Lipid Profile, Cardiovascular Risk Factors and Metabolic Syndrome in a Group of AIDS Patients

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Summary

Background: Since the advent of AIDS, the anti-HIV therapy has developed significantly, including the highly active antiretroviral therapy (HAART) and the disease acquired a chronic characteristic. However, after the introduction of HAART, several metabolic alterations were observed, mainly related to the lipid profile.

Objectives: to evaluate and compare lipid profiles, analyze cardiovascular risk, describe the prevalence of metabolic syndrome in AIDS patients with or without HAART.

Methods: Over an 18-month period, 319 patients treated at outpatient clinics in the city of São Paulo, Brazil were selected.

Results: The final sample included 215 patients receiving HAART and 69 HAART-naive patients. The mean age was 39.5 years, and 60.9% were males. The main cardiovascular risk factors were smoking (27%), hypertension (18%) and family history of atherosclerosis (40%). Mean total cholesterol, HDL-cholesterol, triglycerides and glucose were higher in the HAART group than in the non-HAART group (205 vs. 180 mg/dL, 51 vs. 43 mg/dL, 219 vs. 164 mg/dL and 101 vs. 93 mg/dL respectively; $p < 0.001$ for all). According to the Framingham risk score, the cardiovascular risk was moderate to high in 11% of the patients receiving HAART and 4% of the HAART-naïve patients. According to the Adult Treatment Panel III definition, the metabolic syndrome was observed in 13% and 12% of the patients with or without HAART, respectively.

Conclusions: Although the mean values for total cholesterol, HDL-c and triglycerides were higher in the HAART group, a higher cardiovascular risk was not identified in the former. The prevalence of metabolic syndrome was comparable in both groups. (Arq Bras Cardiol 2009; 93(2):107-111)

Key Words: metabolic syndrome X, lipid metabolism disorders, cardiovascular disease, highly active antiretroviral therapy.

Introduction

The introduction of the highly active antiretroviral therapy (HAART) has changed the course of HIV infection, increasing survival and improving quality of life in HIV-infected individuals[1]. However, it has been shown that a high proportion of patients treated with HAART regimens, especially those including protease inhibitors (PIs), present metabolic disorders (dyslipidemia, insulin resistance) and physiological alterations (lipodystrophy and lipoatrophy), as well as being at greater risk for cardiovascular disease (coronary artery disease and stroke)[2-10]. These findings have changed the scenario of HIV infection and treatment.

In 1998, Carr et al. described HIV-associated lipodystrophy[11], characterized by a dorsocervical fat pad (also known as a "buffalo hump"), larger abdominal girth, increased breast size, as well as by lipoatrophy of the face, buttocks and limbs, together with prominence of the superficial veins in the extremities. In AIDS patients receiving HAART, the overall prevalence of at least one physical abnormality is thought to be approximately 50%, although reported rates range from 18 to 83%[10]. Differences in prevalence rates might be attributable to age, gender or the type/duration of antiretroviral therapy, as well as to the lack of an objective and validated case definition[10].

Data in the literature show that the prevalence of hyperlipidemia ranges from 28% to 80% in patients receiving HAART, including hypertriglyceridemia (40-80%) and high total cholesterol (10-50%)[4-7,12-14]. These lipidic alterations are mainly related to the use of PIs[2,4-9].

There are conflicting data regarding the association between HAART and the incidence of coronary disease (angina or myocardial infarction) in AIDS patients[12-17]. Although differences in study design, sample selection and statistical analyses might explain this disparity, longer exposure to HAART, mainly to PIs, appears to increase the risk of myocardial infarction. The Data Collection on Adverse Events of Anti-HIV Drugs study showed that the relative risk

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increase of myocardial infarction increases by 26% per year of HAART exposure[14].

Several studies have demonstrated that the prevalence of metabolic syndrome is higher in AIDS patients receiving HAART than in HIV-negative individuals[18-20].

To date, there have been no studies evaluating metabolic alterations in AIDS patients receiving HAART in Brazil, which has an estimated 600,000 HIV-infected population, of whom 180,000 receive HAART, mostly in public outpatient health care facilities.

The aim of this study was to evaluate and compare lipid profiles, analyze cardiovascular risk, describe the prevalence of metabolic syndrome in AIDS patients receiving and not receiving HAART.

Methods

This was a descriptive, transversal study conducted at seven outpatient facilities in the city of São Paulo, Brazil: the Federal University of São Paulo and six outpatient clinics operated by the São Paulo Municipal Department of Health.

Consecutive patients were recruited during regularly-scheduled outpatient visits between December 2004 and May 2006. Patients were considered eligible for inclusion in the study if, at the time of data collection, they were undergoing active follow-up treatment, had been receiving HAART for at least two months, were not taking any medications that might affect the lipid profile (diuretics, statins, fibrats, hormones, etc.) or were not receiving antiretroviral therapy. A total of 319 patients met the inclusion criteria and were enrolled in the study.

Upon enrollment, a questionnaire was applied. The questionnaire consisted of questions concerning the use of HAART, family history of coronary heart disease, diabetes mellitus, cigarette smoking, blood pressure and the use of medications that might affect the lipid profile. Total cholesterol, low-density lipoprotein-cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c) and triglycerides, as well as CD4+ cell counts and HIV viral load, were also determined. When the levels of the triglycerides were above 400 mg/dL the Friedewald equation was used to determine the levels of the LDL-c. Cardiovascular risk was calculated using the Framingham risk score[21] and the metabolic syndrome was evaluated based on the Adult Treatment Panel III (APT III) criteria[22]. These rules are: triglycerides $\geq$ 150 mg /dL, abdominal waist for man $\geq$ 102 cm and woman $\geq$ 88 cm, blood glucose $\geq$ 110 mg/dL, HDL-c $<$ 40 mg/dL for man and $<$ 50 mg/dL for woman and blood pressure $\geq$ 130 x 85 mmHg[22].

The sample size was calculated base on a initial analysis of the variables of interest. Mean values and standard deviations were considered. All data were transformed into a standardized format and merged into a central data set. The level of statistical significance was set at 0.05 (α = 5%), and the Statistical Package for the Social Sciences program, version 12.0 for Windows, was used in all analyses. All participating patients gave the written informed consent using a form that had been previously approved by the Federal University of São Paulo Ethics Committee and the São Paulo Municipal Department of Health.

Results

Of the 319 evaluated AIDS patients, 243 were receiving HAART (group 1), and 76 were HAART-naïve (group 2). The mean age was 39.5 years and 60.9% of the patients were male. The main cardiovascular risk factors observed in the sample were smoking (27%), hypertension (18%), family history of atherosclerosis (40%) and diabetes mellitus (4%). Baseline characteristics of the individuals are described in Table 1. In comparison with group 2, group 1 presented higher mean values of total cholesterol (205 vs. 180 mg/dL [$p < 0.001$], HDL-c (51 vs. 43 mg/dL [$p < 0.001$]), triglycerides (219 vs. 164 mg/dL [$p = 0.004$]) and glucose (101 vs. 93 mg/dL [$p < 0.001$) respectively. No significant difference was found between the two groups regarding LDL-c ($p = 0.073$).

Some patients were excluded from the estimation through the Framingham risk score of the risk of coronary artery disease: 41 for being younger than 30 years; 31 because the lipid profile was incomplete; and 5 because blood pressure data were unavailable. Therefore, 242 patients were evaluated (193 patients in group 1 and 49 patients in group 2). According to the Framingham risk score, the cardiovascular risk was moderate to high in 11% (22) of the patients receiving HAART and in 4% (2) of the HAART-naïve patients. As shown in Table 2, no statistically significant differences were found between the two groups. Metabolic syndrome, according to the ATP III criteria[22], was identified in 13% (27) of the patients in group 1 and 12% (8) of the patients in group 2 ($p=0.832$). The characteristics of the metabolic syndrome are described in Table 3.

As shown in Table 4, the patients in group 1 were clustered into five groups according to the HAART regimen used, in order to evaluate the best regimen in terms of its effect on the metabolic profile: group A, receiving zidovudine (AZT)+lamivudine (3TC)+efavirenz; group B, receiving AZT+3TC+lopinavir/ritonavir and AZT+3TC+nelfinavir; group C, receiving AZT+3TC+atazanavir; group D, receiving stavudine (d4T)+3TC+efavirenz; group E, receiving d4T+3TC+lopinavir/ritonavir and d4T+3TC+nelfinavir and d4T+didanosine+lopinavir/ritonavir. Sixty-one patients were excluded because it was not possible to cluster them into one of the 5 more prevalent regimens used; therefore, 154 patients were evaluated. Average HDL-c was lower in group E ($p = 0.049$) than in group A ($p = 0.011$), group B ($p = 0.026$) or group D ($p = 0.026$). The lowest LDL-c and total cholesterol values were observed in group C. Although the highest triglycerides levels were observed in group E, there were no significant differences among the five groups ($p = 0.495$).

Discussion

Average values for total cholesterol, HDL-c, triglycerides and glucose were statistically higher in the patients receiving HAART than in the HAART-naïve patients with the exception

Table 1 – Patients' characteristics

Characteristic	with HAART (n = 243)	without HAART (n=76)	p value
Male*	145 (59.7%)	50 (65.8%)	0.039†
Female*	98 (40.3%)	26 (34.2%)	0.039†
Age (years)	41.0	34.8	< 0.001‡
CD4+ (cells/mm3)*	476.5 (3-1687)	587.2 (51-1746)	0.0012‡
Viral load < 400 copies/mL	207 (85.1%)	9 (11.8%)	< 0.001‡
Duration of HIV infection (years)	5.8	2.8	< 0.001‡
Current smoker	62 (25.5%)	23 (30.3%)	0.250§
High blood pressure (mmHg)	48 (19.9%)	10 (13.3%)	0.132§
Diabetes Mellitus	13 (5.3%)	0 (0.0%)	0.027§
No laboratory test results	28 (11.5%)	8 (10.4%)	
Total cholesterol (mg/dL)*	205 (106-398)	180 (112-279)	< 0.001‡
HDL-c cholesterol (mg/dL)*	51 (15-124)	43 (19-76)	< 0.001‡
LDL-c cholesterol (mg/dL)*	116 (26-297)	107 (48-181)	0.073‡
Triglycerides (mg/dL)*	219 (43-1133)	164 (39-764)	0.004‡
Glucose (mg/dL)*	101 (78-243)	93 (77-127)	< 0.001‡
Body Mass Index	24.4	24.3	0.921‡
Body weight (kg)	67.5	67.4	0.955‡
Height (cm)	1.66	1.67	0.817‡
Abdominal waist (cm)	86.1	83.5	0.048‡

**Results expressed as means and interquartile ranges. Legend: † = χ^2 test , ‡ = t test; § = Fisher test; HAART – highly active antiretroviral therapy; HDL-c – high-density lipoprotein cholesterol; LDL-c – low-density lipoprotein cholesterol*

Table 2 – Framingham risk score classification of cardiovascular risk

10-year risk of cardiovascular disease	with HAART (n = 193)		without HAART (n = 49)		Total (n = 242)	
	n	%	n	%	n	%
Low (0-10%)	171	88.6	47	95.9	218	90.1
Moderate (10-19%)	20	10.4	2	4	22	9.1
High (≥ 20%)	2	1	0	0	2	0.8

Kappa test: p = 0.296

of LDL-c (p = 0.073). These data are in agreement with those in the literature showing that AIDS patients receiving HAART present more metabolic alterations, mainly high triglycerides and cholesterol, than do those not receiving HAART[2]. Of the patients receiving HAART in the present study, 41.4% (89) and 20.5% (44) presented high levels of triglycerides and total cholesterol, respectively. Data in the literature show that the prevalence of hyperlipidemia ranges from 28% to 80%, including hypertriglyceridemia (40-80%) and high total cholesterol (10-50%)[4-7,13,14]. In the Brazilian study by Caramelli et al[23], the hypercholesterolemia was present in 43% and hypertriglyceridemia in 53% of the patients using PIs[23].

In our study sample as a whole, the main cardiovascular risk factors observed were smoking (27%), hypertension (18%) and a family history of atherosclerosis (40%). However, 88% of the patients had at least one cardiovascular risk factor. In the Swiss HIV Cohort Study, 57% of the patients were smokers, 35.7% had high triglyceride levels and 26.1% had high blood pressure[24]. Our study sample was

Table 3 – Characteristics of the metabolic syndrome between the two groups

Characteristic	With HAART (n=215)	Without HAART (n=69)	p (c2 test)
Abdominal waist	14%	9%	0.219
Triglycerides	57%	41%	0.016
Glucose	16%	7%	0.057
HDL-c	28%	49%	0.001
Blood Pressure	16%	19%	0.532
Metabolic Syndrome	13%	12%	0.832

The percentage refers to the value above the normal range according to the ATP III.

Table 4 – Lipid profiles of the patients according to the antiretroviral therapy regimen employed

	Total cholesterol (mg/dL)	HDL-c (mg/dL)	LDL-c (mg/dL)	Triglycerides (mg/dL)	n
Group A	212.5 ± 49.3	53.1 ± 14.2	121.0 ± 42.2	206.6 ± 133.6	80
Group B	202.4 ± 39.9	54.9 ± 23.0	108.3 ± 28.6	196.1 ± 59.7	14
Group C	177.9 ± 32.9	46.1 ± 11.6	88.9 ± 31.7	263.6 ± 193.7	14
Group D	206.6 ± 36.0	53.3 ± 14.0	124.4 ± 34.8	225.6 ± 227.5	27
Group E	210.4 ± 52.4	43.3 ± 8.4	112.8 ± 39.8	263.9 ± 163.8	19
p value	0.136	0.049	0.057	0.495	154

**Results expressed as averages and standard deviations. HDL-c – high-density lipoprotein; LDL-c – low-density lipoprotein; Group A: zidovudine (AZT)+lamivudine (3TC)+efavirenz; Group B: AZT+3TC+lopinavir/ritonavir and AZT+3TC+nelfinavir; Group C: AZT+3TC+atazanavir; Group D: stavudine (d4T)+3TC+efavirenz; Group E: d4T+3TC+lopinavir/ritonavir and d4T+3TC+nelfinavir and d4T+didanosine+lopinavir/ritonavir*

young for the development of cardiovascular disease (CVD). Nevertheless, our findings related to other cardiovascular risk factors (current smoking, high blood pressure and hypertriglyceridemia) are in agreement with those in the literature. Currier et al[6] and Carr et al[25] showed that 60% of AIDS patients have hyperglycemia, dyslipidemia and central obesity, a combination seen in 88.3% of the subjects evaluated in the present study.

According to the Framingham risk score, the cardiovascular risk was moderate to high in 11% of the patients receiving HAART and in 4% of the HAART-naïve patients. The averages of total cholesterol (199 mg/dL) and HDL-c (49 mg/dL), the low frequency of diabetes (4%) and the younger age of the patients (39 years) in the sample as a whole could explain the slightly higher Framingham risk score in the HAART group. These characteristics are similar to those reported in a study conducted in Norway, in which patients receiving HAART were found to have an almost two-fold higher risk for CVD than those in the control group (11.9% vs. 6.3%)[26]. The Framingham risk score has been broadly used for this purpose, as it has been validated in the literature.

According to the APT III criteria[22], metabolic syndrome was present in 13% of patients in group 1 and 12% of patients in group 2. These findings differ from those by Estrada et al[20], who found that 15.8% of patients receiving HAART presented metabolic syndrome, compared with only 3.2% of the control patients.

All the HAART regimens caused alterations in the lipid profile when compared to the patients without HAART. The differences observed among the groups evaluated in terms of the lipid profile were not statistically significant. Consequently, it was not possible to determine the best regimen regarding the metabolic profile. Group C, treated with atazanavir, presented the lowest levels of total cholesterol and LDL-c, although no benefit was observed in terms of triglyceride levels. Unexpectedly, higher HDL-c levels were observed in the HAART group. There is no reasonable explanation for this fact, although it could be speculated that it was due to the fact that the HIV was controlled (85% of the patients in this group achieved an undetectable viral load), which decrease the inflammatory response.

Conclusions

Although it was observed that the mean values of total cholesterol, HDL-c and triglycerides were higher in the HAART group than in the non-HAART group, a higher cardiovascular

risk was not identified in the former. The prevalence of metabolic syndrome was comparable in the two groups, despite the metabolic alterations induced by HAART.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Referências

1. Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med. 1998; 338: 853-60.
2. Mulligan K, Grunfeld C, Tai VW, Algren H, Pang M, Chernoff DN, et al. Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection. J Acquir Immune Defic Syndr. 2000; 23: 35-43.
3. Carr A. HIV protease inhibitor-related lipodystrophy syndrome. Clin Infect Dis. 2000; 30 (Suppl 2): 135-42.
4. Dube M, Sattler F. Metabolic complications of antiretroviral therapies. AIDS Clin Care. 1998; 10: 41-4.
5. Sweet DE. Metabolic complications of antiretroviral therapy. Top HIV Med. 2005; 13 (2): 70-74.
6. Currier JS, Havlir DV. Complications of HIV disease and antiretroviral therapy. Top HIV Med. 2005; 13 (1): 16-23.
7. Stein J. Dyslipidemia in the era of HIV protease inhibitors. Prog Cardiovasc Dis. 2003; 45: 293-304.
8. Barbaro G. Metabolic and cardiovascular complications of highly active antiretroviral therapy for HIV infection. Curr HIV Res. 2006, 4: 79-85.
9. Barbaro G. Highly active antiretroviral therapy-associated metabolic syndrome: pathogenesis and cardiovascular risk. Am J Therapeutics. 2006; 13: 248-60.
10. Grinspoon S, Carr A. Cardiovascular risk and body fat abnormalities in HIV-infected adults. N Engl J Med. 2005; 352: 48-62.
11. Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS. 1998; 12, F51-F58.
12. Hajjar LA, Calderaro D, Yu PC, Giuliano I, Lima EMO, Barbaro G, et al. Cardiovascular manifestations in patients with the human immunodeficiency virus. Arq Bras Cardiol. 2005; 85 (5): 365-77.
13. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. N Engl J Med. 2003; 348: 702-10.
14. Friis-Moller N, Weber R, Reiss P, Thiebaut R, Kirk O, D'Arminio Monforte A, et al. For the D.A.D Study Group. Cardiovascular disease risk factors in HIV patients - associations with antiretroviral therapy: results from the DAD Study. AIDS. 2003; 17: 1179-93.
15. Holmberg SD, Moorman AC, Willianson JM, Tong TC, Ward DJ, Wood KC, et al and the HIV Outpatient Study (HOPS) Investigators. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. Lancet. 2002; 360: 1747-8.
16. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D and the Clinical Epidemiology Group from the French Hospital Database. Increased risk for myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. AIDS. 2003; 17: 2479-86.
17. Currier J, Taylor A, Boyd F, Dezii CM, Kawabata H, Burtcel B, et al. Coronary heart disease in HIV-infected individuals. J Acquir Immune Defic Syndr. 2003; 33: 506-12.
18. Gazzaruso C, Bruno C, Garzaniti A, Giordanetti S, Fratino P, Sacchi P, et al. Hypertension among HIV patients: prevalence and relationships to insulin resistance and metabolic syndrome. J Hypertens. 2003; 21: 1377-82.
19. Bruno R, Gazzaruso C, Sacchi P, Zocchetti C, Giordanetti C, Garzaniti A, et al. High prevalence of metabolic syndrome among HIV-infected patients: link with the cardiovascular risk. J Acquir Immune Defic Syndr. 2002; 31: 363-5.
20. Estrada V, Martinez-Larrad T, Gonzalez-Sanchez JL, de Villar NGP, Zabena C, Fernandez C, et al. Lipodystrophy and metabolic syndrome in HIV-infected patients treated with antiretroviral therapy. Metabolism. 2006; 55 (7): 940-5.
21. Dawber TR, Meadors GF, Moore FE Jr. Epidemiolofical approaches to heart disease: the Framingham Study. Am J Public Health. 1951; 41 (3): 279-81.
22. Third Report of the National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Circulation. 2002; 106: 3143-421.
23. Caramelli B, de Bernoche CYSM, Sartori AMC, Sposito AC, Santos RD, Monachini TS, et al. Hyperlipidaemia related to the use of HIV protease inhibitors: natural history and results of treatment with Fenofibrate. Braz J Infect Dis. 2001; 5 (6): 332-8.
24. Glass TR, Ungsedhapand C, Wolbers M, Weber R, Vernazza PL. Bucher HC, et al. Prevalence of risk factors for cardiovascular disease in HIV-infected patients over time: the Swiss HIV Cohort Study. HIV Med. 2006; 7 (6): 404-10.
25. Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1 protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia and insulin resistance. Lancet. 1998; 351: 1881-3.
26. Bergensen BM, Sandvik L, Brunn JN, Tonstad S. Elevated Framingham risk score in HIV-positive patients on highly active antiretroviral therapy: results from a Norwegian study of 721 subjects. Eur J Clin Microbiol Infect Dis. 2004; 23: 625-30.