ORIGINAL ARTICLE

Metabolic profile and cardiovascular risk factors among Latin American HIV-infected patients receiving HAART

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ABSTRACT

Objective: Determine the prevalence of metabolic abnormalities (MA) and estimate the 10-year risk for cardiovascular disease (CVD) among Latin American HIV-infected patients receiving highly active anti-retroviral therapy (HAART). **Methods:** A cohort study to evaluate MA and treatment practices to reduce CVD has been conducted in seven Latin American countries. Adult HIV-infected patients with at least one month of HAART were enrolled. Baseline data are presented in this analysis. **Results:** A total of 4,010 patients were enrolled. Mean age (SD) was 41.9 (10) years; median duration of HAART was 35 (IQR: 10-51) months, 44% received protease inhibitors. The prevalence of dyslipidemia and metabolic syndrome was 80.2% and 20.2%, respectively. The overall 10-year risk of CVD, as measured by the Framingham risk score (FRF), was 10.4 (24.7). Longer exposure to HAART was documented in patients with dyslipidemia, metabolic syndrome and type 2 diabetes mellitus. The FRF score increased with duration of HAART. Male patients had more dyslipidemia, high blood pressure, smoking habit and higher 10-year CVD than females. **Conclusions:** Traditional risk factors for CVD are prevalent in this setting leading to intermediate 10-year risk of CVD. Modification of these risk factors through education and intervention programs are needed to reduce CVD.

Keywords: HAART, HIV, metabolic parameters, cardiovascular risk factors, metabolic syndrome, dyslipidemia.

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INTRODUCTION

Since the introduction of highly active anti-retroviral therapy (HAART) in 1995, a significant decrease in mortality was observed in HIV-infected patients coupled with a marked reduction in the incidence of opportunistic infections and certain kind of cancers.[1] While these achievements are clearly remarkable, long-term complications of HAART were soon recognized including dyslipidemia, changes in body composition, insulin resistance, and glucose intolerance, mineral bone disease, and lactic acidosis.[2,3] These abnormalities may be associated with the use of certain anti-retrovirals such as stavudine, zidovudine and protease inhibitors, but a net effect of HIV infection can not be ruled-out. Additionally, current evidence suggests that patients on HAART are at risk of developing cardiovascular disease (CVD), and recent studies reported a higher prevalence of traditional risk factors for CVD in HIV-infected patients than in non-infected controls, such as arterial hypertension, dyslipidemia, and diabetes mellitus.[3-9] These complications jeopardize the long-term benefits of HAART, and make the overall management of HIV-infected patients more complex and more costly as well.

The World Health Organization reported in 2007 that 1.6 million people lived with HIV in Latin America; 100,000 new cases were diagnosed that year; 58,000 cases died, and approximately 300,000 cases received HAART.[10] Scaling-up HAART programs are being implemented in the region to a degree that many countries provide anti-retroviral therapy free of charge to a large proportion of patients. As more patients receive HAART in the region, it is expected that a similar trend in metabolic complications and cardiovascular events is likely to be observed. However, the prevalence of metabolic complications in these patients is largely unknown in the region, and the routine evaluation of metabolic parameters is variably undertaken both at regional and national levels. Therefore, the impact of HAART on metabolic abnormalities and CVD has not been elucidat-

ed in Latin America. We report here pre-intervention data on metabolic parameters and risk factors for CVD in a large cohort of Latin American HIV-infected patients on HAART participating in a study designed to evaluate modalities to minimize CVD risk in the region. To our knowledge, this is the first attempt to characterize these problems in Latin America. The results of our study will allow us not only to better understand the long-term complications of HAART in Latin America, but also to develop local guidelines to treat and prevent CVD.

METHODS

Study design

The RAPID II study (Registry and Prospective Analysis of Patients Infected with HIV and Dyslipidemia) is a cohort web-based study designed to prospectively collect data on demographic, metabolic and treatment modalities among HIV-infected patients receiving HAART from Latin America.

Setting

Seven Latin American countries, each one contributing with varying number of participating centers from Argentina (16 centers distributed in Buenos Aires, La Plata and Rosario), Brazil (15 centers distributed in São Paulo, Rio de Janeiro, Campinas, and Porto Alegre), Chile (two centers in the capital Santiago), Colombia (3 centers located in Bogotá and Cali), Ecuador (11 centers distributed in Quito, Cuenca and Guayaquil), Peru (five centers in the capital Lima) and Venezuela (nine centers distributed in Caracas, Valencia, Barquisimeto and San Cristobal) participated in the study.

Study population

Inclusion criteria: Patients older than 18 years of age, or minimum age as determined by local regulations or as legal requirements dictate, of both gender, and with confirmed HIV infection receiving a HAART regimen for at least one month prior to enrollment were selected. A lipid profile had to be obtained on every patient at enrollment or within one month before it. All patients had to be managed as outpatients from November 2006 to September 2007.

Exclusion criteria: Patients were excluded if they had been enrolled in any clinical trial within one month before enrollment or if written consent was not granted.

Procedures

A detailed interview was performed at enrollment to obtain demographic data; details of HIV infection, including time from diagnosis to enrollment and history of prior anti-retroviral medications. Cardiovascular risk factors present before enrollment including history of arterial blood hypertension, diabetes mellitus, metabolic syndrome, dyslipidemia, smoking habits, family history of premature cardio-vascular disease and presence of main arterial bed affection were also ascertained. Information on smoking, exercising and diet, as well as on any medication or lipid lowering intervention implemented the two months prior to enrollment was also obtained. Patients who had a history of dyslipidemia were requested to provide information on any prior lipid intervention undertaken, including diet, exercising and the use of lipid lowering drugs. A complete physical examination was performed, including measurements of blood pressure, weight, height, and waist circumference. A blood sample was taken and processed in each participating centre to measure fasting blood glucose, total cholesterol, HDL-cholesterol and LDL-cholesterol, triglycerides, creatine phosphokinase, and liver enzymes, including AST and ALT, at enrollment and every six months for two years. CD4 cell count and viral load determination were also performed at enrollment and every six months for two years.

Outcomes

The main outcomes of the study were the determination of metabolic risk factors at enrollment and at every six month of follow-up for a total of two-years, the evaluation of cardiovascular events on every follow-up visit, and the lipid lowering behaviors of the participating investigators at enrollment and subsequently for a total of two-years.

The following risk factors were evaluated including older age (age ≥ 45 years for men and ≥ 55 years for women), current cigarette smoking, high blood pressure (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg and/or usage of an antihypertensive drug), low HDL-cholesterol (man with ≤ 40 mg/dL or woman with ≤ 50 mg/dL), high LDL-cholesterol (fasting LDL levels ≥ 130 mg/dL), dyslipidemia (fasting serum triglycerides ≥ 150 mg/dL and/or fasting total serum cholesterol ≥ 240 mg/dL and/or low HDL-cholesterol and/or high LDL-cholesterol), blood lipid normalization (fasting serum triglycerides > 150 mg/dL and fasting total serum cholesterol < 240 mg/dL and HDL-cholesterol > 40 mg/dL and LDL-cholesterol < 130 mg/dL), type 2 diabetes (fasting serum glucose ≥ 126 mg/dL in two measurements at least one week apart and/or usage of oral anti-diabetic drugs), physical inactivity (lack of exercising defined as physical activity for at least 30 minutes three times-a-week), family history of premature cardiovascular disease (presence of cardiovascular disease in either a male first-degree relative < 55 years old or a female first-degree relative < 65 years old), obesity (body mass index > 30 kg/m^2), established coronary heart disease (history of either acute myocardial infarction, or angina, or sudden death, or myocardial revascularization), cardiovascular event (coronary heart disease or stroke or transient ischemic attack or peripheral artery disease or any combination of the above), cardiovascular risk (absolute ten-year-risk of cardiac death or myocardial infarction using the Framingham risk factor algorithm), high risk patients (those with established or pre-

dicted ten-year-cardiovascular risk ≥ 20%), abnormal waist circumference (man waist perimeter ≥ 102 cm or woman waist perimeter ≥ 88 cm), metabolic syndrome following ATPIII criteria[11] (simultaneous presence of at least three out of five of the following: triglycerides ≥ 150 mg/dL, abnormal waist circumference, fasting blood glucose ≥ 110 mg/dL, high blood pressure, low HDL-cholesterol), abnormal body fat distribution (fat loss from the face or extremities, or central fat gain or a mixed pattern).

The lipid lowering therapeutic behavior of the participating investigators in each center was evaluated at enrollment and every six-month period for two years. The behaviors were classified into four groups: group A corresponded to direct lipid treatment and HAART switching, group B corresponded to direct lipid treatment but no HAART switching, group C corresponded to no direct lipid treatment and no HAART switching, and group D corresponded to no direct lipid treatment and HAART switching. The investigators were requested to explain why they have selected a specific behavior.

Sample size determination and statistical analysis

Assuming rates of serum lipid normalization range from 10% to 20% and two ratios of dyslipidemic and non-dyslipidemic patients (1:1 and 3:1), a sample size of 4000 individuals was estimated to provide enough power to conduct the analysis of blood lipid normalization of dyslipidemia following one the four lipid lowering behaviors. Categorical variables were contrasted with the chi-square test with continuity correction or with the Fisher´s exact test. Continuous variables were contrasted with the student´s t-test or the Mann-Whitney test. All tests were two sided, a level of significance was pre-defined at <0.05.

Ethical considerations

The study was approved by local and national regulatory agencies in each participating center. Each patient signed an informed consent form.

RESULTS

A total of 4,010 patients were recruited, three countries contributed to 70% of the sample: Argentina enrolled 1,015 patients, Brazil enrolled 1,001 patients and Venezuela enrolled 807 patients. The remaining patients were enrolled by Colombia (474 patients), Peru (417 patients), Ecuador (252 patients) and Chile (44 patients).

Demographic and anthropometric data

Mean age (SD) of the whole population was 41.9 (10) years, 73.9% of the patients were males. The age and gender distribution of patients is shown in Figure 1. Most of the patients were young adults concentrated in the age group of 28-47 years; only 1.5% had more than 68 years of age. Age distribution by country is shown in Figure 2. No difference across countries was observed. Mean body mass index was 24.6 kg/m^2, which was uniformly distributed across the participating countries.

Figure 1: Age and gender distribution of patients in the RAPID II study. Patients are homogeneously distributed across the countries.

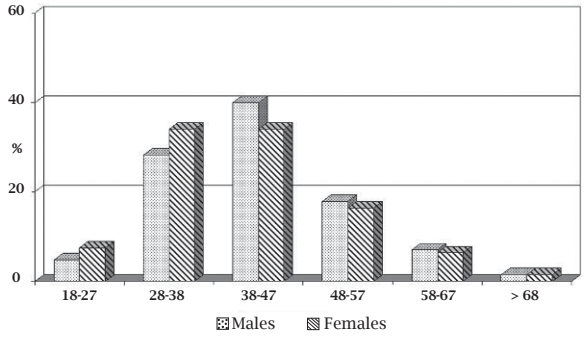
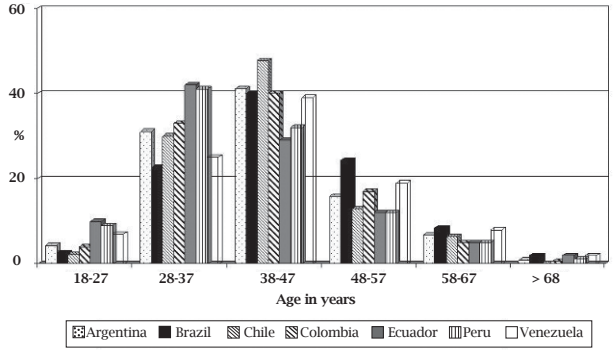


Figure 2: Age distribution of patients by country in the RAPID II study.



HIV related characteristics

All patients were well experienced with HAART, with a median duration on anti-retroviral therapy of 25 months, Table 1. The shortest duration of HAART was observed among Peruvian patients and the longest among Brazilian patients: 18 and 40 months, respectively. A protease inhibitor based HAART was used in 44% of patients; Chile reported the lowest use of protease inhibitors and Venezuela reported the highest: 20% *vs.* 61.5%, respectively. NNRTI based HAART predominated, with 56% of patients receiving such a therapy. Chile reported the highest use of a NNRTI and Venezuela reported the lowest; 81.8% and 38.2%, respectively. The median CD4 cell count was 417 cells/mm^3; ranging from as low as 255 cells/mm^3 in Peru to as high as 474 cells/mm^3 in Brazil. The mean viral load determination was 2.4 log10 copies/mL, which was uniformly distributed across countries.

*Table 1. Demographic, anthropometric, serum biochemical parameters and HIV related characteristics at enrollment**

Characteristic	Argentina (n = 1,015)	Brazil (n = 1,001)	Chile (n = 44)	Colombia (n = 474)	Ecuador (n = 252)	Peru (n = 417)	Venezuela (n = 807)	Overall (n = 4,010)
Age, y	41.6 (9.3)	44 (9.8)	40.6 (9.1)	40.8 (9.4)	39 (10.5)	39.1 (9.9)	42.6 (10.7)	41.9 (10.0)
Male gender, n (%)	70.4	65.4	90.9	86.7	77.8	70.7	80.9	73.9
Body mass index, kg/m^2	24.8 (3.7)	24.8 (3.9)	24.8 (2.7)	23.4 (3.1)	24.4 (3.7)	24.7 (3.6)	25 (3.9)	24.6 (3.8)
Waist circumference, cm	87.9 (11.1)	88.9 (11.2)	85.3 (9.8)	84.6 (8.5)	86.1 (12.9)	86.5 (9.8)	88.6 (10.7)	87.6 (10.8)
Systolic blood pressure, mmHg	119.9 (15.4)	121.6 (15.3)	112.7 (18.4)	114.9 (9.7)	116.1 (16.1)	110.7 (12.3)	119.1 (13.3)	118.3 (14.6)
Glucose, mg/dL	92. 8 (26.9)	97.1 (25.1)	83.4 (26.2)	91.9 (14.1)	95.6 (21.1)	80.9 (18.0)	92.1 (18.8)	92.4 (22.9)
Triglycerides, mg/dL	201.2 (201.6)	192.7 (153.3)	202.7 (129.4)	243.1 (165.3)	233.3 (219.2)	251.7 (191.8)	174.5 (192.9)	214.6 (188.4)
Total cholesterol, mg/dL	196.2 (46.9)	194.7 (44.2)	195.6 (57.1)	206.6 (49.7)	200.6 (66.0)	191.8 (57.9)	192.9 (52.7)	196.2 (50.7)
HDL-cholesterol, mg/dL	45.6 (15.0)	45.9 (14.1)	39.7 (12.2)	45.9 (13.7)	44.5 (13.1)	45.1 (5.3)	40.7 (13.0)	44.6 (13.5)
LDL-cholesterol, mg/dL	113.5 (46.5)	108.9 (41.7)	110.1 (48.5)	114.1 (42.9)	114.9 (44.0)	104.8 (39.4)	106.3 (46.3)	110.1 (44.1)
ALT, IU/l	29.5 (32.0)	29.3 (19.7)	22.2 (9.3)	32.9 (27.5)	34.2 (22.7)	26.7 (18.6)	28.9 (20.6)	29.5 (24.5)
Time on HAART†, m‡	23 (9-49)	40 (16-77)	24.5 (9-43)	23 (9-40)	19 (9-35)	18 (7-27)	27 (10-55)	25 (10-51)
NNRTI based HAART, %§	61.9	51.8	81.8	58.9	70.6	71.7	38.2	56.0
PI based HAART, %¶	36.2	51.4	20.0	38.0	30.6	31.9	61.5	44.0
CD4 cell count, cells/mm3‡	447	474	362	390	363	255	452	417
	(280-661)	(329-677)	(220-537)	(272-589)	(262-544)	(177-376)	(285-661)	(266-621)
Viral load, log10 copies/mL	2.1 (1.0)	2.3 (0.9)	2.2 (0.9)	2.2 (0.9)	2.7 (0.8)	2.8 (0.9)	2.4 (1.1)	2.4 (1.0)

*Values are mean (SD) unless noted otherwise
†HAART = highly active anti-retroviral therapy
‡Median (Interquartile range)
§NNRTI = non-nucleoside reverse transcriptase inhibitor
¶PI = protease inhibitor

Table 2. Metabolic profile and cardiovascular risk factors prior to enrollment

Characteristic	Argentina (n = 1,015)	Brazil (n = 1,001)	Chile (n = 44)	Colombia (n = 474)	Ecuador (n = 252)	Peru (n = 417)	Venezuela (n = 807)	Overall (n = 4,010)
High blood pressure, %	9.2	13.9	6.8	4.2	4.0	4.1	13.1	9.7
Diabetes mellitus, %	3.1	6.5	6.8	0.8	2.4	1.7	3.5	3.6
Dyslipidemia, %	49.3	57.3	59.1	21.1	27.8	31.9	47.3	44.5
Smoking habit, %	56.5	45.6	81.8	37.8	44.4	36.7	45.0	46.7
Family history of cardiovascular disease, %	36.1	33.4	45.5	30.6	28.6	17.8	30.1	31.3
Use of drugs for high blood pressure, %	6.9	12.9	6.8	3.4	5.6	2.6	12.1	8.5
Use of drugs for diabetes mellitus, %	2.6	4.5	6.8	0.6	2.0	1.0	2.9	2.7

Metabolic profile and cardiovascular risk evaluation

Serum biochemical data at enrollment are shown in Table 1, including serum glucose, triglycerides, total cholesterol, HDL and LDL cholesterol, and liver enzymes. Mean values for these tests were evenly distributed across the participating countries.

Cardiovascular and metabolic risk factors prior to enrollment are shown in Table 2. History of dyslipidemia (44.5%) and smoking habit (46.7%) were highly prevalent in this cohort as reported by patients. Family history of cardiovascular disease was reported in almost one third of the patients. History of diabetes mellitus was obtained in 3.6%. The metabolic profile and cardiovascular risk factors at enrollment are shown in Table 3. Cardiovascular risk factors were frequent in this cohort as determined by the high prevalence of dyslipidemia (80.2%) and high blood pressure (31.5%). Dyslipidemia was driven by high hipertrygliceridemia (55.8%) and low-HDL cholesterol values (49.5%). The overall prevalence of type 2 diabetes mellitus was observed in 3.3%, but was as low as 0.8% in Colombia and as high as 6.8% in Chile. Smoking habit was reported in 22.8% of patients at enrollment, but was as high as 50% for Chilean patients and as low as 10.3% for Ecuadorian patients. The 10-year overall risk of developing CVD was intermediate (10.4), as measured by the Framingham risk factor score, but was not evenly distributed. Brazilian and Chilean patients had the highest 10-year risk, while Colombian and Ecuadorian patients had the lowest 10-year risk. The overall proportion of patients in the highest risk group was 10.2%. Longer exposure to HAART was documented in patients with dyslipidemia (35.1 *vs.* 31.6 months, $p = 0.0034$), type 2 diabetes (48.4 *vs.* 33.9 months, $p < 0.001$), and metabolic syndrome (39.4 *vs.* 33.1 months, $p < 0.001$). The exposure to HAART increased also the 10-year risk of developing CVD: 0.09 increase in the Framingham risk score per month of exposure.

A clear gender difference in the risk of developing CVD was observed, Table 4. Males were older: mean age (SD) 42.2 (9.9) *vs.* 40.8 (10.3) years, $p < 0.001$, and had higher prevalence of dyslipidemia and other traditional risk factors for CVD such as high blood pressure and smoking. In contrast, females had more prevalence of obesity, abnormal waist circumference, metabolic syndrome, and lack of exercise. The 10-year risk of developing CVD was higher in males, and more males belonged to the high risk category. Both groups were similar in HIV disease severity.

DISCUSSION

The results of this study indicate that among this cohort of adult HIV-infected patients well experienced with HAART from seven Latin American countries, there is a high prevalence of dyslipidemia and intermediate 10-year risk of developing CVD. Gender differences in the metabolic profile

*Table 3. Metabolic profile and cardiovascular risk factors at enrollment**

Characteristic	Argentina (n = 1,015)	Brazil (n = 1,001)	Chile (n = 44)	Colombia (n = 474)	Ecuador (n = 252)	Peru (n = 417)	Venezuela (n = 807)	Overall (n = 4,010)
Older age	23.2	33.1	22.7	26.6	17.5	18.0	30.2	26.6
Smoking habit	34.1	22.1	50.0	18.9	10.3	15.6	18.2	22.8
High blood pressure	39.2	39.2	25.0	15.6	25.0	14.6	32.7	31.5
Abnormal waist circumference	7.1	7.5	4.6	2.1	6.4	3.6	7.4	6.2
Abnormal body fat distribution	34.6	46.9	20.5	31.2	40.5	28.1	37.2	37.3
Low-HDL	44.1	46.6	59.1	38.4	46.8	35.0	56.0	45.8
High-LDL	31.7	28.2	36.4	34.4	31.4	23.3	26.4	29.2
Dyslipidemia	78.5	79.3	90.9	82.1	84.5	67.9	86.9	80.2
Type 2 diabetes	2.7	6.1	6.8	0.8	2.0	1.7	3.4	3.3
Physical inactivity	46.8	57.9	59.1	63.9	61.1	28.5	60.2	53.4
Obesity	8.2	9.1	2.3	3.4	8.7	6.5	9.5	7.9
Established coronary heart disease	1.2	1.9	0	0.2	0	0.5	0.9	1.0
Cardio vascular event	3.4	5.2	2.3	0.8	1.2	1.7	5.7	3.7
Metabolic syndrome	22.3	25.4	13.6	8.4	19.1	13.7	22.4	20.2
Mean Framingham risk factor (SD)	9.8 (23.5)	14.2 (30)	13.8 (28.3)	5.6 (13.5)	5.8 (17.7)	6.1 (18.3)	12.6 (27.5)	10.4 (24.7)
High risk patients	9.5	14.2	15.9	5.5	5.6	6.5	12.1	10.2

* Values are % unless noted otherwise

*Table 4. Gender comparison of anthropometric, HIV related and cardiovascular risk factors**

Characteristic	Male patients (n = 2963)	Female patients (n = 1047)	p value
Family history of cardiovascular disease	21.84	23.50	0.280
Abnormal waist circumference	9.7	36.7	< 0.001
Obesity	6.6	11.8	< 0.001
Current smoking	25.0	16.7	< 0.001
Lack of exercise	51.7	58.5	< 0.001
High blood pressure	34.3	23.5	< 0.001
Dyslipidemia	81.3	77.3	< 0.001
Metabolic syndrome	19.4	22.7	0.020
Type 2 diabetes	3.7	3.3	0.631
Mean Framingham risk score (SD)	11.4 (24.7)	7.5 (24.6)	< 0.001
High risk category for cardiovascular disease	11.1	6.8	< 0.001
Mean CD4 cell count (SD), cells/mm^3	464.8 (270.4)	479.8 (286.)	0.1407
Mean viral load (SD), $\log_{10}$ copies/mL	2.4 (1.0)	2.3 (1.0)	0.4344

*Values are % unless noted otherwise

and cardiovascular risk were observed, with male patients at higher risk than females. Obesity and metabolic syndrome predominated in females. These results are remarkable and stress the necessity of incorporating the evaluation, treatment and prevention of modifiable risk factors and metabolic derangements in HIV-infected patients under HAART into routine practice in the region.

The 10-year risk of developing CVD as measured by the Framingham risk factor score was intermediate in this cohort of patients, but was not evenly distributed, it was low in three countries (Ecuador, Colombia and Peru, < 10%) and intermediate in the remaining four (Argentina, Brazil, Chile and Venezuela, 10-20%). However, the overall estimated risk of CVD in this large cohort of patients was higher than that reported for HIV-infected patients on HAART from developed countries with similar age distribution of subjects.[12-16] These studies estimated the 10-year risk of CVD in the low risk category (estimated risk < 10%): 7.0% among 403 Italian patients,[12] 7.4% in another Italian study with 1,243 subjects,[13] 6.2% in 603 Spanish patients,[14] 6% in 2,386 American subjects,[15] and 8.8% among 219 Norwegian patients.[16] We did not include a control group from the general population in our study, but a comparison of our results with those published recently from a large cross-sectional study conducted in seven Latin American countries among 11,550 non-HIV infected subjects found similar results for the 10-year risk of CVD, with 83% of these patients in the low risk category and approximately 10% in the high risk category.[17] We used the Framingham risk algorithm to predict CVD in HIV-infected patients, although it was not designed to predict the CVD risk in this population. Its utility to estimate the risk has been questioned more recently, as it may not be fully applicable to this population of patients.[18] The general consensus is that the score performs reasonably well in this population; it tends to over predict the risk in unexposed individuals and under predict the risk in exposed individuals.[18] Better equations are clearly needed to more accurately predict the risk of CVD in HIV-infected patients. Although the Framingham risk factor may not accurately predict the risk of CVD in HIV-infected patients on HAART, compelling evidence of an association between HAART and CVD comes from the largest cohort of HIV-infected patients recruited for the Data Collection on Adverse Events of anti-HIV drugs study (DAD study).[19] The first report of that study in 2003 showed that for any year of exposure to antiretroviral medications there was a 26% increase in the rate of acute myocardial infarction.[19] A more recent report after completing 5 years of follow-up showed 32% increase in the risk of CVD, mainly due to protease inhibitors exposure.[20] In agreement with these findings, we also observed that longer exposure to HAART in our cohort correlated with more risk for CVD, as measured by the Framingham risk score, as well as with higher rates of dyslipidemia, type 2 diabetes mellitus, and metabolic syndrome.

The individual role of traditional risk factors on the risk of CVD has been evaluated recently, concluding that they contribute in the similar direction in HIV positive and negative individuals.[9] However, the prevalence of certain traditional risk factors such as smoking and dyslipidemia is higher in HIV-infected individuals compared to the general population, the latter as a direct result from HIV infection itself or due to the exposure to anti-retrovirals.[19,21-23] Of note, the overall prevalence of dyslipidemia (80.2%) and arterial blood hypertension (31.5%) in our population was higher

compared to that reported from large cohort studies in the developed world (45.9% and 7.2%, respectively),[19,20] and from non-HIV infected subjects in Latin America (6-20% and 9-29%, respectively.[17] Current or past smoking habit in our study was comparable to that reported among HIV-infected patients[23] and non-HIV infected patients in Latin America.[17] On the other hand, the prevalence of type 2 diabetes mellitus (3.3%) was similar to that reported elsewhere,[19] but lower than that reported in non-HIV infected subjects in Latin America (4-8%).[17] The contribution of metabolic syndrome to the risk of CVD in HIV-infected patients on HAART has been challenged recently, as its definition may not have a good sensitivity for this population.[24] The prediction of CVD risk with metabolic syndrome is not more accurate than the conferred by its components. The overall prevalence of metabolic syndrome in our cohort of HIV-infected patients was similar than that reported elsewhere.[25-27]

Gender differences in the risk of CVD among HIV-infected patients on HAART have been reported.[20,28] We found a predominance of dyslipidemia, smoking habit, and high blood pressure among males, resulting in higher risk for CVD. In contrast, females presented more metabolic syndrome and obesity. Interestingly, obesity was more prevalent among females than among males in a large cohort of non-HIV-infected patients in Latin America.[17] Prevalence rates of obesity ranged from 16.8% in Buenos Aires to 30.4% in Mexico City in that study. Data from our cohort seem to correspond with the global obesity epidemic that affects both sexes, but particularly female Latin American subjects.

The study has limitations that should be considered when interpreting our results. Firstly, we did not include controls from the general population. Comparison of certain traditional risk factors for CVD, such as smoking habit and obesity in the general population of Latin America were comparable to those found in our study, but the prevalence of dyslipidemia and high blood pressure were markedly different, which may explain the increase risk of CVD observed in our patients. The purpose of our study was not to compare the CVD risk in HIV-infected patients with that of the general population, but to show the current status of the metabolic profile and CVD risk in HIV-infected patients on HAART. Secondly, our convenient sample may not be representative of the whole population of HIV-infected patients on HAART in Latin America, but to our knowledge this study represents the first attempt to elucidate the CVD risk among these patients in the region, and its results may be used for comparison with studies that might be conducted in the future. Lastly, some risk factors unique to HIV-infected patients on HAART such as altered body composition, including lypoatrophy and lypodistrophy could not be evaluated in this cohort of patients. Some studies have found a correlation between body composition and metabolic derangements that we were not able to ascertain in this study.

In summary, the intermediate 10-year risk of CVD observed in this population resulted from the high prevalence of traditional risk factors for CVD, and points out the necessity of implementing programs to reduce it. Intervention strategies should focus on smoking cessation, dietary counseling, increase exercise, and treatment of arterial blood hypertension and dyslipidemia, together with modification of HAART regimens when needed.

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REFERENCES

1. Palella FJ, Delaney KM, Moorman AC *et al*. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV outpatient study investigators. N Eng J Med 1998; 338:853-60.
2. Carr A, Samaras K, Burton S, Freund J, Chisholm DJ, Cooper DA. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance due to HIV protease inhibitors. AIDS 1998; 12:F51-F58.
3. Grinspoon S, Carr A. Cardiovascular risk and body-fay abnormalities in HIV-infected adults. N Eng J Med 2005; 352:48-62.
4. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab 2007; 92:2506-12.
5. Currier JS, Taylor A, Boyd F *et al*. Coronary heart disease in HIV-infected individuals. J Acquir Immune Defic Syndr 2003; 33:506-12.
6. Obel N, Thomsen HF, Kronborg G *et al*. Ischemic heart disease in HIV-infected and HIV-uninfected individuals: a population-based cohort study. Clin Infect Dis 2007; 44:1625-1631.
7. Iloeje UH, Yuan Y, L´italien G *et al*. Protease inhibitor exposure and increased risk of cardiovascular disease in HIV-infected patients. HIV Med 2005; 6:37-44.

8. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D. Clinical Epidemiology Group From the French Hospital Database. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. AIDS 2003; 17:2479-86.
9. Currier JS, Lundgren JE, Carr AC *et al*. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. Circulation 2008; 118:e29-35.
10. AIDS epidemic update 2007. UNAIDS/07.27E/JC1322E. December 2007.
11. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C; American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation. 2004; 109:433-8 .
12. De Socio GV, Martinelli L, Morosi S *et al.* Is estimated cardiovascular risk higher in HIV-infected patients than in the general population?. Scand J Infect Dis 2007; 39:805-812.
13. De Socio GVL, Parruti G, Quirino T *et al*. Identifying HIV patients with an unfavorable cardiovascular risk profile in the clinical practice: Results from the SIMONE study. J Infect 2008: doi:10.1016/j.jinf.2008:03.007.
14. Santos J, Palacios R, González M, Ruiz J, Márquez M. Atherogenic lipid profile and cardiovascular risk factors in HIV-infected patients (Nétar Study). Int J STD AIDS 2005; 16:677-80.
15. Bergersen BM, Sandvik L, Bruun 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.
16. Kaplan RC, Kingsley LA, Sharrett AR *et al*. Ten-year predicted coronary heart disease risk in HIV-infected men and women. Clin Infect Dis 2007; 45:1074-81.
17. Schargrodsky H, Hernández-Hernández R, Champagne BM *et al*. CARMELA: assessment of cardiovascular risk in seven Latin American cities. Am J Med 2008; 121:58-65.
18. Law MG, Friis-Møller N, El-Sadr WM *et al*. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study. HIV Med 2006; 7:218-30
19. Friis-Møller N, Sabin CA, Weber R *et al*. Combination antiretroviral therapy and the risk of myocardial infarction. N Eng J Med 2003; 349:1993-2003.
20. Friis-Møller N, Reiss P, Sabin CA *et al*. Class of antiretroviral drugs and the risk of myocardial infarction. N Eng J Med 2007; 356:1723-35.
21. Friis-Møller N, Weber R, Reiss P *et al*. Cardiovascular disease risk factors in HIV patients--association with antiretroviral therapy. Results from the DAD study. AIDS 2003; 17:179-3.
22. Savès M, Chêne G, Ducimetière P *et al*. Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. Clin Infect Dis 2003; 37:292-8.
23. Gritz ER, Vidrine DJ, Lazev AB, Amick BC 3rd, Arduino RC. Smoking behavior in a low-income multiethnic HIV/AIDS population. Nicotine Tob Res 2004; 6:71-7.
24. Samaras K, Wand H, Law M, Emery S, Cooper D, Carr A. Prevalence of metabolic syndrome in HIV-infected patients receiving highly active antiretroviral therapy using International Diabetes Foundation and Adult Treatment Panel III criteria: associations with insulin resistance, disturbed body fat compartmentalization, elevated C-reactive protein, and hypoadiponectinemia. Diabetes Care 2007; 30:113-9.
25. Bonfanti P, Giannattasio C, Ricci E *et al*. HIV and metabolic syndrome: a comparison with the general population. J Acquir Immune Defic Syndr 2007; 45:426-31.
26. Mondy K, Overton ET, Grubb J, Tong S, Seyfried W, Powderly W, Yarasheski K. Metabolic syndrome in HIV-infected patients from an urban, midwestern US outpatient population. Clin Infect Dis 2007; 44:726-34.
27. Samaras K. Metabolic consequences and therapeutic options in highly active antiretroviral therapy in human immunodeficiency virus-1 infection. J Antimicrob Chemother 2008; 61:238-45.
28. Neumann T, Woiwod T, Neumann A *et al*. Cardiovascular risk factors and probability for cardiovascular events in HIV-infected patients, Part III: gender differences. Eur J Med Res 2004; 27; 9:55-60.