J Pediatr Endocr Met 2012;25(5-6):529–535 © 2012 by Walter de Gruyter • Berlin • Boston. DOI 10.1515/jpem-2012-0005

Metabolic disorders in vertically HIV-infected children: future adults at risk for cardiovascular disease

Marta Dapena[1,a], Beatriz Jiménez[2,a], Antoni Noguera-Julian[3], Pere Soler-Palacín[1,*], Clàudia Fortuny[3], Rebeca Lahoz[3], Francisco Javier Aracil[2], Concepción Figueras[1] and María Isabel de José[2]

[1] Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron – Universitat Autònoma de Barcelona, Barcelona, Spain
[2] Pediatric Infectious Diseases Unit, Hospital Universitario La Paz, Madrid, Spain
[3] Pediatric Infectious Diseases Unit, Department of Pediatrics, Hospital Universitari Sant Joan de Déu – Universitat de Barcelona, Esplugues de Llobregat, Spain

Abstract

Background: Despite metabolic disorders in HIV-infected children being widely described, there is still a lack of agreed criteria for diagnoses and management. Numerous studies are coming from other settings and results are heterogeneous when assessing several analytical and clinical parameters.
Objectives: To describe the prevalence of metabolic disorders and associated risk factors in the Spanish National cohort of HIV-infected pediatric patients (CoRISpe).
Methods: This was a cross-sectional study following all vertically HIV-infected children and adolescents in three referral centers included in the CoRISpe. Metabolic data (fasting lipids, glucose and insulin levels and thyroid hormone levels) were collected. Fat distribution was clinically assessed by expert clinicians.
Results: We included 157 patients [median age 13 years, interquartile range (IQR) 10–16]. Median duration of antiretroviral therapy was 10.2 years (IQR 5.0–13.0). Almost 20% of patients had insulin resistance and this was associated with hepatitis C co-infection, current use of stavudine (d4T) and hypertriglyceridemia. Hypercholesterolemia and hypertriglyceridemia were found in 23.9% and 24.8% of patients and were associated with current use of protease inhibitors (p=0.042 and p=0.022, respectively). Abnormal fat distribution was observed in 63 patients (40.5%): lipoatrophy in 32 (20.4%), lipohypertrophy in eight (5.1%) and a mixed pattern in 23 patients (14.6%), and it was significantly associated with previous exposure to stavudine (p<0.001).
Conclusions: Metabolic disorders are a significant problem in our HIV-infected pediatric population. We need to encourage the development of global strategies and the creation of consensus guidelines that can decrease the cardiovascular risk in this population.

Keywords: antiretroviral; dyslipidemia; HIV; HIV-associated lipodystrophy syndrome; insulin resistance.

Introduction

Over the past 20 years, the implementation of highly active antiretroviral therapy (HAART) has considerably reduced the mortality and morbidity associated with human immunodeficiency virus (HIV) infection in children living in industrialized countries. Concomitantly, morbidity from the long-term effects of antiretroviral drugs has grown in importance. Among the related complications, metabolic disorders, such as abnormal glucose metabolism, dyslipidemia and abnormalities in body fat distribution, with subcutaneous fat loss and central fat accumulation, are a cause for concern. In children facing the prospect of life-long treatment with HAART, the development of these complications is particularly worrisome because of the potentially increased risk of cardiovascular disease in early adulthood (1–10).

Previous related studies have included a significant number of patients, but have provided relatively heterogeneous results, and the rate of metabolic disorders in this population remains unclear (2, 7, 9, 11). Furthermore, childhood obesity is an increasingly prevalent problem in developed countries, and the similarity between abnormalities occurring in this condition and those of antiretroviral-induced metabolic syndrome further complicates the analysis (12, 13). Despite the first descriptions being reported almost 10 years ago, there are still no standardized criteria or guidelines for the management of this treatment-related complication.

Most studies on this subject come from geographic areas other than Spain and those performed in this setting include small patient numbers (3, 10, 14). To define the status of our pediatric patients in this regard, this study was designed to assess the prevalence of metabolic disorders and related risk factors in a large cohort of vertically HIV-infected Spanish children with lengthy antiretroviral drug exposure.

[a]Marta Dapena and Beatriz Jiménez contributed equally to the manuscript.

*Corresponding author: Dr. Pere Soler-Palacín, Pediatric Infectious Diseases and Immunodeficiencies Unit Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona Passeig de la Vall d'Hebron, 119-129 08035, Barcelona, Spain
Phone: +34 934893140, Fax: +34 934893039,
E-mail: psoler@vhebron.net

Received January 8, 2012; accepted March 1, 2012;
previously published online April 19, 2012

Methods

Study design

A cross-sectional study was carried out in a cohort of vertically HIV-infected children and adolescents followed-up at the outpatient clinics at Hospital Universitario La Paz (Madrid), Hospital Universitari San Joan de Déu (Barcelona) and Hospital Universitari Vall d'Hebron (Barcelona), three tertiary pediatric reference hospitals within the cohort of HIV-infected pediatric patients (CoRISpe). CoRISpe is the Spanish cohort of HIV-infected children of 18 years or below, which currently includes 794 patients in 73 centers in Spain. The study was approved by the Ethics Committees of all three centers, and informed consent for participation was obtained from all patients and parents or legal guardians, as appropriate.

Clinical data

Clinical and immunological stage was assessed according to the Centers for Disease Control and Prevention (CDC) classification criteria (15). Demographic characteristics, a complete history of past and current antiretroviral drug use, and data on hepatitis B virus and hepatitis C virus (HCV) co-infection were obtained from the CoRISpe database.

Outcomes and definitions

At assessment, CD4+T- lymphocyte percentage and absolute count, and HIV-1 viral load (VL) were determined. HIV-VL was defined as undetectable at <50 copies/mL. Blood was drawn after an 8-h fast and the following parameters were analyzed: lipid profile (triglycerides, total cholesterol, high-density cholesterol [HDL-c], and low-density cholesterol [LDL-c]), glucose, insulin and thyroid hormones (thyroid-stimulating hormone and free thyroxine).

Abnormal fasting lipid levels were defined based on American Heart Association criteria, endorsed by the American Academy of Pediatrics (16, 17). Cholesterol and triglyceride levels were analyzed using enzymatic methods. Hypertriglyceridemia was established based on plasma triglyceride levels ≥150 mg/dL and hypercholesterolemia on total plasma cholesterol levels ≥200 mg/dL. The cut-off for abnormal LDL-c was >130 mg/dL, and for abnormal HDL-c was <40 mg/dL. Dyslipidemia was established whenever hypercholesterolemia and/or hypertriglyceridemia were documented.

Plasma glucose concentrations were measured using the glucose oxidase method. Serum insulin concentrations were determined by enzyme immunoassay. According to the International Diabetes Foundation's Metabolic Syndrome in Children and Adolescents consensus report (18), fasting glucose was considered normal at <100 mg/dL. The homeostatic model of insulin resistance (HOMA-IR=fasting insulin (μU/mL)×fasting glucose (mg/dL)/405) was used to assess insulin resistance. A HOMA-IR result >4.0 was considered a marker of resistance (19).

Serum concentrations of thyroid-stimulating hormone and free thyroxine were determined by electrochemiluminescence immunoassay. Reference ranges were 0.25–6.15 μU/mL for thyroid-stimulating hormone and 0.70–1.64 ng/dL for free thyroxine.

Body measurements

Anthropometric measurements included height, weight and body mass index (BMI) and were expressed as Z-scores, adjusted for age and sex based on the Spanish standard growth curves (20). BMI categories, (overweight, obese, and malnourished) were defined according to the World Health Organization Expert Committee statement (21). Puberty was rated using Tanner stages.

The diagnosis of abnormal fat distribution was based on physical examination performed by expert clinicians at the most recent visit and was classified according to the European Paediatric Lipodystrophy Group as follows (22):

- lipohypertrophy (central or cervical fat accumulation, and/or breast enlargement);
- lipoatrophy (peripheral fat loss in face, limbs or buttocks); and
- a mixed pattern when both were present.

Statistical analyses

Results were expressed as the median and interquartile range (IQR) for quantitative variables and as the percentage for qualitative variables. When antiretroviral drugs were analyzed as risk factors, naïve patients were excluded. Comparisons between quantitative variables were performed with the Mann-Whitney U-test or Student's t-test. The Fisher exact test was used to compare categorical variables. Multivariate logistic regression analysis was performed including only variables that were significantly associated with metabolic disorders or abnormal fat redistribution in the bivariate analysis. Results are given as odds ratios (ORs) with 95% confidence intervals (CIs). Significance was set at a p-value of <0.05. Statistical analyses were performed using the Statistical Package for the Social Sciences (v.17) (SPSS, Chicago, IL, USA).

Results

A total of 157 vertically HIV-infected pediatric patients were evaluated. All patients included were 18 years of age or younger and were followed-up at the three participating hospitals; no patients were excluded. Median age was 13 years (IQR: 10–16) and 50.3% of participants were Tanner stage ≥4 at assessment. Fifteen patients (9.6%) were co-infected with HCV and two patients (1.3%) with hepatitis B virus. The main clinical data of the study patients are shown in Table 1.

Plasma HIV-VL was undetectable in two-thirds of patients, and median CD4+ T-cell count/percentage was 777 per mm^3/34%. Almost one-third of patients met the AIDS criteria. Seven of 150 children were naïve to HAART, nine were on structured treatment interruption, and the rest were receiving HAART. Median duration of antiretroviral therapy was 10.2 years (IQR: 5.0–13.0). Median duration of antiretroviral interruption was 60 months (IQR: 6.0–86.5). None of the patients were receiving glucose-lowering or lipid-lowering drugs.

Among the patients on HAART, 90% were currently receiving a nucleoside reverse transcriptase inhibitor-based regimen, 46.7% a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, and 53.3% a protease inhibitor-based regimen. Almost 90% of patients had been exposed to the three main families of antiretroviral drugs at least once.

Ever/current exposure to zidovudine and stavudine (d4T) was 82.2%/36% and 71%/8.6%, respectively.

Median Z-score values for body weight, height and BMI were within normal ranges. Five patients (3.2%) were overweight, eight (5.2%) were obese, and three (1.9%) were

Table 1 Baseline characteristics of the cohort (n=157) at the time of the assessment.

Variable	Number
Age, years	13 (IQR: 10–16)
Female gender, n (%)	94 (59.9%)
Tanner, n (%)	
1	40 (25.5%)
2–3	38 (24.2%)
4–5	79 (50.3%)
CDC clinical category, n (%)	
N/A	66 (42.0%)
B	46 (29.3%)
C (AIDS)	45 (28.7%)
CDC- Immunological category, n (%)	
1 (CD4 ≥25%)	40 (25.5%)
2 (CD4 15%–25%)	60 (38.2%)
3 (CD4 15%)	57 (36.3%)
Hepatitis B virus co-infection, n (%)	2 (1.3%)
HCV co-infection, n (%)	15 (9.6%)
HIV-infection markers	
Viral load <50 copies/mL, n (%)	101 (64.3%)
CD4+ T-cells percentage (%)	34 (26.5–40.0)
CD4+ T-cells per mm^3	777 (579–1144)
Antiretroviral therapy, n (%)	
Naïve patients	7 (4.5%)
No current treatment	16 (10.2%)
Time on ARV, years (n=157)	10.2 (5–13)
Drug in current combination (n=150), n (%)	
NRTI	135 (91.8%)
Zidovudine	46 (30.7%)
Stavudine	12 (8.0%)
NNRTI	71 (47.3%)
Protease inhibitor	80 (53.3%)
Previous exposure (n=150), n (%)	
NRTI	
Zidovudine	125 (82.2%)
Stavudine	108 (71%)
NNRTI	112 (74.7%)
Protease inhibitor	129 (86%)

Values are expressed as median (interquartile range) except when stated otherwise. ARV, antiretroviral therapy; CDC, centers for disease control; HCV, hepatitis C virus; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside analog HIV reverse transcriptase inhibitor.

Table 2 Main endocrine and metabolic results of patients included in the cohort (n=157).

Variable	
Anthropometric values	
Z score weight[a]	–0.49 (–1.17 to 0.18)
Z-score height[a] (n=155)	–0.40 (–1.29 to 0.38)
Z- score BMI[a] (n=155)	–0.37 (–0.96 to 0.32)
Abnormal fat distribution[b]	63 (40.5%)
Lipoatrophy[b]	32 (20.4%)
Lipohypertrophy[b]	8 (5.1%)
Mixed pattern[b]	23 (14.6%)
Thyroid function (n=156)	
Thyroid-stimulating hormone[a], µU/mL	1.80 (1.2–2.5)
Free T4[a], ng/mL	1.07 (0.95–1.16)
Lipid metabolism	
Total cholesterol[a], mg/dL	162 (134.5–195.0)
HDL-c, mg/dL[a] (n=155)	46 (39–56)
LDL-c, mg/dL[a] (n=155)	96 (74–121)
Total cholesterol/HDL-c ratio[a] (n=155)	3.5 (3.0–4.1)
Hypercholesterolemia[b]	37 (23.9%)
LDL-c ≥130 mg/dL	28 (18.1%)
Triglycerides[a], mg/dL	106 (73.8–149.0)
Hypertriglyceridemia[b]	39 (24.8%)
Carbohydrate metabolism	
Fasting glycemia[a], mg/dL	88.0 (83–93)
Fasting hyperglycemia[b]	11.0 (7%)
Fasting insulin[a], µU/mL (n=151)	9.4 (5.0–16.3)
Hyperinsulinemia[b] (n=151)	35.0 (23.2%)
HOMA-IR[a] (n=151)	2.0 (1.0–3.5)
Insulin resistance (HOMA-IR ≥4.0)[b]	30.0 (19.9%)

Values are expressed as: [a]median (interquartile range); and [b]n and percentage. BMI, body mass index; HDL-c, high-density cholesterol; LDL-c, low-density cholesterol; HOMA-IR, homeostatic model assessment to quantify insulin resistance.

malnourished. Among the obese and overweight children, 78% were white.

In 18 patients (11.6%), height was below -2 standard deviations. The main anthropometric, metabolic and hormonal data are summarized in Table 2.

Abnormal fat distribution was observed in 63 patients (40.5%): lipoatrophy in 32 (20.4%), lipohypertrophy in eight (5.1%), and a mixed pattern in 23 (14.6%), with no differences between patients on HAART or structured interruption (p=0.082).

There were no cases of abnormal fat distribution in naïve subjects (p=0.042). On univariate analysis, total antiretroviral exposure was longer in patients with fat redistribution (r+0.45, p<0.001). In addition, ever exposure to d4T, NNRTIs or protease inhibitors (p<0.001, p<0.001, and p=0.012, respectively) and Tanner stage ≥4 (p<0.001) were significantly associated with abnormal fat distribution patterns. On multivariate analysis adjusted for total antiretroviral exposure in years, NNRTI exposure, d4T exposure, protease inhibitor exposure, Tanner stage, fasting insulin, LDL-c plasma levels, HOMA-IR index and CD4+ T-lymphocyte absolute counts, only ever d4T exposure remained significantly associated with abnormal fat distribution (OR 3.8, 95% CI 1.1–13.0; p=0.033).

Hypercholesterolemia was found in 23.9% of patients and hypertriglyceridemia in 24.8%. Twenty-eight patients (18.1%) showed elevated plasma LDL-c levels, 42 (27.1%) low HDL-c levels, and 12 (7.7%) a total cholesterol/HDL-c ratio >5. Hypertriglyceridemia was more frequent in boys (34.9% vs. 18.1%, p=0.023). Hypertriglyceridemia was not related to CDC stage or higher HIV-VL.

Patients with hypercholesterolemia showed higher CD4+ T-cell percentage (36.8±7.8 vs. 31.9±10, p=0.008) and lower HIV-VL (p=0.002) than those with normal cholesterol levels. Subjects who were not currently receiving HAART showed normal total cholesterol and triglyceride levels (r=0.17, p=0.042 and r=0.18, p=0.022, respectively).

On multivariate analysis, hypercholesterolemia and hypertriglyceridemia were both associated with current protease

inhibitor use (OR 3.3, 95% CI 1.4–7.7; p=0.005 and OR 3.3, 95% CI 1.4–7.5; p=0.004, respectively), adjusted for total antiretroviral exposure in years and current antiretroviral therapy.

Fasting plasma glucose levels above normal were observed in 11 patients (7%) and insulin resistance was diagnosed in 19.9%. Three patients (1.9%), had plasma glucose levels >110 mg/dL and HOMA-IR values of 22.40, 13.23, and 19.00, respectively.

There were no significant differences in HOMA-IR based on Tanner stage, sex or BMI Z-score. On multivariate analysis, insulin resistance was significantly associated with HCV co-infection (OR 5.0, 95% CI 1.4–17.3; p=0.009), current d4T use (OR 5.0, 95% CI 1.3–18.8; p=0.016), and hypertriglyceridemia (OR 1.01, 95% CI 1.00–1.01; p=0.006), adjusted for total antiretroviral exposure in years, current antiretroviral therapy, fasting triglyceride plasma levels and HCV infection. No cases of overt diabetes were detected.

Mean free thyroxine level was 1.08 ng/mL (IQR 0.95–1.16) and mean thyroid-stimulating hormone level was 2.06 µU/mL (IQR 1.2–2.5). Among the 157 patients, two cases of subclinical hypothyroidism were detected (1.27%); thyroid-stimulating hormone levels were <10 µU/mL but they normalized in 3 months without no interventions. The most important results obtained are summarized in Table 3.

Discussion

The availability of HAART has shifted concerns regarding the management of HIV-infected patients. The disease now resembles a chronic condition in which the long-term effects of antiretroviral treatment have gained considerably in importance. These effects are of particular consequence in children with HIV, who are expected to have a lengthy survival. As clinicians involved in the care of these patients, we were prompted to review the treatment protocols used in our children to take these aspects into consideration, one, such aspect being antiretroviral-related metabolic disturbances. As the first step in this task, we set out to define the metabolic status of our patients, which can be affected by antiretroviral therapy and have future implications on cardiovascular health.

In keeping with the findings from recent studies (1–11), significant metabolic disorders were detected in a substantial percentage of vertically HIV-infected Spanish children and adolescents. The main factor that was significantly associated with fat redistribution on multivariate analysis was d4T exposure, as has been reported elsewhere (4, 23, 24), although it was more common in Tanner stage ≥4 adolescents and in those with longer exposure to HAART (3–5, 8, 22). The high exposure to d4T at the time of the study can be explained by the older median age of the cohort. Many patients had developed resistances and were receiving antiretroviral rescue therapy, including d4T. Our findings support the notion that d4T should be avoided whenever possible in HIV-infected patients, and confirm that it is a significant risk factor for metabolic disorders and abnormal fat distribution (22, 25).

Of note, although the duration of interruption was lengthy in our cohort, the number of patients on structured HAART interruption was small and there were no significant differences in fat distribution patterns between these patients and those receiving HAART.

Regarding dyslipidemia, it is of interest that individuals with hypercholesterolemia had better immunological status and virological control, which may reflect better adherence to HAART and could be a sign of immune reconstitution (11, 14).

The percentage of patients with impaired fasting glucose was high in our cohort, but in accordance with the results reported by Aldrovandi et al. (2). Other studies have reported lower percentages, although this may be attributable to the lower cut-off we used of 100 mg/dL instead of 120 mg/dL (18). This could correspond to a pre-diabetic stage, but oral glucose tolerance testing was not performed so prediabetes cannot be assumed. Our patients also showed a high prevalence of insulin resistance (19.9%) compared to some previous findings (26, 27), but again, other authors have reported similar values (4). In any case, the high values we found may be related to the relatively older median age of our cohort, greater Tanner stage, and the prevalence of fat redistribution.

Insulin resistance was only related to current d4T use and HCV co-infection on multivariate analysis. If we had used an alternative cut-off of 3.16 for elevated HOMA-IR, as proposed by Tresaco et al. (19), the percentage would have increased to 29.1%. This suggests that a lower HOMA-IR cut-off will enable early identification of metabolic syndrome in children at risk (18).

HIV-infected patients are prone to thyroid dysfunction and regular assessment is recommended in this population (28) as subclinical hypothyroidism has been associated with increased cardiovascular risk (29, 30). In our cohort, however, only two cases of subclinical hypothyroidism were detected, and hormone levels normalized spontaneously within 3 months in both cases.

The strength of our study resides in the characteristics of the cohort: the length of antiretroviral drug exposure and the sample size are the largest published in our setting. Furthermore, the methods used in calculating the fasting profile were appropriate. An interesting finding was the emergent overweight and obesity rate in our cohort, with 8.4% of our patients affected overall. Whereas HIV-infected children living in industrialized countries are healthier and malnourishment has become uncommon, obesity is a global pediatric trend (12, 13) that adds to cardiovascular risk due to the virus itself and the side-effects of antiretroviral treatment.

The cross-sectional design is an obvious limitation of our study, as is its retrospective nature, which is the reason why waist circumference, an independent predictor of insulin resistance in children, and blood pressure were not routinely measured. Thus, the prevalence rate of metabolic syndrome could not be established in our cohort (18). These data will soon be available in a prospective study including the entire cohort. In addition, the assessment of fat redistribution was based on clinical criteria; therefore, a quantitative assessment is not provided. Nonetheless, when clinical assessment is

Table 3 Risk factors for abnormal fat distribution, insulin resistance and dyslipidemia (univariate analysis).

	Abnormal fat distribution			Insulin resistance			Hypercholesterolemia			Hypertriglyceridemia		
	Abnormal (n=63)	Normal (n=94)	p-Value	HOMA≥4 (n=30)	HOMA<4 (n=121)	p-Value	TC≥200 mg/dL (n=37)	TC<200 mg/dL (n=120)	p-Value	TG≥150 mg/dL (n=39)	TG<150 mg/dL (n=118)	p-Value
Sex[c] (female)	35 (55.6%)/ 28 (44.4%)	59 (62.8%)/ 35 (37.2%)	0.408[d]	16 (53.3%)/ 14 (46.7%)	72 (59.5%)/ 49 (40.5%)	0.543[d]	17 (45.9%)/ 20 (54.1%)	77 (64.2%)/ 43 (35.8%)	0.056[d]	17 (43.6%)/ 22 (56.4%)	77 (65.3%)/ 41 (34.7%)	0.023*,[d]
Tanner≥4[c]	45 (71.4%)	34 (36.2%)	<0.001*,[d]	17 (56.7%)	60 (49.6%)	0.544[d]	16 (43.2%)	63 (52.5%)	0.352[d]	19 (48.7%)	60 (50.8%)	0.855[d]
BMI Z-score[b]	–0.2±1.1	–0.2±1.0	0.836[f]	0.1±1.4	–0.2±0.9	0.872[e]	–0.4±0.6	–0.1±1.1	0.114[e]	–0.5±0.9	–0.1±1.1	0.078[e]
HVC[c]	8 (12.6%)	7 (7.4%)	0.283[d]	7 (23.3%)	7 (5.8%)	0.008*,[d]	3 (8.1%)	12 (10.0%)	0.100[d]	3 (11.1%)	5 (9.1%)	1.000[d]
Viral load[a], copies/mL	<50 (<50–1600)	<50 (<50–1300)	0.979[e]	<50 (<50–2600)	<50 (<50–325)	0.613[e]	<50 (<50–<50)	<50 (<50–2525)	0.002*,[e]	<50 (<50–1600)	<50 (<50–1450)	0.317[e]
CD4+ T cells[b]	32.6±10.2	33.3±9.4	0.692[f]	31.1±11.0	33.6±9.1	0.236[e]	36.8±7.8	31.9±10.0	0.008*,[e]	30.7±10.2	33.8.0±9.5	0.090[e]
Time ART[b], years	11.5±3.2	6.9±5.0	<0.001*,[f]	9.6±4.5	8.7±5.03	0.376[e]	9.4±4.4	8.6±5.0	0.601[e]	10.1±4.5	8.3±5.0	0.029*,[e]
PI exposure[c]	59 (93.7%)	70 (80.5%)	0.030*,[d]	26 (86.7%)	98 (86%)	1.000[d]	32 (86.5%)	97 (85.8%)	1.000[d]	34 (87.2%)	95 (85.6%)	0.798[d]
Current PI[c]	32 (50.8%)	48 (55.2%)	0.622[d]	16 (53.3%)	62 (54.4%)	1.000[d]	28 (75.7%)	52 (46%)	0.002*,[d]	29 (74.4%)	51 (45.9%)	0.003*
NNRTI exposure[c]	57 (90.5%)	55 (63.2%)	<0.001*,[d]	23 (76.7%)	84 (73.7%)	0.818[d]	26 (70.3%)	86 (76.1%)	0.516[d]	29 (74.4%)	83 (74.8%)	1.000[d]
Current NNRTI[c]	31 (49.2%)	40 (46%)	0.742 [d]	13 (43.3%)	54 (47.4%)	0.837[d]	15 (40.5%)	56 (49.6%)	0.351[d]	16 (41.0%)	55 (49.5%)	0.456[d]
d4T exposure[c]	59 (93.7%)	49 (56.3%)	<0.001*,[d]	23 (76.7%)	81 (71.1%)	0.650[d]	23 (62.2%)	85 (75.2%)	0.142[d]	26 (66.7%)	82 (73.9%)	0.412[d]
Current d4t[c]	6 (9.5%)	6 (6.9%)	0.560[d]	6 (20.0%)	6 (5.3%)	0.019*,[d]	1 (2.7%)	11 (9.7%)	0.295[d]	3 (7.7%)	9 (8.1%)	1.000[d]
AZT exposure[c]	51 (81.0%)	74 (85.1%)	0.515[d]	26 (86.7%)	93 (81.6%)	0.599[d]	34 (91.9%)	91 (80.5%)	0.132[d]	35 (89.7%)	90 (81.1%)	0.317[d]
Current AZT[c]	17 (27.0%)	29 (33.3%)	0.474[d]	9 (30.0%)	33 (28.9%)	1.000[d]	11 (29.7%)	35 (31.0%)	1.000[d]	16 (41.0%)	30 (27.0%)	0.111[d]

Values are expressed as: [a]median (P25, p75); [b]mean±standard deviation; [c]absolute (percentage). Statistical tests: [d]Fisher exact test; [e]Mann-Whitney U-test; [f]Student's t-test. *Statistically significant: p<0.05. ART, antiretrovirals; AZT, zidovudine; BMI, body mass index, d4T, stavudine; HOMA, insulin resistance index; HVC, hepatitis C virus infection; NNTRI, non-nucleoside analog reverse transcriptase inhibitor; PI, protease inhibitor; TC, total cholesterol level; TG, triglycerides.

performed by expert clinicians, a good correlation with dual-energy X-ray absorptiometer (DXA) measurements has been reported, suggesting that physician- and patient-rated lipoatrophy reports might be useful surrogates for more expensive measures of lipoatrophy (22, 31). Furthermore, interpretation of DXA data in children is difficult because body composition varies considerably with age, sex, and pubertal status and there are no pediatric reference data (31). In addition, DXA cannot distinguish between subcutaneous fat stores and visceral fat (2, 32).

In summary, our data show that Spanish HIV-infected children and young adolescents present the same metabolic complications as those reported in recent large studies in other settings. The increasing obesity rate in Spanish HIV-infected children is also of great concern. Although we have been aware of these complications since the first descriptions almost 10 years ago, there is still a lack of standardized criteria and guidelines for their management (33, 34). Our data highlight and reinforce the need for the creation of specific guidelines for this growing, unique population, that include careful consideration of HAART-related toxicities, promotion of healthy lifestyles, and early implementation of other strategies to decrease cardiovascular risk.

Potential conflicts of interest and transparency declaration

This study was funded in part by the AIDS Research Network (RIS, Red de Investigación en SIDA) and by the Foundation for AIDS Research and Prevention in Spain (FIPSE, Fundación para la Investigación y la Prevención del SIDA en España; grants 36910/10 and 240813/09). Rebeca Lahoz is the recipient of a grant from Hospital Universitari Sant Joan de Déu. The authors do not have any commercial or other associations that might pose a conflict of interest.

Acknowledgments

The authors would like to thank the children who participated in this study and their families, Elia Pérez (Statistics Department, Hospital Universitario La Paz, Madrid) for performing the statistical analysis, and Celine Cavallo for English language advice.

References

1. Viganò A, Cerini C, Pattarino G, Fasan S, Zuccotti GV. Metabolic complications associated with antiretroviral therapy in HIV-infected and HIV-exposed uninfected paediatric patients. Expert Opin Drug Saf 2010;9:431–45.
2. Aldrovandi GM, Lindsey JC, Jacobson DL, Zadzilka A, Sheeran E, et al., for the Pediatric AIDS Clinical Trials Group P1045 team. Morphologic and metabolic abnormalities in vertically HIV-infected children and youth. AIDS 2009;23:661–72.
3. Resino S, Micheloud D, Lorente R, Bellón BM, Navarro ML, et al. Adipokine profiles and lipodystrophy in HIV-infected children during the first 4 years on highly active antiretroviral therapy. HIV Med 2011;12:54–60.
4. Dimock D, Thomas V, Cushing A, Purdy JB, Worrell C, et al. Longitudinal assessment of metabolic abnormalities in adolescents and young adults with HIV-infection acquired perinatally or in early childhood. Metabolism 2011;60;874–80.
5. Viganò A, Brambilla P, Pattarino G, Stucchi S, Fasan S, et al. Long-term evaluation of glucose homeostasis in a cohort of HAART-treated HIV-infected children. Clin Drug Investig 2009;29:101–09.
6. Rhoads MP, Smith CJ, Tudor-Williams G, Kyd P, Walters S, et al. Effects of highly active antiretroviral therapy on paediatric metabolite levels. HIV Med 2006;7:16–24.
7. Tassiopoulos K, Williams PL, Seage III GR, Crain M, Oleske J, et al., for the International Maternal Pediatric Adolescent AIDS Clinical Trials 219C Team. Association of hypercholesterolemia incidence with antiretroviral treatment, including protease Inhibitors, among perinatally HIV-infected children. J Acquir Immune Defic Syndr 2008;47:607–14.
8. Spolou V, Kanaka-Gantenbein C, Bathrellou I, Mora S, Mostrou G, et al. Monitoring of lipodystrophic and metabolic abnormalities in HIV-1 infected children on antiretroviral therapy. Hormones 2011;10:149–55.
9. Rhoads MP, Lanigan J, Smith CJ, Lyall EG. Effect of specific ART drugs on lipid changes and the need for lipid management in children with HIV. J Acquir Immune Defic Syndr 2011;57:404–12.
10. Guzmán-Fulgencio M, Micheloud D, Lorente R, Bellón JM, de José Gomez MI, et al. Cardiovascular risk markers are increased in HIV-infected children with lipodystrophy syndrome. J Infect 2011;62:240–3.
11. Farley J, Gona P, Crain M, Cevia J, Oleske J, et al. Prevalence of elevated cholesterol and associated risk factors among perinatally HIV-infected children (4–19 years old) in Pediatric AIDS Clinical Trials Group 219C. J Acquir Immune Defic Syndr 2005;38:480–7.
12. Yeste D, Carrascosa A. Obesity-related metabolic disorders in childhood and adolescence. An Pediatr (Barc) 2011;75:135.e1–9.
13. CDC Health disparities and inequalities request – United States, 2011. MMWR Morb Mortal Wkly Rep 2011;60(Suppl):73.
14. Resino S, Micheloud D, Larrú B, Bellón JM, León JA, et al. Spanish Group of Paediatric HIV Infection. Immunological recovery and metabolic disorders in severe immunodeficiency HIV type 1-infected children on highly active antiretroviral therapy. AIDS Res Hum Retroviruses 2008;24:1477–84.
15. CDC 1994. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR Morb Mortal Wkly Rep 1994;43:1–10.
16. American Academy of Pediatrics. Cardiovascular risk reduction in high-risk pediatric populations. Pediatrics 2007;119:618–21.
17. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, et al. Cardiovascular risk reduction in high-risk pediatric populations: a scientific statement from the American Heart Association Expert Panel. (Endorsed by the American Academy of Pediatrics). Circulation 2006;114:2710–38.
18. Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, et al. IDF consensus Group. Metabolic syndrome in children and adolescents-an IDF consensus report. Pediatr Diabetes 2007;8:299–306.
19. Tresaco B, Bueno G, Pineda I, Moreno LA, Garagorri JM, et al. Homeostatic model assessment (HOMA) index cut-off values to identify the metabolic syndrome in children. J Physiol Biochem 2005;61:381–8.

20. Carrascosa Lezcano A, Fernández García JM, Fernández Ramos C, Fernández Longás A, López Siquero JP, et al. Grupo Colaborador Español. Spanish cross-sectional growth study 2008. Part II. Height, weight and body mass index values from birth to adulthood. An Pediatr (Barc) 2008;68:552–69.
21. WHO child growth standards and the identification of severe acute malnutrition in infants and children. A joint Statement by the World Health Organization and the United Nations Children's Fund. WHO, Unicef, 2009. Available at: http://www.who.int/nutrition/publications/severemalnutrition/9789241598163_eng.pdf, accessed 3 Aug 2011.
22. European Paediatric Lipodystrophy Group. Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe. AIDS 2004;18:1443–51.
23. Mallal SA, John M, Moore CB, James IR, McKinnon EJ. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. AIDS 2000;14:1309–16.
24. Hartman K, Verweel G, de Groot R, Hartwig NG. Detection of lipoatrophy in human immunodeficiency virus-1-infected children treated with highly active antiretroviral therapy. Pediatr Infect Dis J 2006;25:427–31.
25. Brown TT, Glesby MJ. Management of the metabolic effects of HIV and HIV drugs. Nat Rev Endocrinol 2011;20:11–21.
26. Jaquet D, Lévine M, Ortega-Rodriguez E, Faye A, Polak M, et al. Clinical and metabolic presentation of the lipodystrophic síndrome in HIV-infected children. AIDS 2000;14:2123–8.
27. Lee B, Aurpibul L, Sirisanthana V, Mangklabruks A, Sirisanthana T, et al. Low prevalence of insulin resistance among HIV-infected children receiving nonnucleoside reverse transcriptase inhibitor-based highly active antiretroviral therapy in Thailand. HIV Medicine 2009;10:72–8.
28. Viganò A, Riboni S, Bianchi R, Cafarelli L, Vago T, et al. Thyroid dysfunction in antirretroviral treated children. Pediatr Infect Dis J 2004;23:235–9.
29. Park YJ, Lee YJ, Choi SI, Chun EJ, Jang HC, et al. Impact of subclinical hypothyroidism on the coronary artery disease in apparently healthy subjects. Eur J Endocrinol 2011;165:15–21.
30. Grapin M, Piroth L, Verges B, Sgro C, Mack G, et al. Increased prevalence of subclinical hypothyroidism in HIV patients treated with highly active antiretroviral therapy. AIDS 2000;14:1070–2.
31. Tungsiripat M, O'Riordan MA, Storer N, Harrill D, Ganz J, et al. Subjective clinical lipodystrophy Assessment correlates with DEXA-measured limb fat. HIV Clin Trials 2009;10:314–9.
32. McComsey GA, Leonard E. Metabolic complications of HIV therapy in children. AIDS 2004;18:1753–68.
33. Ross AC, McComsey GA. Cardiovascular disease risk in pediatric HIV: the need for population-specific guidelines. J Acquir Immune Defic Syndr 2011;57:351–4.
34. Soler-Palacín P, Ciria L, Polo R, Couceiro JA, de José MI, et al; Study Group for the Pediatric HIV-patient for the National AIDS Plan (SPNS). Recomendaciones CEVIHP/SEIP/AEP/SPNS para el seguimiento del paciente pediátrico infectado por el Virus de la Inmunodeficiencia Humana (VIH). Sanidad, June 2009. Available at: http://www.mspsi.gob.es/ciudadanos/enfLesiones/enfTransmisibles/sida/publicaciones/profSanitarios/recoSeguimientoPediatricoVIHJunio09.pdf, accessed 3 Aug 2011.