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Metabolic Syndrome in Children and Adolescents Living with HIV

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Text

Introduction

Over the past 20 years in developed countries, implementation of highly active antiretroviral therapy (HAART) for patients infected with human immunodeficiency virus (HIV) has led to a dramatic reduction in AIDS-related mortality in both children and adults [1-4]. At the same time, the prevalence of abnormalities of fat distribution and disorders of lipid and carbohydrate metabolism have significantly increased [5,6]. Thus, cardiovascular disease is now becoming an increasingly more frequent cause of mortality in adults living with HIV [7,8].

HIV-related metabolic alterations are associated with both the infection itself [9,10] and the use of HAART [11-19]. Some treatment regimens, especially those including nucleoside reverse transcriptase inhibitors (NRTIs) and/or protease inhibitors (PIs), have been linked with insulin resistance, diabetes mellitus, dyslipidemia, changes in body fat distribution, and the risk of cardiovascular disease [11-19]. The pathogenic mechanisms involved in these metabolic disorders are complex and include a direct effect of the drugs on lipid metabolism, adipocyte function, endothelial cells, mitochondria, and proinflammatory cytokines; related host risk factors, such as race, age, sex, and lifestyle habits, have also been described in HIV-infected patients [11, 14, 20]. Insulin resistance is increasingly recognized as a chronic, low-level, inflammatory state. Hyperinsulinemia and the action of insulin have been proposed as common factors preceding hypertension, low high-density lipoprotein cholesterol levels, hypertriglyceridemia, abdominal obesity, and altered glucose tolerance, and all these abnormalities are linked to the development of coronary heart disease [21].

In pediatric and adolescent patients, who are exposed to HAART for many years before reaching adulthood, these comorbidities are of particular concern because of the potential risk of developing cardiovascular disease in the future [22-26]. The changes in body composition that normally occur during puberty can hinder the detection of abnormalities of fat distribution [27], although recent studies have demonstrated the existence of this disorder even in prepubertal children [28].

Metabolic syndrome (MetS), a term that includes hypertension, dyslipidemia, obesity with increased waist circumference, and hyperglycemia, is considered an independent risk factor for developing cardiovascular disease in both HIV-positive and -negative individuals. In the HIV-infected pediatric population, some studies report the prevalence of different components of MetS separately [29-31], but there are no data on the prevalence of MetS as a cluster of factors, and consensus criteria for diagnosing the syndrome in these patients are lacking.

Numerous criteria have been proposed to define MetS in the general population of children and adolescents [32,33], the most widely used being the modified National Cholesterol Education Program (NCEP)-Adult Treatment Panel III (ATP III) criteria [34,35]. Nonetheless, there was no universal agreement as to which system to use in the pediatric population until the International Diabetes Federation (IDF) proposed consensus criteria [36]. These were established according to the following age groups: 6-10 years, 10-16 years, and >16 years (the last being comparable to adults) [36]. Currently, the IDF criteria are considered the reference standard for the pediatric population, although they were formulated for obese patients and have not been validated in HIV-infected children or adolescents.

Pediatric patients living with HIV may potentially experience the effects of several factors associated with MetS (eg, the infection itself and antiviral treatment) in addition to those commonly seen in the overall population of children and adolescents (eg, sedentary lifestyle, inappropriate diet, obesity epidemic). Therefore, pediatric HIV patients are expected to show a higher prevalence of MetS than that seen in the general population. Early detection and implementation of preventive and therapeutic measures against MetS in these patients could potentially minimize their risk of developing cardiovascular disease in adulthood.

The aim of this study is to determine the prevalence of MetS in the HIV-infected pediatric population in Spain and to investigate the risk factors for MetS associated with the infection and the antiretroviral therapy used in its treatment.

Patients and methods

A cross-sectional study was carried out in patients included in the *Cohorte Pediátrica de la Red de Investigación en SIDA* (CoRISpe, Pediatric Cohort of the Spanish AIDS Research Network), which comprises patients from 75 centers and is an important epidemiological representation of children currently infected in Spain [37]. At present, data have been collected from 1089 HIV-infected pediatric patients, among whom 482 are currently younger than 18 years of age. The data are collected in a database and updated yearly. All pediatricians involved in CoRISpe were invited to participate in the present study. Seventeen hospitals agreed to participate and provided data from 242 patients (201 younger than 19 years) between January 2012 and July 2013. Patients outside the age range (2-18 years, both inclusive) and those lacking data for any of the

items used to define MetS (waist circumference, triglyceride levels, HDL-cholesterol level, blood pressure, and fasting plasma glucose concentration) were excluded.

Demographic, clinical, immunological, and virological data, and the details of current/previous antiretroviral treatment were obtained from the database. Clinical and immunological stage were assessed according to the Centers for Disease Control and Prevention (CDC) classification criteria [38].

At a routine outpatient visit, the patients' weight, height, and body mass index (BMI) were assessed and expressed as age- and sex-adjusted *z*-scores, based on the Spanish standard growth curves [39]. Waist circumference was measured, and the 90th percentile adjusted for age and sex was defined according to Spanish tables [40]. Puberty was rated using Tanner stages.

The diagnosis of abnormal fat distribution was based on physical examination performed by experienced clinicians and was classified according to definitions contained in the Spanish recommendations for antiretroviral therapy in HIV-infected children and adolescents as follows [41]: 1) lipohypertrophy (intra-abdominal visceral and subcutaneous fat accumulation; cervical fat accumulation and single or multiple lipomas were also included); 2) lipoatrophy (subcutaneous fat loss in face, limbs or buttocks); and 3) a mixed pattern when both were present.

MetS was first defined according to the IDF criteria [36] and then using the modified NCEP-ATP III criteria [34], and separate analyses were performed in the patients who received a MetS diagnosis according to each system. The diagnosis of MetS requires the presence of central obesity plus at least 2 of the 4 other factors in the IDF classification or any 3 or more factors in the NCEP-ATP III criteria, respectively.

Blood pressure was determined with patients at rest, using an electronic sphygmomanometer or a manual oscillometric device, depending on the center. The blood pressure percentiles applied were adjusted for age and sex as reported by the National High Blood Pressure Education Program [42].

The fasting lipid profile (triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol), plasma glucose concentration, and serum insulin concentration were measured, and HIV viral load (HIV-VL) and CD4+T-cell percentage and absolute count were determined. Insulin resistance was defined as a calculated homeostatic model assessment of insulin resistance (HOMA-IR; fasting insulin [mU/L] x fasting glucose [mg/dL]/405) >2.5 in Tanner stage 1 patients or >4.0 in Tanner stage ≥2 patients [43].

The study was approved by the ethics committees of all the participating centers, and informed consent or assent for participation was obtained from all patients and parents or legal guardians, as appropriate.

A descriptive analysis was performed of the characteristics of patients with and without MetS. Qualitative variables were expressed as the frequency and percentage and quantitative variables as the mean and standard deviation (SD) or the median and interquartile range (IQR). Associations with MetS were analyzed using the chi-square or Fisher exact test for qualitative variables and the Student *t* or Mann-Whitney *U* test for quantitative variables, as appropriate. Significance was set at a *p*-value of <0.05. Statistical analyses were performed using Stata 13.1 (Stata Statistical Software: Release 13. College Station, TX, USA).

Results

In total, 152 patients (83 females, 54.61%) aged 2 to 18 (inclusive) years were included. Median age was 13.12 years (IQR: 9.55;15.99) and 68.42% of patients were Tanner stage ≥2 at assessment. Two thirds of patients (67.11%) were born in Spain. Plasma HIV-VL was undetectable in 63.82% and median CD4+T-cell count was 914.66/mm^3 (IQR: 643;1148). More than half the patients (57.89%) met AIDS criteria. Overall, 126 patients (82.89%) were receiving HAART.

Median *z*-score values for weight, height, and BMI were all within the normal ranges (Table 1). The most prevalent disturbance (21.05%) detected was an abnormally low HDL-cholesterol level, followed by hypertriglyceridemia (19.08%), impaired fasting glucose (4.61%), and raised blood pressure (3.95%). Abnormal fat distribution was observed in 39 patients (25.66%) (lipoatrophy 18 patients [11.84%], lipohypertrophy 16 patients [10.53%], mixed pattern 5 patients [3.29%]).

Three patients met the IDF criteria for MetS (1.97%). There were no differences in sex, age, or origin between these patients and those who did not meet the MetS criteria (Table 1). All patients with MetS were Tanner stage ≥2 (p=0.589). Lipohypertrophy was significantly associated with IDF-defined MetS (p=0.029) (Table 1).

Regarding the components of metabolic syndrome, mean triglyceride levels were significantly higher in patients with MetS (292 mg/dL *vs.* 107.36 mg/dL, p=0.006) and HDL-cholesterol was significantly lower (34 mg/dL *vs.* 55.47 mg/dL, p=0.007). Waist circumference, glucose levels, and blood pressure values were also higher in MetS patients, as was expected, but the differences did not reach statistical significance.

All patients meeting the MetS criteria were receiving HAART (p=1). Nonetheless, there was no significant association of the presence of the syndrome with current or ever exposure to any specific antiretroviral or family of antiretrovirals (NRTIs, non-nucleoside reverse transcriptase inhibitors [NNRTIs] or PIs), or with the duration of these treatments.

Based on the modified NCEP-ATP III criteria, the prevalence of MetS in our series was 5.92% (9 patients). In this analysis, MetS was significantly associated with Tanner stage ≥2 (p=0.041), lipohypertrophy (p=0.001), and higher *z*-scores for weight and body mass index (p=0.002 and p<0.001, respectively) (Table 2).

Insulin resistance was observed in 17 patients (11.18%) and was associated with the presence of MetS diagnosed with the modified NCEP-ATP III criteria (p=0.03). Insulin resistance was associated with lower HDL-cholesterol levels (p=0.036), but not with age, sex, Tanner stage, AIDS criteria, viral load, CD4+ T-cell count, or exposure to any type of treatment.

Discussion

The availability of current HAART strategies has modified the course of HIV infection and has transformed the disease into a chronic manageable condition. It has also shifted concerns regarding the management of HIV-infected patients. The long-term effects of antiretroviral treatment and the proinflammatory state produced by the virus have gained considerably in importance. These long-term effects are of particular interest in children living with HIV, many of whom have been exposed to the virus and antiretroviral drugs their entire life and are expected to have lengthy survival. Cardiovascular disease is an increasingly more common cause of morbidity and mortality

in HIV-infected patients [7,8]. As MetS is an independent risk factor for this condition, it is of special interest to detect it at an early stage and, particularly, to prevent its onset.

A recent systematic review of all pediatric studies on MetS published since 2003 reported a median prevalence of 3.3% (range, 0%-19.2%) in the general pediatric population, 11.9% (range, 2.8%-29.3%) in overweight children, and 29.2% (range, 10%-66%) in obese children [35]. Interestingly, the median prevalence of MetS in the general population does not show large differences according to the diagnostic criteria applied: 3.1% with IDF and 4.2% with NCEP-ATP III criteria. However, in a recent population-based survey in Europe including 18,745 children 2.0 to 10.9 years of age, the prevalence of MetS differed according to the definition used: 0.4% with the IDF criteria and 1.4% with the modified NCEP-ATP III criteria (3.6% and 11.6% when considering only obese children) [33]. In our setting, the prevalence of MetS using the IDF criteria was 10.7% in a cohort of 346 obese children and adolescents [44]. To our knowledge, there are no studies reporting the prevalence of MetS in HIV-infected children applying either the IDF criteria (currently the most widely accepted) or the modified NCEP-ATP III criteria.

In HIV-infected adults, the prevalence of MetS ranges from 11.4% to 45.4% [45], depending on the setting and diagnostic criteria used. In Spain, the reported MetS prevalence rates in adult HIV patients are 11.4% [46] and 15.8% [47] using IDF criteria, and 17% [48] using NCEP-ATP III criteria. In the study by Jericó et al. [48], MetS prevalence was described according to age groups: the overall prevalence was 17%, and there was an increase from 5.1% in patients younger than 30 years to 27% in those aged 50 to 59 years.

Taking these data into account, the prevalence of MetS in our cohort is consistent with the value reported for HIV-infected adults in our setting, regardless of the criteria used. Of particular interest is the difference in prevalence according to the criteria applied (1.97% *vs.* 5.92%), which has also yielded discordant results in previous studies in the general pediatric population (3.1% *vs.* 4.2% [35] and 0.4% *vs.* 1.4% [33]). Thus, it is evident that the choice of criteria used to diagnose MetS is important. In our series, the MetS prevalence increased 3-fold when the modified NCEP-ATP III criteria were used rather than the presently accepted IDF consensus definition, and the value was higher than that of the general population. This is also the case in studies in HIV-infected adults [45,49], and is apparently due to the fact that abdominal obesity is a key component and the *sine qua non* in the IDF definition. In adults, insulin resistance and abdominal obesity are considered to be significant causative factors in the development of MetS [50], whereas in HIV-infected individuals, there is evidence that different pathogenic pathways can lead to MetS [51]. This situation would call for a specific MetS definition in the HIV-infected population, including pediatric patients. Of note in our study, lipohypertrophy was associated with MetS using both the IDF and NECP-ATP III criteria. While abdominal obesity may be part of the lipohypertrophy syndrome in HIV-infected patients, not all lipohypertrophic patients have a large waist circumference and qualify for IDF-defined MetS.

In HIV-infected adults, MetS has been associated with lipodystrophy [47,52], increased BMI [46-48], and insulin resistance [47], in keeping with the pediatric findings in our study. Nonetheless, we did not observe a relationship with other reported risk factors such as high cholesterol [52] and exposure to several antiretroviral drugs [48].

Furthermore, we found an association between MetS (as per the modified NCEP-ATP III criteria) and Tanner stage ≥2, which may be attributable to a longer history of infection and antiretroviral treatment and to the physiological insulin resistance increase that occurs during puberty [53].

An abnormally low HDL-cholesterol level and hypertriglyceridemia were the most prevalent components of MetS in our cohort, as has been previously described in HIV-infected adults [54] and children [55].

The prevalence rate of abnormal HOMA-IR values in our patients (11.18%) is another important finding and is consistent with previous reports [56]. The rate doubles that of impaired fasting glucose level (4.61%), suggesting that HOMA-IR could be an early marker of disturbances in glucose metabolism. In a previous study by our group, the prevalence of insulin resistance was even higher [55]. Our data suggest that HOMA-IR should be included in the routine controls performed in these patients.

As was noted above, this is the first study to assess the prevalence of MetS in HIV-infected children in Spain, and, to our knowledge, the sample included is the largest one in which metabolic disorders have been investigated. However, this strength stems from the fact that it is a multicenter study, which implies differences in the laboratory techniques used and inevitable interobserver variation related to clinical aspects such as lipodystrophy assessment. Furthermore, the small number of patients with MetS, the cross-sectional design and the lack of a control group limits the statistical power to analyze associated factors. The fact that new antiretroviral regimens are less likely to cause metabolic disorders also limits to some extent the long-term validity of our results.

In conclusion, MetS is an additional complication of HIV infection and prolonged antiretroviral treatment that can occur in pediatric ages, which implies a serious, ongoing problem that ultimately may affect survival and quality of life. Thus, it seems reasonable that the presence of MetS should be systematically evaluated at least in HIV-infected children with lipohypertrophy. The varying prevalence of MetS found in our cohort according to the diagnostic criteria used is a strong indication of the urgent need to define appropriate criteria for this specific population. Finally, further studies are needed to determine and confirm the risk factors for MetS in HIV-infected pediatric patients, with a focus on potentially modifiable ones, such as those related to the antiretroviral treatment prescribed.

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References

1. World Health Organization. *Antiretroviral therapy for HIV infection in infants and children: towards universal access. Recommendations for a public health approach. 2010 revision*. Geneva: World Health Organization; 2010.
2. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf.
3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
4. Expert Panel of the Spanish Collaborative for Pediatric HIV infection (CEVIHP), the Spanish Society of Pediatric Infectology (SEIP), the Spanish Association of Pediatrics (AEP) and the National AIDS Plan Secretariat (SPNS). Consensus document of CEVIHP/SEIP/AEP/SPNS on antiretroviral treatment in HIV-infected children and adolescents (Updated February 2012). Available at: http://www.msssi.gob.es/ciudadanos/enfLesiones/enfTransmisibles/sida/publicaciones/profSanitarios/DocTARNsAdolescentes26Jun12.pdf.
5. Viganò A, Cerini C, Pattarino G, et al. Metabolic complications associated with antiretroviral therapy in HIV-infected and HIV-exposed uninfected paediatric patients. *Expert Opin Drug Saf.* 2010;9:431-445.

6. Aldrovandi GM, Lindsey JC, Jacobson DL, et al; Pediatric AIDS Clinical Trials Group P1045 team. Morphologic and metabolic abnormalities in vertically HIV-infected children and youth. *AIDS.* 2009;23:661-672.
7. Palella FJ Jr, Baker RK, Moorman AC, et al; HIV Outpatient Study Investigators. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr.* 2006;43:27-34.
8. Morlat P, Roussillon C, Henard S, et al; ANRS EN20 Mortalité 2010 Study Group. Causes of death among HIV-infected patients in France in 2010 (national survey): trends since 2000. *AIDS.* 2014;28:1181-1191.
9. Francisci D, Giannini S, Baldelli F, et al. HIV type 1 infection, and not short-term HAART, induces endothelial dysfunction. *AIDS.* 2009;23:589-596.
10. El-Sadr WM, Mullin CM, Carr A, et al. Effects of HIV disease on lipid, glucose and insulin levels: results from a large antiretroviral-naïve cohort. *HIV Med.* 2005;6:114-121.
11. Resino S, Micheloud D, Lorente R, 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.
12. Bernasconi E, Boubaker K, Junghans C, et al; Swiss HIV Cohort Study. Abnormalities of body fat distribution in HIV-infected persons treated with antiretroviral drugs: The Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr.* 2002;31:50-55.

13. De Wit S, Sabin CA, Weber R, et al. Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. *Diabetes Care.* 2008;31:1224-1229.
14. Murata H, Hruz PW, Mueckler M. The mechanism of insulin resistance caused by HIV protease inhibitor therapy. *J Biol Chem.* 2000;275:20251-20254.
15. Bitnun A, Sochett E, Dick PT, et al. Insulin sensitivity and β-cell function in protease inhibitor-treated and -naïve human immunodeficiency virus-infected children. *J Clin Endocrinol Metab.* 2005;90:168-174.
16. Lainka E, Oezbek S, Falck M, et al. Marked dyslipidemia in human immunodeficiency virus-infected children on protease inhibitor-containing antiretroviral therapy. *Pediatrics.* 2002;110:e56.
17. Zhang B, Macnaul K, Szalkowski D, et al. Inhibition of adipocyte differentiation by HIV protease inhibitors. *J Clin Endocrinol Metab.* 1999;84:4274-4277.
18. Rosso R, Parodi A, d'Annunzio G, et al. Evaluation of insulin resistance in a cohort of HIV-infected youth. *Eur J Endocrinol.* 2007;157:655-659.
19. Haugaard SB, Andersen O, Vølund A, et al. Beta-cell dysfunction and low insulin clearance in insulin-resistant human immunodeficiency virus (HIV)-infected patients with lipodystrophy. *Clin Endocrinol (Oxf).* 2005;62:354-361.
20. Guzmán-Fulgencio M, Micheloud D, Lorente R, et al. Cardiovascular risk markers are increased in HIV-infected children with lipodystrophy syndrome. *J Infect.* 2011;62:240-243.
21. Fernández-Real JM, Ricart W. Insulin resistance and chronic cardiovascular inflammatory syndrome. *Endocr Rev.* 2003;24:278-301.

22. Mondy KE, de las Fuentes L, Waggoner A, et al. Insulin resistance predicts endothelial dysfunction and cardiovascular risk in HIV-infected persons on long-term highly active antiretroviral therapy. *AIDS.* 2008;22:849-856.
23. Cade WT, Overton ET, Mondy K, et al. Relationships among HIV infection, metabolic risk factors, and left ventricular structure and function. *AIDS Res Hum Retroviruses.* 2013;29:1151-1160.
24. Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2010;56:1113-1132.
25. Grunfeld C, Delaney JA, Wanke C, et al. Preclinical atherosclerosis due to HIV infection: carotid intima-medial thickness measurements from the FRAM study. *AIDS.* 2009;23:1841-1849.
26. Ross AC, O'Riordan MA, Storer N, et al. Heightened inflammation is linked to carotid intima-media thickness and endothelial activation in HIV-infected children. *Atherosclerosis.* 2010;211:492-498.
27. Beregszaszi M, Dollfus C, Levine M, et al. Longitudinal evaluation and risk factors of lipodystrophy and associated metabolic changes in HIV-infected children. *J Acquir Immune Defic Syndr.* 2005;40:161-168.
28. Palchetti CZ, Patin RV, Gouvêa Ade F, et al. Body composition and lipodystrophy in prepubertal HIV-infected children. *Braz J Infect Dis.* 2013;17:1-6.
29. Miller TL, Grant YT, Almeida DN, et al. Cardiometabolic disease in human immunodeficiency virus-infected children. *J Cardiometab Syndr.* 2008;3:98-105.

30. Amaya RA, Kozinetz CA, McMeans A, et al. Lipodystrophy syndrome in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2002;21:405-410.

31. Papi L, Menezes AC, Rocha H, et al. Prevalence of lipodystrophy and risk factors for dyslipidemia in HIV-infected children in Brazil. *Braz J Infect Dis.* 2014;18:394-399.

32. Ford ES, Li C. Defining the metabolic syndrome in children and adolescents: will the real definition please stand up? *J Pediatr.* 2008;152:160-164.

33. Ahrens W, Moreno LA, Mårild S, et al; IDEFICS consortium. Metabolic syndrome in young children: definitions and results of the IDEFICS study. *Int J Obes (Lond).* 2014;38(Suppl 2):S4-14.

34. Cook S, Weitzman M, Auinger P, et al. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988-1994. *Arch Pediatr Adolesc Med.* 2003;157:821-827.

35. Friend A, Craig L, Turner S. The prevalence of metabolic syndrome in children: a systematic review of the literature. *Metab Syndr Relat Disord.* 2013;11:71-80.

36. Zimmet P, Alberti K, George MM, et al; IDF Consensus Group. The metabolic syndrome in children and adolescents – an IDF consensus report. *Pediatric Diabetes.* 2007;8:299-306.

37. de José MI, Jiménez de Ory S, Espiau M, et al; working groups of CoRISpe and HIV HGM BioBank. A new tool for the paediatric HIV research: general data from the Cohort of the Spanish Paediatric HIV Network (CoRISpe). *BMC Infect Dis.* 2013;13:2.

38. Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age; Official authorized addenda: human immunodeficiency virus infection codes and official guidelines for coding and reporting ICD-9-CM. *MMWR.* 1994;43:1-10.

39. Carrascosa A, Fernández JM, Ferrández A, et al; and collaborative group. Spanish growth studies 2010. Available at: http://www.aeped.es/sites/default/files/eecweb14_09_10.pdf

40. Serra L, Aranceta J, Pérez C, et al; and AEP-SENC-SEEDO collaborative group. *Consensus Dossier. Reference curves for weight categorization. Children and young population*. Madrid: IM&C; 2002

41. Recommendations of the CEVIHP/SEIP/AEP/PNS on antiretroviral treatment in HIV-infected children and teenagers. March 2008. Available at: http://www.msssi.gob.es/ciudadanos/enfLesiones/enfTransmisibles/sida/docs/guiasAntirretroviral_ninosAdolescentes2008.pdf

42. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics.* 2004;114 (Suppl 2);555-576.

43. Geffner ME, Patel K, Miller TL, et al, for the Pediatric HIV/AIDS Cohort Study. Factors associated with insulin resistance among children and adolescents perinatally infected with HIV-1 in the Pediatric HIV/AIDS Cohort Study. *Horm Res Paediatr.* 2011;76:386–391.

44. Yeste D, Carrascosa A. Obesity-related metabolic disorders in childhood and adolescence. *An Pediatr (Barc).* 2011;75:135.e1-9.

45. Paula AA, Falcão MC, Pacheco AG. Metabolic syndrome in HIV-infected individuals: underlying mechanisms and epidemiological aspects. *AIDS Res Ther.* 2013;10:32.

46. Bernal E, Masiá M, Padilla S, et al. Prevalence and characteristics of metabolic syndrome among HIV-infected patients from a Mediterranean cohort. *Med Clin.* 2007;128:172–175.

47. Estrada V, Martínez-Larrad MT, González-Sánchez JL, et al. Lipodystrophy and metabolic syndrome in HIV-infected patients treated with antiretroviral therapy. *Metabolism.* 2006,55:940–945.

48. Jericó C, Knobel H, Montero M, et al. Metabolic syndrome among HIV-infected patients: prevalence, characteristics, and related factors. *Diabetes Care.* 2005;28:132–137.

49. Alencastro PR, Wolff FH, Oliveira RR, et al. Metabolic syndrome and population attributable risk among HIV/AIDS patients: comparison between NCEP-ATPIII, IDF and AHA/NHLBI definitions. *AIDS Res Ther.* 2012;9:29.

50. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet.* 2005;365:1415-1428.

51. Brown TT, Glesby MJ. Management of the metabolic effects of HIV and HIV drugs. *Nat Rev Endocrinol.* 2011;8:11-21.

52. Jantarapakde J, Phanuphak N, Chaturawit C, et al. Prevalence of metabolic syndrome among antiretroviral-naive and antiretroviral-experienced HIV-1 infected Thai adults. *AIDS Patient Care STDS*. 2014;28:331-340.

53. Yeste D, Betancourth S, Gussinyé M, et al. Glucose intolerance in obese children and adolescents. *Med Clin (Barc).* 2005;125:405-408.

54. Jacobson DL, Tang AM, Spiegelman D, et al. Incidence of metabolic syndrome in a cohort of HIV-infected adults and prevalence relative to the US population (National Health and Nutrition Examination Survey). *J Acquir Immune Defic Syndr.* 2006;43:458-466.

55. Dapena M, Jiménez B, Noguera-Julian A, et al. Metabolic disorders in vertically HIV-infected children: future adults at risk for cardiovascular disease. *J Pediatr Endocrinol Metab.* 2012;25:529-535.

56. Barlow-Mosha L, Eckard AR, McComsey GA, et al. Metabolic complications and treatment of perinatally HIV-infected children and adolescents. *J Int AIDS Soc.* 2013;16:18600.

Table 1. Baseline characteristics and anthropometric values of the cohort at assessment, according to the presence of MetS (IDF criteria).

	Total (n=152)	**Without MetS (n=149)**	**With MetS (n=3)**	**p-value**
Female sex°	83 (54.61)	80 (53.69)	3 (100)	0.251[a]
Age, years†	13.12 (9.55;15.99)	13.05 (9,57; 15.99)	13.19 (9.24; 15.49)	0.868[b]
Tanner stage°	<2: 44 (28.95) ≥2: 104 (68.42) Unkn.: 4 (2.63)	<2: 44 (29.53) ≥2: 101 (67.79) Unkn.: 4 (2.68)	<2: 0(0) ≥2: 3 (100) Unkn.: 0 (0)	0.589[a]
AIDS, yes°	88 (57.89)	87 (58.39)	1 (33.33)	0.573[a]
Undetectable viral load°¥	97 (63.82)	95 (63.76)	2 (66.67)	1[a]
CD4+ T-cell per mm^3†	914.66 [643;1148]	891 [641;1140]	1222 [1025;1311]	0.110[b]
Abnormal fat distribution				
Lipoatrophy°	18 (11.84)	17 (11.41)	1 (33.33)	0.317[a]
Lipohypertrophy°	16 (10.53)	14 (9.4)	2 (66.67)	**0.029[a]***
Mixed pattern°	5 (3.29)	4 (2.68)	1 (33.33)	0.096[a]
Weight *z*-scoreŦ	-0.12 (0.22)	-0.13 (0.22)	-0.00 (0.10)	0.274[b]
Height *z*-scoreŦ	-0.03 (0.06)	-0.03 (0.06)	-0.04 (0.08)	0.910[b]

BMI *z*-score₸	-0.06 (0.15)	-0.06 (0.15)	0.07 (0.15)	0.151[b]

Values are expressed as: °n (percentage); †median [p25;p75]; ₸mean (SD).

¥Undetectable viral load = below 25 copies/mL. Statistical tests: [a]Fisher exact test;

[b]Mann-Whitney U test. *Statistically significant: $p<0.05$. BMI, body mass index; MetS, metabolic syndrome; Unkn, unknown.

Table 2. Baseline characteristics and anthropometric values of the cohort at assessment, according to the presence of MetS (modified NCEP-ATP III criteria).

	Total (n=152)	**Without MetS (n=143)**	**With MetS (n=9)**	**p-value**
Female sex°	83 (56.41)	79 (55.24)	4 (44.44)	0.732[a]
Age, years†	13.12 [9.55;15.99]	12.92 [9,49; 16.04]	14.94 [12.77; 15.09]	0.676[b]
Tanner stage°	<2: 44 (28.95) ≥2: 104 (68.42) Unkn.: 4 (2.63)	<2: 44 (30.77) ≥2: 96 (67.13) Unkn.: 3 (2.1)	<2: 0 (0) ≥2: 8 (88.89) Unkn.: 1 (11.11)	**0.041[a]***
AIDS, yes°	88 (57.89)	84 (58.74)	4 (44.44)	0.494[a]
Undetectable viral load°¥	97 (63.82)	92 (64.34)	5 (55.56)	0.723[a]
CD4+ T-cell per mm^3†	914.66 [643;1148]	891 [641;1144]	1110 [709;1222]	0.337[b]
Abnormal fat distribution				
Lipoatrophy°	18 (11.84)	17 (11.89)	1 (11.11)	1[a]
Lipohypertrophy°	16 (10.53)	11 (7.69)	5 (55.56)	**0.001[a]***
Mixed pattern°	5 (3.29)	4 (2.80)	1 (11.11)	0.266[a]
Weight *z*-scoreŦ	-0.12 (0.22)	-0.14 (0.22)	0.08 (0.14)	**0.002[b]***

Height *z*-score₸	-0.03 (0.06)	-0.03 (0.06)	-0.05 (0.08)	0.691[b]
BMI *z*-score₸	-0.06 (0.15)	-0.07 (0.15)	0.16 (0.14)	**0.000[b]***

Values are expressed as: °n (percentage); †median [p25;p75]; ₸mean (SD). ¥Undetectable viral load = below 25 copies/mL. Statistical tests: [a]Fisher exact test; [b]Mann-Whitney U-test. *Statistically significant: $p<0.05$. BMI, body mass index; MetS, metabolic syndrome; Unkn, unknown.