Age-specific and sex-specific weight gain norms to monitor antiretroviral therapy in children in low-income and middle-income countries

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Background: Viral load and CD4% are often not available in resource-limited settings for monitoring children's responses to antiretroviral therapy (ART). We aimed to construct normative curves for weight gain at 6, 12, 18, and 24 months following initiation of ART in children, and to assess the association between poor weight gain and subsequent responses to ART.

Design: Analysis of data from HIV-infected children younger than 10 years old from African and Asian clinics participating in the International epidemiologic Databases to Evaluate AIDS.

Methods: The generalized additive model for location, scale, and shape was used to construct normative percentile curves for weight gain at 6, 12, 18, and 24 months following ART initiation. Cox proportional models were used to assess the association between lower percentiles (< 50th) of weight gain distribution at the different time points and subsequent death, virological suppression, and virological failure.

Results: Among 7173 children from five regions of the world, 45% were underweight at baseline. Weight gain below the 50th percentile at 6, 12, 18, and 24 months of ART was associated with increased risk of death, independent of baseline characteristics. Poor weight gain was not associated with increased hazards of virological suppression or virological failure.

Conclusion: Monitoring weight gain on ART using age-specific and sex-specific normative curves specifically developed for HIV-infected children on ART is a simple, rapid, sustainable tool that can aid in the identification of children who are at increased risk of death in the first year of ART.

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Introduction

More than three million children live with HIV worldwide, of whom more than 90% live in sub-Saharan Africa [1]. In the absence of antiretroviral therapy (ART), a third of children infected perinatally will not survive to their first birthday, and more than half will not survive to their second birthday [2]. Successful initiation of ART in children is followed by a rapid decline in viral load, a rebound in $CD4^+$ cell count, a reduction in mortality, and a rapid gain in weight, especially in the first 6–12 months of ART [3–7].

In developed nations, routine laboratory tests (HIV viral load, $CD4^+$ cell count) are performed every 3–4 months to monitor patients with HIV receiving ART [8]. The measurement of viral load and to some extent that of $CD4^+$ cell count requires expensive and sophisticated technologies that cannot always be easily transferred or sustained in resource-poor settings. Recent studies in adults showed that routine $CD4^+$ monitoring had small but significant benefits over clinical monitoring, [9,10] and viral load monitoring had no significant additional benefit over $CD4^+$ monitoring [9]. Similar benefits of routine monitoring of $CD4^+$ cell count were reported in the only such trial conducted in children so far [11]. In addition, this trial demonstrated that monitoring of weight gain on ART is a sensitive indicator of first-line treatment failure in African children [11], supporting the WHO recommendations that in settings in which viral load is unavailable, clinical parameters, particularly the improvement in growth, be used for monitoring ART, supported where possible with $CD4^+$ cell count monitoring [12].

Contrary to viral load, which has a clear and simple target cut-point (below detection limit), cut-points for weight gain that correlate with subsequent treatment outcomes have not been clearly established. One important difficulty in establishing those references for children resides in the fact that changes in weight strongly depend on age and sex. Two age-stratified and sex-stratified normative percentiles curves are almost ubiquitously used in pediatric care: the WHO 'Road to Health' for attained weight-for-age [13], and the Fels Institute growth charts for growth velocity [14,15]. In a previous analysis [16] using data from a single clinic in Soweto, South Africa, we demonstrated that the WHO and the Fels Institute growth charts were not valid for use in children receiving ART. Furthermore, although the effectiveness of ART is the same in high-income, middle-income, and low-income countries [17,18], the prevalence of malnutrition and opportunistic infections at ART initiation varies by region, which could affect weight gain following ART initiation.

In this study, we aimed to construct international reference standards for gains in weight at 6, 12, 18, and 24 months following ART initiation and identify the centile curves of weight gain that are correlated with subsequent treatment failure and death.

Methods

Data and data sources

Data for this analysis were provided by the International Epidemiologic Databases to Evaluate AIDS, a US National Institutes of Health initiative launched in 2005 to establish an international research consortium to address research questions not answerable by single cohorts. The initiative funds seven regional data centers of which five contributed data for this analysis: the Asia-Pacific region which includes the Therapeutics Research, Education, and AIDS Training in Asia (TREAT Asia) HIV Observational Database and includes data from Cambodia, India, Indonesia, Malaysia, Thailand, and Vietnam; the West African Database on Antiretroviral Therapy Collaboration which includes cohorts from Benin, Burkina Faso, Côte d'Ivoire, Ghana, Mali, and Senegal; the Central African region with participating sites from Burundi, Cameroon, Democratic Republic of Congo, and Rwanda; the Eastern Africa regional data centers which combine data from cohorts in Kenya, Tanzania, and Uganda; and the Southern African region with data from Lesotho, Malawi, Mozambique, South Africa, Zambia, and Zimbabwe. Detailed descriptions of the database and the main clinical outcomes have been reported elsewhere [19,20].

Statistical analysis

Assessing the homogeneity of weight gain over time by region

To assess the homogeneity of gains in weight, we computed the median weight gain from ART initiation for each 3-month interval through 24 months of ART and plotted the values for each of the five regions. The plotted curves were visually inspected and data were merged if the gains overtime appeared homogeneous across regions (parallel plots). A quantile regression model with weight as response variable and time, region, and the interaction terms between region and time as dependent variable was also used to formally assess whether the change in weight over time after ART initiation varies by region.

Construction of reference curves for weight gain at 6, 12, 18, and 24 months after antiretroviral therapy initiation

We calculated weight gain at each of the 6, 12, 18, and 24 months time points for each individual child. Response curves were obtained by smoothing measurements over the chronological age at time of measurement using locally weighted quadratic regression [21]. Estimates of weight gain were then obtained by subtracting the response curve estimates at each time point from the baseline (at ART initiation) estimates (see reference [16]

for a detailed description of the method). For visits that fell within 3 months of the cut-point, the weight gain was adjusted simply by dividing the measured weight gain by the exact time interval since ART initiation and multiplying it by the corresponding time interval. For example, in a child whose closest weight to 6 months was measured at 5 months, the estimate of weight gain at 6 months was obtained by dividing the difference between the smoothed value of weight at 5 months and the value at ART initiation by 5, and then multi-plying it by 6.

To obtain the normative reference percentile curves, we used methods similar to those used by the WHO to construct recent international growth curves [13]. The 6, 12, 18, and 24 months estimates of weight gain were regressed on chronological age using the generalized additive model for location, scale, and shape, a method that requires a parametric distribution assumption for the response variable while allowing the modeling of the distribution parameter as nonparametric (smooth) functions of the explanatory variables [22]. For the response variable, we assumed a Box-Cox power exponential distribution with four parameters relating to location (μ, median), scale (σ, coefficient of variation), skewness (υ, transformation for symmetry), and kurtosis (τ, power exponential parameter), respectively [23]. To specify the model, the user must choose the number of degrees of freedom (df) to be used for each parameter. Starting with the simplest model that includes age and the fitting of μ and σ curves while keeping the degree of freedom for υ and τ fixed at zero, we searched for df(μ) and then df(σ) that minimized the global deviance as indicated by the generalized Akaike Information Criterion (with penalty 3 for each degree of freedom used). In the next step, using the df(μ) and df(σ) selected in the previous, we sequentially searched for the df(υ) and df(τ) that minimized the global deviance. In the last step, Q statistic [24] and worm plots [25] were used to fine tune the selected df(μ), df(σ), df(υ), and df(τ) [23]. Because of the high variability of weight gain in children after the age of 10 years, only data from children younger than 10 years were used to facilitate model convergence.

Association of lower weight gain with subsequent response to antiretroviral therapy

Three outcomes were considered: time to death (survival), time to viral suppression (first viral load less than 400 copies/ml after ART initiation), and time to virologic failure. The outcome of virologic failure occurred when a child met one of three conditions: a viral load measurement more than 1000 copies/ml after at least 1 year of ART, two consecutive viral load measurements more than 400 copies/ml after initial virologic suppression, or failure to ever achieve virological suppression after at least 1 year of ART.

For each of the three outcomes, separate Cox proportional hazard models were fitted for the 3rd, 10th, 25th, 33rd, and 50th centiles as predictors for each of the 6, 12, 18, and 24 months time points. Age at ART initiation (<2 years, 2–4 years, 5–9 years), weight-for-age *z* score (WAZ) (<−3SD, −3SD ≤ to <−2SD, −2SD ≤ to <−1SD, and ≥−1SD) [26], baseline CD4% (<15, 15–25, >25%), an interaction term between WAZ and the centiles (in case the association differed by baseline WAZ), and year of ART initiation were included in the initial model for death. Baseline viral load (≥5 log, <5 log copies/ml) was also included in the initial models for the two virological outcomes. Using a stepwise backward selection procedure and the Wald test, all covariates that did not contribute significantly to the fit of each multivariate model were dropped. The hazard ratio and 95% confidence interval (CI) from each of the final models are reported. All variables included in the model met the proportional hazards assumption formally evaluated using the Kolmogorov-type supremum test [27].

Analyses were done using SAS 9.2 (SAS Institute, Cary, North Carolina, USA). All tests were conducted using a two-sided 0.05 significance level, without correction for multiple comparisons (or uncertainty because of model selection). The study was approved by the Office of Human Research Ethics at the University of North Carolina at Chapel Hill.

Results

Description of cohorts

Of the 11 802 HIV-infected children younger than 10 years of age in the combined dataset, 8628, 6825, 5241, and 3883, were on ART for at least 6, 12, 18, and 24 months, respectively. Of those children, 7173, 5029, 4288, and 3072 had sufficient data to be included in the analysis at each time point. Half (3657 or 51%) were from Southern Africa, 23% from Eastern Africa,13% from Asia, 9% from Western Africa, and 4% from Central Africa (Table 1). The change in weight overtime following ART initiation was homogeneous across regions. All *P* values for the four interaction terms between region and time were more than 0.20 (Figure 3 and Table 3 supplemental material, http://links.lww.com/QAD/A596).

Few (3.5%) children initiated ART before 2004, the majority (78%) initiated between 2005 and 2007, and the remainder (7%) initiated in 2008 and 2009 (Table 1). Half (52%) were male. At the time of ART initiation, 23% were aged 1 year or younger, and 45% were underweight for age (WAZ ≤−2 SD). Of the 5171 (72.1%) children with pre-ART CD4% available, 74% were severely immunosuppressed (CD4% <15%). Of the 2615 (36.5%) children with pre-ART viral load, 64% had values at least 5 log copies/ml. Children from the Eastern and Southern Africa regions were less likely to be underweight-for-age

Table 1. Characteristics at antiretroviral therapy initiation of 7173 children younger than 10 years of age included in the analysis of 6-month weight gain[a].

	Overall		Asia-Pacific		Central Africa		East Africa		Southern Africa		West Africa	
Characteristics	Number[b]	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Sex												
Men	3719	51.85	470	51.71	150	49.02	873	52.97	1874	51.24	352	53.91
Women	3454	48.15	439	48.29	156	50.98	775	47.03	1783	48.76	301	46.09
CD4%												
<15%	3819	73.85	579	77.10	2	50.0	819	82.81	2116	70.72	303	69.66
15–25%	1060	20.50	140	18.64	2	50.0	139	14.05	681	22.76	98	22.53
>25%	292	5·65	32	4.26	0	–	31	3.13	195	6.52	34	7.82
Viral load												
<100 000 copies/ml	935	35.76	123	32.03	0	–	0	–	800	36.87	12	19.67
≥100 000 copies/ml	1680	64.24	261	67.97	0	–	0	–	1370	63.13	49	80.33
Weight-for-age *z* score[c]												
≥−1 SD	1929	27.14	178	19.82	72	23.76	448	27.40	1072	29.59	159	24.50
<−1 to ≥−2SD	1973	27.76	215	23.94	86	28.38	462	28.26	1035	28.57	175	26.96
<−2 to ≥−3SD	1516	21.33	216	24.05	58	19.14	389	23.79	715	19.74	138	21.26
<−3SD	1690	23.78	289	32.18	87	28.71	336	20.55	801	22.11	177	27.27
Age in years												
0–1	1679	23.41	107	11.77	56	18.30	231	14.02	1130	30.90	155	23.74
2–4	2541	35.42	309	33.99	107	34.97	648	39.32	1239	33.88	238	36.45
5–9	2953	41.17	493	54.24	143	46.73	769	46.66	1288	35.22	260	39.82
Year of ART Initiation												
2003	249	3.47	146	16.06	0	-	0	–	103	2.82		
2004	839	11.70	61	6.71	14	4.58	80	4.85	593	16.22	91	13.94
2005	1959	27.31	151	16.61	93	30.39	281	17.05	1183	32.35	251	38.44
2006	2212	30.84	252	27.72	83	27.12	558	33.86	1124	30.74	195	29.86
2007	1435	20.01	157	17.27	57	18.63	616	37.38	515	14.08	90	13.78
2008	421	5.87	106	11.66	42	13.73	113	6.86	134	3.66	26	3.98
2009	58	0.81	36	3.96	17	5.56	0	–	5	0.14	0	–
Time on ART in months [median (IQR)][d]	7173	23.9 (14.7, 34.4)	909	43.7 (28.9, 55.9)	306	41.3 (23.0, 47.9)	1648	20.4 (13.3, 28.2)	3657	21.5 (13.7, 30.9)	653	25.4 (16.8, 34.9)

ART, antiretroviral therapy; IQR, interquartile range.
[a]Children were included if they had at least 6 months of follow-up on ART and at least a pre-ART and a 6-month measurement needed to estimate the 6-month weight gain.
[b]Totals vary by baseline characteristics due to missing data.
[c]Sex-specific weight-for age and height-for-age *z* scores were obtained by plotting the weight measurements at baseline against the WHO weight-for-age and height-for-age charts.
[d]Minimum = 6 months, Maximum = 59 months.

at ART initiation compared with those from other regions ($P < 0.01$).

The median duration of follow-up was 23.9 months following ART initiation. A total of 111 deaths were recorded, of which 68 (61.3%) occurred between 6 and 12 months, 20 (18.0%) between 12 and 18 months, 12 (10.8%) between 18 and 24 months, and 11 (10.0% after 24 months of ART (Table 5 supplemental material, http://links.lww.com/QAD/A596).

Growth curves and distribution of 6, 12, 18, and 24 months weight gain

Figures 1 and 2 present the age-specific and sex-specific distributions of cumulative weight gained at 6, 12, 18, and 24 months after ART initiation. For example, for a boy who started ART at the age of 6 months, at the 6, 12, 18, and 24 months visits, to remain consistently above the 33rd percentile curves for weight gain, he must have cumulatively gained at least 2.04, 3.42, 4.52, and 5.50 kg, at the corresponding visit, irrespective of his initial weight (Tables 6a–9b, supplemental material, http://links.lww.com/QAD/A596).

Association of poor postantiretroviral therapy weight gain (<50th percentile) and subsequent survival, viral suppression and virologic failure

Children with poor weight gain at 6 and 12 months of ART had a statistically higher hazard of death than those with good weight gain (Table 2). After adjustment for WAZ at ART initiation, the hazard ratios comparing children below the 33rd percentile of weight gain with

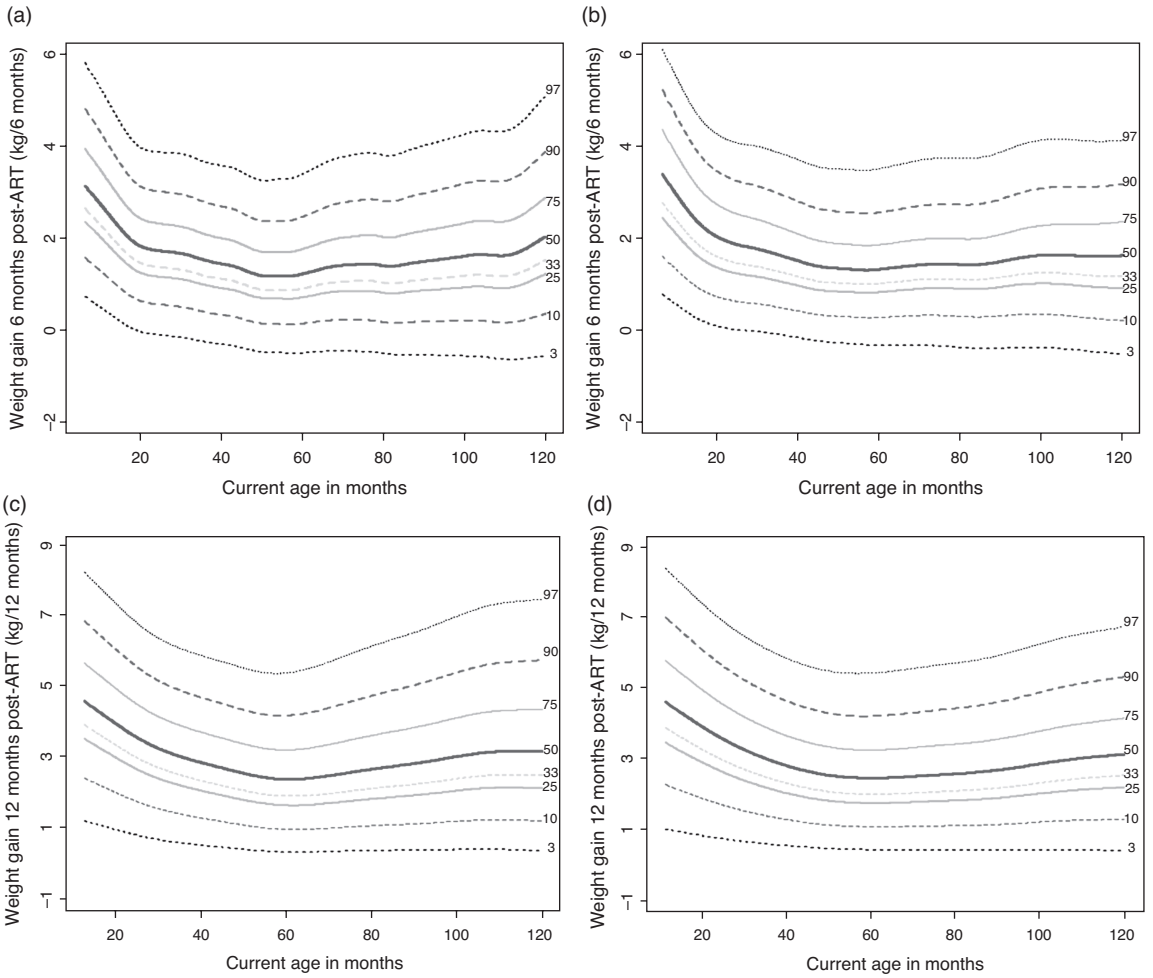

Fig. 1. Six-month and 12-month sex-specific and age-specific weight gain reference curves in children. (a) Centile curves for 6 months post-ART weight gain in females. (b) Centile curves for 6 months post-ART weight gain in males. (c) Centile curves for 12 months post-ART weight gain in females. (d) Centile curves for 12 months post-ART weight gain in males. Curves were obtained using Box Cox power exponential (BCPE) distribution and the generalized additive model for location, scale, and shape. Model for female at 6 months (a): BCPE (age, df(μ) = 12.9, df(σ) = 0.2, df(υ) =1, df(τ)=3). Model for males at 6 months (b): BCPE (age, df(μ) = 9.9, df(σ) = 0.2, df(υ) =2, df(τ)=2). Model for females at 12 months (c): BCPE (age, df(μ) = 4.8, df(σ) = 0, df(υ) =1, df(τ)=0). Model for males at 12 months (d): BCPE (age, df(μ) = 4.8, df(σ) = 0, df(υ) =1.3, df(τ)=0). df, degrees of freedom.

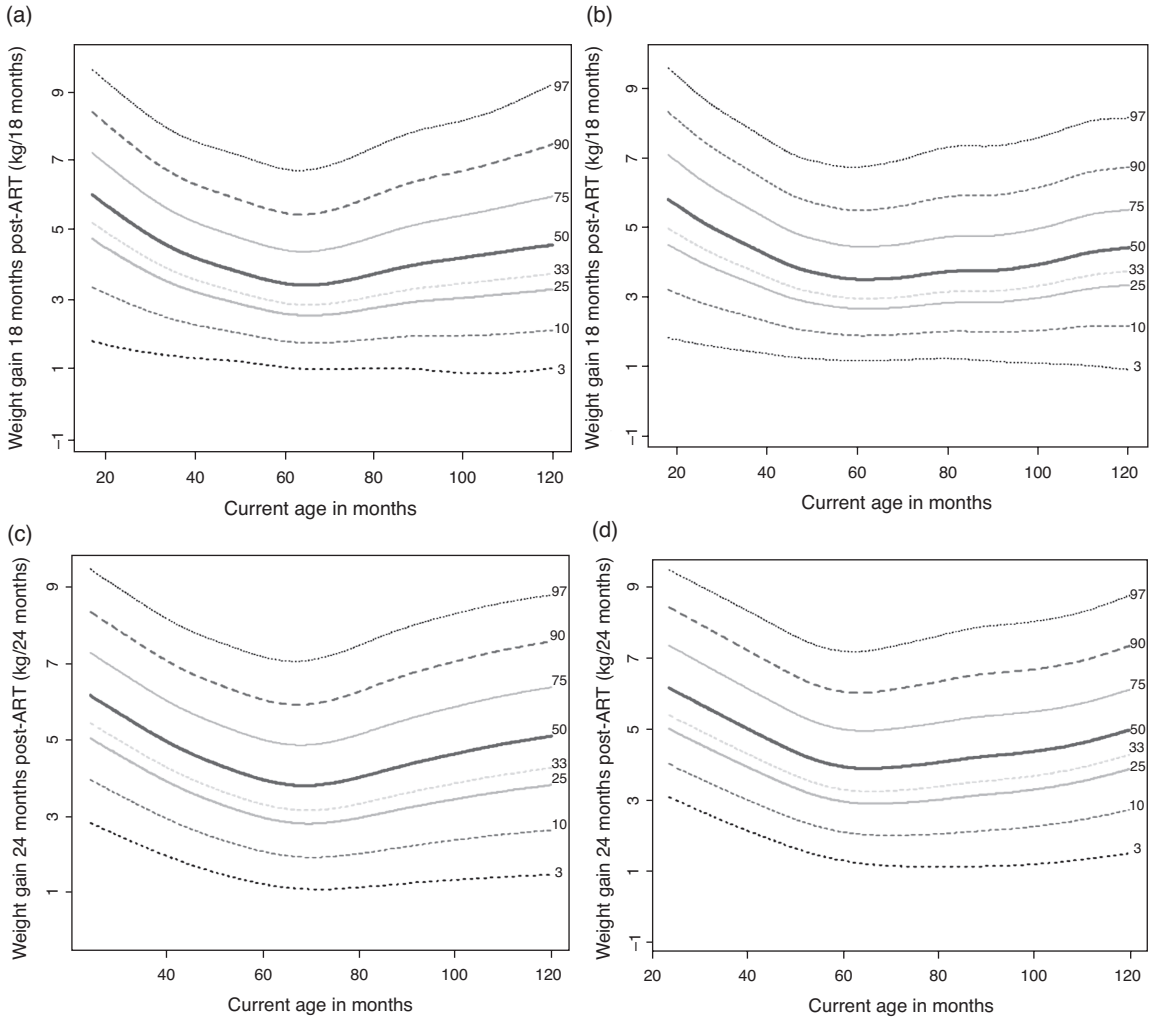

Fig. 2. Eighteen-month and 24-month sex-specific and age-specific weight gain reference curves in children. (a) Centile curves for 18 months post-ART weight gain in females. (b) Centile curves for 18 months post-ART weight gain in males. (c) Centile curves for 24 months post-ART weight gain in females. (d) Centile curves for 24 months post-ART weight gain in males. Curves were obtained using Box Cox power exponential (BCPE) distribution and the generalized additive model for location, scale, and shape. Model for females at 18 months (a): BCPE (age, df(μ) =4.1, df(σ) = 0, df(υ) =3, df(τ)=0). Model for males at 18 months (b): BCPE (age, df(μ) = 6.1, df(σ) = 0, df(υ) =2, df(τ)=0). Model for females at 24 months (c): BCPE (age, df(μ) = 3, df(σ) = 1.5, df(υ) =0.8, df(τ)=0). Model for males at 24 months (d): BCPE (age, df(μ) = 3.8, df(σ) = 1.22, df(υ) =1, df(τ)=0). df, degrees of freedom.

those above was 2.97 (95% CI: 2.03, 4.36) at 6 months and 2.28 (95% CI: 1.23, 4.22) at 12 months. A dose–response effect was observed for these associations with higher hazard ratios at lower weight gains, especially for the first 12 months of ART. For example, children with weight gains at the lowest (3rd) percentile had a nine-fold greater hazard of subsequent death compared with children with greater weight gain. The increased risk of death with lower weight gains persisted after 18 and 24 months of ART, but the estimates were imprecise due to the limited number of deaths that occurred after 18 months.

No statistical association was observed between the distribution of weight gain and time to virological suppression or time to virologic failure (Table 2).

Discussion

Data from recent randomized clinical trials in children [11] and in adults [10] show that routine laboratory monitoring for antiretroviral drug toxicity may not be needed in children and that $CD4^+$ monitoring provides a small but significant reduction in disease progression or death after the second year on ART. In adults, despite results from a large multicountry cohort study showing that virological monitoring might have some added benefit [28], particularly after 2 years, results from a clinical trial shows that adding viral load to $CD4^+$ monitoring provided no further benefits [10]. The trial in children identified monitoring weight gain as a sensitive indicator of first-line treatment failure [11].

Table 2. Association between lower percentile of weight gains at 6, 12, 18, and 24 months of antiretroviral therapy and time to mortality, virological suppression, and virological failure.

	Time to death after 6 months		Time to virological suppression[a]		Time to virological failure[b]	
	Hazard ratio (95% CI)		Hazard ratio (95% CI)		Hazard ratio (95% CI)	
	Crude	Adjusted[c]	Crude	Adjusted[d]	Crude	Adjusted[e]
Percentile	Weight gain at 6 months after ART initiation					
3rd	7.61 (4.64, 12.48)	9.20 (5.51, 15.34)	0.95 (0.69, 1.30)	1.18 (0.86, 1.62)	1.85 (1 02, 3.36)	1.10 (0.46, 2.68)
10th	6.86 (4.62, 10.20)	8.61 (5.74, 12.92)	1.01 (0.83, 1.21)	1.11 (0.92, 1.34)	1.50 (1.02, 2.21)	0.76 (0.43, 1.34)
25th	3.18 (2.19, 4.62)	4.17 (2.84, 6.12)	0.92 (0.83, 1.02)	0.93 (0.84, 1.03)	1.12 (0.91, 1.37)	1.10 (0.85, 1.41)
33rd	2.30 (1.59, 3.34)	2.97 (2.03, 4.36)	0.95 (0.87, 1.04)	0.95 (0.87, 1.04)	1.01 (0.84, 1.21)	0.90 (0.72, 1.13)
50th	1.45 (0.99, 2.12)	1.80 (1.22, 2.66)	0.93 (0.86, 1.01)	0.91 (0.84, 0.99)	0.98 (0.83, 1.15)	0.95 (0.78, 1.16)
	Weight gain at 12 months after ART initiation					
3rd	5.96 (2.65, 13.40)	7.33 (3.20, 16.78)	1.07 (0.81, 1.40)	1.11 (0.86, 1.46)	1.21 (0.67, 2.21)	0.92 (0.45, 1.91)
10th	3.25 (1.60, 6.60)	4.05 (1.96, 8.37)	0.96 (0.81, 1.15)	0.99 (0.83, 1.18)	1.15 (0.80, 1.66)	0.82 (0.49, 1.37)
25th	1.82 (0.98, 3.38)	2.21 (1.17, 4.17)	1.00 (0.90, 1.12)	1.01 (0.90, 1.12)	0.98 (0.79, 1.21)	0.94 (0.72, 1.23)
33rd	1.88 (1.03, 3.41)	2.28 (1.23, 4.22)	1.00 (0.90, 1.10)	0.99 (0.89, 1.09)	0.99 (0.81, 1.20)	0.91 (0.72, 1.15)
50th	1.39 (0.76, 2.54)	1.64 (0.88, 3.04)	0.97 (0.88, 1.07)	0.95 (0.86, 1.04)	0.92 (0.77, 1.10)	0.90 (0.72, 1.11)
	Weight gain at 18 months after ART initiation					
3rd	–	–	0.94 (0.70, 1.25)	1.11 (0.74, 1.67)	1.00 (0.52, 1.93)	0.61 (0.22, 1.68)
10th	1.55 (0.46, 5.20)	1.88 (0.55, 6.43)	1.06 (0.89, 1.26)	0.88 (0.69, 1.12)	0.93 (0.64, 1.34)	0.83 (0.50, 1.36)
25th	1.98 (0.86, 4.58)	2.41 (1.02, 5.68)	1.01 (0.90, 1.13)	0.90 (0.77, 1.05)	0.93 (0.74, 1.17)	0.91 (0.66, 1.24)
33rd	1.59 (0.70, 3.63)	1.92 (0.82, 4.48)	0.98 (0.89, 1.09)	0.98 (0.85, 1.12)	0.92 (0.75, 1.13)	0.84 (0.65, 1.10)
50th	1.90 (0.81, 4.49)	2.32 (0.97, 5.58)	0.94 (0.85, 1.03)	0.93 (0.81, 1.06)	0.99 (0.81, 1.19)	0.96 (0.76, 1.21)
	Weight gain at 24 months after ART initiation					
3rd	2.76 (0.35, 21.53)	3.34 (0.42, 26.34)	0.75 (0.54, 1.02)	0.79 (0.52, 1.21)	1.31 (0.78, 2.21)	1.21 (0.56, 2.64)
10th	2.21 (0.48, 10.23)	2.87 (0.61, 13.48)	0.97 (0.80, 1.18)	0.83 (0.64, 1.08)	1.17 (0.81, 1.68)	1.31 (0.79, 2.16)
25th	3.90 (1.19, 12.80)	4.80 (1.44, 15.93)	1.00 (0.88, 1.14)	0.89 (0.75, 1.06)	1.05 (0.81, 1.35)	0.98 (0.69, 1.40)
33rd	5.65 (1.50, 21.28)	7.17 (1.87, 27.44)	0.93 (0.82, 1.04)	0.87 (0.74, 1.02)	0.95 (0.75, 1.20)	0.87 (0.64, 1.18)
50th	4.79 (1.03, 22.15)	5.99 (1.28, 28.08)	0.93 (0.83, 1.04)	0.92 (0.79, 1.02)	0.90 (0.73, 1.11)	0.89 (0.68, 1.18)

ART, antiretroviral therapy.
[a]Viral load $\leq$ 400 HIV RNA copies/ml.
[b]Viral load measurement after at least 1 year of ART above 1000 copies/ml, two consecutive viral load measurements >400 copies/ml after initial virologic suppression, or failure to achieve virological suppression after at least 1 year of ART.
[c]Adjusted for baseline weight-for-age *z* scores (WAZ).
[d]Adjusted for baseline age, viral load, and region.
[e]Adjusted for baseline age, viral load, and region.

Growth monitoring is routinely performed in the follow-up of children [26]. However, neither of the commonly used WHO and Fels normative references growth curves are valid for HIV-infected children starting ART [16]. This is mainly because the origin used for both of these curves is birth, although ART initiation in resource-limited settings generally does not happen at birth. In this study, we were able to construct normative reference standards for weight gain at 6, 12, 18, and 24 months of ART for HIV-infected children younger than 10 years. At 6 and 12 months on ART, the hazard of dying in children whose weight gain was below the 33rd percentile was at least twice that of children who gained more weight. The strength of the association increased with decreasing weight gain.

We did not observe a correlation between weight gain and virological suppression or virological failure. This is contrary to findings from our single-clinic cohort study of South African children [16]. We speculate that it is because of selection bias, as viral load monitoring was not routinely available or accessible in most clinics and regions. In most regions outside of South Africa, children in routine care are only assessed by viral load in the presence of a clinical indication. As such, children with available viral load measurements are not representative of all children on ART.

The large sample size and extended follow-up allowed us to construct reference distributions through 24 months, and inclusion of five regions representing the regions of the world where virtually all pediatric HIV cases are found were important strengths of our study. Unfortunately, we did not have adequate and unbiased data on viral load and CD4$^+$ to assess the potential of monitoring weight gain alone or in combination with CD4$^+$ as predictors of poor response to ART. Moreover, we had to limit the analysis to children 10 years or younger because of the high heterogeneity of weight gain after 10 years of age. [26] Finally, because of the open nature of the cohorts, occurrence of deaths and loss to follow up, numbers of children included in the analysis reduced with longer follow-up time points. The data thus need to be interpreted conditional on surviving and remaining on ART and in care to the time point of interest.

In conclusion, in areas with limited access to viral load or CD4$^+$ measurement, monitoring weight gain post-ART using normative data developed specifically for HIV-infected children on ART could be a simple and highly

valuable tool to identify those children at highest risk of death.

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Conflicts of interest

There are no conflicts of interest.

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