following HAART

Following 6 months of HAART, median CD4 cell count increased from 342 cells/ μ l (IQR 156, 535) to 621 cells/ μ l (IQR 342, 857) ($P < 0.01$) and to 704 cells/ μ l (IQR 437, 1079) after 12 months of HAART ($P < 0.01$). The rate of CD4 gain and growth reconstitution were correlated in children below 3 year of age (Spearman's ρ 0.48, $P < 0.01$). However, because CD4 changes following HAART may be within the causal pathway of HAART effect on growth, change in CD4 cell count was not included in multivariate analysis.

Discussion

In this cohort of 173 HIV-1-infected children initiating HAART we made several important observations. Following HAART, younger children had a significant and substantially higher rate of return to their population age norms in weight and WHZ than older children. However, gains in height were slower and did not differ significantly based on age. Finally, baseline clinical status and nutritional supplements modified growth reconstitution suggesting a potential role for interventions to improve growth during HAART.

The children in this study experienced marked improvements in catch-up weight gain after HAART comparable to other studies in Africa [6,10,11,14]. We observed a significant difference in the rate of catch-up weight gain in very young children (<3 years) compared to older children (6–10 years). Whereas younger children are expected to grow more rapidly than older children, this does not mean that reconstituting growth to population norms would inevitably be more rapid in younger children. We found that within a year of treatment children below 3 or 3–5 years were two to three-fold more likely to attain normal weight for their age than children 6–10 years old.

There are several mechanisms that may explain our observation of more rapid growth reconstitution in younger children. First, younger children may have sustained less severe intestinal damage due to a shorter duration of HIV-1 disease allowing them to more effectively absorb nutrients after viral suppression [24,25]. HIV-1-related compromises in gastrointestinal permeability may result in malabsorption and may be less quickly restored after longer duration of HIV-1 [26,27]. In addition, longer HIV-1 duration results in chronic systemic immune activation, which may require more time to reverse and thus, exert a more prolonged metabolic cost [28,29]. Finally, weight reconstitution of older children may be limited by the irreversible height compromise from chronic HIV-1 infection.

Height among all children in this study remained well below average irrespective of age at HAART. Factors influencing catch-up height include the age at onset of illness, age at treatment, bone age, and extent of the height deficit [30–34]. HIV-1-infected children in US/European studies have shown height gain to normal values following HAART, with the highest restoration potential in children below 3 years old [6,35]. However, children in our study had much lower height (2nd percentile) at presentation, compared to 29th percentile in a US study [6], and were often malnourished. Vitamin D deficiency, poor calcium intake and/or absorption, and advanced disease may contribute to low bone mineral content in HIV-1-infected children [36–40]. This may be particularly relevant in Africa, where malnutrition further complicates growth reconstitution. We observed that multivitamin use was associated with increases in height gains, which is consistent with studies noting greater bone mineral density following multivitamins [40]. As early childhood is a critical period for bone mineral accrual [30], early HAART initiation may have the greatest impact on height reconstitution.

We found that advanced WHO clinical stage was associated with significantly greater increases in WHZ. There are conflicting data on the effect of baseline HIV-1 disease status

on growth reconstitution following HAART. Our study is consistent with a US-based study that demonstrated that children with advanced disease stage at HAART initiation had greater improvements in body mass index (BMI) [9]. However, other studies have not shown growth reconstitution to be associated with clinical stage, CD4 cell count, or HIV-1 viral load [6,9,15,35]. In this study, we did not find an association between baseline CD4 cell count and growth reconstitution. Contradictory results may be due to population differences, including age and disease status, growth deficits prior to treatment, underlying nutritional status, and length of follow-up. Greater gains in WHZ among sicker children following HAART may be explained by a higher shift in caloric demands from fighting HIV-1 infection to restoring normal growth regulation.

The importance of nutrition in chronically malnourished regions is recognized and empiric nutritional supplementation has been incorporated in many pediatric HIV treatment programs in Africa. However, benefits of nutritional supplementation on CD4 cell count, viral load, long-term growth and physical function in HIV-1-infected children are poorly defined. One study observed higher weight gain 1 month following amino acid-based macronutrient supplements vs. standard nutritional rehabilitation in severely malnourished antiretroviral-naïve Zambian HIV-1-infected children [41]. Systematic reviews have concluded that more evidence regarding macronutrient supplementation is needed [7,42]. It is plausible that HAART alone would reverse growth compromise given adequate caloric intake. However, our data suggest that among children on HAART, food supplements contributed to additional gains in weight and WHZ, and multivitamins contributed to gains in height, even after adjusting for baseline growth and disease stage. We estimate that below 3-year-olds initiating HAART at clinical stage 3 or 4 and normal hemoglobin with WHZ = -2 and receiving food supplements would reach the population norm in 11 months compared to 1.5 years if not on food supplements. It is also possible that more rapid growth in infancy on HAART may have adverse consequences on obesity or lipid metabolism [43,44]. Our data emphasize the need to further evaluate nutritional supplementation effects on long-term growth in HIV-1-infected children on HAART.

Our study has several strengths and limitations. We had excellent retention and survival with less than 8% of children being either lost or dying during follow-up. However, children initiating HAART were necessarily survivors and older children are therefore a selected group. Whereas we were able to look at children below 3 years, there were few infants below 1 year who may be expected to have the most durable and rapid benefit from HAART based on our data. However, the population represents a typical pediatric HIV-1 treatment program population. Although we were able to adjust for confounders, viral loads were not available. As data on receipt of food supplements were limited and the availability of food supplements was inconsistent, these results should be interpreted with caution. Additionally, information on the type and dose of multivitamin taken was unknown.

There are few studies of growth reconstitution in resource-limited settings and emerging literature is often limited to 6–12 months following HAART. Most of these studies have not focused solely on growth reconstitution, but rather on HIV-1 viral load and CD4 cell count. It is important to define rates and establish patterns of growth reconstitution following HAART. These measures, and the role of interrelated factors, can be used to provide estimates for anticipated catch-up growth. It was not expected that younger children would have a higher rate of return to their population norms than older children, particularly since younger children presented with poorer growth. In countries with limited access to virologic monitoring these findings may also be used to help identify children not responding to treatment.

Our data suggest that children starting HAART at an early age have the greatest weight growth reconstitution and potential to catch-up to the average growth standards of their peers. Linear growth occurred markedly slower and it is unclear whether complete linear catch-up can be achieved. Improvements in growth may help to slow disease progression and reduce pediatric morbidity and HIV-related mortality. Finally, food supplementation and multivitamin use may influence the rate of growth reconstitution following HAART. Complementary to the improved survival observed in the CHER study [45], these results emphasize the need for early identification and treatment in HIV-1-infected children as a means by which to prevent or restore growth faltering at the same time as improving childhood survival. Furthermore, these results suggest the need for clinical trials to determine optimal nutritional supplementation regimens for improving growth and morbidity in HIV-1-infected children on HAART in resource-limited settings.

Acknowledgments

The Coptic Hope Center for Infectious Diseases is supported by the President's Emergency Plan for AIDS Relief (PEPFAR) through a cooperative agreement (U62/CCU024512-04) from the US Centers for Disease Control and Prevention (CDC). The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the CDC. C.J.M. is supported by the National Center for Research Resources, a component of the National Institutes of Health (NIH) (TL1RR025016). Other funding sources for this study include a K23 grant (AI065222-04), a K24 grant (HD054314), and support by the NIH funded program, University of Washington Center for AIDS Research (CFAR) (P30 AI027757). We would like to thank the research personnel, clinic staff, and data management teams in Nairobi, Kenya and Seattle, Washington; the Coptic Hope Center for Infectious Diseases for their participation and cooperation.

References

1. UNAIDS. , editor. UNAIDS. Paediatric HIV infection and AIDS: UNAIDS point of view. Geneva, Switzerland: UNAIDS; 2002 Sep. p. 8
2. WHO. Early detection of HIV infection in infants and children. Geneva, Switzerland: WHO; 2007 May.
3. Arpadi SM. Growth failure in children with HIV infection. *J Acquir Immune Defic Syndr*. 2000; 25(Suppl 1):S37–S42. [PubMed: 11126424]
4. McKinney RE Jr, Robertson JW. Effect of human immunodeficiency virus infection on the growth of young children. Duke Pediatric AIDS Clinical Trials Unit. *J Pediatr*. 1993; 123:579–582. [PubMed: 8410511]
5. Miller TL, Evans SJ, Orav EJ, Morris V, McIntosh K, Winter HS. Growth and body composition in children infected with the human immunodeficiency virus-1. *Am J Clin Nutr*. 1993; 57:588–592. [PubMed: 8460616]
6. Nachman SA, Lindsey JC, Moye J, Stanley KE, Johnson GM, Krogstad PA, Wiznia AA. Growth of human immunodeficiency virus-infected children receiving highly active antiretroviral therapy. *Pediatr Infect Dis J*. 2005; 24:352–357. [PubMed: 15818296]
7. Mahlungulu S, Grobler LA, Visser ME, Volmink J. Nutritional interventions for reducing morbidity and mortality in people with HIV. *Cochrane Database Syst Rev*. 2007 CD004536.
8. Anabwani G, Navario P. Nutrition and HIV/AIDS in sub-Saharan Africa: an overview. *Nutrition*. 2005; 21:96–99. [PubMed: 15661483]
9. Verweel G, van Rossum AM, Hartwig NG, Wolfs TF, Scherpbier HJ, de Groot R. Treatment with highly active antiretroviral therapy in human immunodeficiency virus type 1-infected children is associated with a sustained effect on growth. *Pediatrics*. 2002; 109:E25. [PubMed: 11826235]
10. Kekitiinwa A, Lee KJ, Walker AS, Maganda A, Doerholt K, Kitaka SB, et al. Differences in factors associated with initial growth, CD4, and viral load responses to ART in HIV-infected children in Kampala, Uganda, and the United Kingdom/Ireland. *J Acquir Immune Defic Syndr*. 2008; 49:384–392. [PubMed: 18931630]

11. Wamalwa DC, Farquhar C, Obimbo EM, Selig S, Mbori-Ngacha DA, Richardson BA, et al. Early response to highly active antiretroviral therapy in HIV-1-infected Kenyan children. *J Acquir Immune Defic Syndr*. 2007; 45:311–317. [PubMed: 17356470]
12. De Beaudrap P, Rouet F, Fassinou P, Kouakoussui A, Mercier S, Ecochard R, Msellati P. CD4 cell response before and after HAART initiation according to viral load and growth indicators in HIV-1-infected children in Abidjan, Cote d'Ivoire. *J Acquir Immune Defic Syndr*. 2008; 49:70–76. [PubMed: 18667922]
13. Kabue MM, Kekitiinwa A, Maganda A, Risser JM, Chan W, Kline MW. Growth in HIV-infected children receiving antiretroviral therapy at a pediatric infectious diseases clinic in Uganda. *AIDS Patient Care STDS*. 2008; 22:245–251. [PubMed: 18298315]
14. Bolton-Moore C, Mubiana-Mbewe M, Cantrell RA, Chintu N, Stringer EM, Chi BH, et al. Clinical outcomes and CD4 cell response in children receiving antiretroviral therapy at primary healthcare facilities in Zambia. *JAMA*. 2007; 298:1888–1899. [PubMed: 17954540]
15. Chantry CJ, Byrd RS, Englund JA, Baker CJ, McKinney RE Jr. Growth, survival and viral load in symptomatic childhood human immunodeficiency virus infection. *Pediatr Infect Dis J*. 2003; 22:1033–1039. [PubMed: 14688560]
16. Lindsey JC, Hughes MD, McKinney RE, Cowles MK, Englund JA, Baker CJ, et al. Treatment-mediated changes in human immunodeficiency virus (HIV) type 1 RNA and CD4 cell counts as predictors of weight growth failure, cognitive decline, and survival in HIV-infected children. *J Infect Dis*. 2000; 182:1385–1393. [PubMed: 11010839]
17. Denny T, Yogev R, Gelman R, Skuza C, Oleske J, Chadwick E, et al. Lymphocyte subsets in healthy children during the first 5 years of life. *JAMA*. 1992; 267:1484–1488. [PubMed: 1347086]
18. Shearer WT, Quinn TC, LaRussa P, Lew JF, Mofenson L, Almy S, et al. Viral load and disease progression in infants infected with human immunodeficiency virus type 1. Women and Infants Transmission Study Group. *N Engl J Med*. 1997; 336:1337–1342. [PubMed: 9134873]
19. Englund JA, Baker CJ, Raskino C, McKinney RE, Petrie B, Fowler MG, et al. Zidovudine, didanosine, or both as the initial treatment for symptomatic HIV-infected children. AIDS Clinical Trials Group (ACTG) Study 152 Team. *N Engl J Med*. 1997; 336:1704–1712. [PubMed: 9182213]
20. USAID Bureau for Democracy CHA. , editor. USAID. Food aid programs and the President's emergency plan for AIDS relief: HIV and food security conceptual framework. USAID; 2007 Sep.
21. Chung MH, Drake AL, Richardson BA, Reddy A, Thiga J, Sakr SR, et al. Impact of prior HAART use on clinical outcomes in a large Kenyan HIV treatment program. *Curr HIV Res*. 2009; 7:441–446. [PubMed: 19601781]
22. WHO. Recommendations for a public health approach. Geneva, Switzerland: WHO Press; 2006. Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access; p. 152
23. de Onis M, Garza C, Victora CG, Onyango AW, Frongillo EA, Martines J. The WHO Multicentre Growth Reference Study: planning, study design, and methodology. *Food Nutr Bull*. 2004; 25:S15–S26. [PubMed: 15069916]
24. Miller TL, Agostoni C, Duggan C, Guarino A, Manary M, Velasco CA. Gastrointestinal and nutritional complications of human immunodeficiency virus infection. *J Pediatr Gastroenterol Nutr*. 2008; 47:247–253. [PubMed: 18664883]
25. Canani RB, Spagnuolo MI, Cirillo P, Guarino A. Ritonavir combination therapy restores intestinal function in children with advanced HIV disease. *J Acquir Immune Defic Syndr*. 1999; 21:307–312. [PubMed: 10428109]
26. Group TIPIHS. Intestinal malabsorption of HIV-infected children: relationship to diarrhoea, failure to thrive, enteric micro-organisms and immune impairment. *AIDS*. 1993; 7:1435–1440. [PubMed: 8280408]
27. Quesnel A, Moja P, Blanche S, Griscelli C, Genin C. Early impairment of gut mucosal immunity in HIV-1-infected children. *Clin Exp Immunol*. 1994; 97:380–385. [PubMed: 7915975]
28. Pernet P, Vittecoq D, Kodjo A, Randrianarisolo MH, Dumitrescu L, Blondon H, et al. Intestinal absorption and permeability in human immunodeficiency virus-infected patients. *Scand J Gastroenterol*. 1999; 34:29–34. [PubMed: 10048729]

29. Campbell DI, Elia M, Lunn PG. Growth faltering in rural Gambian infants is associated with impaired small intestinal barrier function, leading to endotoxemia and systemic inflammation. *J Nutr.* 2003; 133:1332–1338. [PubMed: 12730419]
30. Gafni RI, Baron J. Catch-up growth: possible mechanisms. *Pediatr Nephrol.* 2000; 14:616–619. [PubMed: 10912529]
31. Kay's SK, Hindmarsh PC. Catch-up growth: an overview. *Pediatr Endocrinol Rev.* 2006; 3:365–378. [PubMed: 16816805]
32. Boersma B, Houwen RH, Blum WF, van Doorn J, Wit JM. Catch-up growth and endocrine changes in childhood celiac disease. Endocrine changes during catch-up growth. *Horm Res.* 2002; 58(Suppl 1):57–65. [PubMed: 12373016]
33. Walters TD, Griffiths AM. Mechanisms of growth impairment in pediatric Crohn's disease. *Nat Rev Gastroenterol Hepatol.* 2009; 6:513–523. [PubMed: 19713986]
34. Wit JM, Boersma B. Catch-up growth: definition, mechanisms, and models. *J Pediatr Endocrinol Metab.* 2002; 15(Suppl 5):1229–1241. [PubMed: 12510974]
35. Steiner F, Kind C, Aebi C, Wyler-Lazarevitch CA, Cheseaux JJ, Rudin C, et al. Growth in human immunodeficiency virus type 1-infected children treated with protease inhibitors. *Eur J Pediatr.* 2001; 160:611–616. [PubMed: 11686506]
36. Arpadi SM, Horlick M, Thornton J, Cuff PA, Wang J, Kotler DP. Bone mineral content is lower in prepubertal HIV-infected children. *J Acquir Immune Defic Syndr.* 2002; 29:450–454. [PubMed: 11981360]
37. Arpadi SM, McMahon D, Abrams EJ, Bamji M, Purswani M, Engelson ES, et al. Effect of bimonthly supplementation with oral cholecalciferol on serum 25-hydroxyvitamin D concentrations in HIV-infected children and adolescents. *Pediatrics.* 2009; 123:e121–e126. [PubMed: 19117833]
38. O'Brien KO, Razavi M, Henderson RA, Caballero B, Ellis KJ. Bone mineral content in girls perinatally infected with HIV. *Am J Clin Nutr.* 2001; 73:821–826. [PubMed: 11273859]
39. Rosso R, Vignolo M, Parodi A, Di Biagio A, Sormani MP, Bassetti M, et al. Bone quality in perinatally HIV-infected children: role of age, sex, growth, HIV infection, and antiretroviral therapy. *AIDS Res Hum Retroviruses.* 2005; 21:927–932. [PubMed: 16386108]
40. Jacobson DL, Spiegelman D, Duggan C, Weinberg GA, Bechard L, Furuta L, et al. Predictors of bone mineral density in human immunodeficiency virus-1 infected children. *J Pediatr Gastroenterol Nutr.* 2005; 41:339–346. [PubMed: 16131991]
41. Amadi B, Mwiya M, Chomba E, Thomson M, Chintu C, Kelly P, Walker-Smith J. Improved nutritional recovery on an elemental diet in Zambian children with persistent diarrhoea and malnutrition. *J Trop Pediatr.* 2005; 51:5–10. [PubMed: 15601655]
42. Hsu, J.; Pencharz, PB.; Macallan, D.; Tomkins, A. *Macronutrients an HIV/AIDS: a review of current evidence.* Geneva, Switzerland: WHO; 2005. p. 41
43. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *BMJ.* 2000; 320:967–971. [PubMed: 10753147]
44. Dulloo AG. Thrifty energy metabolism in catch-up growth trajectories to insulin and leptin resistance. *Best Pract Res Clin Endocrinol Metab.* 2008; 22:155–171. [PubMed: 18279786]
45. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med.* 2008; 359:2233–2244. [PubMed: 19020325]

Fig. 1. Kaplan–Meier estimates of the cumulative proportion of HIV-1-infected children with catch-up growth (Z-score ≥ 0) by age at HAART initiation

Hazard ratios are listed from Cox proportional hazards regression models examining the effect of age at HAART initiation on catch-up growth (Z-score ≥ 0), adjusting for baseline growth indices (WAZ, WHZ or HAZ). HAART, highly active antiretroviral therapy; HAZ, height-for-age Z-score; WAZ, weight-for-age Z-score; WHZ, weight-for-height Z-score.

Fig. 2. Scatter plot of change in growth indices over time by age at HAART initiation
 Lowest curves represent growth reconstitution following HAART, by age at HAART initiation. HAART, highly active antiretroviral therapy.

Table 1

Description of the cohort of HIV-1-infected children initiating HAART.

	Median (IQR) or N (%)	<i>n</i> ^a
Baseline characteristics		
Age (years)	4.7 (2.4, 7.0)	173
<3 years	52 (30)	173
3–5 years	62 (36)	173
6–10 years	59 (34)	173
Female sex	85 (49)	173
Hospitalized in last year	43 (26)	164
WHO clinical stage 3 or 4	72 (42)	171
CD4 cell count below normal for age ^b	90 (62)	145
Underweight (WAZ <−2)	81 (48)	169
Wasted (WHZ <−2)	38 (25)	151
Stunted (HAZ <−2)	81 (48)	169
Weight-for-age Z-score (WAZ)	−1.9 (−3.0, −1.0)	169
Weight-for-height Z-score (WHZ)	−0.8 (−2.0, 0.2)	151
Height-for-age Z-score (HAZ)	−2.0 (−3.1, −1.0)	169
Sociodemographic characteristics		
Family member on HAART	52 (32)	161
Mother deceased	38 (24)	159
Three or more children in household	53 (34)	157
Electricity in home	90 (65)	139
Piped water in home	93 (67)	139
Follow-up characteristics		
Multivitamin use	130 (76)	171
Food supplements	83 (48)	173
Child deaths	12 (7)	173
Children lost during follow-up	7 (4)	173
Duration of follow-up, months	19 (9, 28)	173
NNRTI-based HAART regimen	165 (95)	173
Time to HAART (days)	37 (25, 64)	173

HAART, highly active antiretroviral therapy; IQR, interquartile range; WHO, World Health Organization.

^aNumber of children for whom data was available.^bBased on World Health Organization criteria, the following thresholds were considered below normal for age: below 12 months, CD4 cell count below 1500 cells/μl; 12–35 months, CD4 cell count below 750 cells/μl; 36–59 months, CD4 cell count below 350 cells/μl; and at least 5 years, CD4 cell count below 200 cells/μl [22].

Table 2

Correlates of baseline underweight, wasting, and stunting in HIV-1 infected children prior to HAART.

	Underweight (WAZ <-2)			Wasting (WHZ <-2)			Stunting (HAZ <-2)		
	OR	(95% CI)	P value	OR	(95% CI)	P value	OR	(95% CI)	P value
Baseline characteristics									
Age at HAART initiation									
<3 years	1.11	(0.52, 2.37)	0.79	1.67	(0.69, 4.02)	0.26	1.39	(0.65, 2.96)	0.39
3–5 years	0.55	(0.26, 1.13)	0.10	0.26	(0.09, 0.77)	0.02	0.97	(0.47, 1.99)	0.93
6–10 years	1.00	–	–	1.00	–	–	1.00	–	–
WHO clinical stage									
3 or 4	3.19	(1.68, 6.05)	<0.01	2.03	(0.96, 4.28)	0.06	1.65	(0.89, 3.06)	0.11
1 or 2	1.00	–	–	1.00	–	–	1.00	–	–
CD4 cell count									
Below normal for age	1.23	(0.62, 2.42)	0.55	1.83	(0.76, 4.36)	0.18	1.09	(0.55, 2.14)	0.80
Above normal for age	1.00	–	–	1.00	–	–	1.00	–	–
Sociodemographic characteristics									
Family member on HAART									
Yes	0.48	(0.24, 0.96)	0.04	0.43	(0.17, 1.06)	0.07	0.67	(0.34, 1.30)	0.24
No	1.00	–	–	1.00	–	–	1.00	–	–
Mother's status									
Mother deceased	1.16	(0.56, 2.41)	0.68	1.20	(0.48, 3.02)	0.69	1.17	(0.56, 2.43)	0.68
Mother alive	1.00	–	–	1.00	–	–	1.00	–	–
Number of children in home									
3	1.29	(0.66, 2.51)	0.46	0.95	(0.41, 2.22)	0.91	1.53	(0.79, 2.98)	0.21
<3	1.00	–	–	1.00	–	–	1.00	–	–
Piped water in home									
Yes	0.82	(0.40, 1.67)	0.59	1.23	(0.52, 2.95)	0.63	0.46	(0.22, 0.95)	0.04
No	1.00	–	–	1.00	–	–	1.00	–	–
Electricity in home									
Yes	0.72	(0.36, 1.46)	0.37	1.30	(0.55, 3.09)	0.56	0.61	(0.30, 1.23)	0.17
No	1.00	–	–	1.00	–	–	1.00	–	–

CI, confidence interval; HAART, highly active antiretroviral therapy; HAZ, height-for-age Z-score; OR, odds ratio; WAZ, weight-for-age Z-score; WHZ, weight-for-height Z-score.

Table 3
Univariate predictors of monthly change in growth in HIV-1 infected children following HAART initiation.

	Weight-for-age Z-score			Weight-for-height Z-score			Height-for-age Z-score		
	Mean change ^a (95% CI)	P value ^b		Mean change ^a (95% CI)	P value ^b		Mean change ^a (95% CI)	P value ^b	
Baseline characteristics									
Age at HAART initiation									
<3 years	0.07 (0.03, 0.10)	0.001		0.06 (0.02, 0.11)	0.005		0.005 (−0.02, 0.03)	0.72	
3–5 years	0.02 (−0.02, 0.05)	0.33		−0.02 (−0.06, 0.02)	0.36		0.005 (−0.02, 0.03)	0.71	
6–10 years	Reference	–		Reference	–		Reference	–	
WHO clinical stage									
3 or 4	0.03 (0.001, 0.07)	0.05		0.07 (0.03, 0.11)	<0.001		−0.01 (−0.03, 0.02)	0.59	
1 or 2	Reference	–		Reference	–		Reference	–	
CD4 cell count									
Below normal	0.005 (−0.03, 0.04)	0.77		0.004 (−0.04, 0.05)	0.83		0.003 (−0.02, 0.03)	0.81	
Above normal	Reference	–		Reference	–		Reference	–	
Hemoglobin									
<9 g/dl	0.05 (0.02, 0.09)	0.001		0.06 (0.03, 0.10)	0.001		0.005 (−0.02, 0.03)	0.68	
9 g/dl	Reference	–		Reference	–		Reference	–	
Sociodemographic characteristics									
Family member on HAART									
Yes	−0.02 (−0.05, 0.01)	0.19		−0.02 (−0.06, 0.02)	0.37		−0.01 (−0.04, 0.01)	0.30	
No	Reference	–		Reference	–		Reference	–	
Mother's status									
Deceased	−0.02 (−0.06, 0.01)	0.22		−0.03 (−0.08, 0.02)	0.24		−0.003 (−0.03, 0.02)	0.80	
Alive	Reference	–		Reference	–		Reference	–	
Number of children in home									
3	0.01 (−0.02, 0.05)	0.50		0.01 (−0.03, 0.05)	0.54		0.008 (−0.01, 0.03)	0.45	
<3	Reference	–		Reference	–		Reference	–	
Piped water in home									
Yes	−0.01 (−0.05, 0.03)	0.59		0.02 (−0.03, 0.06)	0.44		−0.002 (−0.03, 0.03)	0.91	
No	Reference	–		Reference	–		Reference	–	
Follow-up characteristics									
Food supplements ^c									
Yes	0.06 (0.03, 0.10)	0.001		0.08 (0.02, 0.13)	0.007		0.02 (−0.01, 0.05)	0.17	
No	Reference	–		Reference	–		Reference	–	
Multivitamin use ^c									
Yes	0.01 (−0.01, 0.02)	0.35		0.01 (−0.01, 0.02)	0.33		0.01 (0.003, 0.02)	0.008	
No	Reference	–		Reference	–		Reference	–	

^aValues represent the difference between the mean change in Z-score per month for children with the characteristic compared to the mean change in Z-score per month for children in the reference group.

^bThis P value represents the result of a statistical test of the difference in the average rate of Z-score change between children with and without the characteristic.

c_T Food supplements and multivitamin use were treated as time-varying covariates.

Table 4

Multivariate models of monthly change in growth in HIV-1-infected children following HAART initiation.

	Weight-for-age Z-score			Weight-for-height Z-score			Height-for-age Z-score		
	Mean change ^a (95% CI)	Adjusted P value ^b		Mean change ^a (95% CI)	Adjusted P value ^b		Mean change ^a (95% CI)	Adjusted P value ^b	
Model 1									
Age at HAART initiation									
<3 years	0.05 (0.01, 0.08)	0.01		0.05 (0.01, 0.09)	0.01		-0.01 (-0.04, 0.02)	0.64	
3-5 years	0.02 (-0.02, 0.05)	0.31		-0.002 (-0.04, 0.04)	0.91		0.002 (-0.02, 0.03)	0.88	
6-10 years	Reference	-		Reference	-		Reference	-	
WHO clinical stage									
3 or 4	0.02 (-0.01, 0.05)	0.25		0.05 (0.02, 0.08)	0.003		-0.01 (-0.04, 0.01)	0.36	
1 or 2	Reference	-		Reference	-		Reference	-	
Hemoglobin									
<9 g/dl	0.03 (-0.003, 0.07)	0.08		0.04 (-0.001, 0.07)	0.05		-	-	
9 g/dl	Reference	-		Reference	-		-	-	
Multivitamin use ^a									
Yes	-	-		-	-		0.01 (0.003, 0.02)	0.009	
No	-	-		-	-		Reference	-	
Model 2									
Age at HAART initiation									
<3 years	0.05 (0.01, 0.09)	0.006		0.06 (0.02, 0.10)	0.005		-0.01 (-0.03, 0.02)	0.66	
3-5 years	0.02 (-0.01, 0.05)	0.26		0.001 (-0.04, 0.04)	0.97		0.003 (0.02, 0.03)	0.83	
6-10 years	Reference	-		Reference	-		Reference	-	
WHO clinical stage									
3 or 4	0.02 (-0.01, 0.05)	0.25		0.05 (0.02, 0.08)	0.002		-0.01 (-0.04, 0.01)	0.31	
1 or 2	Reference	-		Reference	-		Reference	-	
Hemoglobin									
<9 g/dl	0.02 (-0.02, 0.05)	0.29		0.03 (-0.01, 0.06)	0.16		-	-	
9 g/dl	Reference	-		Reference	-		-	-	
Food supplements ^c									
Yes	0.06 (0.03, 0.10)	0.001		0.08 (0.03, 0.14)	0.005		0.02 (-0.01, 0.06)	0.15	
No	Reference	-		Reference	-		Reference	-	
Multivitamin use ^c									
Yes	-	-		-	-		0.01 (0.004, 0.02)	0.003	
No	-	-		-	-		Reference	-	

^aValues represent the difference between the mean change in Z-score per month for children with the characteristic compared to the mean change in Z-score per month for children in the reference group after adjusting for other variables listed in the model, baseline growth (WAZ, WHZ or HAZ) and duration of follow-up.

^bThis P value represents the result of a statistical test of the difference in the adjusted average rates of change in growth between children with and without the characteristic.

c_T Food supplements and multivitamin use were treated as time-varying covariates.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript