ORIGINAL ARTICLE

Metabolic syndrome in HIV-infected patients receiving antiretroviral therapy in Latin America

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Submitted on: 07/27/2009
Approved on: 12/03/2009

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The study was supported by research grant from Bristol-Myers Squibb. We would like to thank the following people from Bristol Myers Squibb for their contribution to the study: Cochon N., Guevara R, Castagneto J, Fernández B, Calenda M, Barbosa E, Andrade P., Montenegro J, Olivera M, Isaza A, Gutierrez R, Coronado A, Conrrado S.

ABSTRACT

Objective: To evaluate the prevalence of and the associated factors for metabolic syndrome (MS) among Latin American HIV-infected patients receiving antiretroviral therapy (ART) using baseline data from the RAPID II study. **Methods**: A longitudinal study to evaluate the metabolic profile, cardiovascular disease (CVD) risk and associated treatment practices to reduce this risk has been conducted in seven Latin American countries (the RAPID II study). Adult HIV patients with at least six months of RT were enrolled. MS was defined following ATP-III criteria. Demographic and anthropometric data, serum biochemical and clinical parameters were compared in patients with and without MS using bivariate and multivariate analysis. **Results**: A total of 4,010 patients were enrolled, 2,963 (74%) were males. Mean age (SD) was 41.9 (10.0) years. The prevalence of MS was 20.2%. Females had higher prevalence of MS than males (22.7% vs. 19.4%, p = 0.02). MS was driven by high triglycerides, low HDL-cholesterol and high blood pressure (HBP). Patients with MS had higher 10-year CVD risk: 22.2% vs. 7.4%, p < 0.001. Age (OR: 1.05 per year), female gender (OR: 1.29), family history of CVD (OR: 1.28), CD4 cell count (OR: 1.09 per 100 cell increase), and protease inhibitor based-ART (OR: 1.33) correlated with MS in the multivariate analysis. **Conclusions**: Prevalence of MS in this setting was similar to that reported from developed countries. MS was driven by high triglycerides, low-HDL and HBP, and it was associated with higher risk of CVD. Traditional risk factors, female gender, immune reconstitution, and protease inhibitor based-ART correlated with MS.

Keywords: metabolic syndrome (MS), HIV, ART, Latin America.

[Braz J Infect Dis 2010;14(3):256-263]

INTRODUCTION

Metabolic syndrome (MS) includes derangements in glucose metabolism, insulin resistance, lipid abnormalities, hypertension and abdominal obesity.[1] Patients with MS from the general population have more risk to develop type 2 diabetes and carry a significant increased risk of dying due to cardiovascular disease (CVD).[2,3] Therefore, identifying individuals with MS may allow implementation of measures to halt the progression to diabetes and CVD.

Since the introduction of effective antiviral treatment through combined antiretroviral therapy (RT) in the 1990s, a significant improvement in survival of HIV-infected patients has been observed, together with a dramatic decrease in the incidence of many opportunistic infections.[4] However, metabolic abnormalities and abnormal body fat redistribution, following a very similar pattern to that described for MS, were soon observed.[5,6] In addition, several early studies disclosed that HIV-infected patients receiving ART had high prevalence rates of MS, even higher than those reported from the general population in certain settings.[7-9] While the real contribution of MS to detect patients at risk to develop CVD compared to other traditional risk evaluations in both non-HIV and HIV-infected populations is currently under debate, most experts agree that components of MS may be used to predict risk of CVD and type 2 diabetes mellitus.[1,10]

Scaling-up programs to provide ART are being implemented across the world thanks to initiatives promoted by several organizations. The net results of these interventions is a marked benefit in survival and quality of life among ART recipients, but it is also expected that all short and long-term complications of ART, including metabolic abnormalities will be observed in these patients, although the magnitude of the problem has not been explored yet. Latin American countries are not the exception of this situation, as reported by WHO using

data up to 2007; approximately 300,000 patients received ART in Latin America that year.[11] Therefore, we undertook this study to evaluate the prevalence and determinants of metabolic syndrome among Latin American HIV-infected patients receiving ART, using baseline data gathered from the RAPID II study. The results of this study may be used by regional and local policy makers to incorporate interventions aimed at reducing the burden of long-term metabolic complications of ART in the region.

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 ART in Latin America.

Setting

Sixty one centers from seven Latin American countries are participating in the study: Argentina (16 centers in Buenos Aires, La Plata and Rosario), Brazil (15 centers in Sao Paulo, Rio de Janeiro, Campinas, and Porto Alegre), Chile (2 centers in Santiago), Colombia (3 centers in Bogotá and Cali), Ecuador (11 centers in Quito, Cuenca and Guayaquil), Peru (5 centers in Lima) and Venezuela (9 centers in Caracas, Valencia, Barquisimeto and San Cristobal).

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 genders, and with confirmed HIV infection receiving ART for at least six months prior to enrollment were selected. A lipid profile had to be obtained on every patient at enrollment or within one month. 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 current and prior antiretroviral medications. Cardiovascular risk factors present before enrollment including history of hypertension, diabetes mellitus, dyslipidemia, smoking habit, and family history of premature CVD. Information on smoking, exercising and diet, as well as on any medication or lipid lowering intervention implemented during 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, exercise and the use of lipid lowering drugs. A complete physical examination was performed, including measurements of blood pressure, weight, height, and waist circumference. A fasting blood sample was taken and processed in each participating centre to measure 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.

Definition of metabolic syndrome

The main outcome of this study was to determine the prevalence and the determinants of metabolic syndrome at the first study visit. Metabolic syndrome was defined following National Cholesterol Education Program Adult Treatment Panel III definition.[1] Based on that definition, three or more of the following criteria need to be met for defining metabolic syndrome: 1) fasting serum triglycerides ≥ 150 mg/dL; 2) abnormal waist circumference: waist perimeter ≥ 102 cm in man, or ≥ 88 cm in women); 3) fasting blood glucose ≥ 100 mg/dL; 4) hypertension: systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg, and/or use of an antihypertensive drug); 5) low HDL-cholesterol: man with ≤ 40 mg/dL or woman with ≤ 50 mg/dL.

Statistical analysis

Demographic and clinical variables were compared between patients with and without metabolic syndrome including age, gender, family history of CVD, body mass index, obesity, current smoking, lack of exercise, duration of HIV infection, time on ART, current use of protease inhibitors (PI), current use of nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI), CD4 cell count, viral load determination, and serum biochemical evaluations including glucose and lipid parameters. The Framingham risk algorithm was used to estimate the 10-year risk of developing CVD.

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, the level of significance was pre-defined at < 0.05. Odds ratios and 95% confidence intervals were calculated. Associated factors for metabolic syndrome were evaluated in bivariate and multivariate analysis following backward stepwise unconditional regression analysis.

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, 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). Mean age (SD) of the population was 41.9 (10.0) years, 73.9% of the patients were males. Most of the patients were concentrated in the age group of 28-47 years; only 1.5% had more than 68 years of age. Median CD4 cell count was 417 cells/mm^3 (IQR: 266-621), and mean viral load determination was 2.4 (1.0) $\log_{10}$ copies/mL. A protease inhibitor based ART was used in 44% of patients.

The overall prevalence of MS was 20.2% (812/4,010); it was higher in female than in male patients: 22.7% vs. 19.4%, respectively, p = 0.02. The distribution of individual components of the MS by gender is shown in Figure 1. High triglycerides (55.8%), low-HDL cholesterol (49.5%) and hypertension (31.5%) were the most prevalent individual components of MS in this population. Male patients had higher prevalence of hypertriglyceridemia, elevated fasting blood glucose and hypertension than females. In contrast, female patients had higher prevalence of low-HDL cholesterol and abdominal obesity than male patients.

The prevalence of MS by age and gender is shown in Figure 2. A trend towards higher prevalence rates of MS by age was observed; females disclosed higher prevalence rates than males. Figure 3 illustrates the distribution of MS by country and gender. Chile and Colombia had the lowest prevalence rates of MS, while the remaining five countries showed comparable rates. Female patients of five countries; Brazil, Colombia, Ecuador, Peru and Venezuela had higher prevalence rates of MS than males, the opposite was observed in Argentina and Chile.

Figure 2: Prevalence of metabolic syndrome by age and gender.

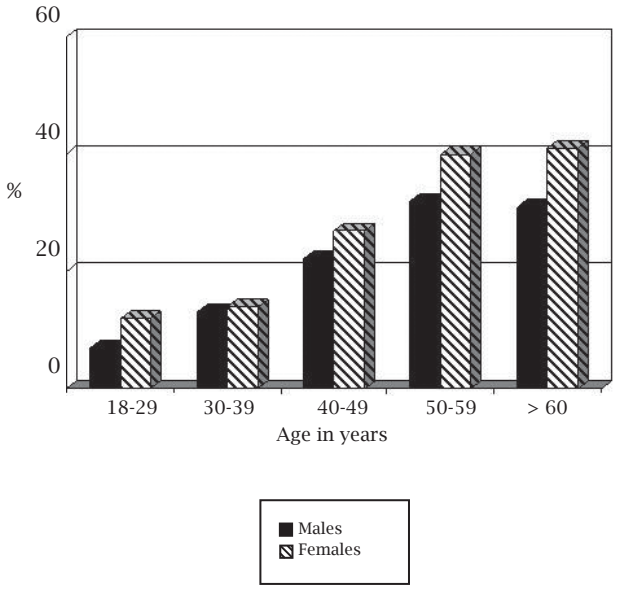

Figure 1: Components of the metabolic syndrome by gender.

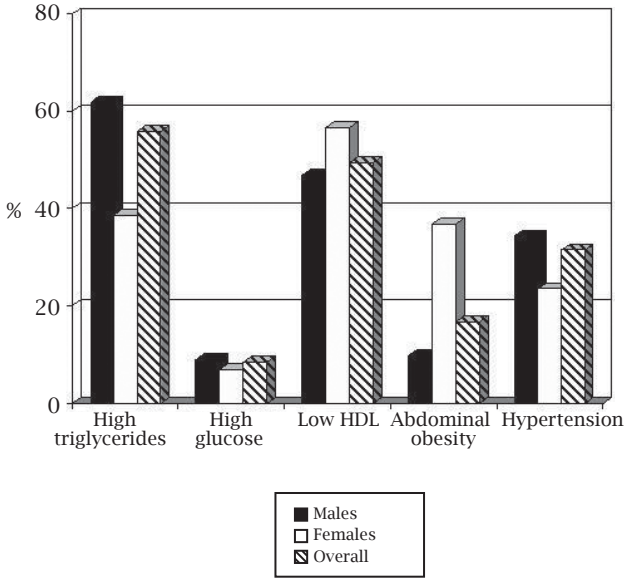

Figure 3: Prevalence of metabolic syndrome by country and gender.

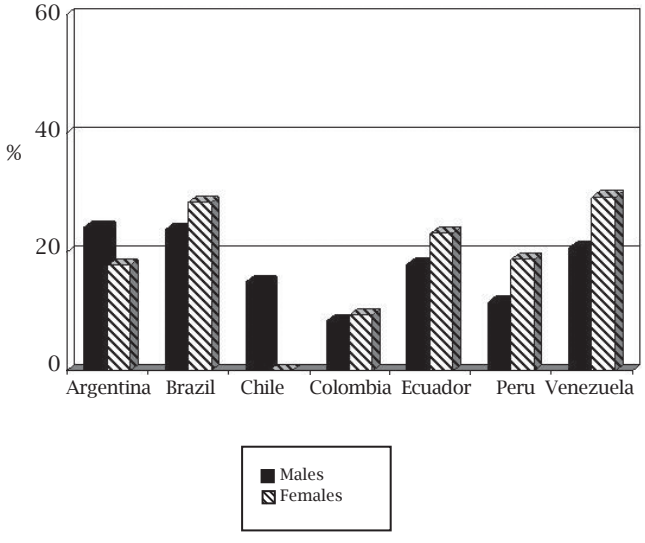

*Table 1. Bivariate analysis of characteristics associated with metabolic syndrome**

Characteristic	Metabolic syndrome (n = 812)	No metabolic syndrome (n = 3,198)	Odd ratio (95% CI)	p-value
Age, y	45.88	40.84	1.05 (1.04-1.06)	< 0.001
Gender, %				
Male	19.37	80.63	1.0	
Female	22.73	77.27	1.22 (1.03-1.45)	0.020
Family history of cardiovascular disease, %				
No	19.06	80.94	1.0	
Yes	24.41	75.59	1.37 (1.15-1.64)	< 0.001
Duration of HIV infection, y	7.19	6.26	1.05 (1.03-1.07)	< 0.001
Duration of combination antiretroviral treatment, y	3.87	2.76	1.08 (1.05-1.11)	< 0.001
CD4 cell count, 10^3 cells/mm^3	0.53	0.45	2.65 (2.03-3.46)	< 0.001
Viral load, $\log_{10}$ copies/mL	2.27	2.37	0.90 (0.83-0.98)	0.011
Current protease inhibitor use, %				
No	17.85	82.15	1.0	
Yes	23.27	76.73	1.40 (1.20-1.63)	< 0.001
Current non-nucleoside reverse transcriptase inhibitor use, %				
No	22.75	77.25	1.0	
Yes	18.29	81.71	0.76 (0.65-0.89)	0.001
Current nucleoside reverse transcriptase inhibitor use, %				
No	27.5	72.5	1.0	
Yes	20.2	79.8	0.66 (0.29-1.51)	0.352
Body mass index, kg/m^2	27.44	23.91	1.30 (1.27-1.33)	< 0.001
Waist circumference, cm	96.05	85.45	1.11 (1.10-1.12)	< 0.001
Obesity, %				
No	16.65	83.35	1.0	
Yes	62.15	37.85	8.22 (6.44-10.48)	< 0.001
Hypertension, %				
No	6.73	93.27	1.0	
Yes	49.64	50.36	13.65 (11.34-16.44)	< 0.001
Elevated fasting blood glucose, %				
No	18.47	81.53	1.0	
Yes	67.59	32.41	9.20 (6.44-13.15)	< 0.001
Current smoking, %				
No	20.69	79.31	1.0	
Yes	18.78	81.22	0.89 (0.74-1.07)	0.207
Lack of exercise, %				
No	18.59	81.41	1.0	
Yes	21.70	78.30	1.21 (1.04-1.42)	0.015
Fasting serum glucose, mg/dL	106.69	88.77	1.04 (1.03-1.05)	< 0.001
Fasting serum total cholesterol, mg/dL	209.0	192.19	1.01 (1.0-1.02)	< 0.001
Fasting serum HDL, mg/dL	37.27	46.39	0.93 (0.92-0.94)	< 0.001
Fasting serum LDL, mg/dL	114.3	109.1	1.03 (1.01-10.04)	< 0.001
Fasting serum triglycerides, mg/dL	324.4	186.8	1.04 (1.03-1.05)	< 0.001

*Values are mean unless noted otherwise

*Table 2. Multivariate analysis of characteristics associated with metabolic syndrome**

Characteristic	Adjusted Odds Ratio	95% Confidence interval	p-value
Age at enrollment, per year	1.05	1.04-1.06	< 0.001
Female gender	1.29	1.08-1.54	0.006
Family history of cardiovascular disease	1.28	1.07-1.54	0.007
CD4 cell count per 100 cell increase	1.09	1.06-1.12	< 0.001
Protease inhibitor based ART#	1.33	1.13-1.57	0.001
Zidovudine based ART	0.86	0.73-1.01	0.069

*corrected for anthropometric parameters, duration of HIV infection, time on antiretroviral treatment, viral load, smoking, hypertension, lack of exercise, and current use of nucleoside and non-nucleoside reverse transcriptase antiretroviral treatment.
ART: antiretroviral therapy

The overall (SD) 10-year risk of developing CVD, as measured by the Framingham risk equation was 10.4% (24.7). Patients with MS had higher 10-year CVD risk compared to patients without MS: 22.2% vs. 7.4%, respectively, $p < 0.001$. The bivariate analysis to identify determinants of MS is presented in Table 1. Patients with MS were older, had higher body mass index, more obesity and higher abdominal waist circumference than patients without MS. Most of the variables studied correlated with MS in this analysis including age, gender, family history of CVD, HIV related features such as duration of HIV infection, duration of ART, CD4 cell count and viral load, current use of PIs and NNRTIs, anthropometric data, lack of exercise, diabetes and hypertension, as well as serum values of glucose and lipids. No association was found for current smoking and current use of NRTIs. We further explore the association of the most commonly used NRTIs in the region with MS, and confirmed no association for stavudine (OR: 0.93, 95% CI: 0.74-1.18, $p = 0.600$), abacavir (OR: 1.13, 95% CI: 0.91-1.40, $p = 0.263$), and lamivudine (OR: 0.83, 95% CI: 0.65-1.06, $p = 0.136$), but a protective effect of zidovudine was observed (OR: 0.820, 95% CI: 0.70-0.961, $p = 0.016$).

The multivariate analysis is presented in Table 2. Age at enrollment (5.0% increase per year), female gender (28% increase), current use of PIs (33% increase), CD4 cell count (9% increase per 100 cell raise) and family history of CVD (28% increase) correlated with metabolic syndrome. The association of time living with HIV infection and time on ART, and the protective effect of zidovudine on MS were not confirmed in the multivariate analysis.

DISCUSSION

This cross sectional study analyzed pre-intervention data from the RAPID II study and demonstrates that Latin American HIV-infected patients receiving ART have a similar overall prevalence rate of MS than that reported from comparable populations in developed countries.[9, 12-17] High triglycerides, low-HDL cholesterol, and hypertension were the most prevalent individual components of MS. Interestingly, female patients had higher prevalence rate of MS than males, with higher rates of abdominal obesity and lower-HDL cholesterol values than males. Patients with MS had higher risk of developing CVD and had nine fold higher prevalence of type 2 diabetes mellitus compared to patients without MS. We identified risk factors for MS including traditional hazards such as age and family history of CVD, and unique factors to this setting such as female gender, cellular immune-reconstitution and use of PIs. These finding are to our knowledge the first attempt to characterize MS among HIV-infected patients on ART in the region and have important implications for designing regional preventive measures.

The prevalence of MS found in our study, 20.2%, is comparable to that reported from the developed world.[9, 12-17] Several studies have compared the prevalence of MS among HIV-infected and non-HIV infected patients, finding similar or higher prevalence rates among HIV infected patients.[9,12,13] We did not include a non-HIV control group; therefore, we are not able to determine whether HIV-infected patients differ or not from the general population of Latin America. However, a recently published study in the region that recruited a large

sample size (11,500 subjects from six Latin American countries: Argentina, Colombia, Ecuador, Chile, Mexico and Peru) with a similar age distribution to our sample showed an overall prevalence rate of MS of 20%.[18] Interestingly, female subjects in that study had higher prevalence rate of MS than males (21.5% vs. 19.3%, respectively), and disclosed similar gender differences in the prevalence of MS per country as seen in our study (higher female prevalence rate of MS in Ecuador, Peru and Colombia, and male predominance in Argentina). The authors attributed the difference to the growing diabetic and obesity pandemics in the region that affect mostly females. These data suggest that the prevalence of MS among HIV-infected patients in Latin America does not differ from the general population, but also suggest that different risk patterns may exist between these two populations.

The most prevalent individual components of the MS in our study were high triglycerides, low-HDL cholesterol and hypertension. This pattern has been consistently seen across several studies in HIV-infected patients receiving ART.[9,14,15] Gender differences in the frequency of each component of MS were observed in our study; males had higher frequency of elevated triglycerides, HBP and elevated blood glucose, while females had higher prevalence of low-HDL cholesterol and abdominal obesity. These gender differences in the contribution of each component of the MS have not been adequately explored in the literature, and may reflect real differences pertinent to the Latin American population that merit further investigation. Expectedly, MS patients had significantly higher 10-year risk of developing CVD compared to patients without MS as measured by the Framingham risk algorithm.

Our study identified several independent risk factors for MS through multivariate analysis that controlled for potential confounders. Among them, age and family history of CVD are well recognized risk factors for MS and CVD.[9,14] We found a 9% increase in the risk of MS per 100 cell increment in CD4 cell count, implying that the most immune reconstituted patients had higher risk of developing MS. This finding is somewhat surprising, but has been observed by others.[9,16,19] Higher CD4 cell count was a predictor of MS in a cohort study of male HIV-infected patients,[9] and more recent data from the DAD study (Data Collection on Adverse Events of Anti-HIV Drugs) found higher CD4 cell counts and lower viral load values among patients with MS.[19] Similarly, a study conducted in Italy found that higher CD4 cell counts correlated with more CVD risk, hypothesizing that more immune-reconstituted patients represent a subset of patients with longer exposure to ART showing cumulative higher risk of CVD.[16] Others have found that patients with higher CD4 cell counts (> 200 cells/mm^3) had higher rates of vessel thickening, a surrogate marker for CVD, than patients with lower CD4 cell counts.[20]

Female gender was one of the strongest predictors of MS in our study, despite a male predominance in the sample population. While a very high prevalence of MS among females from the USA has been reported recently,[21] this finding is rather unique in the literature, and may represent a distinctive feature of the Latin American region. A higher prevalence of MS among females in six Latin American countries has been reported recently, which may correspond with our findings,[18] Unfortunately, the authors of that large study did not look at independent predictors of MS to confirm the presumed female predisposition. Finally, we found that HIV-related features such as time living with HIV and time on ART did not correlate with MS, but that a specific component of ART, current use of PIs independently correlated with MS, not finding an association with NRTI and NNRTI use. The literature has conflicting information regarding specific contribution of ART itself and its components to MS. Jacobson *et al.* found that ART did not correlate with MS.[12] However, use of lopinavir/r boosted by ritonavir and didanosine were independently associated with MS in the multivariate analysis in that study. In another study, Mondy *et al.* found that current use of ART was not different in subjects with and without MS, but use of PIs was associated with higher triglyceride levels only.[9] Another study conducted in Spain found that past and current use of a PI correlated with MS; that study also found that current use of stavudine correlated with MS.[8] These dissimilar findings may be explained by different patterns of lipid derangements associated with specific components of ART, including thymidine analogues and PIs, in particular with ritonavir-boosted PI regimens, but may also be explained by different patient populations and probably by gender and race differences that have not been adequately explored.

Our study has limitations including the non-random selection of the study participants that may affect the representativeness of the sample, and the absence of controls from the general population, that makes difficult to draw conclusions regarding the significance of our data. On the other hand, the large sample size, and the participation of patients from seven countries that collectively manage the largest number of HIV-infected patients in South America are strengths of the study. Additionally, the findings of similar results for the overall prevalence of MS and for the higher prevalence of MS among females, when compared to a larger study conducted among non-HIV subjects from the region pro vide further support on the relevance of the information

presented here. The cohort design of the RAPID II study will allow us to corroborate the results obtained in this cross sectional study, in particular to evaluate the incidence of MS, to provide more information on the contribution of individual components of the syndrome, and to compare its predictive value in calculating CVD risk compared to other available risk determinations.

In conclusion, the prevalence of MS in this large group of HIV-infected patients receiving ART is comparable to that reported from similar populations from developed countries and from non-HIV infected subjects from the region. Patients with MS had higher estimated risk for CVD. MS was associated with traditional risk factors but with somewhat unique features such as female gender, immune-reconstitution and current PI use. Latin American physicians should be aware of the magnitude of the problem, and should incorporate into daily practice interventions to reduce MS, targeting the risk groups identified in this study.

ACKNOWLEDGEMENTS

We are very grateful to the researchers of the RAPID II Study Group:

Argentina: Zala C, Cahn P, Galindez J, Lopardo G, Altclas J, Ruiz MC, Corrales JL, Lupo SH, Pallone E, Vera MA, Rodríguez CG, Cassetti I, García O, Levalle J, Belloso WH, Losso MH.

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Chile: Wolff M, Muñoz R.

Colombia: Alvarez C, Leal R, Sussmann O, Lenis W.

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Venezuela: Castrillo M, Pineda A, Ducharne M, Roldán Y, Contreras K, Vivas J, Deibis L, Salcedo M, Semeco J, Rosales A, Rivera M, Arzola A, Muller G, Torres A, Quintero V, Flores ME, Rojas N, Silva M, Riera J, Figueredo A, Alayo E.

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