Published in final edited form as:

Trop Med Int Health. 2010 August ; 15(8): 934–944. doi:10.1111/j.1365-3156.2010.02561.x.

Growth response to antiretroviral treatment in HIV-infected children: A cohort study from Lilongwe, Malawi

Ralf Weigel¹, Sam Phiri², Fred Chiputula², Joe Gumulira², Martin Brinkhof³, Thomas Gsponer³, Hannock Tweya², Matthias Egger³, and Olivia Keiser³

¹Ministry of Health and Lighthouse Trust at Kamuzu Central Hospital, Lilongwe, Malawi

²Lighthouse Trust at Kamuzu Central Hospital, Lilongwe, Malawi ³International epidemiological Databases to Evaluate AIDS in Southern Africa (IeDEA-SA), Institute for Social and Preventive Medicine, University of Bern, Switzerland

Summary

Objective—Malnutrition is common in HIV-infected children in Africa and an indication for antiretroviral treatment (ART). We examined anthropometric status and response to ART in children treated at a large public-sector clinic in Malawi.

Methods—All children aged <15 years who started ART between January 2001 and December 2006 were included and followed until March 2008. Weight and height were measured at regular intervals from 1 year before to 2 years after the start of ART. Sex- and age-standardized z-scores were calculated for weight-for-age (WAZ) and height-for-age (HAZ). Predictors of growth were identified in multivariable mixed-effect models.

Results—A total of 497 children started ART and were followed for 972 person-years. Median age (inter-quartile range; IQR) was 8 years (4 to 11 years). Most children were underweight (52% of children), stunted (69%), in advanced clinical stages (94% in WHO stages 3 or 4) and had severe immunodeficiency (77%). After starting ART median (IQR) WAZ and HAZ increased from −2.1 (−2.7 to −1.3) and −2.6 (−3.6 to −1.8) to −1.4 (−2.1 to −0.8) and −1.8 (−2.4 to −1.1) at 24 months, respectively ($p < 0.001$). In multivariable models, baseline WAZ and HAZ scores were the most important determinants of growth trajectories on ART.

Conclusions—Despite a sustained growth response to ART among children remaining on therapy, normal values were not reached. Interventions leading to earlier HIV diagnosis and initiation of treatment could improve growth response.

Keywords

children; HIV infection; growth; antiretroviral therapy; Malawi

Introduction

Growth monitoring identifies HIV-infected children eligible for ART and helps to assess their response to ART (WHO 2006; Benjamin, Jr. et al. 2004b). Studies on growth response to ART from resource-limited settings have only been published recently (Bandyopadhyay & Bhattacharyya 2008; Kabue et al. 2008; Kekitiinwa et al. 2008; Bolton-Moore et al. 2007). Several studies from sub-Saharan Africa described positive short-term responses of

weight-for-age z-scores (WAZ) and length/height-for-age z-scores (HAZ) to ART (Song et al. 2007; Walker et al. 2007; Wamalwa et al. 2007; Ellis & Molyneux 2007; Fassinou et al. 2004). However, only few studies reported growth response to ART beyond 12 months (Kabue et al. 2008; Bolton-Moore et al. 2007; Nyandiko et al. 2006). Of note, growth response in the first year of ART was less pronounced in children treated in Uganda than in children who started ART in the United Kingdom and Ireland, despite similar virological and immunological control (Kekitiinwa et al. 2008). In India the growth response over 18 months of ART was less pronounced in malnourished children than in children with normal nutritional status (Bandyopadhyay & Bhattacharyya 2008).

In 2005, Malawi had an adult HIV prevalence of 12.4% and 239,000 adults and 19,000 children below 15 years of age were in need of ART (Ministry of Health of Malawi 2008). The prevalences of underweight and stunting in children under five years in the Lilongwe district were 24%, and 52.3% respectively (National Statistical Office (NSO) [Malawi] & ORC Macro 2005). Studies from Malawi highlight the high prevalence of HIV infection in children with severe acute malnutrition (Heikens et al. 2008; Thurstans et al. 2008; Kessler et al. 2000), their high mortality associated with HIV (Chinkhumba et al. 2008; Fergusson et al. 2008) and malnutrition as a risk factor for death in HIV-infected children not on ART and on ART (3Cs4kids collaboration 2008; Bong et al. 2007; Laufer et al. 2006). More information is needed about growth response beyond 12 months on ART in children with and without malnutrition and the predictors of this response under routine public-sector service conditions.

Methods

Setting

Lighthouse is part of Kamuzu Central Hospital (KCH), the tertiary health facility for the central region of Malawi and its capital, Lilongwe. It provides HIV testing and counselling, clinical and community home based care for adults and children. ART was at cost until it became free in June 2004 through the national programme. After HIV-infected patients have registered and provided basic demographic information including place of residence at the clinic reception, clinicians diagnose and treat opportunistic infections, prescribe Cotrimoxazole prophylaxis and assess patients for ART eligibility according to national guidelines (Ministry of Health of Malawi 2003, 2006b). Children aged <15 years with WHO stages 3 and 4 or absolute or relative CD4 count below the age-dependent threshold for severe immunosuppression (WHO 2006) are started on ART as soon as caregivers have attended a group education session. Until December 2003, a weight-band based regimen of AZT, 3TC and NVP, in form of generic syrups, capsules and split tablets and from January 2004, a combination of generic adult split tablets of d4T/3TC and NVP tablets was used as initial therapy. For the first 6 months children in stable health condition visit the clinic monthly, thereafter 2-monthly. Patients' outcomes (alive and on ART, dead, stopped ART for any reason, transfer-out to another ART facility and lost to follow-up) are updated at least quarterly. Patients not eligible for ART are followed up less frequently, usually every 2–3 months, and receive Cotrimoxazole prophylaxis. Children aged <15 years comprise about 5% of registered patients.

Data collection

Clinic aids measured weight and height at every visit with a weekly calibrated mechanical weighing scale and a height scale (both Fa. Seca, Germany). They referred to standard weight-for-height look-up tables according to the NCHS/CDC/WHO reference to identify children with acute malnutrition, and entered the results in patients' files and patient-held health passports. Children with acute malnutrition received ready-to-use food as plumpy-

nut, a high calorie commercial peanut butter therapeutic food supplement. Severe cases were admitted to the nutritional rehabilitation unit at KCH (Ministry of Health of Malawi 2006a). Between 2002 and 2004 a data clerk entered key clinical information including weight, height and outcomes into an MS Access database. Since 2005 an electronic data system with touch-screens and real-time data entry was used. In 2006, we merged the data from the two sources and started tracing patients who missed their appointments. Children who never started ART were not traced.

Inclusion criteria and definitions

All children younger than 15 years at ART initiation with a first visit and documented ART start date between 1st January 2001 and 31st December 2006 were included in the study. Data until 31st March 2008 were analysed. We excluded children who were transferred from another ART site and for whom the ART start date was unknown. A child was considered lost to follow-up if the time between the last visit of the child and the closing date of the cohort on 31st of March 2008 was longer than 3 months. Weight and height measurements were converted into age- and sex-adjusted z-scores using data of the NCHS/CDC/WHO international reference population (Hamill et al. 1977) and underweight was defined as weight-for-age (WAZ) <-2 and stunting as height-for-age (HAZ) <-2. In sensitivity analyses we used the WHO reference data (WHO 2010a,b) for weight for age up to 10 years and for height for age.

Z-scores below or above 10 were deemed erroneous and excluded from the analysis. In addition we inspected individual trajectories over time and deleted values that were clearly inconsistent. We took weight and height measurements and WHO clinical staging closest to the starting date of ART (within 3 months) as baseline values. For CD4 cell counts the post-ART window was restricted to 1 week after start of ART. CD4 cell percentages were grouped into the categories 'severe', 'moderate' and 'no suppression' according to WHO criteria (WHO 2004).

Statistical analysis

Medians and interquartile ranges of WAZ, HAZ and CD4 percentage were calculated from start of ART up to two years. The trajectories of the anthropometric measurements on ART over time were analyzed using the best-fitting second order fractional polynomials with WAZ and HAZ as outcomes in mixed-effect models (Royston & Altman 1994). All available weight and height measurements from start of ART up to the last follow-up visit (including patients who were lost to follow-up, who were transferred out or who died) were included in the analysis, provided the child had all baseline variables and at least one subsequent weight or height measurement recorded.

The model included the following co-variables: sex, age (<2, 2–4, 5–9, 10 years), baseline WAZ and HAZ (–3, >–3 to –2, >–2 to –1, >–1), baseline WHO clinical stage, degree of immunodeficiency and time period of ART start. The years before June 2004 were combined in one category as the patients had to pay for ART during this period. We also included coefficients for the interaction between time and baseline z-scores since it can be expected that children with low baseline z-scores will have steeper trajectories than children with high baseline z-scores. Random effects per child were considered for the coefficients of the fractional polynomial to account for the correlation of repeated measurements within the same child and the heterogeneity of children's trajectories. The model was fit using a fully probabilistic approach (see Appendix for further details). The model fit was visually assessed by plotting the predicted median with 95% prediction intervals and the observed trajectories for individual children over time. In a sensitivity analysis missing values of stage of disease and degree of immunodeficiency at start of antiretroviral therapy were imputed.

We used multinomial regression models with stage of disease and degree of immunodeficiency as outcome and age, sex, year of starting ART and WAZ at start of ART as predictors. Missing data were imputed by randomly sampling from the corresponding predictive multinomial distribution.

All analyses were done in Stata version 10.2 (College Station, Texas, USA), R (The R Development Core Team. 2009) and WinBUGS (Lunn et al. 2010).

Ethical approval

The National health sciences research committee of Malawi gave permission to analyse and disseminate these data, which were collected during routine care.

Results

Study population and baseline characteristics

The selection of the children and their contribution to different analyses is shown in Figure 1. Since 2001, a total of 1,024 HIV-infected children aged <15 years had at least one visit at the Lighthouse clinic and 497 children started ART. Among the 527 children who did not start ART, two (0.4%) were transferred out, 489 (92.8%) were lost to follow up and 36 (6.8%) are still under follow up. After starting ART, 21 (4.3%) children died, 140 (28.2%) were lost to follow up and 136 (27.4%) were transferred out. Table 1 shows the characteristics of the 497 children at ART initiation. Median age was 8 years (IQR 4–11 years) and about one-third were 10 years or older. The majority lived in the city of Lilongwe or in Lilongwe district. Most children were severely immunosuppressed, in WHO clinical stage 3 or 4, underweight and stunted.

Anthropometric measurements

At least one weight or height measurement was recorded for 450 (90.5%) and 441 (88.7%) of children, respectively. The median number of weight measurements before starting ART was 3 (IQR 2–5), and it was 15 (IQR 6–22) thereafter. For height, the corresponding numbers were 2 (IQR 1–4) and 7 (3–10). The 497 children included in the analysis contributed 8,030 weight measurements and 4,281 height measurements. The time on ART was 972 person-years overall, 916 person-years in the analysis of weights and 908 person-years in the analysis of heights. Patients without any weights or heights (n=47) were more likely to have started ART before June 2004 (40.4% versus 16.0%, $p<0.001$) and their duration on ART was shorter (8 months versus 25 months, $p<0.001$). The other characteristics were similar. Of these children, 2 (4.3%) died, 13 (27.7%) were transferred out and 32 (68.1%) were lost to follow-up.

Growth and CD4 cell response

During the year before starting ART WAZ and HAZ scores were fairly stable, with median (IQR) scores at ART initiation of -2.1 (-2.7 to -1.3) and -2.6 (-3.6 to -1.8), respectively. After starting ART catch up growth was observed. Median (IQR) WAZ increased to -1.4 (-2.1 to -0.8) ($p<0.001$) and HAZ to -1.8 (-2.4 to -1.1) ($p<0.001$) at 24 months. Overall 691 CD4 cell percentage values were recorded after the start of ART (median number of 1 value (IQR 0–3) per child). The median (IQR) CD4 percent increased from 10.8% (7.2% to 15.7%) at month 0 to 26.9% (17.5% to 33.9%) at month 24 ($p<0.001$).

Predictors of growth response

Table 2 shows the predictors of growth response from the analysis that included children with complete data only (complete case analysis) and the analysis using multiple imputation

to fill in missing values. Figure 2 shows the predicted trajectories from the model together with the observed medians. The model parameters are presented in full in the Appendix. The main effects listed in Table 2 correspond to a vertical shift of the z-score trajectories compared to the baseline category, for WAZ and HAZ. In summary, a low z-score at the start of ART was the most important predictor for later growth response. Children who were stunted or wasted at the start of antiretroviral therapy did not reach normal values within the 2-year study period.

Children with missing CD4 and clinical stage at baseline were more likely to have started ART in the year 2006 (33% versus 14%, $p=0.001$) and they were followed for a shorter time (13 months versus 27 months, $p<0.001$). Imputation of missing values of baseline stage of disease and degree of immunodeficiency or the use of the WHO growth reference data (results not shown) did not materially alter the results: although girls have a slightly higher weight-for-age z-score at start of antiretroviral therapy after multiple imputation, the effect is small compared to the effect of the baseline z-score (Table 2).

Trajectories of z-scores for individual children

Figure 3 shows individual growth trajectories of WAZ and HAZ together with the predicted median and 95% prediction intervals by baseline z-score. Although there is some variability between children, overall response patterns are similar between children. The four panels in Figure 3 illustrate the interaction between time and baseline WAZ and HAZ. The trajectories differ across categories of baseline z-scores. In general, children with the lowest baseline z-score category show the steepest increase in their trajectories after starting ART, and the strongest attenuation over time. This effect is more pronounced for weight than for height.

Discussion

This cohort study of children starting ART in Lilongwe, Malawi, found that about half of the children were underweight and two-thirds were stunted when initiating therapy. Median WAZ and HAZ increased with ART, but underweight and stunted children did not reach normal growth after 2 years on ART. In children who started with WAZ and HAZ scores of less than -3 , catch up on growth was better than in children with less depressed growth at baseline. In multivariable analysis, low z-scores at ART initiation were the most important predictor for growth response. Conversely, there was little evidence for an association of growth response with age, sex, the degree of immunodeficiency at baseline or clinical stage.

As in other African cohorts, children started ART with advanced disease and median WAZ and HAZ scores at ART initiation were also similar to previous studies (Arrive et al. 2008; Bandyopadhyay & Bhattacharyya 2008; Sutcliffe et al. 2008). Other studies in Africa also showed an increase of WAZ and HAZ (Fassinou et al. 2004; Song et al. 2007; Walker et al. 2007; Wamalwa et al. 2007) without reaching normal values. In our study this was also the case, despite observing growth over an extended period of time. In contrast, in a study of ART-naïve children in the United States normal WAZ and HAZ were reached after one and two years of ART, respectively (Nachman et al. 2005), but baseline z-scores were much higher. A European study (Guillen et al. 2007), which enrolled predominantly children who were not ART-naïve, showed that it took five years to reach normal WAZ, and HAZ did not reach normal values. Further studies are needed to define how long it takes to reach normal z-scores in African settings. We did not have access to viral load measurements, but all our patients were ART-naïve and, based on the immunological response, may have had sustained virological suppression. Indeed, growth response has been proposed as a surrogate marker for viral suppression in children treated in resource-limited settings (Benjamin, Jr. et al. 2003, 2004a,b). Suppression of viral replication and prevention of opportunistic

infections through successful ART allows substantial catch up growth, at least in the large proportion of underweight and stunted children, but this needs confirmation in studies with viral load measurements.

Our results show that severely undernourished and stunted children benefit most from ART in terms of catch up growth. In contrast, a study from India showed that lower WAZ and HAZ scores at baseline were associated with poorer growth response (Bandyopadhyay & Bhattacharyya 2008). A study comparing children from Uganda and the United Kingdom and Ireland (Kekitiinwa et al. 2008) found that the median change in HAZ after 12 months on ART was smaller in children treated in Uganda with differences being attributed to lower baseline levels in Ugandan children. Better access to food among children treated at Lighthouse, better virological control and the prevention and prompt treatment of opportunistic infections as well as the longer observation of the children in Lilongwe might explain the discrepant results. In the absence of data on food security and viral load, this explanation remains speculative, however. Also in contrast to earlier studies (Bolton-Moore et al. 2007; Nachman et al. 2005) we did not find that growth response was associated with age.

WHO clinical stage did not influence growth in our cohort. To our knowledge clinical stage at baseline and growth on ART has not been examined previously in African children. Results from European studies are conflicting: Clinical CDC stage did not predict WAZ scores (Guillen et al. 2007; Verweel et al. 2002) but HAZ response was worse in children in clinical stage C compared to children with less advanced disease in a Spanish study (Guillen et al. 2007), but not in a small study from Switzerland (Steiner et al. 2001). In contrast to findings from Uganda (Kekitiinwa et al. 2008), the degree of immunodeficiency was not associated with growth response in our cohort. Similarly, studies from the US and Europe failed to show that baseline CD4 count predicted HAZ response to ART and analyses correlating changes in CD4 count with changes in HAZ scores showed conflicting results (Nachman et al. 2005; Verweel et al. 2002; Steiner et al. 2001). Due to the limited amount of data we were not able to examine the association between CD4 percentage or change in CD4 cell counts and growth.

Our study has a number of limitations. First, the proportion of missing data was relatively high. Faced with substantial increases in patient numbers health care workers in Malawi must focus on service provision, and time for documentation is limited (Muula et al. 2007). Results were, however, similar when filling in missing values for clinical stage and degree of immunodeficiency by multiple imputation. Second, a high proportion of children were lost to follow-up or transferred to another clinic. The growth response of these children may well differ from the response in the children who remained in care. We therefore stress that our results are applicable only to children who remained under observation and care. Third, with a median age of 8 years at ART start, our cohort consists mainly of surviving children and our results are less applicable to infants and young children, which increasingly access ART in sub Saharan Africa. The National therapeutic feeding programme in Malawi provides ready-to-use food to patients with acute moderate malnutrition (children with weight-for-height 70–79% of the median of the NCHS/CDC/WHO reference population). Overworked staff in ART clinics may perceive the use of tables and charts to determine growth indicators as too time-consuming if children are not acutely malnourished, and therefore not eligible for therapeutic feeding. In this situation many chronically malnourished children who would be eligible for ART according to the National guidelines (Ministry of Health of Malawi 2003,2006b) will not receive it, with their nutritional status deteriorating further, to the point that it may no longer be reversible on ART. Pre-ART services should receive more attention: HIV-exposed infants with unknown HIV-status

should be registered and followed up in ART clinics and their growth monitored (Filteau 2009).

In conclusion, our results should motivate health workers in Malawi and elsewhere to consistently monitor growth indicators, both to establish eligibility for ART in a timely fashion and to monitor response to ART. This requires the correct ascertainment of date of birth, regular and accurate measurements of weight and height, and comparison to weight-for-age and height-for-age reference charts, and careful documentation of these results.

Acknowledgments

We thank all children and care givers and all staff at the Lighthouse clinic and Mary Ann Davies and Lynne Mofenson for their very helpful comments. The work was funded by the Ministry of Health of Malawi and the Office of AIDS Research (OAR) of the National Institutes of Health and the National Institute of Allergy and Infectious Diseases. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. 3Cs4kids collaboration. Markers for predicting mortality in untreated HIV-infected children in resource-limited settings: a meta-analysis. *AIDS*. 2008; 22:97–105. [PubMed: 18090397]
2. Arrive E, Kyabayinze DJ, Marquis B, et al. Cohort profile: the paediatric antiretroviral treatment programmes in lower-income countries (KIDS-ART-LINC) collaboration. *Int.J.Epidemiol*. 2008; 37:474–480. [PubMed: 17998240]
3. Bandyopadhyay A, Bhattacharyya S. Effect of pre-existing malnutrition on growth parameters in HIV-infected children commencing antiretroviral therapy. *Ann.Trop.Paediatr*. 2008; 28:279–285. [PubMed: 19021944]
4. Benjamin DK Jr, Hirschfeld S, Cunningham CK, McKinney RE Jr. Growth as a part of the composite endpoint in paediatric antiretroviral clinical trials. *J.Antimicrob.Chemother*. 2004a; 54:701–703. [PubMed: 15355940]
5. Benjamin DK Jr, Miller WC, Benjamin DK, et al. A comparison of height and weight velocity as a part of the composite endpoint in pediatric HIV. *AIDS*. 2003; 17:2331–2336. [PubMed: 14571184]
6. Benjamin DK Jr, Miller WC, Ryder RW, et al. Growth patterns reflect response to antiretroviral therapy in HIV-positive infants: potential utility in resource-poor settings. *AIDS Patient Care STDS*. 2004b; 18:35–43. [PubMed: 15006193]
7. Bolton-Moore C, Mubiana-Mbewe M, Cantrell RA, et al. Clinical outcomes and CD4 cell response in children receiving antiretroviral therapy at primary health care facilities in Zambia. *JAMA*. 2007; 298:1888–1899. [PubMed: 17954540]
8. Bong CN, Yu JK, Chiang HC, et al. Risk factors for early mortality in children on adult fixed-dose combination antiretroviral treatment in a central hospital in Malawi. *AIDS*. 2007; 21:1805–1810. [PubMed: 17690580]
9. Chinkhumba J, Tomkins A, Banda T, Mkangama C, Fergusson P. The impact of HIV on mortality during in-patient rehabilitation of severely malnourished children in Malawi. *Trans.R.Soc.Trop.Med.Hyg*. 2008; 102:639–644. [PubMed: 18534649]
10. Ellis J, Molyneux EM. Experience of anti-retroviral treatment for HIV-infected children in Malawi: the 1st 12 months. *Ann.Trop.Paediatr*. 2007; 27:261–267. [PubMed: 18053342]
11. Fassinou P, Elenga N, Rouet F, et al. Highly active antiretroviral therapies among HIV-1-infected children in Abidjan, Cote d'Ivoire. *AIDS*. 2004; 18:1905–1913. [PubMed: 15353976]
12. Fergusson P, Chinkhumba J, Grijalva-Eternod C, et al. Nutritional recovery in HIV infected and uninfected children with severe acute malnutrition. *Arch.Dis.Child*. 2008
13. Filteau S. The HIV-exposed, uninfected African child. *Trop.Med Int.Health*. 2009; 14:276–287. [PubMed: 19171011]
14. Guillen S, Ramos JT, Resino R, Bellon JM, Munoz MA. Impact on weight and height with the use of HAART in HIV-infected children. *Pediatr.Infect.Dis.J*. 2007; 26:334–338. [PubMed: 17414398]

15. Hamill PV, Drizd TA, Johnson CL, Reed RB, Roche AF. NCHS growth curves for children birth-18 years. United States. Vital Health Stat. 1977; 11:i-74.
16. Heikens GT, Bunn J, Amadi B, et al. Case management of HIV-infected severely malnourished children: challenges in the area of highest prevalence. Lancet. 2008; 371:1305–1307. [PubMed: 18406865]
17. Kabue MM, Kekitiinwa A, Maganda A, et al. 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]
18. Kekitiinwa A, Lee KJ, Walker AS, 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]
19. Kessler L, Daley H, Malenga G, Graham S. The impact of the human immunodeficiency virus type 1 on the management of severe malnutrition in Malawi. Ann.Trop.Paediatr. 2000; 20:50–56. [PubMed: 10824214]
20. Laufer MK, van Oosterhout JJ, Perez MA, et al. Observational cohort study of HIV-infected African children. Pediatr.Infect.Dis.J. 2006; 25:623–627. [PubMed: 16804433]
21. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS - a Bayesian modelling framework: concepts, structure, and extensibility. Statistics and Computing. 2010; 10:325–337.
22. Ministry of Health of Malawi. First Edition. Government of Malawi; 2003. Treatment of AIDS. Guidelines for the use of antiretroviral therapy in Malawi.
23. Ministry of Health of Malawi. Lilongwe, Malawi: Government of Malawi and UNICEF; 2006a. Interim guidelines for the management of acute malnutrition in adolescents and adults.
24. Ministry of Health of Malawi. Second Edition. Government of Malawi; 2006b. Treatment of AIDS. Guidelines for the use of antiretroviral therapy in Malawi.
25. Ministry of Health of Malawi. Government of Malawi; 2007. ANC Sentinel Surveillance and National HIV Prevalence and AIDS Estimates.
26. Muula AS, Chipeta J, Siziya S, et al. Human resources requirements for highly active antiretroviral therapy scale-up in Malawi. BMC.Health Serv.Res. 2007; 7:208. [PubMed: 18093318]
27. Nachman SA, Lindsey JC, Moye J, et al. Growth of human immunodeficiency virus-infected children receiving highly active antiretroviral therapy. Pediatr.Infect.Dis.J. 2005; 24:352–357. [PubMed: 15818296]
28. National Statistical Office (NSO) [Malawi] and ORC Macro. Calverton, Maryland: NSO and ORC Macro; 2005. Malawi Demographic and Health Survey 2004.
29. Nyandiko WM, Ayaya S, Nabakwe E, et al. Outcomes of HIV-infected orphaned and non-orphaned children on antiretroviral therapy in western Kenya. J.Acquir.Immune.Defic.Syndr. 2006; 43:418–425. [PubMed: 17099313]
30. Royston P, Altman DG. Regression using fractional polynomials of continuous covariates: parsimonious parametric modelling. Appl.Statist. 1994; 43:429–467.
31. Song R, Jelagat J, Dzombo D, et al. Efficacy of highly active antiretroviral therapy in HIV-1 infected children in Kenya. Pediatrics. 2007; 120:e856–e861. [PubMed: 17846147]
32. Steiner F, Kind C, Aebi 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]
33. Sutcliffe CG, van Dijk JH, Bolton C, Persaud D, Moss WJ. Effectiveness of antiretroviral therapy among HIV-infected children in sub-Saharan Africa. Lancet Infect.Dis. 2008; 8:477–489. [PubMed: 18652994]
34. Rubin, D. New York: Wiley; 1987. Multiple imputation for non-response in surveys.
35. The R Development Core Team. R: A Language and Environment for Statistical Computing. Reference Index. Version 2.10.1. 2009 Available at <http://cran.r-project.org/doc/manuals/refman.pdf>.
36. Thurstans S, Kerac M, Maleta K, Banda T, Nesbitt A. HIV prevalence in severely malnourished children admitted to nutrition rehabilitation units in Malawi: geographical & seasonal variations a cross-sectional study. BMC.Pediatr. 2008; 8:22. [PubMed: 18495024]

37. Verweel G, van Rossum AM, Hartwig NG, et al. 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]
38. Walker AS, Mulenga V, Ford D, et al. The impact of daily cotrimoxazole prophylaxis and antiretroviral therapy on mortality and hospital admissions in HIV-infected Zambian children. *Clin.Infect.Dis*. 2007; 44:1361–1367. [PubMed: 17443476]
39. Wamalwa DC, Farquhar C, Obimbo EM, 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]
40. WHO. 2003 revision. Geneva, Switzerland: WHO; 2004. Scaling up antiretroviral therapy in resource- limited settings: Treatment guidelines for a public health approach.
41. WHO. Geneva, Switzerland: WHO; 2006. Antiretroviral Therapy of HIV infection in infants and children: Towards universal Access. Recommendations for a public health approach.
42. WHO. [Accessed 21/03/2010] Growth reference data for 5–19 years. 2010a. Last updated 2010. Available at <http://www.who.int/growthref/en/>
43. WHO. [Accessed 21/03/2010] WHO Child Growth Standards. 2010b. Last updated 2010. Available at <http://www.who.int/childgrowth/standards/en/>

Appendix

1) Full probability model

Let $Y_j(t)$ denote the anthropometric measure be it WAZ or HAZ for child $j=1, \dots, N$ at time $t=1, \dots, T$, with time in years. The model can be written as

$$Y_j(t) = \alpha_0 + \alpha_j + \alpha_{\text{Female}} \cdot \text{Female}_j + \alpha_{\text{Age1}} \cdot \text{Age1}_j + \alpha_{\text{Age2}} \cdot \text{Age2}_j + \alpha_{\text{Age3}} \cdot \text{Age3}_j + \alpha_{\text{Start1}} \cdot \text{Start1}_j + \alpha_{\text{Start2}} \cdot \text{Start2}_j + \alpha_{\text{Start3}} \cdot \text{Start3}_j + \alpha_{\text{Z1}} \cdot \text{Z1}_j + \alpha_{\text{Z2}} \cdot \text{Z2}_j + \alpha_{\text{Z3}} \cdot \text{Z3}_j + \alpha_{\text{WHO1}} \cdot \text{WHO1}_j + \alpha_{\text{WHO2}} \cdot \text{WHO2}_j + \alpha_{\text{Immuno1}} \cdot \text{Immuno1}_j + \alpha_{\text{Immuno2}} \cdot \text{Immuno2}_j + (\beta_0 + \beta_j + \beta_{\text{Z1}} \cdot \text{Z1}_j + \beta_{\text{Z2}} \cdot \text{Z2}_j + \beta_{\text{Z3}} \cdot \text{Z3}_j) \cdot t + (\gamma_0 + \gamma_j + \gamma_{\text{Z1}} \cdot \text{Z1}_j + \gamma_{\text{Z2}} \cdot \text{Z2}_j + \gamma_{\text{Z3}} \cdot \text{Z3}_j) \cdot t \log t + \varepsilon_j$$

where all the variables (non-greek letters) are indicator variables taking the value 1 if child j is in the corresponding category. For example, female children in ART start age group 2 (i.e. between 5 and 9 years old), ART start group 3 (i.e. started ART 2006), in baseline z-score group 1 (i.e. baseline z-score less than -3), WHO clinical stage 3 and with no immunodeficiency have the following model:

$$Y_j(t) = \alpha_0 + \alpha_j + \alpha_{\text{Female}} \cdot \text{Female}_j + \alpha_{\text{Age2}} \cdot \text{Age2}_j + \alpha_{\text{Start3}} \cdot \text{Start3}_j + \alpha_{\text{Z1}} \cdot \text{Z1}_j + \alpha_{\text{WHO1}} \cdot \text{WHO1}_j + \alpha_{\text{Immuno1}} \cdot \text{Immuno1}_j + (\beta_0 + \beta_j + \beta_{\text{Z1}} \cdot \text{Z1}_j) \cdot t + (\gamma_0 + \gamma_j + \gamma_{\text{Z1}} \cdot \text{Z1}_j) \cdot t \log t + \varepsilon_j$$

The error term ε represents the measurement error for each child and is a centered Student t -distribution with 3 degrees of freedom and standard deviation σ . The random effects distributions are centered Student t -distributions as well with 3 degrees of freedom and standard deviations σ_α , σ_β and σ_γ . Student t -distribution were preferred because these heavy tailed distributions yield robust estimates.

The prior distributions for α_0 , β_0 and γ_0 are centered normal with standard deviation 5. For the other α , β and γ parameters the priors are centered normal with standard deviation 10.

The prior distributions for all σ parameters are inverse gamma distributions with shape and rate parameters equal to 0.01.

2) Additional parameters (random effects and interaction with time) from multivariable model presented in table 2

α , β and γ correspond to the parameters in the model which is described in detail above.

Variables at start of ART	Weight-for-age Complete case analysis (n=342)	Weight-for-age Multiple imputation (n=417)	Height-for-age Complete case analysis (n=307)	Height-for-age Multiple imputation (n=358)
Interaction with time (β)				
z-score				
> -1	0	0	0	0
> -2 to -1	0.18 (0.00 to 0.34)	0.13 (-0.06 to 0.33)	0.18 (-0.05 to 0.42)	0.42 (0.18 to 0.67)
> -3 to -2	0.36 (0.18 to 0.54)	0.38 (0.18 to 0.58)	0.39 (0.17 to 0.64)	0.66 (0.43 to 0.90)
-3	1.00 (0.79 to 1.19)	1.03 (0.78 to 1.27)	0.51 (0.28 to 0.76)	0.81 (0.58 to 1.04)
Interaction with ln time (γ)				
z-score				
> -1	0	0	0	0
> -2 to -1	-0.03 (-0.19 to 0.13)	0.08 (-0.10 to 0.26)	-0.04 (-0.22 to 0.16)	-0.15 (-0.35 to 0.06)
> -3 to -2	-0.12 (-0.26 to 0.03)	-0.10 (-0.29 to 0.08)	-0.12 (-0.30 to 0.07)	-0.23 (-0.42 to -0.03)
-3	-0.45 (-0.65 to -0.26)	-0.52 (-0.73 to -0.30)	-0.01 (-0.19 to 0.18)	-0.23 (-0.43 to -0.04)
Overall intercept α_0	-0.56 (-1.06 to -0.06)	0.38 (-0.46 to 1.29)	-0.62 (-1.42 to 0.08)	0.11 (-0.78 to 0.94)
Standard deviation α_0	0.30 (0.26 to 0.34)	0.84 (0.78 to 0.91)	0.37 (0.32 to 0.42)	0.76 (0.70 to 0.83)
β_0	0.04 (-0.09 to 0.18)	0.14 (-0.01 to 0.31)	-0.02 (-0.24 to 0.19)	-0.25 (-0.45 to -0.04)
Standard deviation β_0	0.38 (0.33 to 0.44)	0.57 (0.51 to 0.63)	0.29 (0.25 to 0.34)	0.39 (0.34 to 0.44)
γ_0	-0.10 (-0.23 to 0.02)	-0.18 (-0.33 to -0.03)	-0.08 (-0.25 to 0.08)	0.03 (-0.14 to 0.21)
Standard deviation γ_0	0.26 (0.22 to 0.31)	0.44 (0.38 to 0.52)	0.17 (0.14 to 0.21)	0.19 (0.13 to 0.25)

The interaction parameters with time (beta and gamma) are related to catch up growth for each baseline category of WAZ and HAZ. Large values of beta indicate a large catch up growth shortly after ART start. Negative values for gamma indicate that catch up growth is increasingly attenuated over time on ART, meaning that a child will not catch up forever.

Figure 1.
Flowchart of selection of children and contribution to different analyses

Figure 2.

Evolution of z-scores for weight-for-age (top) and height-for-age (bottom) from start of antiretroviral therapy (ART) up to 2 years after start of ART.

Lines represent fit of mixed-effect model. Dots represent medians with interquartile ranges (IQR). The four trajectories represent children with baseline z-scores > -1, > -2 to -1, > -3 to -2, and > -4 to -3.

Figure 3. Trajectories of z-scores for weight-for-age (n=313) and height-for-age (n=280) for individual children by baseline z-scores with lines representing predicted median z-scores and corresponding 95% prediction intervals.

Table 1

Characteristics of 497 children starting ART at the Lighthouse clinic, Lilongwe.

Year of starting ART	
2001–2003	65 (13.1%)
2004	136 (27.4%)
2005	215 (43.3%)
2006–07	81 (16.3%)
Sex	
Girls	242 (48.7%)
Boys	255 (51.3%)
Age (years)	
Median (IQR)	8 (4 to 11)
<2	11 (2.2%)
2–4	115 (23.1%)
5–9	197 (39.6%)
10	174 (35.0%)
Area of residence <i>n=424</i>	
Outside Lilongwe	66 (15.6%)
Lilongwe district	143 (33.7%)
Lilongwe city	215 (50.7%)
Degree of immunodeficiency* <i>n=383</i>	
None	13 (3.4%)
Moderate	75 (19.6%)
Severe	295 (77.0%)
WHO clinical stage <i>n=402</i>	
Stage 1	2 (0.5%)
Stage 2	22 (5.5%)
Stage 3	234 (58.2%)
Stage 4	144 (35.8%)
Weight for age <i>n=419</i>	
Median (IQR)	−2.1 (−2.7 to −1.3)
Underweight (%) **	217 (51.8%)
Height for age <i>n=363</i>	
Median (IQR)	−2.6 (−3.6 to −1.8)
Stunted (%) **	251 (69.2%)
Duration of follow-up(months)	
Median (IQR)	23.4 (11.1 to 33.7)

Number of children (%) shown unless otherwise indicated.

Data incomplete for area of residence, degree of immunodeficiency, WHO clinical stage, weight-for-age and height-for-age.

* Severe: CD4% <15% or absolute CD4 cell count < 750, <500, <200 for children aged <12 months, 1–5 years, 6–12 years. Moderate: CD4% 15%–24% or absolute CD4 cell count < 750–1499, 500–999, 200–499. none: CD4% ≥25% or absolute CD4 cell count ≥ 1500, 1000, 500

**
Z-score below -2

Table 2

Change in weight and height z-scores after starting antiretroviral therapy associated with baseline z-scores and other characteristics at baseline

	Coefficients for main effects (95% confidence intervals)			
	Weight-for-age Complete case analysis (n=342)	Weight-for-age Multiple imputation (n=417)	Height-for-age Complete case analysis (n=307)	Height-for-age Multiple imputation (n=358)
Z-score				
> -1	0	0	0	0
> -2 to -1	-0.96 (-1.11 to -0.82)	-1.44 (-1.70 to -1.17)	-1.05 (-1.28 to -0.81)	-1.53 (-1.88 to -3.47)
> -3 to -2	-1.76 (-1.91 to -1.61)	-2.25 (-2.50 to -1.98)	-1.92 (-2.15 to -1.71)	-2.43 (-2.76 to -2.11)
-3	-2.96 (-3.14 to -2.79)	-3.44 (-3.76 to -3.15)	-3.18 (-3.41 to -2.94)	-3.78 (-4.10 to -3.47)
Age (years)				
< 2	0	0	0	0
2 - 4	-0.02 (-0.42 to 0.42)	-0.28 (-1.03 to 0.43)	-0.09 (-0.70 to 0.59)	-0.55 (-1.25 to 0.17)
5 - 9	0.08 (-0.32 to 0.49)	-0.11 (-0.86 to 0.61)	0.00 (-0.61 to 0.59)	-0.28 (-0.96 to 0.41)
10	0.00 (-0.38 to 0.43)	-0.20 (-0.95 to 0.51)	-0.10 (-0.72 to 0.59)	-0.39 (-1.09 to 0.31)
Sex				
Male	0	0	0	
Female	0.01 (-0.07 to 0.11)	0.20 (0.03-0.39)	0.08 (-0.03 to 0.18)	0.14 (-0.02 to 0.30)
Time period				
Jan 2001 - Jun 2004	0	0	0	0
Jun 2004 - Dec 2004	-0.10 (-0.26 to 0.05)	-0.04 (-0.32 to 0.25)	0.00 (-0.20 to 0.19)	0.01 (-0.28 to 0.31)
Jan 2005 - Dec 2005	-0.19 (-0.32 to -0.05)	-0.10 (-0.36 to 0.16)	0.00 (-0.18 to 0.17)	0.08 (-0.16 to 0.34)
2006	-0.21 (-0.39 to -0.03)	0.06 (-0.23 to 0.34)	0.10 (-0.12 to 0.33)	0.09 (-0.23 to 0.40)
Degree of immunodeficiency				
None	0	0	0	0
Moderate	0.09 (-0.22 to 0.41)	-0.48 (-0.98 to 0.07)	0.08 (-0.26 to 0.44)	0.01 (-0.50 to 0.52)
Severe	0.04 (-0.26 to 0.34)	-0.42 (-0.90 to 0.07)	0.04 (-0.36 to 0.31)	-0.14 (-0.62 to 0.35)
WHO clinical stage				
stage 4	0	0	0	0
stage 3	0.00 (-0.10 to 0.10)	0.02 (-0.17 to 0.20)	0.01 (-0.13 to 0.11)	0.10 (-0.07 to 0.28)
stage 1 or 2	0.01 (-0.20 to 0.21)	0.10 (-0.30 to 0.49)	0.02 (-0.20 to 0.23)	0.05 (-0.29 to 0.41)

Children with a baseline and at least one subsequent WAZ and HAZ value are included.

The coefficients show the vertical shift of the trajectories compared to each baseline category (0) for WAZ and HAZ. Results are adjusted for all variables shown in the table. The model is described in detail in the statistical appendix, which reports the coefficients for random effects and the interaction with time.