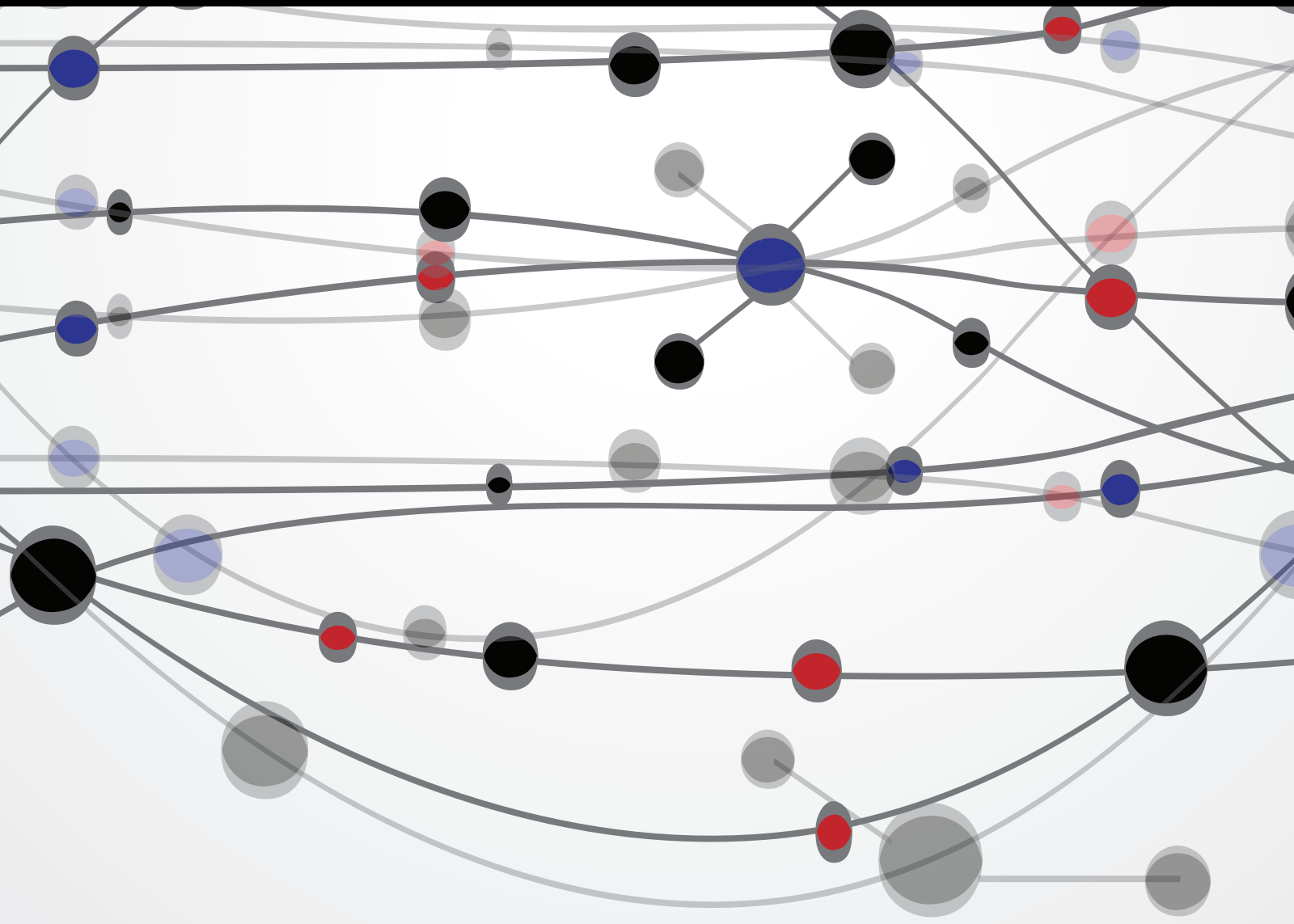
The Scientific World Journal

# HIV Infection and Cardiovascular Disease

Guest Editors: Sandra C. Fuchs, Marina Beltrami-Moreira, Bolanle Oyeledun, Papa Salif Sow, and Marco Vitoria



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*Editorial*

# HIV Infection and Cardiovascular Disease

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HIV infection has been considered as one of the major global public health threats of the last century, increasing several times the mortality rate in comparison to the cholera epidemic that swept London in the nineteenth century. Unlike the contamination caused by cholera bacillus, prevention of HIV infection requires other interventions than basic sanitation, and the antiretroviral agents currently remain the touchstone to transform the disease from subacute into a chronic condition. The introduction of highly active antiretroviral therapy (HAART) in the treatment of HIV-infected patients, in 1990s, has allowed better health status and greater longevity among people living with HIV, associated with a reduction in the viral transmission rate. For a while, it has been believed that universal access to HAART and the progressive increase in the efficiency of the prevention methods could save future generations [1]. However, it requires an enormous effort to expand HIV testing, maintenance of sustained treatment, and implementation of prevention programs. Nevertheless, HAART is not free of adverse effects.

With the significant reduction of the mortality and morbidity associated with HIV induced immunodeficiency in patients using HAART, the HIV infection is behaving as a long-term sickness [2]. HIV infection and its treatment have been associated with abnormal metabolic profile [3]; increased prevalence of noncommunicable diseases [4, 5] and mortality rate of AIDS-related have shifted to non-AIDS-related conditions [6, 7]. In the pre-HAART era, mortality from cardiovascular disease in infected persons occurred almost two decades earlier than in the general population. After the introduction of HAART, this difference went on to about nine years [8]. Even though the HIV-infected population is getting older, most still ar less than 50 years old and, in the United States, only half of the population will be 50 years in 2015 [9]. Therefore, the long-term management of patients with HIV infection has to be expanded to diagnosis, treatment, and prevention of cardiovascular risk factors and coronary heart disease. Even so, most current guidelines for the treatment of HIV infection are still focused only on antiretroviral treatment and do not take into account the treatment and prevention of comorbidities not related to AIDS [10–12]. However, bringing the paradigm of cardiovascular disease prevention for the scenario of HIV infection requires detection of the prevalence of cardiovascular risk factors and coronary heart disease in HIV-infected patients.

In this edition of this journal, a portrait of the Brazilian scenario of cardiovascular disease among HIV-infected patients was presented. Brazil is a country that has provided free access to HIV treatment for the entire population of infected people in the last two decades, and the use of HAART had a great impact on the costs of health care and

the demand for the public health system. D. V. Araújo et al. showed that, in the last five years, the number of HIV/AIDS cases increased approximately by 40%, among patients under 50-years of age, yet the hospital admissions due to AIDS remained stable. Conversely, there was a marked increase in the hospitalizations due to acute myocardial infarction. R. K. Lazzaretti et al. provided data on genetic basis for understanding the complexity of the dyslipidemia in HIV infection. They detected that single nucleotide polymorphisms in six candidate genes (APO B, APO A5, APO E, APO C3, SCAP, and LDLR) were associated with dyslipidemia, showing that genetic factors contribute to determining the lipid profile in HIV-infected individuals on antiretroviral therapy.

Even so, there is a lack of robust evidence for prescribing agents to reduce dyslipidemia in HIV-infected patients. The new guidelines for cholesterol treatment highlighted the lack of randomized clinical trials on the potential benefits of statin therapy to reduce the risk of atherosclerotic cardiovascular disease in HIV-infected patients exceeding the risk of adverse events or drug interactions [13].

Another approach, previously described for the general population [14, 15], was to determine whether the association between consumption of alcoholic beverages and hypertension was modified by race in HIV-infected individuals. Among lifestyle characteristics, the consumption of large amounts of alcohol was independently associated with hypertension in white and nonwhite HIV-infected individuals. M. L. R. Ikeda et al. showed that there was an association of blood pressure with the frequency of consumption among the whites, while for nonwhite participants the amount of alcohol consumed was more important than the pattern of consumption in raising blood pressure. Although some of lifestyle characteristics are not modifiable, alcohol consumption is suitable for intervention.

In an attempt to compare some tools available to assess the overall cardiovascular risk profile of HIV-infected patients, M. W. Nery et al. calculated the traditional Framingham risk score, the Prospective Cardiovascular Münster (PROCAM) score; both originally developed for non-HIV-infected population; and the Data Collection on Adverse Effects on Anti-HIV Drugs (DAD) score, validated on HIV-infected patients. They found that the proportion of patients classified as being at moderate risk or higher was larger for the Framingham than for the PROCAM score. While these results have clinical follow-up and management implications, there was no comparison with data collected for the incidence of events. The use of Framingham score seems to have the advantage of allowing the comparison with other studies conducted in non-HIV-infected population [16]. Finally, a pooled analysis carried out in three cities of the Northeast, Midwest, and Southern Brazil showed that, irrespective of HIV status or treatment, classically risk-associated conditions, such as hypertension and diabetes, persist as the most relevant risk factors for cardiovascular disease. Moreover, these conditions were present at a younger age in the studied population. Of note is also the high prevalence of moderate and high risk according to the Framingham risk score among women. In this group, the diagnosis of cardiovascular disease and ischemic heart disease frequently occurs later than in men. This study reminds us that it is never too early to approach these problems and emphasize primary prevention of cardiovascular disease, even among populations with chronic conditions such as the HIV infection. We believe that the spectrum of cardiovascular manifestations among patients infected by HIV, pictured in this edition, allows the design and implementation of initiatives aimed at controlling and preventing the impact of cardiovascular disease.

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*Research Article*

# The Economic Burden of HIV/AIDS and Myocardial Infarction Treatment in Brazil

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*Objective*. To analyze the expenses of HIV/AIDS and acute myocardial infarction (AMI) treatment in Brazil. *Methods*. A search in the Brazilian epidemiological database (DATASUS) on AMI and AIDS hospitalizations and their costs was done from January 1998 to December 2011. The number of HIV/AIDS cases and antiretroviral treatment (ART) costs was obtained from public Brazilian databases. *Results*. In 5 years, HIV/AIDS cases increased 38.5%, mainly in patients aged 25–49. There were 180,640 patients in ART in 2007 at a cost of R$ 3,920 per patient/year. The hospitalizations due to AIDS were stable over the last 13 years; however, the hospitalizations due to AMI have increased 78%. In 2007, the expenses with hospitalizations for HIV/AIDS and AMI (25–49 years) were approximately 0.12 and 1.52% of the Ministry of Health budget allocated to reimburse inpatient costs. The expenses on ART totaled 1.5% of the total budget (all age groups). *Conclusion*. The prevalence of HIV/AIDS is still increasing in Brazil. There are scientific evidences suggesting an increased incidence of AIM in this population. Considering the high costs for the treatment of both diseases, an economic analysis is important to alert health managers to strengthen the preventive measures to guarantee the financial sustainability of such treatment.

## 1. Introduction

The Brazilian HIV/AIDS Program was established in May 1985 [1]. In 1996, the Brazilian Unified Health System (SUS) ensured the coverage of antiretroviral drugs (ART) to all those living with HIV/AIDS in Brazil, resulting in AIDS mortality reduction [2].

Following the development of drug resistance in HIV patients, the Brazilian Ministry of Health had to provide new drugs at higher costs, investing up to R$ 551 million in antiretroviral treatment in 2003. There was an increase in the investment in subsequent years due to the acquisition of patented drugs (up to R$ 960 million in 2006). The introduction of the first fusion inhibitor, enfuvirtide, in the therapeutic regimen of multidrug-resistant patients had a strong impact on total costs. It was provided to 1,030 patients at a daily cost of US$ 22.19, the accounting for 4.4% of antiretroviral expenditure in 2006 [3].

It remains controversial whether the exposure to combination antiretroviral (ART) treatment increases the risk of acute myocardial infarction (AMI). Friis-Møller et al. conducted a prospective observational study with 23,468 patients with HIV from 11 previously established cohorts to evaluate the risk factors and the incidence of myocardial infarction. The authors concluded that ART therapy was independently associated with a 26-percent relative increase in the rate of myocardial infarction per year of exposure during the first four to six years of use [4]. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study assessed the risk of AMI in 13 anti-HIV drugs in an observational study. Over 178,835 person-years, 580 patients developed AMI. Of the drugs considered, only indinavir, lopinavir ritonavir,

Table 1: Number of patients covered in the HIV/AIDS Program (antiretroviral drugs) and their related costs in the Brazilian Unified Health System (SUS).

| Year | Number of patients | Cost (reais) | Cost per patient (reais) |
|---|---|---|---|
| 2002 | 125,175 | R$668,783,673 | R$5,342 |
| 2003 | 139,868 | R$495,900,996 | R$3,545 |
| 2004 | 156,670 | R$596,016,153 | R$3,804 |
| 2005 | 164,547 | R$567,045,691 | R$3,446 |
| 2006 | 174,270 | R$1,002,732,562 | R$5,753 |
| 2007 | 180,640 | R$708,178,407 | R$3,920 |

Source: Vieira 2009 [8], monthly report for Assessment and Use of HIV Drugs, and STD/AIDS Program Care and Treatment Unit.

didanosine, and abacavir were associated with a significantly increased risk of AMI (12 to 13%) [5]. Islam et al. estimated the relative risk of cardiovascular disease (CVD) among people living with HIV (PLHIV) compared with the HIV-uninfected population. The authors conducted a systematic review and meta-analysis of studies and showed that the relative risk of CVD was 1.61 (95% CI 1.43–1.81) among PLHIV without ART compared with HIV-uninfected people. The relative risk of CVD was 2.00 (95%CI 1.70–2.37) among PLHIV on ART compared with HIV-uninfected people and 1.52 (95% CI 1.35–1.70) compared with treatment-naïve PLHIV [6].

Given the importance and the high costs of treating both conditions in Brazil, this analysis aimed to estimate and analyze the costs of HIV/AIDS and AMI treatment and their impact on the public budget of the Brazilian Unified Health System.

## 2. Methods

A search in the Brazilian epidemiological database (DATASUS) on AMI and AIDS hospitalizations and their costs was done from January 1998 to December 2011. The survey was restricted to patients aged 25–49 (group with the highest prevalence of HIV/AIDS in the Brazil). Data were registered as the number of hospitalizations and reimbursed expenditures in Reais (R$). The annual number of HIV/AIDS reported cases was obtained from the TABNET database of the Brazilian Ministry of Health [7].

Data from a previously published study about the antiretroviral treatment costs were analyzed. The authors analyzed the Ministry of Health's total spending on drugs and its programs between 2002 and 2007 [8]. The Federal Government antiretroviral drug acquisitions were analyzed separately, obtained from a federal purchase website (ComprasNet) [9].

The Brazilian Public Health System perspective, which considers only direct costs that are reimbursed to health care providers was adopted. In this scenario, indirect costs are not computed in the database.

## 3. Results

From 1980 to June 2007, 474,273 HIV/AIDS cases were reported. In June 2012, this number increased to 656,701 registered cases (Figure 1). Data on the number of patients on antiretroviral therapy between 2002 and 2007 and the annual total and per patient costs of HIV/AIDS treatment are described in Table 1, comprising almost 100% HIV of the reported cases (Brazilian Ministry of Health, 2008).

The number of hospitalizations for AMI and AIDS and their costs (patients aged 25–49; 1998–2011) is shown in Figures 2 and 3, respectively.

## 4. Discussion

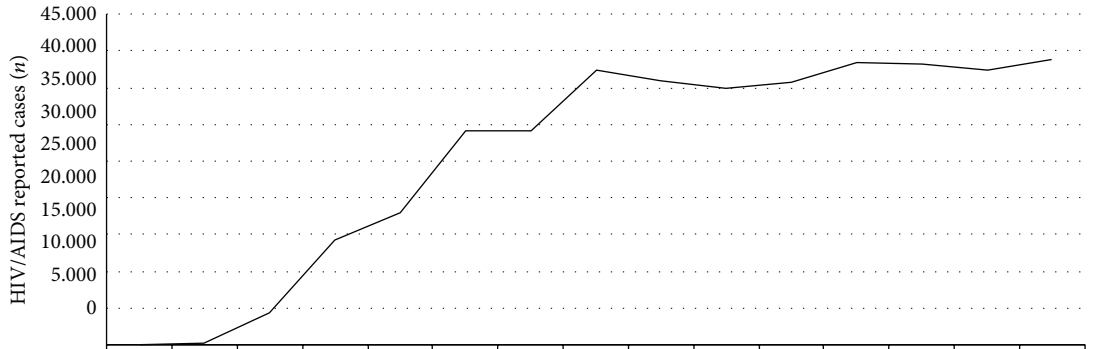
In Brazil, the age-standardized mortality from cardiovascular diseases decreased by 26% in the last decade, and this decrease was partially due to the successful implementation of health policies that led to the reduction of smoking and the expansion of access to basic health care [10]. However, the prevalence of diabetes, arterial hypertension, and HIV/AIDS is increasing parallel with the prevalence of overweight and aging population, which may be reflected in unfavorable trends in mortality from cardiovascular diseases in the next decade.

Cardiovascular diseases represented the third leading cause of hospitalizations in the Brazilian Unified Health System, having been responsible for the greater spending on hospitalization, accounting for a total of R$ 1.9 billion or 19% of the total cost of hospitalizations. Acute coronary syndrome (unstable angina and acute myocardial infarction) accounted for 7% of all deaths in Brazil, associated with substantial direct and indirect costs to healthcare systems and society [11].

In the last 5 years, the number of HIV/AIDS registered cases increased 38.5% [12]. The age group where AIDS is more prevalent in both sexes is the one with 25–49 year olds, reflecting an early age group with an increased risk of developing cardiovascular events. The indirect costs, such as productivity loss in this age group, are a major concern to health policy makers and the whole society.

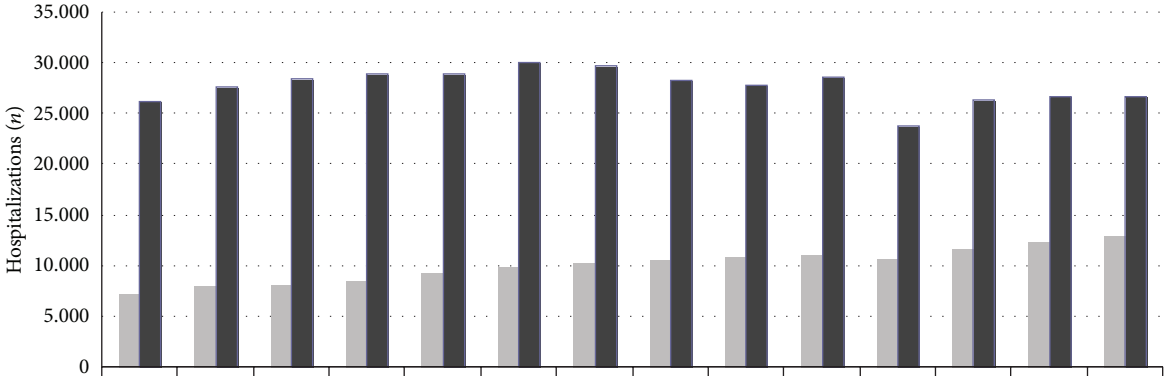
The number of hospitalizations due to AIDS related conditions was stable over the last 13 years; however, the number of hospitalizations due to AMI in patients aged 25 to 49 has increased approximately 78% in the same period. This age group has a low risk of cardiovascular events, but the combination of HIV exposure and HIV/AIDS treatment could be a possible reason for this increase in the incidence of AIM.

The total costs with hospitalization have increased in both conditions, but with a more substantial growth in the AMI



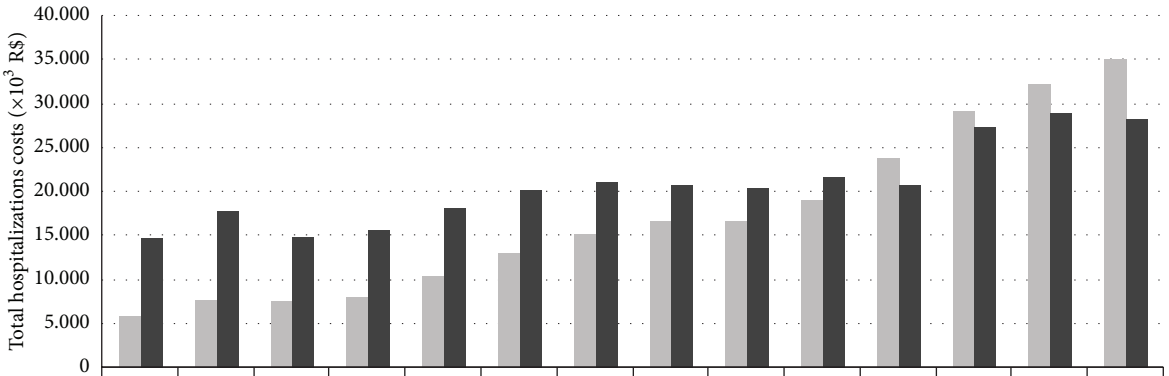

| | 1980 | 1984 | 1988 | 1992 | 1994 | 1998 | 2000 | 2002 | 2004 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients | 1 | 130 | 4.323 | 14.258 | 18.040 | 29.109 | 29.233 | 37.379 | 35.947 | 34.931 | 35.718 | 38.529 | 38.188 | 37.359 | 38.776 |

Figure 1: Annual HIV/AIDS reported cases in Brazil, 1980–2011.




| | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AMI | 7.252 | 7.989 | 8.152 | 8.463 | 9.236 | 9.924 | 10.327 | 10.613 | 10.900 | 11.147 | 10.724 | 11.650 | 12.344 | 12.947 |
| AIDS | 26.132 | 27.585 | 28.384 | 28.879 | 28.847 | 30.047 | 29.630 | 28.229 | 27.747 | 28.639 | 23.703 | 26.281 | 26.602 | 26.608 |

Figure 2: Annual hospitalizations due to AMI and AIDS (25–49 years).




| | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AMI | 5.807 | 7.699 | 7.521 | 8.106 | 10.403 | 12.951 | 15.280 | 16.668 | 16.663 | 19.122 | 23.927 | 29.083 | 32.357 | 35.113 |
| AIDS | 14.713 | 17.849 | 14.806 | 15.650 | 18.229 | 20.259 | 21.145 | 20.705 | 20.327 | 21.642 | 20.764 | 27.282 | 28.939 | 28.264 |

Figure 3: Annual costs with AMI and AIDS hospitalizations (25–49 years).

hospitalizations costs (92% versus 504% increase for AIDS and AIM, resp.). This cost increase can be due to changes in clinical practice, such as the use of thrombolytic agents and revascularization procedures during admissions.

The total budget of the Brazilian Ministry of Health in 2007 was R$ 44.3 billion and of this total, R$ 23 billion were allocated to reimburse outpatient and inpatient treatment costs. In the same year, the expenses with hospitalizations for HIV/AIDS-related conditions and AIM (25–49 years) were approximately 0.12 and 1.52% of this budget, respectively. Its worth mentioning that, in the same year, spending on antiretroviral treatment totaled 1.5% of the total budget (all age groups).

There are 18 antiretroviral drugs and 37 formulations available in Brazil for the treatment of people living with HIV (for children and adults). Ten of these drugs are produced by multinational companies and eight are locally produced (one private and six state-run Brazilian laboratories). It has been noted that for most of these medications (79%, 11 of 14 antiretroviral drugs) there was a significant reduction in the prices between 2006 and 2007, reaching 50% reduction in some cases [8]. An analysis of the expenditures with the Brazilian antiretroviral drug program suggests that the universal access policy will not be sustainable in long term without compromising investments in other areas [13].

This study has some limitations. Firstly it adds only the indirect evidence that the rising cost of hospitalization for AMI among the low coronary risk may be due to HIV infection and the use of antiretroviral agents. Secondly, it was not possible to compare the costs of AMI in both HIV positive and negative populations, mainly due to the lack of information available in the Brazilian databases. Further work is needed to clarify this important and relevant issue.

## 5. Conclusion

The prevalence of HIV/AID is still increasing among young adults and all these individuals will have access to long-term antiretroviral treatment in Brazil. There are scientific evidences suggesting an increased incidence of myocardial infarction in this population. Considering the high costs for the treatment of both diseases, health managers and decision-makers should be aware of strengthening preventive measures in order to guarantee the financial sustainability of the treatment in public health units in Brazil.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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*Clinical Study*

# Cardiovascular Risk Assessment: A Comparison of the Framingham, PROCAM, and DAD Equations in HIV-Infected Persons

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This study aims to estimate the risk of cardiovascular disease (CVD) and to assess the agreement between the Framingham, Framingham with aggravating factors, PROCAM, and DAD equations in HIV-infected patients. A cross-sectional study was conducted in an outpatient centre in Brazil. 294 patients older than 19 years were enrolled. Estimates of 10-year cardiovascular risk were calculated. The agreement between the CVD risk equations was assessed using Cohen's kappa coefficient. The participants' mean age was 36.8 years (SD = 10.3), 76.9% were men, and 66.3% were on antiretroviral therapy. 47.8% of the participants had abdominal obesity, 23.1% were current smokers, 20.0% had hypertension, and 2.0% had diabetes. At least one lipid abnormality was detected in 72.8%, and a low HDL-C level was the most common. The majority were classified as having low risk for CV events. The percentage of patients at high risk ranged from 0.4 to 5.7. The PROCAM score placed the lowest proportion of the patients into a high-risk group, and the Framingham equation with aggravating factors placed the highest proportion of patients into the high-risk group. Data concerning the comparability of different tools are informative for estimating the risk of CVD, but accuracy of the outcome predictions should also be considered.

## 1. Introduction

Highly active antiretroviral therapy (HAART) has significantly reduced morbidity and mortality among AIDS patients in many parts of the world [1, 2]. In addition, broad coverage of HAART is also associated with the reduction in the risk of HIV transmission at the population level [3]. The World Health Organization and the Joint United Nations Program on HIV/AIDS have set an international goal for expanding HAART to 15 million people by 2015 [4]. Brazil has a well-established HIV control program, and HAART has been universally offered to all eligible individuals at no charge since 1996. By 2011, approximately 200,000 HIV-infected patients were receiving antiretroviral therapy (ART), resulting in a remarkable survival benefit in the last decade [5, 6].

HAART has enhanced the life expectancy and improved the quality of life for HIV-infected patients. However, the aging of the population and the cumulative adverse effects caused by long periods of exposure to antiretroviral drugs

have markedly increased the prevalence of dyslipidaemia, insulin resistance, impaired glucose metabolism, and abnormal fat distribution among HIV patients [7, 8]. Patients with metabolic syndrome have an increased risk of developing chronic nontransmissible conditions such as diabetes and cardiovascular diseases [9, 10].

Overall, the benefits of HAART in reducing mortality significantly outweigh the risks of metabolic abnormalities. Nevertheless, reducing metabolic abnormalities and identifying groups at high risk for cardiovascular diseases (CVD) are an important part of HIV management. Guidelines about managing dyslipidaemia in the general population [11] and in HIV-infected patients [12, 13] recommend identifying and treating patients at high risk for cardiovascular events. Traditional cardiovascular risk factors, such as smoking, lack of physical activity, and metabolic syndrome, play a very important role in determining cardiovascular events. Assessing and addressing those modifiable risk factors are important for CVD prevention.

Over the past decade, an increasing number of studies have assessed the cardiovascular risk profile of HIV-infected patients [14–22]. The majority of the studies used cardiovascular risk equations developed for a non-HIV-infected population, such as the Framingham or the Prospective Cardiovascular Münster Study (PROCAM) scores. The accuracy of these risk scores for predicting cardiovascular events in HIV-infected patients is not well established. Generally, these scores have been proposed and validated in high-income populations of older patients. In the last decade, a growing number of studies estimated CVD risk in HIV-infected populations, mainly using the Framingham score and less frequently using other cardiovascular risk equations, such as the PROCAM and Systematic Coronary Risk Evaluation (SCORE) equations [14–17, 19–25]. The prevalence of patients at high risk for coronary events in the next 10 years varies largely among these studies, ranging from less than 1% to 21% [15, 16]. These equations were not developed to assess cardiovascular risk in HIV-infected patients, and their accuracy is still uncertain [26, 27].

Presently, there is only one cardiovascular risk score specifically developed for HIV-infected patients [18]. It was based on the results of a large multicentre cohort study (The Data Collection on Adverse Effects on Anti-HIV Drugs Cohort-DAD), conducted mainly in Europe and North America. The DAD equation takes antiretroviral drug exposure into account as a potential risk factor for cardiovascular events. To date, the DAD risk equation has only been applied for CVD risk estimation in one developing country [22]. This study aims to estimate the cardiovascular risk for HIV-infected patients in Brazil using the Framingham, PROCAM, and DAD equations and to compare the results.

## 2. Methods

This study is a cross-sectional analysis of a cohort of HIV-infected patients (PRECOR study) attending an outpatient public referral centre for infectious diseases in central Brazil. HIV-infected patients between 20 and 75 years old were consecutively enrolled between October 2009 and January 2011. The study protocol was approved by the local Institutional Review Board. The participants showed no clinical evidence of active opportunistic diseases at the time of enrolment.

*Clinical and Epidemiological Investigation.* At the time of enrolment, all the participants were interviewed and examined by the same cardiologist, a member of the research team. A structured questionnaire that addressed sociodemographic variables and general medical history was used to collect data.

The participants were also asked about the time of their HIV diagnosis, previous opportunistic diseases, antiretroviral exposure, and cardiovascular risk factors. Smoking status was classified as never, former, or current (those who had stopped smoking within the past 30 days were considered current smokers). The participants were considered to have a history of cardiovascular disease if they had a convincing history of myocardial infarction (MI), angina, stroke, peripheral arterial disease, or an intervention for coronary artery disease. Family history was defined as cardiovascular disease in a first-degree male before the age of 55 or in a first-degree female relative before the age of 65.

Arterial blood pressure was measured. The patients on antihypertensive therapy or with systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg were classified as having hypertension [28].

Afterward, the participants met with a multidisciplinary research team including nutritionists, a pharmacist, a biomedical professional, anthropometrists, and a physiotherapist. Waist circumference (WC) was measured as the narrowest circumference between the lower rib margin and the anterior superior iliac crest using a standard inelastic anthropometric tape. A WC ≥94 centimetres (cm) for men and ≥80 cm for women was considered a risk factor for CVD [29].

*Laboratory Investigation.* The participants were advised to fast overnight for 12 h, to avoid alcohol consumption for 3 days prior to blood collection. All of the analyses were performed at the same laboratory.

Serum total cholesterol (TC), high-density lipoprotein (HDL) cholesterol and triglycerides (TG) were assayed. Serum low-density lipoprotein (LDL) cholesterol was estimated using the Friedewald formula when TG was ≤400 mg/dL [30]. Dyslipidaemia was defined as LDL cholesterol ≥160 mg/dL, HDL cholesterol <40 mg/dL for men and <50 mg/dL for women or diabetics or triglycerides ≥150 mg/dL [11, 31].

High sensitivity C-reactive protein (hsCRP) was quantified. hsCRP values <1 mg/L were classified as normal, between 1 and 3 mg/L were classified as intermediate risk, and >3 mg/L were classified as high risk [32].

Diabetes was defined as a fasting serum glucose level greater than 125 mg/dL [33] or a self-reported diagnosis of diabetes and use of specific therapy. The glomerular filtration rate (GFR) was calculated based on the Cockcroft-Gault equation [34]. A GFR below <60 mL/min or a serum creatinine level equal to or higher than 1.5 mg/dL indicated impaired renal function [35].

A urine sample was collected to determine the albumin/creatinine ratio (ACR) [36]. Patients were categorised as having normoalbuminuria (<30 mcg/mg), microalbuminuria (30 to 299 mcg/mg), or clinical albuminuria (>300 mcg/mg) [37].

CD4 counts and the HIV RNA levels were obtained from the patient's medical chart. HAART data were obtained from the patients' medical and pharmaceutical records.

Metabolic syndrome was defined in accordance with the standards of the International Diabetes Federation [29].

*Calculation of Cardiovascular Risk*. Framingham and PROCAM scores were calculated to predict 10-year CVD risk. DAD equations were used to calculate 5-year CVD risk. The participants with a history of CVD or were older than 75 were excluded from this analysis.

*Framingham Equation*. The following variables were included in the equation: age, sex, systolic blood pressure, antihypertensive therapy (yes or no), serum TC and HDL-cholesterol values, and current smoking status (yes or no). The 10-year risk of CVD was classified as low (<10%), moderate (10% to 20%), or high (>20%) [38]. The patients with diabetes were classified as high risk [11, 31]. The participants who had low or moderate 10-year risk according to the Framingham equation were also reevaluated based on the presence of aggravating factors: family history of CVD, metabolic syndrome, serum creatinine ≥1.5 mg/dL, hsCRP >3.0 mg/L, or albuminuria >30 mcg/mg. Patients presenting at least one of these aggravating factors were reclassified into the high-risk category for CVD over 10 years (Framingham equation with aggravating factors, according to the IV Brazilian Guideline for Dyslipidemia and Atherosclerosis Prevention) [31].

*PROCAM Equation*. The following variables were included in the equation: age; sex; known diabetes or fasting blood glucose level ≥120 mg/dL; systolic blood pressure; serum TG, LDL, and HDL-cholesterol levels; current nicotine consumption and family history of CVD. The 10-year risk of acute coronary events was classified as low (<10%), moderate (10% to 20%), or high (>20%) [39].

*DAD Equation*. The following variables were included in the equation: age; sex; systolic blood pressure; serum CT and HDL-cholesterol level; diabetes; smoking status; family history of CVD; current use of abacavir, indinavir, or lopinavir; and the number of years on indinavir or lopinavir. The 5-year risk of coronary heart disease was classified as low (<1%), moderate (1 to 5%), high (5 to 10%), or very high (>10%) [18].

*Statistical Analysis*. Normally distributed continuous variables were expressed as means and standard deviations; otherwise, they were expressed as medians and interquartile ranges (IQR). Categorical variables were expressed as percentages with 95% confidence intervals (95% CI). A $\chi^2$ test or Fisher's test was used to compare proportions.

The agreement between the CVD risk equations was assessed using Cohen's kappa coefficient with 95% CIs. The participants at high or very high risk according to the DAD equation were considered high-risk patients for the comparison with the Framingham, Framingham with aggravating factors, and PROCAM equations.

Two-sided $P$ values <0.05 were considered statistically significant. The data were analysed using IBM SPSS Statistics base 18.0 for MAC (Chicago, IL, USA).

## 3. Results

A total of 335 HIV-infected adults were enrolled during the study period. Clinical and laboratory data were obtained from 299 patients (89.3%). Thirty-six participants (10.7%) were excluded because their laboratory analyses were incomplete. There was a higher proportion of previous intravenous drug users (IDU) among the individuals with incomplete laboratory data ($P < 0.01$). There were no statistically significant differences in sex, age, educational level, or monthly income ($P > 0.05$) between these two groups. Five patients reported a previous cardiovascular event and were excluded, resulting in 294 participants.

Table 1 presents the sociodemographic and clinical characteristics of the 294 participants. The study population was predominantly male (76.9%). The mean age was 36.8 (SD = 10.3), and the ages ranged from 20 to 71 years. Approximately 80% (185/226) of the males were younger than 45, and approximately 90% (59/68) of the females were younger than 55. The majority of the participants (72.4%) had more than 8 years of schooling. A total of 92.2% reported being exposed to HIV through a sexual route; among these participants, 54.1% declared that they were homosexual males or bisexual. Previous IDU was reported by 2.7%.

The median time since receiving the HIV diagnosis was 2.0 years (IQR: 0.7–5.0 years). At least one opportunistic disease in the previous 12 months was reported by 5.8% of those recruited. At the time of enrolment, 54.1% presented an undetectable HIV viral load, and 72.6% had a CD4 count ≥350 cells/mm$^3$. Overall, 195 (66.3%) out of 294 participants were receiving HAART, with a median duration of 19.0 months (IQR: 5.0–54.0 months) (Table 1).

Figure 1 shows the prevalence of cardiovascular risk factors among the participants. A history of smoking was reported by 46.9% (138/294), and 23.1% (68/294) were current smokers. Seven participants reported a family history of premature atherosclerotic disease. Twenty-three patients had high blood pressure (HBP), and 47.8% of them were receiving antihypertensive therapy. At the time of the physical examination, 55 participants had HBP. In total, 20.0% (59/294) of the participants were considered hypertensive. Abdominal obesity was detected in 47.8% of the participants. The proportion of females with abdominal obesity (82.4%) was higher than the proportion of males (23.0%) ($P < 0.001$).

Most (72.8%) participants had at least one abnormality in their lipid profile. The most common dyslipidaemia was a low HDL-C level, which was found in 61.9% of the participants. The prevalence of isolated hypertriglyceridemia and isolated hypercholesterolemia was 36.4% and 3.5%, respectively. The prevalence of low HDL-C combined with high TG was 46.6%. For 11 participants, LDL cholesterol was not estimated because TG was higher than 400 mg/dL. The mean values

Table 1: Sociodemographic and clinical characteristics of 294 HIV-infected patients.

| Characteristics | Values | 95% CI |
|---|---|---|
| Sociodemographic | | |
| Males | 226 (76.9) | 71.4–81.9 |
| Age, years mean (SD) | 36.8 (10.3) | — |
| Male <45 y | 185 (81.9) | 76.5–86.5 |
| Female <55 y | 59 (86.8) | 78.7–94.8 |
| ≥8 y schooling | 213 (72.4) | 63.0–82.9 |
| Exposure categories | | |
| Sexual route | 271 (92.2) | 81.5–103.8 |
| Homosexual or bisexual[a] | 142 (51.4) | 43.3–60.6 |
| Previous IDU[b] | 7 (2.7) | 1.0–5.5 |
| Clinical HIV history | | |
| HIV diagnosis, years median (IQR) | 2.0 (0.7–5.0) | — |
| Opportunistic disease in previous 12 months[c] | 16 (5.8) | 3.5–8.9 |
| Undetectable HIV viral load[d] | 153 (54.1) | 48.1–60.2 |
| CD4 ≥350 cells/mm$^3$[e] | 207 (72.6) | 22.4–32.7 |
| Antiretroviral therapy | 195 (66.3) | 61.3–71.7 |
| ART duration, months, median (IQR) | 19.0 (5.0–54.0) | — |

IDU: intravenous drug users; ART: antiretroviral therapy.
[a]18 missing, [b]33 missing, [c]17missing, [d]11 missing, [e]9 missing.
Continuous variables are presented as means (SD), median (IQR), and categorical variables are presented as absolute value and percentage with 95% CI.

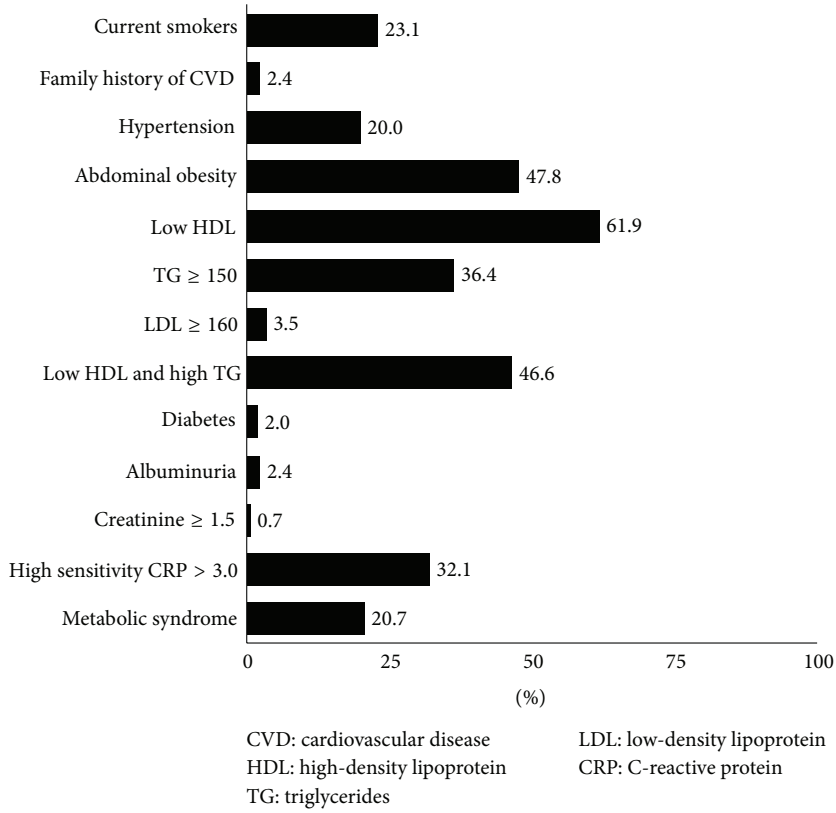


Figure 1: Prevalence of cardiovascular risk factors among 294 HIV-infected patients.

were 169.5 (SD = 42.7) mg/dL for TC, 42.5 (SD = 11.3) mg/dL for HDL cholesterol, 96.6 (SD = 32.5) mg/dL for LDL cholesterol, and 151.4 (SD = 104.5) mg/dL for TG.

A total of 6 patients (2.0%) were categorised as having diabetes. Seventeen patients had albuminuria, and two had creatinine levels equal to or higher than 1.5 mg/dL. High sensitivity C-reactive protein >3 mg/L was detected in 32.1% of the participants. Sixty-one (20.7%) participants had metabolic syndrome. The prevalence of metabolic syndrome was higher among females (36.8%) than among males (16.0%) ($P < 0.001$).

Table 2 presents the antiretroviral regimens at the baseline interview by 195 patients receiving treatment. Of the participants, 62.6% were taking a combination of zidovudine, lamivudine, and efavirenz. The second most frequent antiretroviral regimen was a combination of zidovudine, lamivudine, and lopinavir boosted by ritonavir (12.8%). Twenty-nine patients (15.1%) were using a regimen containing tenofovir. Fifty-one (26.2%) patients were using a protease inhibitor (PI) regimen; among these participants, 28 were taking a lopinavir regimen (25 were taking a regimen boosted by ritonavir). Additional 6 patients used lopinavir in a previous regimen. The median duration of lopinavir-based therapy was 13.0 months (IQR: 4.0–23.5). One participant was taking abacavir. None of the participants were ever exposed to indinavir.

Figure 2 presents the estimated CVD risk of the 283 HIV-infected patients based on the Framingham, Framingham with aggravating factors, PROCAM, and DAD risk equations. Eleven participants were excluded because they had TG >400 mg/dL. The majority of participants were classified at low risk for future CV events. The percentage of patients classified as having a high risk of future CVD ranged from 0.4 to 5.7 using these four scoring systems.

*Framingham Equation.* Based on the Framingham equation, 94.0% of the participants were classified as low-risk, 3.2% as moderate-risk, and 2.8% as high-risk patients.

*Framingham with Aggravating Factors.* Of the participants, 54.4% were classified as low-risk patients, 39.9% as moderate-risk patients, and 5.7% as high-risk patients for CVD. At least one aggravating cardiovascular risk factor was detected in 42.0% of the participants. The most frequent aggravating factor was hsCRP >3.0 mg/L (32.1%), followed by the presence of metabolic syndrome (20.7%). Impaired renal function was identified in 0.7% of the participants, and 2.4% reported a family history of CVD.

*PROCAM Equation*. Of the participant, 98.2% were classified as low-risk patients, 1.4% as moderate-risk patients, and 0.4% as high-risk patients for CVD.

*DAD Equation*. Of the participants, 74.2% were classified as low-risk patients, 23.7% as moderate-risk patients, and 2.1% as high-risk patients. None had a very high risk for CVD.

The agreement of the DAD equation with the Framingham equation was 77.4% ($k = 0.23$; 95% CI 0.07–0.39), with the Framingham with aggravating factors was 56.7% ($k = 0.14$; 95% CI 0.02–0.25), and with the PROCAM equation was 75.3% ($k = 0.07$; 95% CI 0.00–0.26). The agreement was good, but low kappa values were detected for all three comparisons (Table 3).

## 4. Discussion

The present study was conducted in a population of HIV-infected individuals, mainly composed of young adult males, who were clinically stable. One-third of them were naïve to antiretroviral drugs. Less than 3.0% of the patients were at high risk for cardiovascular events over the next 10 years according to equations developed for the general population, such as the Framingham and PROCAM equations. A similar profile was obtained using the DAD equation, which was specifically constructed for HIV patients. When aggravating factors were incorporated into the Framingham equation, as recommended by the Brazilian Guidelines for clinical management, the proportion of the participants classified in the high-risk group increased twofold: almost 40% of the patients were classified in the intermediate-risk group for CV events. Similarly, the DAD equation placed a higher proportion of the patients in the moderate-risk category.

Initially, CVD risk equations were conceived for those over 30 in the general North American and European populations. However, these risk estimations were applied to younger age groups in other settings and, more recently, to people living with HIV [15]. In alignment with our results, other Latin American studies also found a low risk of future CV events using the conventional cardiovascular equations among predominantly male HIV patients in their 30s and 40s [16, 19]. In contrast, a high risk of cardiovascular events was found among older populations, those with greater exposure to antiretroviral drugs, or populations with a higher prevalence of well-known risk factors, such as smoking, diabetes, or hypertension [14, 15, 24].

In our study, the participants were young and had relatively short exposure to antiretroviral drugs. The prevalence of diabetes was low, but the prevalence of abdominal obesity was high, especially among the female participants. Furthermore, most of our patients had low incomes. Obesity and low income were associated with an increased 10-year risk for CVD in a large study conducted in the USA [23]. In addition, aging, abdominal obesity, and the duration of antiretroviral drug exposure are intrinsically associated with the development of diabetes [40], leading to an increased risk for CVD disease in the study population in the near future.

A high triglyceride level is one of the most common lipid abnormalities described among HIV-infected patients [40, 41]. A similar lipid profile was found in the current study and in a previous evaluation in the same setting [42]. One potential disadvantage of using Framingham scores for HIV-infected patients is that triglyceride values are not incorporated into the CVD risk equations. However, the use of elevated triglycerides as a marker for future CVD is still a controversial issue [43].

In the PROCAM equation, triglycerides and LDL levels are incorporated into the risk equation. Nevertheless, for patients with triglyceride levels higher than 400 mg/dL, it is

Table 2: Antiretroviral regimen in 195 HIV-infected patients.

| Antiretroviral regimen | Class of drug | *N* (%) | 95% CI |
|---|---|---|---|
| ZDV + 3TC + EFZ | 2NRTI + 1NNRTI | 122 (62.6) | 51.9–74.7 |
| ZDV + 3TC + LPV/RTV | 2NRTI + 1PI/Booster | 25 (12.8) | 8.3–18.9 |
| 3TC + TDF + EFZ | 2NRTI + 1NNRTI | 15 (7.7) | 4.3–12.7 |
| 3TC + TDF + ATV + RTV | 2NRTI + 1PI/Booster | 5 (2.6) | 0.8–5.9 |
| ZDV + 3TC + TDF + LPV + RTV | 3NRTI + 1PI/Booster | 3 (1.5) | 0.3–4.5 |
| ZDV + 3TC + NVP | 2NRTI + 1NNRTI | 3 (1.5) | 0.3–4.5 |
| Others | — | 22 (11.3) | 7.0–17.0 |

ATV: atazanavir; ZDV: zidovudine; 3TC: lamivudine; EFZ: efavirenz; LPV: lopinavir; NNRT: nonnucleoside reverse transcriptase inhibitor; NRTI: nonnucleoside reverse transcriptase inhibitor; NVP: nevirapine; PI: protease inhibitor; RTV: ritonavir; TDF: tenofovir.

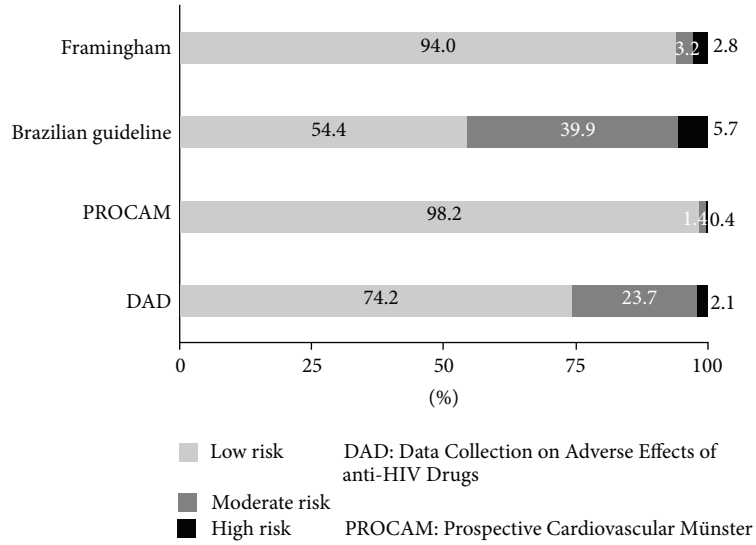


Figure 2: Prevalence of estimated CVD risk according to Framingham, Framingham with aggravating factors (Brazilian Guideline for Dyslipidemia and Atherosclerosis Prevention), PROCAM and DAD risk equations for 283 HIV-infected patients.

not possible to estimate LDL levels, which hampers CVD risk calculation. Similar to our results, other studies using PROCAM equations [14, 15, 19, 24, 25] have found a lower percentage of patients with high 10-year risk for CV events compared with the risk estimates using the Framingham equation. In two studies [19, 25], the coefficient of agreement between the PROCAM and Framingham equations was evaluated. In one study [19], the low- and moderate-risk groups were combined to compare the Framingham and PROCAM scores, yielding weak agreement between these equations. Another study found good agreement between these scores [25]. Determining the proportion of patients with high or moderate 10-year cardiovascular risk has clinical and economic repercussions. It has not been determined which of these two equations is more accurate, and the answer most likely will not be determined [27]. Large cohort studies conducted in HIV-infected populations with different clinical and demographic profiles would be needed to approach this question [27].

In the present study, the Framingham equation with aggravating risk factors most likely overestimated the 10-year cardiovascular risk. The percentage of participants in the high-risk group increased from 2.8% to 5.7%, and the percentage of moderate-risk patients increased more than 10 times (from 3.2% to 39.9%), mainly because of the high sensitivity C-reactive protein (hsCRP) values. hsCRP is a nonspecific marker for inflammation and is considered an independent cardiovascular risk predictor [32]. HIV infection itself and opportunistic infections can lead to a proinflammatory state. The accuracy of CRP as a cardiovascular risk predictor has not been well established in HIV-infected populations [44].

Few large cohort studies have investigated the accuracy of the conventional risk equations to predict cardiovascular events in HIV-infected populations [18, 45, 46]. To date, the DAD equation is the only tool for estimating cardiovascular risk developed specifically for an HIV-infected population. In our study, the proportion of patients in the high-risk

Table 3: Comparison between CVD risk estimation using different equations (283 patients).

| | Cardiovascular risk | Framingham | | | Brazilian Guideline | | | PROCAM | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Low | Moderate | High | Low | Moderate | High | Low | Moderate | High |
| DAD | Low | 210 | 0 | 0 | 126 | 85 | 0 | 210 | 0 | 0 |
| | Moderate | 56 | 6 | 5 | 28 | 29 | 10 | 65 | 2 | 0 |
| | High and very high | 0 | 3 | 3 | 0 | 0 | 6 | 3 | 2 | 1 |
| Agreement | | | 77.4% | | | 56.7% | | | 75.3% | |
| Kappa | | | 0.23 | | | 0.14 | | | 0.07 | |
| 95% CI | | | 0.07–0.39 | | | 0.02–0.25 | | | 0–0.26 | |

DAD: Data Collection on Adverse Effects of Anti-HIV Drugs; PROCAM: Prospective Cardiovascular Münster; CI: confidence Interval.

group for CV events was low using the DAD equation and conventional risk equations (Framingham and PROCAM). Another study from Thailand found a low prevalence of patients with high CVD risk using the DAD equation and the Framingham equation, with good agreement between these scores [22]. However, the Framingham equation predicted higher CVD risk compared with the DAD equation. In our results, the DAD equation placed a higher proportion of the patients in the moderate category of risk for CVD compared with the Framingham and PROCAM scores; this result has implications for clinical followup and management.

Methodological issues regarding the comparability and applicability of these different CVD risk scores, particularly among people living with HIV, have been thoroughly discussed, most recently by D'Agostino [27]. In addition to the differences in the composition of the cardiovascular risk scores and the differences in the relevant outcomes, the comparison of CVD scores using kappa coefficients may have some limitations. Our findings pointed out good agreement for the risk predictions produced by the DAD equations compared with Framingham or PROCAM in constrast with low statistical kappa estimates. Other studies also found good agreement between different risk systems but calculated low kappa values [22, 25]. This apparent paradox could be explained by the imbalanced distribution of the values and by kappa's dependence on the prevalence of the measured event [47]. However, the clinical significance of these inconsistencies is not completely understood.

## 5. Conclusions

Comparing different tools that predict the risk of CVD is informative, but these comparisons do not assess the accuracy of the outcome. Because HAART is offered to large cohort of HIV patients in Brazil, it seems promising to address this issue by monitoring patients and CV events using the existing official surveillance system. These data would be valuable for individual clinical management and for economic evaluations from a public health perspective. Large cohort studies including different HIV-infected groups would be necessary to address these questions.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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*Research Article*

# Association of Blood Pressure and Hypertension with Alcohol Consumption in HIV-Infected White and Nonwhite Patients

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*Introduction.* Although alcohol abuse is associated with hypertension in whites and nonwhites, it has been scarcely investigated in HIV-infected patients. *Objective.* To investigate whether the association of alcohol abuse with hypertension is influenced by skin color in HIV-infected individuals. *Methods.* Cross-sectional study in HIV-infected individuals aged 18 years or older. Demographic characteristics, lifestyle, and HIV infection were investigated. Alcohol abuse was defined as ≥15 (women) and ≥30 g/alcohol/day (men), and binge drinking by the intake of ≥5 drinks on a single occasion. Hypertension was defined by blood pressure ≥140/90 mmHg or use of blood pressure-lowering agents. *Results.* We studied 1,240 individuals, with 39.1 ± 10 years, 51% males and 57% whites. Age and body mass index were associated with blood pressure, and there was an independent association of alcohol abuse with hypertension in whites (RR = 1.9, 95% CI 1.1–3.3) and nonwhites (RR = 2.4, 95% CI 1.4 to 4.0). Among nonwhite individuals who were alcohol abusers, systolic (9.3 ± 3.2; $P = 0.001$) and diastolic blood pressures (6.4 ± 2.1; $P = 0.008$) were higher than in nonabusers. *Conclusion.* Alcohol abuse is a risk factor for hypertension in white and nonwhite HIV-infected individuals. The association of ethanol consumption with blood pressure is not explained by AIDS-related conditions.

## 1. Introduction

Hypertension is a major cardiovascular risk factor worldwide. Projections are that, by the year of 2025, 75.0% (or 1.17 billion people) of the people with hypertension in the world will be living in emerging nations [1]. In Brazil, about 29% of the Brazilian population has hypertension [2]. Alcohol abuse is associated with elevated blood pressure [3], regardless of other risk factors [4–6]. Different studies have shown prevalence rates of hypertension attributed to alcohol consumption ranging from 5 to 30% [7].

Risk factors for cardiovascular diseases, including hypertension and dyslipidemia, are determinants of reduced life expectancy in HIV-infected patients [8]. Hypertension prevalence in HIV-infected individuals ranges from 5.9 to 56.4% [9–12] and has been associated with alcohol abuse and other factors related to HIV infection [9, 10, 13]. In these individuals, the prevalence of alcohol abuse ranges from 8% [14, 15] to 50% [16–18], exceeding the rates in general populations of the United States [19], Europe [20], and Brazil [21], where the prevalence is between 2 and 41% in men and 0.1 and 21% in women [20].

The relationship between alcohol consumption and hypertension may be influenced by some characteristics, such as skin color [3, 22]. Skin color has been identified as a marker of lifestyle [3, 23, 24] and, in some countries, it may also be

characterized as the socioeconomic status of the individuals [4]. In Brazil, the HIV-infected population tends to be more homogeneous in terms of socioeconomic status, affecting the less privileged ones. High blood pressure has been associated with low socioeconomic status [4] and skin color may also be a risk factor. Therefore, the objective of the present study was to investigate if the association between alcohol abuse, blood pressure, and hypertension in HIV-infected patients is influenced by skin color.

## 2. Materials and Methods

We conducted a cross-sectional study including HIV-infected individuals who were being followed up at the Outpatient Clinic of the Care and Therapy Service (SAT), Hospital Sanatório Partenon, State Department of Health of Rio Grande do Sul, Brazil. This clinic and all public health care centers provide medical care, antiretroviral therapy (ART), antihypertensives, and other medications free of charge for HIV-infected patients. We consecutively enrolled female and male patients, aged 18 or older, who were seen between June 2006 and December 2008. Pregnant women, individuals who were unable to provide written consent, or those incarcerated were excluded. Participants who were under the influence of alcohol or drugs at the time of the interview were asked to return for evaluation at another time.

Participants were interviewed on the day of the regular medical appointments. Since they had to consult every month, in order to get antiretroviral medication, they were seen often, which contributed to achieving high participation rate. Information was collected, using standardized questionnaires, for the following characteristics: demographic (age and skin color self-reported, classified as white or nonwhite), socioeconomic (educational attainment, number of school years), and lifestyle characteristics (alcohol consumption, physical activity, and smoking), as well as the use of antiretroviral therapy (ART), and time since diagnosis of HIV infection (in years, classified as ≥6 years, from 3.0 to 5.9 years, and <3 years). Data related to HIV infection as CD4 lymphocyte count ($mm^3$/mL), viral load (copies per mL of blood), and clinical information were confirmed by medical records. Alcohol consumption was investigated using a validated quantity-frequency questionnaire based on the kind of beverage consumed [21], administered by a physician or healthcare professional, containing questions about type, frequency, and amount of alcohol consumed in the last six months. Alcohol consumption was categorized into abstemious drinking, social drinking (>0 and <15 grams/day for women and >0 and <30 grams/day for men), or abusive drinking (≥15 grams/day for women and ≥30 grams/day for men) [21, 22, 25]. Binge drinking was characterized by a consumption of five or more drinks on a single occasion [22]. Frequency of consumption was classified as weekly (consumption on some days of the week, but not daily) or monthly (consumption on some days of the month but not every week), regardless of the amount. Physical activity was investigated using the IPAQ (International Physical Activity Questionnaire) [26], which investigates frequency and duration of physical activity. The intensity of exercise was classified as moderate or high versus low physical activity according to the IPAQ protocol [27]. Smoking was defined according to the information provided by the participants, classifying the amount of consumption in at least 100 cigarettes during their lifetimes.

Weight (Kg) and height (m) were measured twice with the participants being barefoot and wearing light clothes, using an anthropometric scale (Filizola, model 31 adult, Indústria Filizola S.A., São Paulo, SP, Brazil). Body mass index (BMI; $kg/m^2$) was calculated as the weight (kg) divided by the square of the height (m) and classified as normal (<25.0), overweight (25–29.9), and obesity (≥30.0). Standardized measurements of blood pressure were obtained in duplicate in two visits, using a validated oscillometric device (OMRON CP-705) [28]. The average of four BP measurements was used to detect hypertension if systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or in use of blood pressure-lowering agents [25].

Certified researchers performed the interviews and measured anthropometric parameters and blood pressure. Approximately 5% of the interviews were repeated for quality control. Data were entered twice into the database of Epinfo, version 2000. The study was approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre, which is accredited by the Office of Human Research Protections. All participants signed an informed consent form.

*Sample Size Calculation and Statistical Analysis*. Sample size calculation was based on the estimated prevalence of hypertension between white and nonwhite participants with abusive alcohol consumption (30 and 35%, resp.) and abstemious drinking (18%), with 80% of power and a significance level of 0.05 (two-tailed). A sample size of 738 white and 398 nonwhite participants with a 1 : 5 ratio for exposed and unexposed participants to excessive alcohol consumption would be required to detect a hazard ratio of at least 1.7. The estimates were based on previous studies [22, 29].

Characteristics of the sample were expressed as mean and standard deviation. We used Pearson's chi-square test for the analysis of categorical variables and analysis of variance (continuous variables) to assess the association between these factors and the different outcomes. Confounding factors were controlled using the modified Poisson regression (robust variance estimates) [30] and analysis of covariance. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA), version 18.0. Confounding factors were selected based on the literature [3, 31, 32] and $P$ values lower than or equal to 0.2 in unadjusted analysis. Age, sex, educational attainment, smoking, physical activity, body mass index, time since HIV infection, and lifetime HAART use were considered confounding factors used in the multivariate models for whites and nonwhites. Partially adjusted models of alcohol consumption with systolic or diastolic blood pressure, including age, sex, and educational attainment, were run in order to better understand the associations and to interpret the risk ratios. A trend for association was determined by $P$ values between 0.05 and 0.1.

Table 1: Characteristics of HIV-infected individuals according to skin color ($n$ (%) or mean ± SD).

| | Total ($n$ = 1240) | Whites ($n$ = 710) | Nonwhites ($n$ = 530) | $P$ value |
|---|---|---|---|---|
| Male | 628 (50.6) | 391 (55.1) | 237 (44.7) | <0.001 |
| Age (years) | 39.1 ± 10.0 | 39.3 ± 10.3 | 38.9 ± 9.7 | 0.5 |
| Educational attainment (years) | 7.5 ± 4.1 | 8.3 ± 4.2 | 6.4 ± 3.7 | <0.001 |
| Smoking | 525 (42.3) | 298 (42.0) | 227 (42.8) | 0.4 |
| Physical activity | | | | 0.049 |
| Low | 321 (25.9) | 199 (28.0) | 122 (23.0) | |
| Moderate | 398 (32.1) | 232 (32.7) | 166 (31.3) | |
| High | 521 (42.0) | 279 (39.3) | 242 (45.7) | |
| Alcohol consumption | | | | 0.7 |
| Abstemious | 414 (33.4) | 233 (32.8) | 181 (34.2) | |
| Social drinking | 757 (61.0) | 440 (62.0) | 317 (59.8) | |
| Abusive drinking | 69 (5.6) | 37 (5.2) | 32 (6.0) | |
| Frequency of alcohol consumption | | | | 0.7 |
| Abstemious | 414 (33.4) | 233 (32.8) | 181 (34.2) | |
| Monthly | 440 (35.5) | 249 (35.1) | 191 (36.0) | |
| Weekly | 386 (31.1) | 228 (32.1) | 158 (29.8) | |
| Binge drinking | 211 (17.0) | 117 (55.5) | 94 (44.5) | 0.7 |
| Abstemious | 414 (33.4) | 233 (32.8) | 181 (34.2) | |
| No | 616 (49.7) | 360 (50.7) | 255 (48.1) | |
| Yes | 210 (16.9) | 117 (16.5) | 94 (17.7) | |
| Body mass index (kg/m$^2$) | 24.9 ± 4.4 | 24.8 ± 4.3 | 25.0 ± 4.7 | 0.4 |
| Systolic blood pressure (mmHg) | 121.8 ± 18.2 | 121.8 ± 17.7 | 121.8 ± 18.8 | 0.9 |
| Diastolic blood pressure (mmHg) | 76.6 ± 11.4 | 76.0 ± 10.7 | 77.3 ± 12.3 | 0.06 |
| Hypertension | 241 (19.4) | 120 (16.9) | 121 (22.8) | 0.009 |
| Time since HIV infection (years) | | | | 0.005 |
| ≥6.0 | 404 (32.6) | 250 (35.3) | 154 (29.1) | |
| 3.0–5.9 | 350 (28.2) | 176 (24.8) | 174 (32.8) | |
| <3.0 | 485 (39.1) | 283 (39.9) | 202 (38.1) | |
| HIV/HCV coinfection | 261 (22.2) | 143 (21.2) | 118 (23.5) | 0.3 |
| AIDS diagnosis | 892 (72.2) | 510 (72.0) | 382 (72.3) | 0.9 |
| Lifetime HAART use | 815 (65.7) | 467 (65.8) | 348 (65.7) | 0.9 |
| Lifetime protease inhibitor use | 468 (37.7) | 277 (39.0) | 191 (36.0) | 0.3 |
| CD4 (cell/mm$^3$) | | | | 0.08 |
| <350 | 476 (38.8) | 258 (36.7) | 218 (41.6) | |
| ≥350 | 751 (61.2) | 445 (63.3) | 306 (58.4) | |

HAART: highly active antiretroviral therapy; HCV: hepatitis C virus; HIV: human immunodeficiency virus; SD: standard deviation.

## 3. Results

Of the 1,295 HIV-infected patients screened, 1,255 were eligible and 1,240 were included. Thus, forty patients had not confirmed eligibility due to age under 18 years, incarceration, or pregnancy; fifteen refused to participate, and two patients were included in a second attempt due to alcohol intoxication at the first visit. Characteristics of the overall sample are presented in Table 1 by skin color. Participants were aged 39.1 ± 10, half of them were males, and 57% had white skin color. Overall, the distribution of most characteristics was similar among whites and nonwhites, but whites had higher education and time since HIV infection, and nonwhites had high physical activity and prevalence of hypertension.

Risk factors for hypertension among whites and nonwhites are shown in Table 2. The unadjusted analysis showed that only age and BMI were positively associated with hypertension for both categories of skin color. White smokers had lower prevalence of hypertension, whereas among nonwhites there was a trend for the association of alcohol abuse with hypertension. There was no association between variables related to HIV and hypertension.

Table 3 shows that association among the different patterns of alcoholic beverages consumption is roughly similar in whites and nonwhites; abusive consumption of alcohol was associated with hypertension in white and nonwhite HIV-infected individuals, independently of a large set of confounding variables. The frequency of alcohol consumption

Table 2: Risk factors for hypertension among HIV-infected individuals by skin color (*n* (%)).

| | Whites ($n$ = 710) | | Nonwhites ($n$ = 530) | |
|---|---|---|---|---|
| | Hypertension (%) | RR (95% CI) | Hypertension (%) | RR (95% CI) |
| Sex | | | | |
| Female | 48 (15.0) | 1.0 | 65 (22.2) | 1.0 |
| Male | 72 (18.4) | 1.2 (0.9–1.7) | 56 (23.6) | 1.1 (0.8–1.5) |
| *P* value | | 0.2 | | 0.7 |
| Age (years) | | | | |
| 18–34 | 20 (7.4) | 1.0 | 23 (11.4) | 1.0 |
| 35–49 | 56 (16.9) | 2.3 (1.4–3.7) | 63 (24.3) | 2.1 (1.4–3.3) |
| 50–78 | 44 (40.4) | 5.4 (3.4–8.8) | 35 (50.7) | 4.5 (2.8–7.0) |
| *P* value | | <0.001 | | <0.001 |
| Educational attainment (years) | | | | |
| ≥9 | 58 (17.8) | 1.0 | 23 (17.8) | 1.0 |
| 5–8 | 38 (16.2) | 0.9 (0.6–1.3) | 51 (22.2) | 1.2 (0.8–1.9) |
| 0–4 | 24 (16.0) | 0.9 (0.6–1.4) | 47 (27.5) | 1.5 (1.0–2.4) |
| *P* value | | 0.8 | | 0.14 |
| Smoking | | | | |
| No | 85 (20.6) | 1.0 | 76 (25.1) | 1.0 |
| Yes | 35 (11.7) | 0.6 (0.4–0.8) | 45 (19.8) | 0.8 (0.6–1.1) |
| *P* value | | 0.002 | | 0.16 |
| Physical activity | | | | |
| High | 39 (14.0) | 1.0 | 48 (19.8) | 1.0 |
| Moderate | 44 (19.0) | 1.4 (0.9–2.0) | 38 (22.9) | 1.2 (0.8–1.7) |
| Low | 37 (18.6) | 1.3 (0.9–2.0) | 35 (28.7) | 1.4 (1.0–2.1) |
| *P* value | | 0.3 | | 0.16 |
| Alcohol consumption | | | | |
| Abstemious | 41 (17.6) | 1.0 | 41 (22.7) | 1.0 |
| Social drinking | 70 (15.9) | 0.9 (0.6–1.3) | 68 (21.5) | 0.9 (0.7–1.3) |
| Abusive drinking | 9 (24.3) | 1.4 (0.7–2.6) | 12 (37.5) | 1.7 (1.0–2.8) |
| *P* value | | 0.4 | | 0.08 |
| Frequency of alcohol consumption | | | | |
| Abstemious | 41 (18.0) | 1.0 | 41 (22.7) | 1.0 |
| Monthly | 41 (17.6) | 0.9 (0.6–1.3) | 42 (26.6) | 0.9 (0.6–1.3) |
| Weekly | 38 (15.3) | 1.1 (0.7–1.5) | 79 (21.2) | 1.2 (0.8–1.7) |
| *P* value | | 0.7 | | 0.3 |
| Binge drinking | | | | |
| Abstemious | 41 (17.6) | 1.0 | 41 (22.7) | 1.0 |
| No | 60 (16.7) | 0.9 (0.7–1.4) | 60 (23.4) | 1.0 |
| Yes | 19 (16.2) | 0.9 (0.6–1.5) | 20 (21.5) | 1.0 (0.6–1.5) |
| *P* value | | 0.9 | | 0.8 |
| Body mass index (kg/m$^2$) | | | | |
| <25.0 | 36 (8.7) | 1.0 | 45 (15.3) | 1.0 |
| 25–29.9 | 58 (26.6) | 3.1 (2.1–4.5) | 40 (24.7) | 1.6 (1.1–2.4) |
| ≥30.0 | 26 (32.9) | 3.8 (2.4–5.9) | 36 (49.3) | 3.2 (2.3–4.6) |
| *P* value | | <0.001 | | <0.001 |
| HIV/HCV coinfection | | | | |
| No | 96 (18.0) | 1.0 | 85 (22.1) | 1.0 |
| Yes | 22 (15.4) | 0.9 (0.6–1.3) | 29 (24.6) | 1.1 (0.8–1.6) |
| *P* value | | 0.5 | | 0.6 |

Table 2: Continued.

| | Whites ($n$ = 710) | | Nonwhites ($n$ = 530) | |
|---|---|---|---|---|
| | Hypertension (%) | RR (95% CI) | Hypertension (%) | RR (95% CI) |
| AIDS diagnosis | | | | |
| No | 29 (14.6) | 1.0 | 36 (24.7) | 1.0 |
| Yes | 90 (17.6) | 0.8 (0.6–1.2) | 84 (22.0) | 1.1 (0.8–1.6) |
| $P$ value | | 0.3 | | 0.5 |
| Time since HIV infection (years) | | | | |
| <3.0 | 47 (16.6) | 1.0 | 44 (21.8) | 1.0 |
| 3.0–5.9 | 23 (13.1) | 0.8 (0.5–1.2) | 34 (19.5) | 0.9 (0.6–1.3) |
| ≥6.0 | 50 (20.0) | 1.2 (0.8–1.7) | 43 (27.9) | 1.3 (0.9–1.8) |
| $P$ value | | 0.18 | | 0.17 |
| Lifetime HAART use | | | | |
| No | 34 (14.0) | 1.0 | 46 (25.3) | 1.0 |
| Yes | 86 (18.4) | 1.3 (0.9–1.9) | 75 (21.6) | 0.9 (0.6–1.2) |
| $P$ value | | 0.14 | | 0.3 |
| Lifetime protease inhibitor use | | | | |
| No | 77 (22.7) | 1.0 | 68 (15.7) | 1.0 |
| Yes | 44 (23.0) | 1.0 (0.7–1.4) | 52 (18.8) | 1.2 (0.9–1.7) |
| $P$ value | | 0.9 | | 0.3 |
| CD4 (cell/mm$^3$) | | | | |
| <350 | 39 (15.1) | 1.0 | 50 (22.9) | 1.0 |
| ≥350 | 80 (18.0) | 0.8 (0.6–1.2) | 69 (22.5) | 1.0 (0.7–1.4) |
| $P$ value | | 0.3 | | 0.9 |

HAART: highly active antiretroviral therapy; HCV: hepatitis C virus; HIV: human immunodeficiency virus; RR: risk ratio.

Table 3: Association between alcohol consumption and hypertension according to skin color.

| | Whites | Nonwhites |
|---|---|---|
| | RR (95% CI)* | RR (95% CI)* |
| Alcohol consumption | | |
| Abstemious | 1.0 | 1.0 |
| Social drinking | 1.2 (0.8–1.7) | 1.1 (0.8–1.5) |
| Abusive drinking | 1.9 (1.1–3.3) | 2.4 (1.4–4.0) |
| $P$ value | 0.09 | 0.004 |
| Frequency of alcohol consumption | | |
| Abstemious | 1.0 | 1.0 |
| Monthly | 1.1 (0.7–1.6) | 1.0 (0.7–1.5) |
| Weekly | 1.4 (1.0–2.0) | 1.3 (0.9–1.9) |
| $P$ value | 0.2 | 0.18 |
| Binge drinking | | |
| Abstemious | 1.0 | 1.0 |
| No | 1.2 (0.8–1.7) | 1.1 (0.6–1.8) |
| Yes | 1.2 (0.8–1.9) | 1.2 (0.8–1.6) |
| $P$ value | 0.6 | 0.7 |

* RR adjusted for age, sex, educational attainment, smoking, physical activity, BMI, time since diagnosis of HIV infection, and use of highly active antiretroviral therapy.

and acute intake of large amounts were not associated with hypertension.

Systolic and diastolic blood pressure was higher exclusively in nonwhite participants who abused alcohol, independently of confounding factors (Table 4). Systolic blood pressure was on average 9.3 ± 3.2 mmHg, and diastolic 6.4 ± 2.1 mmHg greater among abusers. These differences were independent of age, sex, and educational attainment (data not shown) and of full control for confounding factors. Among white participants, there were an association of diastolic blood pressure with weekly consumption of alcoholic beverages in comparison with nondrinkers and a borderline association versus monthly consumers.

## 4. Discussion

In this study, we found that the consumption of large amounts of alcohol was independently associated with hypertension in white and nonwhite HIV-infected individuals. Blood pressure, on the other hand, was higher exclusively in nonwhite abusers of ethanol, demonstrated after adjustment for confounding factors. However, even partially adjusted models showed the presence of negative confounding factors. Among, whites there was an association of blood pressure with the frequency of consumption. Taken together, these findings suggest that among nonwhite participants quantity is more important than the pattern of consumption, while for whites the frequency of drinking is more relevant.

The association between alcohol abuse and hypertension identified in our study is in agreement with findings from other populations [33]. The association of blood pressure with abusive consumption exclusively in nonwhites was similar to the observed one in the ARIC cohort study (Atherosclerosis Risk in Communities) [3] and in a cohort carried out in southern Brazil [22]. It is unlikely that this differential association of alcohol abuse and blood pressure by skin color is due

Table 4: Association of systolic and diastolic blood pressure with alcohol consumption by skin color.

| Skin color | Alcohol consumption | BP ± SE (mmHg) | Delta of BP ± SE (mmHg)*† | *P* value*† | Delta of BP ± SE (mmHg)**† | *P* value**† |
|---|---|---|---|---|---|---|
| *Systolic BP (mmHg)* | | | | | | |
| Whites | Abstemious | 120.5 ± 1.0 | — | | — | |
| | Social drinking | 122.5 ± 0.7 | 2.0 ± 1.3 | 0.3 | — | |
| | Abusive drinking | 123.3 ± 2.5 | 2.8 ± 2.8 | 0.7 | 0.9 ± 2.7 | 1.0 |
| Nonwhites | Abstemious | 120.8 ± 1.3 | — | | — | |
| | Social drinking | 121.6 ± 0.9 | 0.8 ± 1.6 | 0.9 | — | |
| | Abusive drinking | 130.9 ± 3.0 | 10.1 ± 3.3 | 0.007 | 9.3 ± 3.2 | 0.01 |
| *Diastolic BP (mmHg)* | | | | | | |
| Whites | Abstemious | 74.9 ± 0.6 | — | | — | |
| | Social drinking | 76.6 ± 0.5 | 1.7 ± 0.8 | 0.1 | — | |
| | Abusive drinking | 77.4 ± 1.6 | 2.6 ± 1.7 | 0.4 | 0.9 ± 1.7 | 0.9 |
| Nonwhites | Abstemious | 76.6 ± 0.9 | — | | — | |
| | Social drinking | 77.1 ± 0.6 | 0.5 ± 1.1 | 0.9 | — | |
| | Abusive drinking | 83.4 ± 2.0 | 6.9 ± 2.2 | 0.006 | 6.4 ± 2.1 | 0.008 |
| | Frequency of alcohol consumption | | | | | |
| *Systolic BP (mmHg)* | | | | | | |
| Whites | Abstemious | 120.5 ± 1.0 | — | | | |
| | Monthly | 121.6 ± 1.0 | 1.1 ± 1.4 | 0.9 | — | |
| | Weekly | 123.5 ± 1.0 | 3.0 ± 1.5 | 0.4 | 2.3 ± 1.8 | 0.5 |
| Nonwhites | Abstemious | 120.8 ± 1.3 | — | | | |
| | Monthly | 121.3 ± 1.2 | 0.5 ± 1.8 | 0.8 | — | |
| | Weekly | 123.6 ± 1.4 | 2.8 ± 2.0 | 0.12 | 1.9 ± 1.4 | 0.5 |
| *Diastolic BP (mmHg)* | | | | | | |
| Whites | Abstemious | 74.9 ± 0.6 | | | | |
| | Monthly | 75.7 ± 0.6 | 0.8 ± 0.9 | 0.8 | | |
| | Weekly | 77.6 ± 0.6 | 2.8 ± 0.9 | 0.008 | 2.0 ± 0.9 | 0.079 |
| Nonwhites | Abstemious | 76.7 ± 0.9 | | | | |
| | Monthly | 77.5 ± 0.8 | 0.8 ± 1.2 | 0.9 | | |
| | Weekly | 77.7 ± 0.9 | 1.0 ± 1.3 | 0.8 | 0.2 ± 1.2 | 0.9 |

SE: standard error; *delta in relation to abstemious drinking; **delta in relation to social drinking or monthly consumption; †analyses of covariance adjusted for age, sex, educational attainment, smoking, physical activity, body mass index, time since HIV infection, and lifetime HAART use.

to race or ethnicity, but probably relies on other behavioral characteristics of nonwhite individuals [34]. Anyway, blood pressure was higher exclusively in nonwhite abusers, suggesting that these individuals are at higher risk of the harmful effects of ethanol.

Our study adds a piece of mind in the investigation of the influence of HIV-related characteristics and higher incidence of cardiovascular disease. It has been suggested that the use of HAART may be associated with increasing blood pressure [9, 10, 35, 36]. In some studies, longer time of HAART was associated with hypertension [13, 37]. These associations were not identified in our study, since the use of antiretrovirals, time of HIV infection, AIDS, and CD4 count were not associated with hypertension.

Some limitations of our study deserve to be mentioned. The cross-sectional design does not allow inferring causality. Data on alcohol consumption were obtained from a standardized questionnaire containing detailed information, but it relies on memory, and because it was applied in the context of medical care, this might have led individuals to underreport consumption. Another aspect to be considered is the fact that blood pressure measurements were performed at the medical consultation, and therefore the possibility of a white coat effect cannot be discarded. Even underreporting alcohol consumption or the white coat effect, the association of alcohol abuse with hypertension has been confirmed by ambulatory monitoring of blood pressure [38]. The prospective planning, together with the extensive and detailed measurement of AIDS-related and nonrelated characteristics and adequate statistical power, is a strength of our investigation.

## 5. Conclusions

In conclusion, alcohol abuse is associated with increased risk of hypertension in white and nonwhite HIV-infected individuals. Blood pressure is higher only in nonwhite individuals

who abuse alcoholic beverages and in whites who drink weekly. The association of ethanol consumption with blood pressure is not explained by AIDS-related conditions.

## Conflict of Interests

The authors declare that they have no conflict of interests.

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*Research Article*

# Risk of Coronary Heart Disease among HIV-Infected Patients: A Multicenter Study in Brazil

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Cardiovascular disease has emerged as a crescent problem among HIV-infected population. This study aimed to determine the 10-year risk of coronary heart disease using the Framingham risk score among HIV-infected patients from three regions of Brazil. This is a pooled analysis of three cohort studies, which enrolled 3,829 individuals, 59% were men, 66% had white skin color, and mean age 39.0 ± 9.9 years. Comparisons among regions showed that there were marked differences in demographic, socioeconomic, clinical, and HIV-related characteristics. Prevalence of Framingham score ≥10 was 4.5% in the Southern, 4.2% in the Midwest, and 3.9% in the Northeast of Brazil. The Framingham score ≥10 was similar between regions for males, patients aged ≥60 years, with obesity, central obesity, hypertension, and diabetes mellitus. Women were three times more likely to have coronary heart disease in 10 years than men. Hypertension and diabetes increased more than four times the risk of coronary heart disease, followed by central obesity, obesity, and prehypertension. The use of antiretroviral agents and time since HIV diagnosis were not risk factors for coronary artery disease in 10 years. In conclusion, hypertension and diabetes are the strongest independent predictors of 10-year risk of coronary heart disease among HIV-infected population.

## 1. Introduction

Cardiovascular disease (CVD) has emerged as a growing problem among HIV-infected population. With the advent of highly active antiretroviral therapy (HAART), there was a reduction in AIDS-related mortality, increasing of life expectancy, and the exposure to traditional cardiovascular risk factors [1–3]. On the other hand, the infection itself, as well as HAART, seems to be involved in changing the profile of cardiovascular risk factors [4, 5]. Dyslipidemia and hyperglycemia are adverse effects of HAART, which were associated with metabolic syndrome and are intermediate steps in the development of cardiovascular events [6, 7].

In Brazil, the use of antiretroviral therapy (ART) is available to the public free of charge, as well as blood

pressure-lowering agents, and other medications to control risk factors and prevent CVD. However, there are limited data on coronary heart disease (CHD) in the HIV-infected population [8, 9]. Cardiovascular risk can be evaluated by means of equations that combine several risk factors to provide a quantitative estimate of the risk [10]. The Framingham risk equation has been widely used to estimate the risk of development coronary heart disease over a fixed period of time, usually 10 years, in the general population [11], but the information in the HIV-infected population need to be further addressed [12].

Since the creation of the original equation [11], the Framingham risk score has been modified [13], and some concerns about its use were raised [14]. Although it has been suggested that a specific score needs to be used [15, 16], it is still uncertain the magnitude of CHD burden in the HIV-infected population. Moreover, the diversity of exposure to risk factors and socioeconomic conditions among patients from different clinical settings in Brazil may require the inclusion of different components in the score. Therefore, this study aimed to determine the 10-year risk of coronary heart disease using the Framingham risk score in HIV-infected patients from three regions of Brazil.

## 2. Methods

This is a cross-sectional with joint database analysis of baseline characteristics of three cohort studies, conducted in the Northeast, Midwest, and Southern Brazil, addressing characteristics associated with the Framingham risk score among HIV-infected individuals. In Recife, capital of the state of Pernambuco (Northeast), HIV-infected patients, aged 17 to 74 years, seen in two of the largest public outpatient centers (Hospital Universitario Oswaldo Cruz, from Universidade de Pernambuco, and Hospital Estadual Correia Picanço, from Health Secretariat of the state) for HIV/AIDS were enrolled. In Goiania, capital of the state of Goias (Midwest), HIV-infected patients, attending an outpatient public referral center for infectious diseases (Hospital das Clinicas da Universidade Federal de Goias), aged 20 to 75 years, with no clinical evidence of active opportunistic diseases at enrollment, were eligible to participate. In Porto Alegre, capital of the state of Rio Grande do Sul (Southern Brazil), HIV-infected patients aged 18 years or older, who have been seen in the outpatient clinic of the Hospital Sanatorio Partenon (SAT), of the Health State Department, were enrolled. In all studies, pregnant women, patients with mental retardation, and under restriction of freedom were excluded. The data collection was conducted in 2007–2009 (Recife), 2009–2011 (Goiania), and 2006–2008 (Porto Alegre). All research projects have been approved by the Institutional Review Board of the institutions, which are accredited by the Office of Human Research Protections, and all participants signed an informed consent.

Patients were interviewed using similar standardized questionnaires, anthropometric and blood pressure measurements, while HIV-related variables were obtained from medical records. Data collection was performed on routine visits, by certified physicians and research assistants, using similar questions pertaining demographic characteristics (age, categorized as <50, 50–59, or ≥60 years; self-reported skin color, categorized as white or nonwhite), socioeconomic level (number of years of formal education completed successfully, further categorized as ≥10 or <10), lifestyle (physical activity, categorized as yes or no; lifetime smoking, and binge drinking), clinical characteristics (self-reported previous morbidity, blood pressure lowering agents, antidiabetic agents, and drugs used in the dyslipidemia treatment), HIV-related characteristics (current or past cocaine or crack cocaine use, categorized as yes or no; reported use of antiretroviral medicine, also confirmed by medical records, and duration of HIV infection since the date of diagnosis, categorized as <8 or 8–29 years), and other risk factors for coronary heart disease (body mass index, waist circumference, diabetes mellitus, and hypertension status). In all studies, smoking was investigated by several questions: current status, number of cigarettes smoked per day, and smoking cessation, which allowed classifying individuals as never, former or current smokers. In two studies (in the Northeast and Southern Brazil), these questions were asked to those who reported having smoked at least 100 cigarettes during lifetime [17]. Alcohol consumption was investigated using a standardized questionnaire [18], including type, quantity, and frequency of each beverage consumed and binge drinking, defined by a consumption of five or more drinks on a single occasion [19].

Weight and height were obtained to calculate body mass index ($kg/m^2$), classified as <25, 25–29, or ≥30 $kg/m^2$. Central obesity was determined by waist circumference, which was measured in duplicate and classified as ≥102/88 cm for men and women, respectively. In Porto Alegre, there were four standardized measurements of blood pressure in two visits, using oscillometric monitor OMRON CP-705, and blood pressure was classified based on the average. In Recife and Goiania, there were two and three, respectively, measurements of blood pressure using calibrated aneroid sphygmomanometer (WelchAllyn/Tycos), and the average was used to classify blood pressure on <120/80, 80–89 and 120–139, or ≥140/90 mmHg, or use of antihypertensive medication. Laboratory tests were performed on fasting blood samples, with three months around the date of the interview. Diabetes mellitus was diagnosed based on fasting glucose ≥126 or use of antidiabetic agents.

Framingham scoring was calculated based on age, sex, total cholesterol, HDL cholesterol, LDL cholesterol, smoking status, diabetes mellitus, and blood pressure [11, 20], besides the reported use of using blood pressure, diabetes, or cholesterol lowering agents. Estimates of the Framingham score are more robust for total cholesterol than for LDL-cholesterol [21], and since LDL is the main treatment target [13], the lipid profile (total cholesterol, HDL, and LDL cholesterol) was maintained in the score calculation. The total score was calculated based on the original score sheets, which provide risk of CHD compared to people of the same age and sex [11]. The 10-year risk of CHD score was categorized as <10 (low) or ≥10 (intermediate or high risk, due to the expected low number of participants with high scores) to calculate prevalence and independent risk ratios with 95%CI (confidence intervals). This cutoff was based on the recommendations of the Adult Treatment Panel III (ATP III), which identified categories of cardiovascular risk to determine goals for lipid-lowering therapy [13].

Table 1: Characteristics of HIV-infected patients from regions of Brazil [$n$ (% or mean ± SD)].

| | Total ($n$ = 3829) | Northeast ($n$ = 2016) | Midwestern ($n$ = 289) | Southern ($n$ = 1224) | $P$ value |
|---|---|---|---|---|---|
| Men | 2086 (59.1) | 1249 (62.0) | 221 (76.5) | 616 (50.3) | <0.001 |
| Age (years) | 39.0 ± 9.9 | 39.5 ± 9.6 | 37.3 ± 11.0 | 38.6 ± 10.1 | <0.001 |
| Nonwhite skin color | 1194 (33.8) | 529 (26.2) | 145 (50.2) | 520 (42.5) | <0.001 |
| Years at school ≥10 | 1419 (40.2) | 846 (42.0) | 172 (59.5) | 401 (32.8) | <0.001 |
| Lifetime smoking | 1424 (40.4) | 480 (23.8) | 137 (47.4) | 807 (65.9) | <0.001 |
| Physical activity | 1171 (33.2) | 389 (19.3) | 74 (25.6) | 708 (57.8) | <0.001 |
| Binge drinking | 747 (21.2) | 475 (23.6) | 66 (22.8) | 206 (16.8) | <0.001 |
| Current or past cocaine use | 618 (17.5) | 220 (10.9) | 33 (11.6) | 365 (29.8) | <0.001 |
| Body mass index (kg/m$^2$) | | | | | <0.001 |
| ≤25.0 | 2240 (63.9) | 1357 (67.3) | 184 (68.9) | 699 (57.1) | |
| 25.0–29.9 | 961 (27.4) | 517 (25.6) | 69 (25.8) | 375 (30.6) | |
| ≥30.0 | 306 (8.7) | 142 (7.0) | 14 (5.2) | 150 (12.3) | |
| Waist circumference ≥102/88 cm | 666 (19.0) | 379 (18.8) | 31 (11.6) | 256 (20.9) | 0.002 |
| Hypertension status | | | | | <0.001 |
| Normal | 1406 (39.8) | 721 (35.8) | 102 (35.3) | 583 (47.6) | |
| Prehypertension | 1107 (31.4) | 574 (28.5) | 129 (44.6) | 404 (33.0) | |
| Hypertension | 1016 (28.8) | 721 (35.8) | 58 (20.1) | 237 (19.4) | |
| Diabetes mellitus | 473 (13.4) | 364 (18.1) | 10 (3.5) | 99 (8.1) | <0.001 |
| Antiretroviral use | 2544 (72.1) | 1544 (76.6) | 192 (66.4) | 808 (66.0) | <0.001 |
| Time >8 years since HIV diagnosis | 864 (24.5) | 553 (27.4) | 39 (13.5) | 272 (22.2) | <0.001 |

*2.1. Statistical Analysis.* A conceptual model through a hierarchical procedure was adopted in the data analysis in order to take confounding factors into account. The construction of the hierarchical model was based in two levels, and details are provided elsewhere [22]. Briefly, independent variables were grouped into socioeconomic (education), demographic factors (sex, age, and skin color), lifestyle (smoking, cocaine use, binge drinking, and physical activity), HIV characteristics (ARV use, length of HIV diagnosis) leading to direct determinants (obesity, hypertension, and diabetes mellitus) of cardiovascular disease [23]. Characteristics of the samples are expected to vary by regions, so an additional variable—the study site—was included in the multivariate analysis. At each hierarchical level, one regression equation was fitted including confounding factors which have been associated with Framingham score in the bivariate analysis ($P$ level <0.2) or based on the literature. At the first level, the risk ratios (95% CI) were adjusted for the study site, sex, age, years at school, smoking, cocaine use, binge drinking, antiretroviral therapy, and years of the HIV diagnosis, and, at the second level, there was additional control for waist circumference, hypertension status, and diabetes mellitus. Multivariate analysis was performed using modified Poisson regression (robust variance estimates) [24], and analysis of prevalence of risk factors by regions was carried out using the chi-squared test, in the Statistical Package for Social Sciences (SPSS Inc., version 18, Chicago, IL, USA).

Statistical power was calculated to assess the size of odds ratios that could be detected in this joint analysis using the Epidata statistical software (version 3.1, Pan-American Health Organization, Washington D.C., USA). The association between Framingham risk score ≥10 among participants with prehypertension versus normal blood pressure, for instance, with a 1.27 ratio of unexposed to exposed, significance level of 0.05 (two tailed), and 80% of statistical power would require a sample size of 1284 unexposed and 1011 prehypertensive participants to detect a risk ratio of 2.5.

## 3. Results

Table 1 shows the characteristics of 3,829 men (59.1%) and women (40.9%) evaluated in this pooled analysis of patients infected with HIV. Most were white (66%) had, on average, 39.0 ± 9.9 years, ranging from 18 to 84 years, but only 1.8% were older than 60 years and 40% finished 10 years or more in school. Comparisons among regions showed that there were marked differences in demographic, socioeconomic, clinical, and HIV-related characteristics. Compared with smoking prevalence detected in Southern Brazil, in the Midwest was about twice and in the Northeast three times more prevalent. In the Midwest, the prevalence of central obesity was about half of the prevalence identified in the Northeast and Southern Brazil.

The prevalence of Framingham score ≥10 was 4.5% in the Southern, 4.2% in the Midwest, and 3.9% in the Northeast of Brazil. The prevalence of intermediate or high Framingham score was similar between regions for males, patients aged ≥60 years, with obesity, central obesity, hypertension, and diabetes mellitus (Table 2). The association between alcohol abuse and intermediate or high Framingham score was detected only in the Northeast, while cocaine use was not associated with risk of CHD in Midwestern.

Results of the multivariate analysis showed that age over 50 years was an independent risk factor for coronary heart disease in 10 years (Table 3). Women were three times more likely to have coronary heart disease than men, regardless

Table 2: Association of risk factors with intermediate and high Framingham risk score among HIV-infected patients by regions of Brazil ($n$ (%)).

| | Northeast ($n$ = 2016) | Midwestern ($n$ = 289) | Southern ($n$ = 1224) |
|---|---|---|---|
| Sex | | | |
| Men | 24 (1.9) | 3 (1.4) | 18 (2.9) |
| Women | 55 (7.2) | 9 (13.2) | 37 (6.1) |
| $P$ value | <0.001 | <0.001 | 0.008 |
| Age (years) | | | |
| <50 | 20 (1.2) | 1 (0.4) | 9 (0.9) |
| 50–59 | 42 (16.9) | 7 (26.9) | 24 (17.9) |
| ≥60 | 17 (35.4) | 4 (40.0) | 22 (55.0) |
| $P$ value | <0.001 | <0.001 | <0.001 |
| Skin color | | | |
| Nonwhite | 28 (5.3) | 4 (2.8) | 18 (3.5) |
| White | 51 (3.4) | 8 (5.6) | 37 (5.3) |
| $P$ value | 0.06 | 0.2 | 0.13 |
| Years at school | | | |
| <10 | 53 (4.5) | 8 (6.8) | 38 (4.6) |
| ≥10 | 26 (3.1) | 4 (2.3) | 17 (4.2) |
| $P$ value | 0.1 | 0.06 | 0.8 |
| Lifetime smoking | | | |
| No | 58 (3.8) | 4 (2.6) | 14 (3.4) |
| Yes | 21 (4.4) | 8 (5.8) | 41 (5.1) |
| $P$ value | 0.6 | 0.17 | 0.17 |
| Physical activity | | | |
| No | 64 (3.9) | 9 (4.2) | 25 (4.8) |
| Yes | 15 (3.9) | 3 (4.1) | 30 (4.2) |
| $P$ value | 0.9 | 0.9 | 0.6 |
| Binge drinking | | | |
| No | 72 (4.7) | 7 (3.1) | 50 (4.9) |
| Yes | 7 (1.5) | 5 (7.6) | 5 (2.4) |
| $P$ value | 0.002 | 0.11 | 0.12 |
| Current or past cocaine use | | | |
| No | 77 (4.3) | 10 (4.0) | 50 (5.8) |
| Yes | 2 (0.9) | 1 (3.0) | 5 (1.4) |
| $P$ value | 0.02 | 0.8 | <0.001 |
| Body mass index (kg/m$^2$) | | | |
| ≤25.0 | 45 (3.3) | 4 (2.2) | 17 (2.4) |
| 25.0–29.9 | 20 (3.9) | 6 (8.7) | 25 (6.7) |
| ≥30.0 | 14 (9.9) | 1 (7.1) | 13 (8.7) |
| $P$ value | 0.001 | 0.06 | <0.001 |
| Waist circumference (cm) | | | |
| <102/88 | 46 (2.8) | 5 (2.1) | 27 (2.8) |
| ≥102/88 | 33 (8.7) | 6 (19.4) | 28 (10.9) |
| $P$ value | <0.001 | <0.001 | <0.001 |
| Hypertension status | | | |
| Normal | 12 (1.7) | 0 | 3 (0.5) |
| Prehypertension | 11 (1.9) | 3 (2.3) | 15 (3.7) |
| Hypertension | 56 (7.8) | 9 (15.5) | 37 (15.6) |
| $P$ value | <0.001 | <0.001 | <0.001 |
| Diabetes mellitus | | | |
| No | 25 (1.5) | 6 (2.2) | 32 (2.8) |

Table 2: Continued.

| | Northeast ($n$ = 2016) | Midwestern ($n$ = 289) | Southern ($n$ = 1224) |
|---|---|---|---|
| Yes | 54 (14.8) | 6 (60.0) | 23 (23.2) |
| $P$ value | <0.001 | <0.001 | <0.001 |
| Antiretroviral use | | | |
| No | 22 (4.7) | 2 (2.1) | 14 (3.4) |
| Yes | 57 (3.7) | 10 (5.2) | 41 (5.1) |
| $P$ value | 0.3 | 0.2 | 0.17 |
| Time since HIV diagnosis (years) | | | |
| 8–29 | 27 (34.2) | 3 (25.0) | 7 (12.7) |
| <8 | 52 (65.8) | 9 (75.0) | 48 (87.3) |
| $P$ value | 0.17 | 0.2 | 0.08 |

of age, socioeconomic status, lifestyle, and characteristics related to HIV. Age was the strongest predictor of CHD, even after the control for confounding factors. Binge drinking reduced CHD prevalence, independently of confounding factors, but there was a borderline significance. Hypertension and diabetes mellitus increased more than four times the risk of coronary heart disease, compared with the absence of these conditions, even after adjustment for confounding factors. Hypertension and diabetes were the strongest predictors of intermediate or high CHD risk, followed by central obesity, obesity, and prehypertension. The use of antiretroviral agents and time since HIV diagnosis were not independent risk factors for coronary artery disease in 10 years. Since most of risk factors are established at the age of 60 years, a subanalysis was carried out among participants younger than 50 years. Most of the associations between risk factors and intermediate or high Framingham score were also detected for those less than 50 years old, but some of the associations had even greater risk estimates, such as BMI, hypertension, and diabetes (data not shown). Independent of other confounding factors, an annual increase of age elevated by 30% a 10-year risk of an intermediate or high score (RR = 1.3, 95% CI: 1.2–1.4).

## 4. Discussion

The main objective of this study was to evaluate the association of risk factors and coronary heart disease in 10 years among HIV-infected patients from three regions of Brazil. Traditional risk factors such as age, hypertension, and diabetes mellitus were confirmed as independent risk factors, while HIV-related characteristics were not independently associated. Prehypertension was also independently associated with risk of CHD, which has been described in subjects not infected with HIV. Furthermore, the prevalence of risk factors by regions showed marked differences, suggesting that HIV-infected individuals living in several parts of Brazil did not share many characteristics besides infection.

These findings were not surprising, since age is a strong predictor of CHD risk and one of the main drivers of the Framingham score [20], while hypertension is prevalent and has accounted for almost half of ischemic heart disease cases worldwide [25]. Diabetes mellitus has been pointed out as an important risk factor for CHD [26] in HIV-infected individuals, but the risk detected in this pooled analysis was higher than previously described [27]. Among HIV-positive residents near Kampala, Uganda, in Africa, it was found that more than a quarter had hypertension, similar to the overall prevalence detected in this study, but it was assumed that no participant was smoker. Even so, there was an excessively high prevalence of Framingham score above 10% among men (42% versus 3.7% of women) [28]. In another study, conducted in Germany, about half of HIV-infected participants were smokers and a fifth had high blood pressure. However, approximately 22% and 18% of patients, respectively, were categorized as being at moderate or high 10-year risk for CHD [29]. Results of theoretical models [1, 30] and based on clinical data suggest an increased risk of myocardial infarction, due to the use of antiretroviral treatment. However, these results were found to be specific antiretroviral agents such as indinavir, lopinavir, ritonavir, didanosine, and abacavir [30–32]. In Brazil, most of these agents has been withdrawn or has not been employed in the public health system, and two non-NRTI agents, out of seven, were associated with risk of myocardial infarction.

In this study, prevalence of high 10-year CHD risk (>10%) was very low, as previously reported in Brazil [12, 33]. Among potential explanations, one is that the HIV-infected population was under 60 years old and had low prevalence of cardiovascular risk factors. Furthermore, the Framingham risk score may not be the best tool for assessing cardiovascular risk [34]. Furthermore, it was developed in a subsample of the American population—middle-aged, mostly Caucasians—free of CHD at baseline, whereas the HIV-infected population has a diverse ethnicity and is, on average, younger [15]. It also has been pointed out that the 10-year risk model may underestimate the lifetime risk [35]. However, Framingham risk score has been largely validated against risk detected in the individual data of cohort studies [36], and its simplicity matches the aims of prevention [37].

Besides that, other limitations should be taken into account when interpreting the results. The use of the Framingham score may not capture the true risk for the HIV-infected population, and a specific score, taking into account the use of specific antiretroviral agents, might work differently [16]. In addition, the number of possible combinations of ARV agents and the duration of treatment makes it difficult to isolate individual effects on the risk of coronary heart disease.

Table 3: Risk factors for intermediate and Framingham risk score among HIV-infected patients from Brazil.

| | RR (95% CI) | *P* value |
|---|---|---|
| Study site in Brazil* | | 0.12 |
| Northeast | 1.0 | |
| Midwestern | 0.8 (0.4–1.4) | |
| Southern | 0.7 (0.5–0.9) | |
| Sex* | | <0.001 |
| Men | 1.0 | |
| Women | 3.0 (2.1–4.2) | |
| Age (years)* | | <0.001 |
| <50 | 1.0 | |
| 50–59 | 16.3 (10.8–24.7) | |
| ≥60 | 43.4 (28.5–66.0) | |
| Skin color* | | 0.7 |
| Nonwhite | 1.0 | |
| White | 1.1 (0.8–1.4) | |
| Years at school* | | 0.9 |
| <10 | 1.0 | |
| ≥10 | 1.0 (0.7–1.4) | |
| Lifetime smoking* | | <0.001 |
| No | 1.0 | |
| Yes | 2.2 (1.6–3.0) | |
| Physical activity* | | 0.9 |
| No | 1.0 | |
| Yes | 1.0 (0.7–1.4) | |
| Binge drinking* | | 0.04 |
| No | 1.0 | |
| Yes | 0.6 (0.4–1.0) | |
| Current or past cocaine use* | | 0.13 |
| No | 1.0 | |
| Yes | 0.6 (0.3–1.2) | |
| Body mass index (kg/m$^2$)* | | <0.001 |
| ≤25.0 | 1.0 | |
| 25.0–29.9 | 1.3 (0.9–1.8) | |
| ≥30.0 | 2.3 (1.5–3.4) | |
| Waist circumference (cm)* | | 0.001 |
| <102/88 | 1.0 | |
| ≥102/88 | 1.7 (1.3–2.4) | |
| Hypertension status** | | <0.001 |
| Normal | 1.0 | |
| Prehypertension | 2.1 (1.2–3.6) | |
| Hypertension | 4.6 (2.7–7.9) | |
| Diabetes mellitus** | | <0.001 |
| No | 1.0 | |
| Yes | 4.7 (3.4–6.5) | |
| Antiretroviral use* | | 0.7 |
| No | 1.0 | |
| Yes | 0.9 (0.7–1.3) | |
| Time since HIV diagnosis (years)* | | 0.6 |
| <8 | 1.0 | |
| 8–29 | 0.8 (0.4–1.4) | |

*Risk ratio was adjusted for study site, sex, age, years at school, smoking, binge drinking, cocaine use, antiretroviral use, and length of the HIV diagnosis.

**Risk ratio additionally adjusted for waist circumference, hypertension, and diabetes mellitus.

In conclusion, this study showed that cardiovascular risk factors are present in the HIV-infected population and account for risk of coronary heart disease in 10 years. Even with the variation on risk factor prevalence among regions, the main risk factors—hypertension and diabetes mellitus—were identified in all settings as risk factors for coronary heart disease.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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*Research Article*

# Genetic Markers Associated to Dyslipidemia in HIV-Infected Individuals on HAART

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This study evaluated the impact of 9 single nucleotide polymorphisms (SNPs) in 6 candidate genes (*APOB, APOA5, APOE, APOC3, SCAP*, and *LDLR*) over dyslipidemia in HIV-infected patients on stable antiretroviral therapy (ART) with undetectable viral loads. Blood samples were collected from 614 patients at reference services in the cities of Porto Alegre, Pelotas, and Rio Grande in Brazil. The SNPs were genotyped by conventional polymerase chain reaction (PCR) and real-time PCR. The prevalence of dyslipidemia was particularly high among the protease inhibitors-treated patients (79%). *APOE* (rs429358 and rs7412) genotypes and *APOA5* −1131T>C (rs662799) were associated with plasma triglycerides (TG) and low-density-lipoprotein cholesterol levels (LDL-C). The *APOA5* −1131T>C (rs662799) and *SCAP* 2386A>G (rs12487736) polymorphisms were significantly associated with high-density-lipoprotein cholesterol levels. The mean values of the total cholesterol and LDL-C levels were associated with both the *APOB* SP *Ins/Del* (rs17240441) and *APOB XbaI* (rs693) polymorphisms. In conclusion, our data support the importance of genetic factors in the determination of lipid levels in HIV-infected individuals. Due to the relatively high number of carriers of these risk variants, studies to verify treatment implications of genotyping before HAART initiation may be advisable to guide the selection of an appropriate antiretroviral therapy regimen.

## 1. Introduction

The use of antiretroviral therapy (ART) as a standard of care has changed the prognosis of human immunodeficiency virus (HIV) infection by decreasing mortality and improving quality of life [1, 2]. Despite the clinical benefits, long-term ART is associated with a complex spectrum of unwanted metabolic effects, including dyslipidemia that eventually might lead to increased risk of cardiovascular diseases [3].

Nevertheless, these side effects are not universal to all individuals on ART and even vary in individuals with comparable ART, demographic, immunologic, and virological characteristics. This variability suggests that host genetic factors and inherited predispositions may have a significant influence on the appearance of metabolic alterations [4].

The exact mechanism of dyslipidemia is not fully understood but is most likely multifactorial. In the general population, genetic variation accounts for approximately 43%–83% of the variability in lipid plasma levels [5]. Recent candidate gene studies [6–11] as well as genome-wide-based association studies have identified certain single nucleotide polymorphisms (SNPs) that could account for a significant portion of the variation in blood lipid levels [12–14].

In HIV infection, genetic predisposition may help to explain the variability among patients with respect to the effects of protease inhibitors (PIs) on lipid metabolism [10, 11]. We have hypothesized that this variation is attributable to the joint effect of HIV infection and ART together with the underlying genetic predisposition present in these individuals. The aim of this study was to investigate the frequencies of 9 SNPs in 6 candidate genes and to identify associations between these SNPs and the plasma lipid levels of patients on stable ART with undetectable viral loads.

## 2. Methods

*2.1. Subjects.* We conducted a cross-sectional study with 614 patients who were diagnosed with HIV-1 infection according to the criteria of the Centers for Disease Control and Prevention [15]. All subjects were more than 17 years old, had regularly used ART for at least 12 months, had a viral load below the detection limit of the test (50 copies/mL; Versant HIV-1 RNA 3.0 Assay (bDNA), Siemens, Germany), and were recruited from three referral centers in southern Brazil (HIV/AIDS Ambulatory Unit of Hospital de Clínicas from Porto Alegre/RS, HIV Ambulatory Care of Hospital Universitário Dr. Miguel Riet Correa Jr. from Rio Grande/RS, and HIV/AIDS Specialized Assistance Service from Pelotas/RS) from March 2006 to November 2008. Pregnant women and those with neurological disease that prevented understanding and proper consent were not included in the study. The study protocol was approved by the Research Ethics Committees of the three centers and of the Universidade Federal de Ciências da Saúde de Porto Alegre, and all participants signed an informed consent statement before they were included in the study (protocol numbers: 05/295, 718/08, 154/07, and 141/06, resp.).

*2.2. Study Protocol.* The routine evaluation consisted of visits every 4 months in each center for an evaluation by the patients' attending physicians as well as laboratory evaluations that included measurements of CD4 cell counts, viral load, and lipid levels. The patients were invited to participate in the study and had their information and a blood sample for DNA extraction collected during one of these visits.

An interview was performed at enrollment to obtain demographic and lifestyle information. Details of HIV infection (time from diagnosis as well as current and prior antiretroviral medications), lipid-lowering intervention, and relevant clinical variables were obtained from medical records. The interviewer phenotypically defined the patients' ethnicities because there might be a strong cultural tendency to claim European ancestry in Brazil [16]. Patients were classified as Euro- or Afro-descendants because the Amerindian contribution is very low in the Brazilian South Region [17].

*2.3. Laboratory Analysis.* Blood samples were collected and sent to the Molecular Biology Laboratory for DNA extraction. Lipid profiles included determinations of total cholesterol (TC), high-density lipoprotein (HDL-C), triglycerides (TG), and, when possible, low-density lipoprotein (LDL-C) after fasting for 12 hours. LDL-C was calculated using the Friedewald formula, LDL-C = TC − HDL-C − TG/5, if triglyceride levels were below 400 mg/dL.

Dyslipidemia was defined by fasting triglycerides plasma levels ≥150 mg/dL and/or fasting total cholesterol ≥200 mg/dL and/or LDL-C ≥130 mg/dL and/or HDL-C <40 mg/dL. Participants were instructed not to perform any vigorous physical activity or ingest alcohol in the 24 hours prior to the blood collection [18].

Genomic DNA was obtained from peripheral leukocytes by a standard salting-out technique [19]. The genotypes of apolipoprotein B gene (*APOB*) polymorphisms were determined using polymerase chain reaction (PCR) based procedures in 410 individuals from the outpatient clinic of the Hospital de Clínicas de Porto Alegre. The polymorphism of insertion/deletion of signal peptide SP *Ins/Del* (rs17240441) was amplified by PCR using primers as previously described [20] and directly analyzed by electrophoresis in 8% polyacrylamide gels. The *Xba*I, 7673C>T (rs693) polymorphism was amplified by PCR using the primers described by Pan et al. [21], and genotypes were determined by digestion with *Xba*I restriction endonuclease and electrophoresis in 2% agarose gels.

The SNPs of apolipoprotein A-V (*APOA5*) −1131T>C (rs662799) and S19W (56C>G; rs3135506), apolipoproteinE (*APOE*) 334T>C (E4; rs429358) and 472C>T (E2; rs7412), apolipoprotein C-III (*APOC3*) 3238C>G (rs5128), sterol regulatory element-binding factor cleavage-activating protein (*SCAP*) 2386A>G (rs12487736), and low-density lipoprotein receptor (*LDLR*) intron 19G>T (rs6511720) were genotyped by real-time PCR using the TaqMan methodology and are listed in Table 1. Candidate SNPs were selected via review of PubMed reports of SNP associations with dyslipidemia in the general population or among HIV-infected individuals [6–11].

*2.4. Statistical Analyses.* The results are expressed as the mean ± standard deviation (SD) for continuous variables and as proportions for categorical variables. Variables that did not have a normal distribution (triglycerides) were transformed into natural logarithms before the statistical tests were applied. Allele frequencies were estimated by gene counting. $\chi^2$ analysis that was used to test for deviations in genotype frequencies from the Hardy-Weinberg equilibrium (HWE).

For the *APOC3* 3238C>G (rs5128), *APOA5* −1131T>C (rs662799) and S19W (56C>G) (rs3135506), *SCAP* 2386A>G (rs12487736), and *LDLR* intron 19G>T (rs6511720) polymorphisms, the association analyses were performed according

Table 1: Genotypic and allelic frequencies of polymorphisms analyzed.

| Polymorphisms | Genotypic frequency | Allelic frequency | | |
|---|---|---|---|---|
| *APOA5* –1131T>C (rs662799)[a] | | T | C | |
| T/T | 515 (84.7) | 0.92 | 0.08 | |
| T/C | 90 (14.8) | | | |
| C/C | 3 (0.5) | | | |
| Total | **608** | | | |
| *APOA5* S19W (56C>G; rs3135506)[a] | | C | G | |
| C/C | 500 (82) | 0.90 | 0.10 | |
| C/G | 103 (16.9) | | | |
| G/G | 7 (1.1) | | | |
| Total | **610** | | | |
| *APOB* SP *Ins/Del* (rs17240441)[a] | | *Ins* | *Del* | |
| *Ins/ins* | 193 (47.3) | 0.70 | 0.30 | |
| *Ins/del* | 176 (43.1) | | | |
| *Del/del* | 39 (9.6) | | | |
| Total | **408** | | | |
| *APOB XbaI*, 7673C>T (rs693)[a] | | C | T | |
| C/C | 122 (30) | 0.55 | 0.45 | |
| C/T | 203 (49.9) | | | |
| T/T | 82 (20.1) | | | |
| Total | **407** | | | |
| *APOC3* 3238C>G (rs5128)[b] | | C | G | |
| C/C | 478 (78.8) | 0.89 | 0.11 | |
| C/G | 127 (20.9) | | | |
| G/G | 2 (0.3) | | | |
| Total | **607** | | | |
| *APOE*[a] | | E2 | E3 | E4 |
| E2/E2 | 5 (0.8) | 0.07 | 0.79 | 0.14 |
| E2/E3 | 67 (11.2) | | | |
| E2/E4 | 9 (1.5) | | | |
| E3/E3 | 379 (63.6) | | | |
| E3/E4 | 120 (20.1) | | | |
| E4/E4 | 16 (2.7) | | | |
| Total | **596** | | | |
| *LDLR* intron 19G>T (rs6511720)[a] | | G | T | |
| G/G | 487 (80.2) | 0.90 | 0.10 | |
| G/T | 113 (18.6) | | | |
| T/T | 7 (1.2) | | | |
| Total | **607** | | | |
| *SCAP* 2386A>G (rs12487736)[a] | | A | G | |
| A/A | 168 (27.7) | 0.52 | 0.48 | |
| A/G | 296 (48.9) | | | |
| G/G | 142 (23.4) | | | |
| Total | **606** | | | |

The difference in the number of individuals among single nucleotide polymorphisms (SNPs) is due to failure in genotyping some SNPs in the whole sample. Genotypic frequencies presented as number of patients (%).

[a] $\chi^2$ test for Hardy-Weinberg equilibrium; $P > 0.05$.

[b] $\chi^2$ test for Hardy-Weinberg equilibrium; $P = 0.032$.

Table 2: Characteristics of the study participants.

| | All study participants $n = 614$ | PI-sparing ART $n = 311$ | PI-based ART $n = 303$ | $P$ value |
|---|---|---|---|---|
| Demographic | | | | |
| Age, years | 43.0 ± 10 | 42 ± 10 | 43 ± 9 | 0.114[§] |
| Male sex, *n* (%) | 341 (55.5) | 179 (58) | 162 (54) | 0.348[*] |
| Ethnicity, *n* (%) | | | | |
| Euro-Brazilians | 349 (57) | 166 (48) | 183 (60) | 0.094[*] |
| Afro-Brazilians | 265 (43) | 145 (47) | 120 (40) | |
| Physical activity, *n* (%) | 156 (25) | 74 (24) | 82 (27) | 0.389[*] |
| Cigarette smoking, *n* (%) | 186 (30) | 103 (33) | 83 (28) | 0.153[*] |
| Clinical | | | | |
| CD4, cells/uL | 533 ± 266 | 516 ± 255 | 552 ± 277 | 0.095[§] |
| Therapy time (months) | 68 ± 41 | 57 ± 38 | 76 ± 41 | <0.001[§¥] |
| Lipid-lowering drugs, *n* (%) | 105 (17) | 42 (14) | 63 (21) | 0.021[*] |
| Metabolic | | | | |
| Triglycerides, mg/dL | 196 ± 171 | 170 ± 131 | 223 ± 202 | <0.001[¶¥] |
| Total cholesterol, mg/dL | 192 ± 48 | 189 ± 44 | 196 ± 52 | 0.056[§] |
| HDL-C, mg/dL | 48 ± 16 | 51 ± 17 | 46 ± 14 | <0.001[§] |
| LDL-C, mg/dL | 107 ± 37 | 105 ± 34 | 109 ± 40 | 0.175[§] |
| Dyslipidemia, *n* (%) | 455 (74) | 215 (69) | 240 (79) | 0.006[*] |
| Hypertriglyceridemia | 293 (49) | 122 (40) | 171 (59) | <0.001[*] |
| Hypercholesterolemia | 245 (41) | 118 (39) | 127 (44) | 0.267[*] |
| Low HDL-C | 185 (31) | 74 (24) | 111 (38) | <0.001[*] |

Data presented as mean ± SD or number of patients (%).
PI: protease inhibitors; ART: antiretroviral therapy; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein.
[¥] $P$ value expressed with tests performed with ln-transformed variable.
[§] Student $t$-test for independent samples.
[*] $\chi^2$-Test with Yates correction.
[¶] Student $t$-test for independent samples with ln-transformed variable.

to the dominant model due to the low number of individuals who were homozygous for the minor allele and were pooled with subjects with the heterozygous genotype. As for *APOE* SNPs 334T>C (rs429358) and 472C>T (rs7412), which together define the *APOE* E2, E3, and E4 alleles, the subjects were analyzed in 3 genotype categories: E2/E3, homozygotes for the E3 allele and E3/E4. Subjects with the rare genotypes E2/E2 ($n = 5$), E2/E4 ($n = 9$), and E4/E4 ($n = 16$) were excluded from the statistical analyses.

The Testing Haplotype Effects in Association Studies Program (version 3.1, THESIAS, Paris, France) was used for the analysis of linkage disequilibrium between polymorphisms within the same gene [22].

General linear model analyses were used to test for the interaction between SNPs and variables and to adjust the lipid profile for covariables. The following variables were included in the models and underwent stepwise removal according to the greatest $P$ values: ethnic group, gender, age, physical activity, cigarette smoking, use of lipid-lowering agents, PI use, body mass index (BMI), and the presence of polymorphism. Only those variables that were significant predictors were included in the final model. Correction for multiple testing was performed using the Bonferroni method. The data were analyzed with the Statistical Package for Social Sciences (version 20.0, SPSS, Chicago, Illinois). The value indicating statistical significance was $P < 0.05$.

## 3. Results

*3.1. Study Participants.* The main demographic, clinical, and metabolic characteristics of the individuals enrolled in the study are shown in Table 2. Of the 614 patients, 55.5% were males, 57% were characterized as Euro-descendants, and the mean patient age was 43 ± 10 years. The mean duration of ART was 68 ± 41 months. Regarding metabolic parameters, 245 (41%) patients had hypercholesterolemia, 293 (49%) had hypertriglyceridemia, and 185 (31%) had low HDL-C levels.

The total patient population was stratified according to current PI use or nonuse. The prevalence of dyslipidemia was particularly high among the PI-treated patients (79% versus 69% in nonusers; $P = 0.006$). Although the mean levels of TC and LDL-C did not differ significantly between the PI-treated and non-PI-treated subjects, the latter had higher

Table 3: Mean metabolic variables according to polymorphisms analyzed.

| Polymorphisms | Total cholesterol (mg/dL) | | LDL-C (mg/dL) | | HDL-C (mg/dL) | | Triglycerides (mg/dL) | |
|---|---|---|---|---|---|---|---|---|
| | *N* | M ± SD | *N* | M ± SD | *N* | M ± SD | *N* | M ± SD |
| *APOA5* −1131T>C (rs662799) | | | | | | | | |
| T/T | 499 | 191 ± 80 | 458 | 106 ± 72 | 498 | 48 ± 88 | 499 | 187 ± 157 |
| T/C + C/C | 92 | 196 ± 78 | 83 | 107 ± 12 | 92 | 45 ± 16 | 92 | 243 ± 230 |
| *P* value | | 0.549 | | 0.953 | | 0.047[$] | | 0.003[*£] |
| *P* value *corrected*[**] | | 1.000 | | 1.000 | | 0.376 | | 0.024 |
| *APOA5* S19W (56C>G; rs3135506) | | | | | | | | |
| C/C | 486 | 192 ± 49 | 443 | 106 ± 37 | 485 | 48 ± 15 | 486 | 199 ± 177 |
| C/G + G/G | 106 | 197 ± 43 | 99 | 112 ± 35 | 107 | 50 ± 17 | 107 | 183 ± 144 |
| *P* value | | 0.330 | | 0.047[#] | | 0.130 | | 0.398[*] |
| *P* value *corrected*[**] | | 1.000 | | 0.376 | | 1.000 | | 1.000 |
| *APOB* SP *Ins/Del* (rs17240441) | | | | | | | | |
| *Ins/ins* | 192 | 189 ± 42[a] | 176 | 99 ± 31[c] | 192 | 52 ± 15 | 193 | 195 ± 167 |
| *Ins/del* | 175 | 193 ± 51[ab] | 158 | 106 ± 36[cd] | 175 | 50 ± 14 | 176 | 195 ± 193 |
| *Del/del* | 39 | 210 ± 45[b] | 37 | 120 ± 41[d] | 39 | 54 ± 13 | 39 | 187 ± 103 |
| *P* value | | 0.036[§] | | 0.006[§] | | 0.245 | | 0.996[*] |
| *P* value *corrected*[**] | | 0.288 | | 0.048 | | 1.000 | | 1.000 |
| *APOB XbaI*, 7673C>T (rs693) | | | | | | | | |
| C/C | 122 | 183 ± 42[e] | 112 | 95 ± 35[g] | 122 | 52 ± 15 | 122 | 187 ± 126 |
| C/T | 202 | 194 ± 42[ef] | 185 | 107 ± 31[h] | 201 | 50 ± 14 | 203 | 193 ± 163 |
| T/T | 81 | 203 ± 59[f] | 73 | 110 ± 41[ih] | 82 | 51 ± 12 | 82 | 212 ± 248 |
| *P* value | | 0.007[§] | | 0.002[§] | | 0.705 | | 0.791[*] |
| *P* value *corrected*[**] | | 0.056 | | 0.016 | | 1.000 | | 1.000 |
| *APOC3* 3238C>G (rs5128) | | | | | | | | |
| C/C | 464 | 193 ± 48 | 424 | 107 ± 37 | 465 | 49 ± 16 | 440 | 191 ± 162 |
| C/G + G/G | 125 | 192 ± 49 | 115 | 108 ± 39 | 124 | 47 ± 15 | 124 | 210 ± 214 |
| *P* value | | 0.718 | | 0.833 | | 0.295 | | 0.905[*] |
| *P* value *corrected*[**] | | 1.000 | | 1.000 | | 1.000 | | 1.000 |
| *APOE* genotype | | | | | | | | |
| E2/E3 | 64 | 188 ± 60 | 56 | 93 ± 34[j] | 63 | 46 ± 14 | 64 | 263 ± 350[l] |
| E3/E3 | 365 | 193 ± 47 | 333 | 109 ± 37[k] | 366 | 49 ± 16 | 366 | 186 ± 128[m] |
| E3/E4 | 119 | 198 ± 47 | 112 | 112 ± 38[k] | 119 | 48 ± 17 | 119 | 195 ± 153[m] |
| *P* value | | 0.209 | | 0.002[¶] | | 0.371 | | 0.033[*§] |
| *P* value *corrected*[**] | | 0.836 | | 0.008 | | 1.000 | | 0.132 |
| *LDLR* intron 19G>T (rs6511720) | | | | | | | | |
| G/G | 475 | 193 ± 48 | 430 | 107 ± 36 | 476 | 48 ± 16 | 473 | 198 ± 184 |
| G/T + T/T | 114 | 191 ± 51 | 107 | 105 ± 41 | 113 | 50 ± 16 | 114 | 183 ± 109 |
| *P* value | | 0.612 | | 0.427 | | 0.120 | | 0.971[*] |
| *P* value *corrected*[**] | | 1.000 | | 1.000 | | 1.000 | | 1.000 |

Table 3: Continued.

| Polymorphisms | Total cholesterol (mg/dL) | | LDL-C (mg/dL) | | HDL-C (mg/dL) | | Triglycerides (mg/dL) | |
|---|---|---|---|---|---|---|---|---|
| | *N* | M ± SD | *N* | M ± SD | *N* | M ± SD | *N* | M ± SD |
| *SCAP* 2386A>G (rs12487736) | | | | | | | | |
| A/A | 164 | 195 ± 49 | 146 | 107 ± 39 | 164 | 50 ± 17[n] | 164 | 201 ± 162 |
| A/G | 287 | 194 ± 48 | 263 | 107 ± 35 | 287 | 49 ± 15[no] | 287 | 197 ± 197 |
| G/G | 137 | 188 ± 47 | 129 | 107 ± 41 | 137 | 45 ± 14[o] | 138 | 188 ± 124 |
| *P* value | | 0.443 | | 0.970 | | 0.032[¥] | | 0.971[*] |
| *P* value *corrected*[**] | | 1.000 | | 1.000 | | 0.128 | | 1.000 |

HDL-C: high-density lipoprotein; LDL-C: low density lipoprotein.
[*] *P* value expressed with tests performed with logn-transformed variable.
[**] *P* value after Bonferroni correction for multiple testing.
[§] Adjusted for gender, age, and lipid-lowering agents use.
[¶] Adjusted for age, and lipid-lowering agents use.
[$] Adjusted for gender, cigarette smoking, and PI use.
[£] Adjusted for gender, age, lipid-lowering agents use, and PI.
[#] Adjusted for gender, age, ethnic group, BMI, and lipid-lowering agents use.
[¥] Adjusted for gender, cigarette smoking, ethnic group, and lipid-lowering agents use.
[ab] Tukey test, *Ins/Ins* versus *Ins/Del*, $P = 0.619$; *Ins/Ins* versus *Del/Del*, $P = 0.027$; *Ins/Del* versus *Del/Del*, $P = 0.145$.
[cd] Tukey test, *Ins/Ins* versus *Ins/Del*, $P = 0.231$; *Ins/Ins* versus *Del/Del*, $P = 0.006$; *Ins/Del* versus *Del/Del*, $P = 0.071$.
[ef] Tukey test, C/C versus C/T, $P = 0.053$; C/C versus T/T, $P = 0.007$; C/T versus T/T, $P = 0.598$.
[ghi] Tukey test, C/C versus C/T, $P = 0.006$; C/C versus T/T, $P = 0.008$; C/T versus T/T, $P = 0.830$.
[jk] Tukey test, E2/E3 versus E3/E3, $P = 0.011$; E2/E3 versus E3/E4, $P = 0.005$; E3/E3 versus E3/E4, $P = 0.628$.
[lm] Tukey test, E2/E3 versus E3/E3, $P = 0.003$; E2/E3 versus E3/E4, $P = 0.029$; E3/E3 versus E3/E4, $P = 0.875$.
[no] Tukey test, A/A versus A/G, $P = 0.594$; A/A versus G/G, $P = 0.014$; A/G versus G/G, $P = 0.071$.

plasma HDL-C levels (51 ± 17 mg/dL versus 46 ± 14 mg/dL; $P < 0.001$) and lower triglycerides levels (170 ± 131 mg/dL versus 223 ± 202 mg/dL, $P < 0.001$) than the PI-treated subjects. Therefore, PI use was tested as a covariate in all statistical analyses and was included when significant.

The genotype and allele frequencies of the analyzed SNPs are shown in Table 1. For all studied polymorphisms, there was no departure from Hardy-Weinberg equilibrium, except for *APOC3* 3238C>G (rs5128). Table 3 summarizes the association analysis of the SNPs with serum lipid concentrations.

*3.2. Triglycerides.* Two SNPs contributed significantly to the modification of TG levels. The plasma TG levels were different among *APOE* genotypes ($P = 0.033$), the E2 allele being associated with increased TG levels (Tukey test, E2/E3 versus E3/E3, $P = 0.003$; E2/E3 versus E3/E4, $P = 0.029$). However, this result was no longer significant after correction for multiple testing ($P_{corrected} = 0.132$).

The effect of the *APOA5* −1131T>C (rs662799) polymorphism on plasma lipids was observed in C-allele carriers, who presented higher triglyceride levels than those with the TT genotype (243 ± 230 mg/dL and 187 ± 157 mg/dL, respectively; $P = 0.003$). This nominal *P*-value remained statistically significant after Bonferroni correction for multiple comparisons ($P_{corrected} = 0.024$).

*3.3. HDL Cholesterol.* The *APOA5* −1131T>C (rs662799) polymorphism was also significantly associated with HDL-C levels. The TT homozygotes presented higher HDL-C concentrations than C-carriers ($P = 0.047$) after the same statistical approach and adjustment for covariates. Furthermore, a statistically significant association of the *SCAP* 2386A>G (rs12487736) variant was observed with HDL-C levels ($P = 0.032$). As shown in Table 3, the 2386GG homozygotes had lower HDL-C levels, while the 2386AA homozygotes showed an increase of 5 ± 2 mg/dL when compared to GG homozygotes (Tukey test, AA versus GG, $P = 0.014$). However, both associations were no longer significant after the Bonferroni correction for multiple comparisons.

*3.4. Total Cholesterol and LDL Cholesterol.* Initially, the average TC levels were associated with both the *APOB* SP *Ins/Del* (rs17240441; Table 3, $P = 0.036$) and *APOB Xba*I, 7673C>T (rs693; $P = 0.007$) polymorphisms. The *post hoc* test showed that there were differences between the homozygotes for both polymorphisms (Tukey test, *Ins/Ins* versus *Del/Del*, $P = 0.027$ and C/C versus T/T, $P = 0.007$, resp.). Neither results were significant after Bonferroni correction was applied ($P_{corrected} = 0.320$ and $P_{corrected} = 0.056$, resp.).

The mean LDL-C levels were also different between the genotypes ($P = 0.007$ and $P = 0.002$, resp.) for both polymorphisms and were statistically significant after Bonferroni correction was applied ($P_{corrected} = 0.048$ and $P_{corrected} = 0.016$, resp.). The Tukey test showed that, in the polymorphism of the signal peptide, differences were found between the homozygotes (*Ins/Ins* versus *Del/Del*, $P = 0.006$) and in the polymorphism in exon 26 of the gene the homozygous group with regard to the C allele differed from

Table 4: Effect of *APOB* Del T haplotype in total cholesterol and LDL-C.

| Risk haplotype | TC (mg/dL) | | | LDL-C (mg/dL) | | |
|---|---|---|---|---|---|---|
| | *N* | Mean ± SD | *P* value | *N* | Mean ± SD | *P*-value |
| Noncarriers | 213 | 188 ± 42[a] | 0.036 | 196 | 100 ± 32[b] | 0.011 |
| Heterozygous *Del* T | 163 | 195 ± 51 | | 147 | 108 ± 36 | |
| Homozygotes *Del* T | 27 | 212 ± 48[a] | | 25 | 118 ± 43[b] | |

TC: total cholesterol; LDL-C: low density lipoprotein.
Results from analysis of variance.
[a]Tukey test noncarriers versus homozygous for *Del* T, $P = 0.036$.
[b]Tukey test noncarriers versus homozygous for *Del* T, $P = 0.038$.

the other groups (C/C versus C/T, $P = 0.006$; C/C versus T/T, $P = 0.008$).

A significant linkage disequilibrium ($D' = 0.72$, $P < 0.001$) was detected between polymorphisms associating alleles *Del* and T, as well as *Ins* and C. Based on these results, we analyzed the effect of the haplotype combining alleles *Del* and T on the levels of these lipid parameters. The haplotype analysis showed that homozygotes for the risk haplotype showed significantly higher mean levels of TC and LDL-C (Table 4). The *post hoc* test showed that the differences were found between noncarriers and homozygotes for the *Del* T haplotype (Tukey test, $P = 0.036$ and $P = 0.038$, resp.).

The *APOE* genotype was associated with elevated plasma LDL-C levels ($P = 0.002$; $P_{\text{corrected}} = 0.008$; Table 3). In contrast to what was observed regarding the TG levels, the E2 allele was associated with a decrease in the LDL-C levels, while the E4 allele was associated with an increase, as the differences were found between the E2 and E4 allele carriers (Tukey test, E2/E3 versus E3/E3, $P = 0.011$; E2/E3 versus E3/E4, $P = 0.005$).

Regarding *APOA5* S19W (56C>G) (rs3135506), there was a marginal association with LDL-C levels. Carriers of the G allele and C/C genotype showed a mean and an SD of 112 ± 35 mg/dL and 106 ± 37 mg/dL, respectively ($P = 0.047$), that was adjusted for gender, age, BMI, and use of lipid-lowering agents. However, it did not remain significant after Bonferroni correction.

No significant contribution to plasma TC, TG, HDL-C, or LDL-C was identified in the present dataset with regard to *APOC3* 3238C>G (rs5128) and *LDLR* intron 19G>T (rs6511720).

Analyses were also performed separately for users and nonusers of IPs (data not shown), and similar effects were observed in both groups, although in some cases these effects were not significant.

## 4. Discussion

The contributions of several polymorphisms to dyslipidemia in 614 HIV-1-infected patients on HAART were addressed in the present multicenter study. Nine polymorphisms in 6 candidate genes were analyzed for their association with dyslipidemia. As expected according to the literature, this adverse effect was more prevalent in patients receiving PIs ([23] and references therein). However, we found no statistically significant difference in TC and LDL-C levels between PI-treated and non-PI-treated patients, probably associated with the more prevalent use of lipid-lowering agents by the PI group (21 versus 14%, $P = 0.021$).

The allelic frequencies of the *APOB*, *APOA5*, *APOE*, *SCAP,* and *LDLR* genotypes were similar to those previously described in populations from the same geographical region or ethnicity [8–11]. The *APOC3* 3238C>G (rs5128) genotypic frequencies were not distributed according to what was expected under Hardy-Weinberg equilibrium ($P = 0.032$; Table 1). This small deviation was most likely due to the lower number of homozygotes (2 patients, 0.3%) for the rare allele observed in our study; 7 were expected according to Hardy-Weinberg's proportions. Nevertheless, the allele frequencies ($G = 0.11$) were very close to those found in previous studies of individuals not infected with HIV who live in Southern Brazil ($G = 0.10$), as shown by Fiegenbaum et al. [8], and to participants in the Swiss HIV Cohort Study (SHCS), which were $G = 0.10$ and $G = 0.09$, as shown by Rotger et al. [11] and Tarr et al. [24], respectively.

Our study demonstrated a strong association between the E3/E4 genotype and elevated plasma LDL-C, which is in agreement with the results of previous studies [25, 26]. The E4 variant is typically associated with increased levels of LDL-C and low plasma TG levels, whereas the E2 variant is associated with lower LDL-C levels in the general population [25, 26]. In a large meta-analysis, the E4 variant was associated with a 42% increase in cardiovascular disease risk [27]. Although E2 isoforms bind to LDL receptors much more weakly than E3 or E4 isoforms, the catabolism of the particle containing isoform E2 is slower; this may result in a lower rate of LDL-C formation. Moreover, according to the conclusion of the meta-analysis of Bennet et al. [28], there is an approximately linear relationship between the *APOE* genotypes and both LDL-C levels and to the risk of cardiovascular disease.

Carriers of non-E3/E3 genotypes of *APOE* appear to be at risk of ritonavir-associated hypertriglyceridemia, and this risk appears to be enhanced by the association with *APOC3* variants [29]. According to the SHCS, the interaction between *APOE* and *APOC3* is associated with an extreme risk of developing hypertriglyceridemia in individuals treated with ritonavir [24]. Our data did not allow us to perform the same analyses, as the vast majority of our PI-users were on ritonavir. Nevertheless, our findings are in agreement

with these data reinforcing the association of E2 allele and increased TG levels. With respect to the E3/E3 genotype, according to our data as well as to those of [30], HIV-positive patients have a lower risk of developing high triglyceride levels after starting HAART than non-E3/E3 genotypes.

*APOA5* also plays an important role in the modulation of blood lipid metabolism; it is predominantly synthesized in the liver and is secreted into the plasma, where it plays a central role in regulating TG metabolism [31, 32]. Two polymorphisms in the *APOA5* gene, −1131T>C and S19W (56C>G), have been shown to be associated with elevated triglyceride levels in different populations [31, 33]. In our study, for *APOA5* −1131T>C, individuals with at least one C allele had higher TG levels and lower levels of HDL-C. However, only the association with TG levels remained significant after the Bonferroni correction was applied. These results are consistent with previous study in HIV-infected patients, indicated that −1131C carriers experienced marked increases in triglyceride levels during a 3-year follow-up, while no change was recorded in patients carrying the −1131T normal allele [34]. A similar effect, but of lesser magnitude, was demonstrated regarding changes in cholesterol [34].

To our knowledge, this is the first study conducted in an HIV-positive setting to assess the association of *SCAP* 2386A>G rs12487736 with dyslipidemia. The SCAP pathway controls cellular cholesterol homeostasis. Initially, in our analysis, we found that AA homozygous patients showed higher HDL-C levels; however, this result was no longer significant after Bonferroni correction was applied. Carriers of the 2386G allele from non-HIV-infected Brazilians treated with simvastatin exhibit reduced TC and TG levels, as shown by Fiegenbaum et al. [7], but no association was found with HDL-C levels.

The mean TC and LDL-C levels showed statistically significant differences for genotypes of both polymorphisms in the *APOB* gene: SP *Ins/Del* (rs17240441) and *Xba*I, 7673C>T (rs693). The homozygotes for the alleles T and *Del* had higher levels of these lipids than individuals heterozygous for both alleles, who had intermediate levels; this result is compatible with a co-dominant effect of these polymorphisms. These results are in agreement with published data showing that the *Del* and T alleles are associated with increased levels of TC and/or LDL-C in different populations with distinct diseases [9, 35–37]. However, Xu et al. and Ye et al. found no association of the polymorphism in the signal peptide of the gene with TC and LDL-C levels in the Finnish and Chinese populations, respectively [38, 39].

The significant linkage disequilibrium observed between polymorphisms, as reported in other studies [20, 39], led to an analysis of risk haplotype (patients with a combination of alleles *Del* and T). The patients who were homozygous for the risk haplotype showed higher total cholesterol and LDL-C, while an intermediate effect was observed in patients with the heterozygous haplotype. Rios et al. [9] also observed the association of the haplotype with LDL-C levels in a Brazilian population in a comparison of patients with and without coronary artery disease.

There are two possible causes for these changes in lipid metabolism related to both polymorphisms in the *APOB* gene. The first cause is that three amino acids, leu-ala-leu, that are included in the allele *Ins* and deleted in the allele *Del* could alter the hydrophobicity of the signal peptide of the protein and, thereby, alter the rate of translocation of new *APOB* peptides synthesized in the cytoplasm to the endoplasmic reticulum [38]. The second hypothesis is based on the fact that there is no amino acid change in the functional protein in both polymorphisms. These could then be in linkage disequilibrium with an unknown change in the DNA that may cause lipid abnormalities [20].

Two further SNPs that were proposed in the literature (*APOC3* 3238C>G (rs5128) and *LDLR* intron 19G>T (rs6511720) did not contribute to the plasma lipid levels in the present dataset, which may reflect a limited effect of these SNPs in HIV-infected patients.

All analyses were also performed by stratifying the patients according to PI use (data not shown); however, similar effects were observed in both groups. Furthermore, the variables were not statistically significant in some analyses, and this was most likely attributable to the reduction in the number of individuals when they are analyzed separately. This finding suggests that in our sample, the lipid-gene interaction is independent of the type of HAART used and that the variation observed is similar to that found in the general population.

We acknowledge some limitations of the present study. The cross-sectional design and the inclusion of patients receiving several different antiretroviral regimens, which is a difficulty inherent to any study involving current HAART, as by definition should include at least three different drugs. This fact might hinder the accomplishment of any pharmacogenomics study regarding this therapy. Furthermore, we found a deviation from the HWE observed in the current population for the *APOC3* 3238C>G (rs5128) SNP. Although this deviation may indicate genotyping error, laboratory procedures were in place to detect errors, including blinded, no-template controls and DNA sample replicates. Another limitation that we might acknowledge is the restricted number of SNPs analyzed. We cannot rule out the possibility that other SNPs in the genes investigated here are associated with the phenotypes studied.

In conclusion, our data support the importance of genetic factors on of lipid levels in HIV-infected individuals from a previously uninvestigated region of the world. We found no evidence of interaction of these genetic variants with the use of non-nucleoside transcriptase reverse inhibitors or protease inhibitors. Due to the relatively high number of carriers of these risk variants (e.g., *APOA5* −1131T>C = 15%, *APOB* risk haplotype = 47%, *APOE* = 20.1%), studies to verify treatment implications of genotyping are desirable.

## Authors' Contribution

Eduardo Sprinz and Vanessa S. Mattevi were joint senior authors on this work. Aline S. Gasparotto and Marina G. de M. Sassi genotyped the patients and performed the experiments. Rosmeri K. Lazzaretti, Eduardo Sprinz, Regina Kuhmmer, Jussara M. Silveira, Rossana P. Basso, Cezar

A. T. Pinheiro, and Mariângela F. Silveira were responsible for recruiting and clinical evaluation of patients. Vanessa S. Mattevi conceived and designed the experiments. Carísi A. Polanczyk reviewed the paper. Rosmeri K. Lazzaretti and Vanessa S. Mattevi performed the statistical analyses. Rosmeri K. Lazzaretti, Vanessa S. Mattevi, and Eduardo Sprinz wrote the paper.

## Disclosure

The number of contributors is justified by the performance of sample collections and patients' evaluations in three different reference centers.

## Conflict of Interests

The authors declare that there is no conflict of interests.

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