

Body composition in HIV-infected children: relations with disease progression and survival¹⁻³

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ABSTRACT

Background: Malnutrition is common in HIV-infected children, but the body compartment that is most affected has been ill defined.

Objectives: Our objectives were to 1) compare the fat-free mass (FFM) of children with HIV infection with that of control children, 2) assess the contribution of FFM to body weight in HIV-infected children compared with that of control children, and 3) study the relations between body weight, FFM, and mortality.

Design: A cross-sectional study was performed in 86 HIV-infected and 113 uninfected children (mean ages: 6.9 and 7.7 y, respectively). FFM was estimated from single-frequency bioelectrical impedance analysis by using 3 different published equations; a further estimate was obtained from triceps-skinfold-thickness measurements.

Results: All 4 estimates of body composition showed that FFM in HIV-infected children was significantly less than in control children of similar age. However, FFM as a percentage of body weight was not significantly different between groups. In the whole group of infected children, an age-specific *z* score < -2 for weight and for FFM was significantly associated with an increased risk of death [relative risk (95% CI) = 11.4 (3.1, 41.0) and 5.1 (1.5, 18.2), respectively]; when only children with more severe disease were considered, only *z* score for weight was significantly associated with an increased risk [4.6 (1.4, 14.9)].

Conclusions: These findings suggest that no preferential catabolism of FFM occurs in HIV-infected children and that body weight for age is a better prognostic indicator than is FFM estimated by bioelectrical impedance analysis. *Am J Clin Nutr* 1999;69:1282-6.

KEY WORDS HIV, human immunodeficiency virus, acquired immune deficiency syndrome, AIDS, body composition, bioelectrical impedance analysis, children, malnutrition, prognosis, survival, cachexia, wasting syndrome, fat-free mass, lean body mass

INTRODUCTION

Malnutrition is a frequent finding in HIV-infected children and wasting syndrome is among the criteria for including these children in clinical category C (severely symptomatic) according to the Centers for Disease Control and Prevention (CDC) 1994 classification system (1, 2). At present, the pathogenesis of weight loss or growth failure in HIV infection is largely speculative;

many factors, including poor oral intake, malabsorption, and hypermetabolism, may be involved. Loss of fat and fat-free mass (FFM) could both contribute to body weight loss, but studies of their relative contribution have yielded conflicting results. Body cell mass (the metabolically active component of FFM) was found to be lower than normal in 193 HIV-infected adult patients studied by bioelectrical impedance analysis (BIA) (3) and in otherwise asymptomatic patients. Very young HIV-infected children were found to have significantly less lean body mass (as assessed by midarm circumference and triceps skinfold thickness) than control children of similar age (4). These observations suggest that a preferential loss of FFM occurs early in the disease progression and that cachexia, rather than protein-energy malnutrition, is the most important mechanism of weight loss.

On the contrary, Sharpstone et al (5), using whole-body dual-energy X-ray absorptiometry in adult, HIV-infected asymptomatic men, found that fat mass was the most severely affected body compartment, FFM being apparently increased. More recently, Paton et al (6), using 4 different techniques, found that the weight loss of a group of adult patients with symptomatic HIV infection was not due to excessive FFM catabolism, but was compatible with undernutrition.

Assessment of FFM in HIV-infected patients might prove useful in predicting survival (7), in clinical staging (8), and in evaluating responses to both nutritional and pharmacologic interventions (9, 10). BIA is a safe, noninvasive, and inexpensive technique for estimating FFM in children. Its ability to predict FFM has been confirmed in adults with AIDS (11). The aim of this work was to study FFM in a large group of HIV-infected children and its correlation with the different stages of illness and with survival.

SUBJECTS AND METHODS

Eighty-six prepubertal children with vertically transmitted HIV infection, as defined by the CDC criteria (2), were recruited

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TABLE 1
Characteristics of the HIV-infected and control children¹

	Control children (n = 113)	HIV-infected children				All (n = 86)
		N (n = 11)	A (n = 23)	B (n = 22)	C (n = 30)	
Age (y)	7.7 ± 3.3 (0.8–14.2) ²	7.1 ± 4.1 (1.6–13.1)	7.5 ± 2.6 (1.2–10.4)	6.1 ± 3.2 (0.8–12.2)	6.8 ± 2.8 (0.9–12.0)	6.9 ± 3.1 (0.8–13.1)
Males:females	50:63	3:8	10:13	6:16	17:13	36:50
CDC category of immunologic suppression						
1, none	—	7	5	5	2	19
2, moderate	—	4	9	9	10	32
3, severe	—	0	9	8	18	35

¹There were no significant differences between either HIV-infected and control children or between children in different clinical categories and control children (Student's *t* test, ANOVA, and multiple-range test for age; chi-square test for the proportions of males and females). CDC, Centers for Disease Control and Prevention; N, asymptomatic; A–C, mildly, moderately, and severely symptomatic, respectively.

² $\bar{x} \pm SD$; range in parentheses.

between January 1995 and December 1996 from the First and the Fourth Pediatric Departments of the University of Milan. They were compared with 113 children attending the department clinics for well visits or for scheduled minor surgery; these children were normally nourished at clinical assessment and free from acute or chronic medical conditions that could potentially affect their nutritional status. Informed consent was obtained from the legal guardians of the children, and the study was approved by the local ethics committee. All procedures were performed only after they had been clearly described and explained to the children.

The characteristics of the children studied according to CDC classification criteria are given in **Table 1**. The clinical categories are as follows: N, asymptomatic; A, B, and C, mildly, moderately, and severely symptomatic, respectively.

The HIV-infected children were studied the first time they attended the departments after the beginning of the study if they were free from acute complications. Four children (3 in category C and 1 in category B) with acute febrile diseases (2 with otitis media and 2 with pneumonia) were studied 3 mo later, after they had recovered. Four children had chronic cytomegalovirus infection, 3 were colonized by *Cryptosporidium* and had mild-to-moderate chronic diarrhea, 3 had pulmonary tuberculosis, and 2 were infected with *Mycobacterium avium* complex. Ten children in category A, all children in category B, and 25 children in category C were taking zidovudine (600 mg·m⁻²·d⁻¹). Didenosine (270 mg·m⁻²·d⁻¹) was also given to 4 children in category B and to the remaining 5 children in category C. Standard dietary advice was offered to the parents or guardians of all HIV-infected children and most children in category C were consuming lactose-free diets; no child was being given enteral or parenteral nutritional support.

All measurements were performed in the morning after the children fasted overnight. Weight (to the nearest 0.1 kg), standing height (0.1 cm), nondominant upper arm circumference (0.1 cm), and triceps skinfold thickness (0.1 mm) were measured by the same operator using standard techniques (12, 13). BIA was performed with a tetrapolar bioelectrical analyzer (model Human HI-Scan; Dietosystem, Milan, Italy) after the children voided and rested in bed for 15 min; electrodes were placed as recommended by the manufacturer and a standard, 800- μ A, 50-kHz oscillating current was applied.

Upper arm area and upper arm muscle area were derived from measurements of arm circumference and triceps skinfold thick-

ness as described by Frisancho (13). To predict FFM (in kg) from BIA measurements, the following published equations for children were selected:

Goran et al (14):

$$\text{FFM} = [0.59(\text{RI}) + 0.065(\text{wt}) + 0.04] / [0.769 - 0.0025(\text{A}) - 0.019(\text{G})] \quad (1)$$

Houtkooper et al (15):

$$\text{FFM} = 0.61(\text{RI}) + 0.25(\text{wt}) + 1.31 \quad (2)$$

Arpadi et al (16):

$$\text{FFM} = 0.68(\text{RI}) + 0.70(\text{A}) + 1.34 \quad (3)$$

where RI is resistance index [height (cm)²/resistance (ω)], wt is weight (kg), A is age (y), and G is sex (0 for females and 1 for males).

To allow comparison of patients of different age groups because body composition is known to change with age (though these differences were not statistically significant), standardized differences from the age-specific means were calculated [*z* score = (patient's value – age-specific mean)/age-specific SD]. The EPI-INFO software package (CDC, Atlanta) was used to calculate weight-for-age and height-for-age *z* scores (WAZ and HAZ, respectively). To calculate *z* scores of FFM, control children were divided in 3-y age groups (0–3, 3–6, 6–9, 9–12, and 12–15 y), the mean and SD of the appropriate age group was then used to calculate the FFM *z* score of an individual patient. To test for accuracy, this procedure was also applied to 37 children with nonorganic recurrent abdominal pain (age range: 3.4–12.8 y); mean values between 0.08 and –0.03 were obtained for the *z* scores of different estimates of FFM, and the corresponding SDs ranged between 0.97 and 1.12.

All statistical analyses were performed by using the STATGRAPHICS software package (version 6.0; Manugistics, Inc, Rockville, MD). Categorical variables were compared by using the chi-square test. Continuous variables were compared with one-way analysis of variance (ANOVA) after confirming their normal distribution by standardized coefficients of skewness and kurtosis within the range of –2 to 2. When the ANOVA *F* ratio was statistically significant, a post hoc multiple range analysis was performed by using Tukey's test to compare infected children in different clinical categories and control children.

TABLE 2
Anthropometric and body-composition measures of the HIV-infected and control children¹

	Control children (n = 113)	HIV-infected children				
		CDC clinical category				All ² (n = 86)
		N (n = 11)	A (n = 23)	B (n = 22)	C (n = 30)	
Weight (kg)	27.8 ± 12.3 ^a	27.8 ± 14.3 ^{a,b}	24.1 ± 7.0 ^{a,b}	19.8 ± 9.1 ^b	20.2 ± 6.6 ^b	22.1 ± 9.0 ³
Weight-for-age z score	0.09 ± 1.00 ^a	0.44 ± 0.90 ^a	-0.31 ± 0.75 ^{a,b}	-0.81 ± 1.13 ^b	-0.91 ± 1.17 ^b	-0.55 ± 1.11 ³
Height (cm)	124.5 ± 21.5 ^a	120.0 ± 26.7 ^{a,b}	121.3 ± 16.7 ^{a,b}	110.2 ± 19.9 ^b	112.8 ± 18.3 ^b	115.3 ± 19.7
Height-for-age z score	0.00 ± 0.91 ^a	-0.06 ± 0.84 ^{a,b}	-0.29 ± 0.91 ^{a,b}	-0.82 ± 1.28 ^{b,c}	-1.19 ± 1.01 ^c	-0.71 ± 1.11 ³
FFM (kg)						
Goran et al (14)	20.5 ± 8.4 ^a	19.6 ± 9.9 ^a	18.2 ± 5.5 ^a	14.4 ± 6.7 ^b	14.9 ± 5.2 ^b	16.3 ± 6.6 ³
Houtkooper et al (15)	21.9 ± 8.3 ^a	21.3 ± 10.1 ^a	19.5 ± 5.4 ^a	15.9 ± 6.7 ^b	16.3 ± 5.0 ^b	17.8 ± 6.6 ³
Arpadi et al (16)	22.0 ± 8.2 ^a	20.9 ± 10.0 ^a	20.2 ± 5.7 ^a	16.4 ± 6.9 ^b	17.2 ± 5.5 ^b	18.3 ± 6.8 ³
Upper arm area (cm ²)	3079 ± 1112 ^a	3214 ± 1145 ^a	2582 ± 550 ^a	2475 ± 985 ^a	2341 ± 626 ^b	2554 ± 827 ³
Upper arm muscle area (cm ²)	2157 ± 663 ^a	2162 ± 691 ^a	1890 ± 398 ^a	1730 ± 624 ^b	1678 ± 402 ^b	1811 ± 525 ³

¹ $\bar{x} \pm SD$. Means with different superscript letters are significantly different, $P < 0.05$ (Tukey's test after ANOVA on 5 groups). CDC, Centers for Disease Control and Prevention. FFM, fat-free mass. N, asymptomatic; A–C, mildly, moderately, and severely symptomatic, respectively.

²Significantly different from control children, $P < 0.01$ (Scheffe's test).

³Significant effect of clinical category among HIV-infected children, $P < 0.05$ (ANOVA).

Scheffe's method was used to test the difference between control children and the whole group of HIV-infected children.

With the above sample size and a type I error fixed at 0.05, the study had a probability of ≥ 0.80 of detecting a 10% difference between HIV-infected and control children for weight and FFM (type II error = 0.20). Survival probabilities were estimated with the Kaplan-Meier product-limit procedure; survival rates were compared with the log-rank test.

RESULTS

The anthropometric and body-composition data of the children are shown in **Table 2**. HIV-infected children were significantly lighter and shorter than control children; all prediction equations showed significantly lower FFM and upper arm muscle area for HIV-infected children. The different groups of HIV-infected children differed significantly for all variables studied, except for height, for which only children belonging to categories B and C had mean values significantly lower than those of the control children.

The z scores of body weight, FFM, and upper arm muscle area in the different groups of children studied are shown in **Figure 1**. Scores for children in clinical categories B and C, but not N or A, were significantly different from those of control children. This analysis confirmed that both FFM and WAZ are compromised in children with more severe disease. Moreover, it showed that the different estimations of lean body mass are highly consistent within each group of children and that their changes parallel body weight changes.

When FFM and upper arm muscle area were given as percentages of body weight and upper arm area, respectively (**Table 3**), no statistically significant differences were observed between HIV-infected children and control children or between children in the different HIV categories.

Eleven HIV-infected children had a WAZ < -2 (3 in category B and 8 in C) and 14 had an FFM z score < -2 according to the Houtkooper equation (1, 4, and 9 in categories A, B, and C, respectively). Eight children, in category C3 (the children in clinical category C with the most severe immunologic suppression),

died before the end of the study, 1–17 mo after the evaluation (median: 3.9 mo). The WAZ was < -2 in 5 of them and between -1 and -2 in 3; the FFM z score was < -2 in 4 children, between -1 and -2 in 3, and > -1 in 1 child. In the whole group of HIV-infected children, a WAZ or an FFM z score < -2 was associated with an increased risk of death; when only children in clinical category C were considered, only WAZ was (**Table 4**). This figure did not change when FFMs estimated by the equations of Goran et al or Arpadi et al were used (data not shown).

DISCUSSION

Several equations have been published predicting FFM from BIA. However, most of them have been developed in healthy

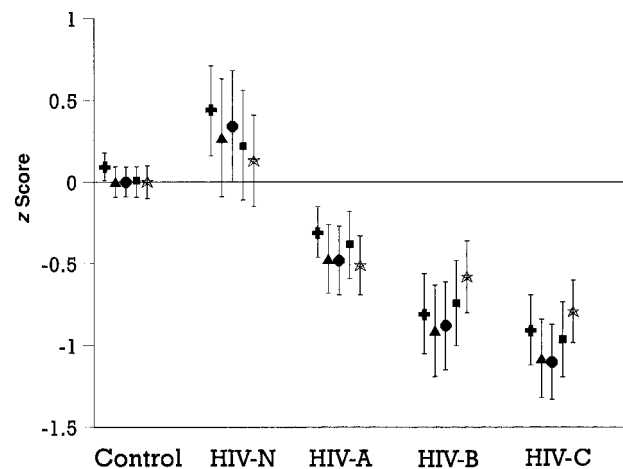


FIGURE 1. Mean (\pm SE) age-specific z scores of body weight (+) and of different estimates of lean body mass in control children and in HIV-infected children in 4 different clinical categories (HIV-N, asymptomatic; and HIV-A–C, mildly, moderately, and severely symptomatic, respectively). \blacktriangle , Fat-free mass as estimated by Goran et al (14); \bullet , fat-free mass as estimated by Houtkooper et al (15); \blacksquare , fat-free mass as estimated by Arpadi et al (16); \star , upper arm muscle area.

TABLE 3

Fat-free mass and upper arm muscle area of the HIV-infected and control children as percentages of body weight and upper arm area, respectively¹

	Control children (n = 113)	HIV-infected children				All (n = 86)
		CDC clinical category			All	
		N (n = 11)	A (n = 23)	B (n = 22)		C (n = 30)
		%				
Fat-free mass						
Goran et al (14)	74.8 ± 8.7	71.1 ± 5.3	75.2 ± 5.7	73.1 ± 7.5	73.8 ± 8.3	73.6 ± 7.1
Houtkooper et al (15)	81.1 ± 7.8	79.0 ± 6.3	81.7 ± 4.8	82.4 ± 8.2	81.8 ± 6.4	81.5 ± 6.5
Arpadi et al (16)	81.6 ± 10.6	77.8 ± 5.3	84.2 ± 6.5	84.6 ± 8.1	85.1 ± 10.2	84.0 ± 8.6
Upper arm muscle area	71.4 ± 6.9	68.0 ± 6.6	73.3 ± 5.1	70.5 ± 5.5	72.7 ± 8.2	71.7 ± 6.7

¹ $\bar{x} \pm SD$. There were no significant differences among clinical categories (by ANOVA), between children in individual categories and control children (Tukey's test after ANOVA on 5 groups), or between all HIV-infected and control children (Scheffe's test). N, asymptomatic; A-C, mildly, moderately, and severely symptomatic, respectively.

children belonging to selected ethnic groups. Their application to children with a different ethnic background or to children with diseases like HIV infection, which progressively affect nutritional status, deserves caution.

We selected 2 equations developed in healthy, white children. The equation of Goran et al was developed from that of Kushner et al (17) divided by an age- and sex-related constant for the hydration of FFM; the final equation was further validated in 2 different groups of healthy children by measuring ¹⁸O dilution space (14). More recently, Reilly et al (18) addressed the ability of 4 published equations to estimate FFM from BIA in a group of healthy prepubertal British children using hydrodensitometry as the reference method; only the equation of Houtkooper et al (15) predicted FFM with negligible bias. The third equation we selected was developed by Arpadi et al (16) in a group of 20 non-white HIV-infected children with dual-energy X-ray absorptiometry as the reference method; to our knowledge, this is the only published equation developed in HIV-infected children. Its applicability to healthy children has not yet been assessed.

These 3 equations use very different subsets of variables to predict FFM. As expected, different equations provided different estimates of FFM in healthy as well as in HIV-infected children, but discussing these differences is beyond the scope of the present work. However, bearing in mind the need to develop and validate specific prediction equations for white, HIV-infected children (and possibly for children in different clinical categories), our study

found remarkably similar figures for FFM, both as absolute values and as percentages of body weight, with the equations of Arpadi et al and Houtkooper et al. In addition, trends in results were observed irrespective of the predictive equation chosen. Moreover, these results are consistent with data from skinfold-thickness measurements, a completely different technique. These findings strongly suggest that a low FFM is common in HIV-infected children belonging to clinical categories B and C (moderately and severely symptomatic), but not in children with no or mild symptoms (categories N and A).

In contrast, loss of body cell mass was found to occur even in otherwise symptomless adult patients (3). Differences in classification criteria may partly explain differences between our asymptomatic pediatric patients and adult patients in other studies, or it is possible that subtle differences in body cell mass are not observed when FFM is estimated by BIA. No other body-composition data are available in asymptomatic children.

The degree of FFM loss was found to be related to the time of death from AIDS in adults (7). McKinney et al (19) retrospectively assessed data from children with severe HIV infection enrolled in a clinical trial of oral zidovudine therapy; they found that a WAZ < -2 was associated with a relative risk of death of 1.53. We found such a WAZ to be associated with remarkably higher relative risks of death (11.4 for the whole group of HIV-infected children and 4.6 for children in category C). Besides different selection criteria (mainly age and disease severity) and

TABLE 4

Mortality of HIV-infected children according to their age-specific weight and fat-free mass (FFM) z scores

	Weight-for-age z score		FFM z score	
	> -2	< -2	> -2	< -2
All HIV-infected children				
Number of deaths (%)	3/75 (4.0)	5/11 (45.4) ¹	4/72 (5.6)	4/14 (28.6) ¹
Survival time (mo)	32.4 ± 0.8	20.2 ± 4.1 ¹	31.9 ± 0.9	25.0 ± 3.4 ¹
Frequency of death (deaths/100 child-months)	0.17	2.80 ¹	0.24	1.41 ¹
Relative risk of death (95% CI)	—	11.36 (3.15, 41.03)	—	5.14 (1.46, 18.17)
Only children in category C				
Number of deaths (%)	3/22 (13.6)	5/8 (62.5) ¹	4/22 (18.2)	4/8 (50.0)
Survival time (mo)	28.9 ± 2.7	15.7 ± 4.3 ¹	27.6 ± 2.8	18.4 ± 4.4
Frequency of death (deaths/100 child-months)	0.63	4.45 ¹	0.87	3.11
Relative risk of death (95% CI)	—	4.58 (1.41, 14.93)	—	0.61 (0.30, 1.26)


¹Significantly different from children with z scores > -2.

possible differences in prognostic indicators derived from small numbers of patients, the very much higher mortality rate observed in that study (49% compared with 26% in our patients) could account for these differences.

An FFM z score < -2 (which indicates an FFM below the 3rd percentile of our control children) seemed to have a weaker association with the risk of death than did WAZ. In our study, lower FFM grossly reflected the reduction of body weight and, as a result, the percentage of body weight provided by FFM (body composition, strictly speaking) was not different either between healthy and HIV-infected children, or among children in different clinical categories. This finding suggests that differences in fat mass and FFM could both contribute in similar proportion to body weight differences in HIV-infected children. Reduced energy intake was reported previously in these children (20) and could account for a loss of body fat as an initial response to starvation. On the other hand, reduced FFM could result either from long-lasting semistarvation or from preferential and inappropriate catabolism of muscle mass, as seen in cachexia. Miller et al (4) reported a selective reduction of muscle mass, as measured by arm muscle circumference, in HIV-infected children < 2 y of age with apparently no changes in fat mass. The children we studied were older, and from our data it is difficult to state whether changes in fat mass preceded the changes in FFM or, on the contrary, both processes proceeded together.

Also, in adult patients it was recently shown that the relative contribution of FFM loss to weight loss, as estimated by several different techniques, is $\approx 60\%$ (6), which suggests that the weight loss is neither catabolic nor cachectic. Neither the results of our study nor these observations support the hypothesis of disproportionate catabolism of FFM.

Obviously, all cross-sectional studies are potentially biased by early mortality. Because 26% of HIV-infected children are estimated to die before the age of 6 y and an estimated 21% of children die within 1 mo of developing a category C illness (21), underrepresentation of children with both asymptomatic and early-onset symptomatic disease is likely to occur in cross-sectional studies. The question of whether the body-composition changes of these children are similar to those of other HIV-infected children who are in other cross-sectional studies is still unanswered.

Further studies, mainly longitudinal cohort studies, are needed to precisely describe the time course of body-composition changes in HIV-infected children. Nevertheless, the whole-body data from our study show that there is no apparent, preferential reduction in FFM in HIV-infected children by the age of 7 y. This suggests that poor energy intake could be the main cause of their weight loss or growth faltering. If confirmed, these results could advocate for vigorous nutritional support, either enteral or parenteral, early in the course of the disease. 

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