

# Abnormalities in body composition and nutritional status in HIV-infected children and adolescents on antiretroviral therapy

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**Summary:** This cross-sectional study aimed to compare growth, nutritional status and body composition outcomes between a group of 94 HIV-infected children and adolescents on antiretroviral therapy (ART) and 364 healthy controls, and to evaluate their association with clinical and lifestyle variables within the HIV-infected group. When compared with the control group, HIV patients had higher risk of stunting (odds ratio [OR] 5.33, 95% confidence interval [CI]: 2.83–10.04) and thinness (OR 4.7, 95% CI: 2.44–9.06), higher waist-to-hip ratios (medians 0.89 versus 0.82 for boys and 0.90 versus 0.77 for girls,  $P < 0.001$ ), and lower prevalence of overweight or obesity (OR 0.33, 95% CI: 0.14–0.78). Protease inhibitor usage was associated with thinness (OR 3.51, 95% CI 1.07–11.44) and lipoatrophy (OR 3.5, 95% CI 1.37–8.95). HIV-infected children on ART showed significant nutritional status and body composition abnormalities, consistent with the severity of vertical HIV infection and the consequences of prolonged ART.

**Keywords:** body composition, nutritional status, children and adolescents, HIV, antiretroviral therapy

## INTRODUCTION

The health and wellbeing of Brazilian children and adolescents have been historically jeopardized by several threats. HIV infection is a relatively recent one, exacting a significant toll in terms of morbidity and mortality. From 1980 to November 2009, more than 18,000 cases of HIV infection in children younger than 13 years old were reported to the Brazilian epidemiological registry. Around 91% of them were due to vertical transmission. A significant number of new cases are still being reported in this age group (around 800 a year), despite the availability of preventive measures.<sup>1</sup>

Growth and nutrition can be severely and precociously compromised in untreated or insufficiently treated HIV-infected children, as demonstrated by regional and international cohort studies.<sup>2,3</sup> In the last 10 years, the implementation of combination antiretroviral therapy (ART) in developed countries has significantly changed this picture, providing improvement in survival, reduction in the incidence of opportunistic infections and recovery of normal growth patterns.<sup>4,5</sup> Similar changes have also been observed for adults and children in Brazil, where ART is universally and freely provided by public health authorities.<sup>6</sup>

The enthusiasm derived from the encouraging results of ART has been somewhat overshadowed by the diversity of its

adverse effects. Metabolic abnormalities and disturbances in body composition have been reported since the introduction of ART. Such abnormalities may be detected clinically or by laboratory tests, and raise concerns related mainly to the risk of further cardiovascular disease (CVD). Protease inhibitors (PIs) and the nucleoside reverse transcriptase inhibitor drug stavudine (D4T) are the agents most frequently associated with such side-effects.<sup>7,8</sup> The interplay between ART-related body changes and lifestyle factors, such as food intake and physical activity, has been a matter of recent evaluation in adult and paediatric cohorts.<sup>9–11</sup> Patients with HIV infection are nowadays a group of individuals with a chronic but controllable disease. Acknowledging this reality, this study aimed to compare body composition outcomes, such as height, weight and fat distribution, between HIV-infected children and adolescents on ART and healthy controls, and to evaluate their association with clinical, immunological and lifestyle variables, within the HIV-infected group.

## PATIENTS AND METHODS

We conducted a cross-sectional study between May 2008 and September 2009. The eligible population comprised 99 children and adolescents being followed up at the Paediatric Immunodeficiency Clinic at the State University of Campinas Hospital, Campinas, São Paulo, Brazil, a tertiary referral center. Five patients were excluded, due to immobility or wheelchair restriction, which prevented anthropometric evaluation. The study population consisted of 94 subjects, all of them on ART. Fifty-five were boys, aged 7.68–19.76 years (median 12.72) and

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39 girls, aged 8.15–18.35 years (median 12.07). All had a diagnosis of HIV infection, confirmed according to Centers for Disease Control and Prevention (CDC) criteria,<sup>12</sup> adapted by the Brazilian Ministry of Health. Three hundred and sixty-four healthy children and adolescents (178 boys and 186 girls) comprised the control group. Control group children studied in public schools from nearby suburban areas, and were socially and demographically comparable with HIV-infected patients.

The Internal Review Board of the State University of Campinas Faculty of Medical Sciences approved the study (statement no. 818/2007). All legal caretakers and teenagers signed an informed consent form.

Anthropometric evaluations and blood sample collections were performed after a 12-hour fast, in the morning. Height and weight were measured according to recommendations from the Anthropometric Standardization Reference Manual.<sup>13</sup> Normal stature was defined as a value above the  $-2$  Z-score from the 2000 National Center for Health Statistics reference.<sup>14</sup> Overweight, obesity and thinness were defined according to body mass index international standards proposed by Cole *et al.*<sup>15,16</sup> Waist and hip circumferences were determined with flexible metric tape (precision of 1 mm). Skinfold measurements were performed with a Lange caliper (Beta Technology Inc, Cambridge, MA, USA), according to procedures established by Lohman *et al.*<sup>13</sup> and skinfold thickness equations were calculated for fat percentage.<sup>17</sup> Adolescents were considered pubertal if they were at least on stage P2 and G2 for male and M2 and P2 for female.<sup>18</sup>

Lipodystrophy was defined by clinical examination.<sup>19</sup> Clinical and immunological HIV categories were defined according to CDC standards, adapted by the Brazilian Ministry of Health.<sup>1</sup> Physical activity was measured with the physical activity questionnaire for children,<sup>20</sup> for patients up to 12 years old, and the international physical activity questionnaire,<sup>21</sup> for patients older than 12 years. Food energy intake was measured by 24-hour recall and its adequacy evaluated according to Recommended Dietary Allowances.<sup>22</sup> HIV viral load was measured by RNA-PCR (Versant<sup>®</sup> bDNA HIV-1 RNA 3.0, Siemens, SP, Brazil) and lymphocyte subpopulations were determined by flow cytometry (FACS Count<sup>®</sup>, Becton Dickinson and Co, SP, Brazil).

Statistical analysis was performed using SPSS<sup>®</sup> software, version 16.0 (SPSS Inc, Chicago, IL, USA). Due to well-established sex differences in body composition in healthy children and adolescents, the comparison of continuous dependent variables between HIV-infected and control subjects was performed separately for boys and girls. Within the HIV-infected group, due to the diversity and potentially confounding effects of independent variables, multivariate analysis was performed, employing the method of logistic regression for categorical variables and multiple linear regression for continuous variables. Association between categorical variables was assessed by  $2 \times 2$  tables, in the form of odds ratios (ORs) and 95% confidence intervals (CIs), and between continuous variables with the employment of Mann-Whitney test or Spearman Coefficient Correlation ( $\rho$ ). Significance was attributed to  $P$  values lower than 0.05.

## RESULTS

### Comparison between HIV-infected and control groups

As shown in Table 1, HIV-infected children and teenagers had a higher risk of short stature and malnutrition, and a lower risk

**Table 1 Analysis of differences in growth and nutritional status between HIV-infected children and adolescents on ART and controls**

Characteristic	HIV (n = 94) n (%)	Control (n = 364) n (%)	(95% CI)
Short stature	24 (25.5)	22 (6.0)	5.33 (2.83–10.04)
Thinness	21 (22.3)	22 (6.0)	4.70 (2.44–9.06)
Overweight/obese	6 (6.4)	62 (17.0)	0.33 (0.14–0.78)

ART = antiretroviral therapy; OR (95% CI) = odds ratio (95% confidence interval)

for being obese or overweight, when compared with subjects in the control group.

Regarding body composition variables, HIV-infected boys had a significantly higher waist-to-hip-ratio. Girls from the infected group had significantly higher waist circumferences and waist-to-hip ratios, and lower subscapular-to-tricipital (SS/TR) skinfold ratios (Table 2).

### Analysis within the HIV-infected group

The 94 subjects from the patient group had been on ART for a median of 7.8 years (range, 0.2–15.5 years). The median age for beginning ART was 4.09 years (range, 0.4–17.07 years). As shown in Table 3, the prevalence of antiretroviral drugs associated with fat distribution abnormalities was 60.6% for PI and to 29.8% for D4T. Clinically, 31.9% of the patients were classified in category C and, immunologically, 37.2% were in category 3. Regarding diet and lifestyle, 26.6% were sedentary and 55.3% did not meet the recommendations for energy intake.

The prevalence of lipodystrophy and lipohypertrophy in this group was 38.3% and 40.4%, respectively. The results from multivariate analysis demonstrated that patients in CDC clinical category C had a higher risk of short stature (OR = 3.68; 95% CI 1.39–9.73). Children on PIs had a higher risk of lipoatrophy and malnutrition (OR = 3.5; 95% CI 1.37–8.95 and OR = 3.51; 95% CI 1.07–11.44, respectively). The risk for abdominal lipohypertrophy was significantly increased in children in immunological category 3 (OR = 2.5; 95% CI 1.06–5.91).

Additionally, independently of gender, children in immunological category 3 had higher waist-to-hip ratios (medians 0.91 versus 0.89,  $P = 0.004$ ). Older age was associated with higher waist circumference ( $P = 0.58$ ,  $P < 0.001$ ), higher SS/TR skinfold ratios ( $P = 0.32$ ,  $P = 0.021$ ), and lower waist-to-hip ratios ( $P = -0.24$ ,  $P = 0.003$ ).

No significant associations were found between body composition abnormalities and physical activity or dietary adequacy.

## DISCUSSION

The high risk of short stature and its association with clinical severity was a striking feature of the study population. Such findings could be explained by the cross-sectional design of the study, which included a significant proportion of teenagers. Those subjects went through their early ages, a critical phase for growth, in the period before the establishment of ART, which effectively took place from 1998 thereafter. These results agree with former observations from the same cohort, which also demonstrated a high prevalence of growth compromise, beginning very early at three months of age; also with a higher

Table 2 Analysis of differences in body composition variables between HIV-infected children and adolescents on ART and controls

Characteristic	HIV (n = 55)		Control (n = 178)		P*
	Median	Range	Median	Range	
<b>Boys</b>					
Waist circumference <sup>†</sup>	61	49–85	60	49–94	0.553
Body fat% <sup>‡</sup>	12.68	6.84–37.50	12.10	4.70–45.40	0.189
Waist-to-hip ratio	0.89	0.78–1.06	0.82	0.70–0.99	<0.001
SS/TR <sup>§</sup>	0.83	0.40–1.50	0.80	0.33–2.33	0.793
<b>Girls</b>					
Waist circumference <sup>†</sup>	65	48–86	61	45–82	0.011
Body fat% <sup>‡</sup>	21.21	8.94–44.85	20.75	9.30–39.73	0.972
Waist-to-hip ratio	0.90	0.71–1.06	0.77	0.65–0.99	<0.001
SS/TR <sup>§</sup>	0.63	0.37–1.20	0.76	0.41–1.44	0.002

ART = antiretroviral therapy; \*Mann-Whitney test; <sup>†</sup>centimetres; <sup>‡</sup>body fat percentage; <sup>§</sup>SS/TR = subscapular/triceps skinfold ratio

proportion in category C children.<sup>2,23</sup> A similar pattern was observed by the European Collaborative Study, which, analysing a much larger cohort, also demonstrated the association between the magnitude of the growth deficit and clinical severity, in all ages.<sup>24</sup> Recent data from cohorts of ART-treated children, however, show that a catch-up in growth is feasible when effective therapy is started early.<sup>25,26</sup>

Another very relevant issue was the significantly higher risk for thinness in the HIV-infected population. Our data suggest that the risk for thinness is not related to inadequate food intake, measured by adequacy compared with RDA. Several international reports stress the association between HIV infection and thinness. In an Indian report, the prevalence of malnutrition varied from 17% to 62%.<sup>27</sup> Data from a South African

cohort of children born to HIV-infected mothers also show an early and sustained prevalence of malnutrition between vertically infected subjects, when compared with seroreverters.<sup>28</sup> It is worth remembering that disturbances in growth and nutrition in HIV-infected children have a complex pathophysiology, encompassing nutrient intake, a catabolic state mediated by chronic inflammation and recurrent infections, and endocrine factors.<sup>29</sup> The association between PI usage, thinness and lipodystrophy, observed in our population, suggests that PIs may also contribute to the decrease in body fat, similar to what has been observed by other groups.<sup>30,31</sup>

The lower overweight or obesity risk, observed in HIV-infected children, when compared with healthy controls, is an original finding from our study. The finding of a significantly lower SS/TR skinfold ratio, a marker of truncal adiposity, observed in infected girls when compared with controls, reinforces these results. Similar results, regarding overweight and obesity risks, were found in another recent Brazilian report.<sup>11</sup> Contrasting with these findings, an American report of HIV-infected young patients revealed a 49.4% prevalence of overweight and obesity, similar to that observed in the uninfected controls (54.3%).<sup>32</sup> Additionally, reports from studies in adult HIV-infected patients show a similar prevalence of obesity between ART-treated patients and the general population.<sup>33</sup> We hypothesize that our study population still maintains the consequences of early-age malnutrition, and that, with prolonged survival, overweight and obesity rates may increase. Also, cultural differences regarding lifestyle variables, such as diet and physical exercise, may be partially responsible.<sup>32</sup>

Some findings from our study population suggest that, despite a low risk of becoming obese or overweight, HIV-infected children on ART may face an increased risk of body composition abnormalities. Clinically identified abdominal lipohypertrophy had a high prevalence, and was associated with past or present severity of immunological compromise. Also, waist circumference and waist-to-hip ratio, both surrogate markers for abdominal lipohypertrophy and risk of CVD, were significantly higher in the infected group. Similar findings were reported by McComsey *et al.*,<sup>8</sup> Aurpibul *et al.*,<sup>34</sup> and the European Paediatric Lipodystrophy Group,<sup>25</sup> who also found an association between the degree of lipohypertrophy and disease severity. Due to the association between lipohypertrophy and dyslipidaemia, as observed in the larger European study population,<sup>22</sup> studies are being conducted in adult and paediatric populations to investigate the association of disturbances in body composition and risk of accelerated CVD. However, the results available so far are inconclusive.<sup>35</sup>

Table 3 Distribution of independent variables in 94 HIV-infected children and adolescents

Variables	Boys		Girls		Total	
	n	%	n	%	n	%
<b>Current PI usage</b>						
Yes	35	63.6	22	56.4	57	60.6
No	20	36.4	17	43.6	37	39.4
<b>Any PI usage</b>						
Yes	48	87.3	33	84.6	81	86.2
No	7	12.7	6	15.4	13	13.8
<b>D4T usage</b>						
Yes	16	29.1	12	30.8	28	29.8
No	39	70.9	27	69.2	66	70.2
CDC immunological class 1 and 2	32	58.2	27	69.2	59	62.8
CDC immunological class 3	23	41.8	12	30.8	35	37.2
CDC clinical class N, A and B	39	70.9	25	64.1	64	68.1
CDC clinical class C	16	29.1	14	35.9	30	31.9
<b>HIV RNA</b>						
Undetectable	27	49.1	13	33.3	40	42.6
Detectable	28	50.9	26	66.7	54	57.4
<b>CD4<sup>+</sup> Cell count</b>						
>500	40	72.7	28	71.8	68	72.3
≤500	15	27.3	11	28.2	26	27.7
<b>CD4/CD8 ratio</b>						
≥1	8	14.5	4	10.3	12	12.8
<1	47	85.5	35	89.7	82	87.2
<b>Physical activity</b>						
Active	47	85.5	22	56.4	69	73.4
Sedentary	8	14.5	17	43.6	25	26.6
<b>Dietary adequacy</b>						
Adequate	27	49.1	15	38.5	42	44.7
Inadequate	28	50.9	24	61.5	52	55.3
Total	55	100.0	39	100.0	94	100.0

PI = protease inhibitor; D4 T = stavudine; CDC = Centers for Disease Control and Prevention

In our study, we did not find significant associations between body composition abnormalities and lifestyle variables, such as physical activity and dietary intake. Results from recent controlled trials suggest that exercise and nutrition can modulate body composition in noninfected obese children;<sup>36</sup> however, we did not find similar reports in the context of paediatric HIV infection.

Our study certainly has limits imposed by the cross-sectional design, since variables related to growth, nutrition and body composition are prone to rapid changes in children and teenagers. However, we feel that the use of a control group, matched by age, sex and social condition, strengthens the power of our results. The use of a control group is important given the regional differences in ethnicity and lifestyle. Additionally, for some variables, such as waist-to-hip ratios, there are still no widely accepted international standards.

We conclude that our study population of HIV-infected teenagers and children on ART, a significant proportion of them survivors from the pre-ART era, shows significant compromise in growth, nutritional status and body composition markers. These abnormalities are consistent with the precocity of clinical impairment in vertically acquired HIV infection, and with prolonged exposure to ART.

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(Accepted 9 March 2011)