

Rosuvastatin and Ciprofibrate in the Treatment of Dyslipidemia in Patients with HIV

Hamilton Domingos, Rivaldo Venâncio da Cunha, Anamaria Mello Miranda Paniago, Albert Schiaveto de Souza, Renata London Rodrigues, João Américo Domingos

Faculdade de Medicina da Universidade Federal de Mato Grosso do Sul (UFMS), Campo Grande, MS - Brazil

Abstract

Background: Dyslipidemia secondary to highly active antiretroviral therapy in patients with HIV is associated with a significant increase in cardiovascular morbidity and mortality due to atherosclerotic disease, requiring, thus, immediate and effective treatment.

Objective: To demonstrate the effectiveness and safety of rosuvastatin and ciprofibrate in the treatment of dyslipidemia associated with highly active antiretroviral therapy in patients with HIV.

Methods: Three hundred and forty-six patients with dyslipidemia underwent pharmacological treatment as follows: 200 patients with hypertriglyceridemia received ciprofibrate (Group I); 79 patients with hypercholesterolemia received rosuvastatin (Group II); and 67 patients with mixed dyslipidemia received ciprofibrate associated with rosuvastatin (Group III). The lipid profile was assessed before and after the lipid-lowering treatment, and the Wilcoxon test was used for statistical comparison. Liver transaminases and creatine phosphokinase were measured to assess liver and muscle toxicity.

Results: The serum concentrations of triglycerides and total cholesterol were significantly lower than those obtained before the lipid-lowering treatment in the three experimental groups ($p < 0.002$). A significant increase in HDL-cholesterol was observed in Groups I and III ($p < 0.002$). In Groups I and II, LDL-cholesterol was significantly lower ($p < 0.001$). None of the patients experienced elevations in transaminases or creatine phosphokinase to significantly toxic levels.

Conclusion: The results of this study show that ciprofibrate and rosuvastatin or a combination of both can be considered an effective, safe and well-tolerated lipid-lowering treatment for patients with AIDS on highly active antiretroviral therapy. (Arq Bras Cardiol 2012;99(5):997-1007)

Keywords: Dyslipidemias; antiretroviral therapy, highly active; HIV; anticholesteremic agents; fibric acids.

Introduction

In 2005, the human immunodeficiency virus (HIV) infection affected 42 million people in the world, of whom, 1.8 million were in Latin America. Brazil was the most affected country in that region in absolute numbers, with approximately 1.2 million infected people, of whom, 257,780 had AIDS¹. According to the UNAIDS 2008 Report, HIV affects 33.4 million people in the world, 2.0 million in Latin America, and 536,000 in Brazil².

AIDS treatment has advanced significantly after the introduction of highly active antiretroviral therapy (HAART), which has determined a significant reduction in the disease-associated mortality and morbidity³. The year 1996 was a turning point in the history of HIV infection, dividing it into pre- and post-HAART eras⁴. Until 1996, early diagnosis of HIV and treatment of opportunistic infections were performed. After 1996, with the advent of HAART, disease control has significantly improved, with consequent increase in survival and improvement in the quality of life of those infected with HIV⁵.

The use of HAART has not only increased the patients' life expectancy, but has significantly reduced the prevalence of opportunistic infections, resulting in the emergence of chronic diseases and conditions related to risk factors common to the general population and that group of patients. Cardiovascular complications associated with HIV infection and related to the adverse effects of antiretroviral agents have become more frequent⁶. Despite the initial benefits of HAART, some studies have shown that treatment with those medications is associated with metabolic changes, such as lipodystrophy (body fat redistribution), insulin resistance, hyperglycemia, and dyslipidemia, with consequent elevation in the risk for atherosclerosis^{7,8}.

Despite the limited knowledge about the disease and about the epidemiology of atherosclerosis in the HIV-infected population, the cardiovascular disease can be due to reasons similar to those of the general population. However, it is worth assessing whether HIV infection and the metabolic changes associated with HAART can accelerate the atherothrombotic process⁹.

Several studies have reported the association between HAART and the risk of cardiovascular events. The DAD study has reported an increased incidence of acute myocardial infarction after long exposure to antiretroviral medication, showing an elevation in the risk of infarction from 0.3%

Mailing Address: Hamilton Domingos •

Rua das Garças, 100, Vila Alta. Postal Code 79010-020, Campo Grande, MS - Brazil

E-mail: hdomingos66@hotmail.com

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pre-HAART to 1.07% in patients undergoing HAART. In addition, a 1.26% increase in the risk of cerebrovascular disease has been identified after the use of HAART⁹.

Statins are the agents of choice to treat hypercholesterolemia and hypertriglyceridemia, because they reduce by 18% to 55% the serum concentrations of LDL-cholesterol and by 7% to 30% the concentrations of triglycerides, and increase by 5% to 10% the concentrations of HDL-cholesterol. Most agents of that group are metabolized by cytochrome P₄₅₀^{CYP}, which also metabolizes the protease inhibitors (PI). Thus, the serum levels of statins can increase, causing toxicity in the skeletal muscles and liver, and other adverse effects. Thus, statins that act in distinct metabolism sites, such as pravastatin, fluvastatin and rosuvastatin, should be preferred, avoiding those with exclusive metabolism by the cytochrome P₄₅₀^{CYP}, such as simvastatin. Atorvastatin can be cautiously used, and data on rosuvastatin are favorable, although limited¹⁰.

Fibrates are fibric acid derivatives used as first-line agents in the treatment of mixed dyslipidemia. They act like agonists of PPAR- α , modulating genes that increase the expression of lipoprotein lipase and apolipoproteins A I and A II, reducing apolipoprotein C III. Gemfibrozil, a representative of that group, is well tolerated, significantly reducing total cholesterol and triglycerides, especially when associated with atorvastatin. Niacin reduces LDL-cholesterol and increases HDL-cholesterol, but has many side effects, such as flushing, itching, hyperglycemia, and hepatotoxicity¹.

Considering that AIDS should be currently approached as a chronic disease, which can be controlled with HAART, managing the side effects of that therapy is important to prevent the development of early atherosclerotic complications already reported in the literature after the advent of HAART.

Methods

This study was prospectively carried out through clinical outpatient follow-up of 648 patients with HIV undergoing HAART. The patients were followed up from 2004 to 2009 at the outpatient clinics of infectology and cardiology of the Hospital Universitário of the UFMS and the Center of Infectious-Parasitic Diseases, both in the city of Campo Grande, state of Mato Grosso do Sul, Brazil.

After anamnesis focused on cardiovascular history, including the major risk factors for atherosclerotic disease (systemic arterial hypertension, smoking habit, dyslipidemia, diabetes or impaired glucose tolerance, visceral obesity, and family history of early atherosclerosis), the patients underwent complete physical examination, including measuring anthropometric data, body mass index, and abdominal circumference, and ectoscopy for assessing HAART-associated lipoatrophy and/or lipoaccumulation.

All patients followed up in this study underwent cardiometabolic assessment. At the first consultation, after anamnesis and physical examination, the following routine complementary tests were performed: fasting glycemia; lipid profile; thyroid stimulating hormone (TSH); creatine phosphokinase (CPK); liver transaminases (GOT and GPT); and creatinine.

The use of ciprofibrate and/or rosuvastatin was indicated to patients who remained persistently dyslipidemic even after being instructed on changes in lifestyle. They were divided into three groups as follows:

Group I: with hypertriglyceridemia over 300 mg/dL;

Group II: with LDL-cholesterol over the limits established by the NCEP, considering the estimated cardiovascular risk according to the Framingham Score as follows: LDL < 100 mg/dL for high-risk patients (> 20%); LDL < 130 mg/dL for moderate-risk patients (10% to 20%); and LDL < 160 mg/dL for low-risk patients (< 10%);

Group III: with mixed dyslipidemia (high cholesterol and triglycerides).

In all groups, patients were treated pharmacologically and instructed about changes in lifestyle as an adjuvant measure. In Group I, ciprofibrate was used at doses ranging from 100 to 200 mg/day, the dose of 200 mg being used only in cases of severe hypertriglyceridemia (concentrations over 1,000 mg/dL), or when 100 mg of ciprofibrate were insufficient to push triglycerides below 400 mg/dL. In Group II, rosuvastatin was used at doses ranging from 10 to 40 mg/day. In Group III, ciprofibrate and rosuvastatin were associated at the same doses used in Groups I and II. LDL-cholesterol was not directly measured, but estimated only by use of the Friedewald equation. Thus, patients with triglyceride levels over 400 mg/dL received initially ciprofibrate and had their LDL-cholesterol concentrations reassessed.

To demonstrate the efficacy of the lipid-lowering treatment, three reassessments of the serum lipid concentrations were performed after 30, 60 and 90 days, and the highest serum lipid level (triglycerides or cholesterol) before lipid-lowering therapy and the lowest serum concentration achieved after 90 days of treatment were considered for statistical assessment.

The safety of the lipid-lowering treatment regarding possible liver and muscle toxicities was determined by use of serial dosages of the enzymes GOT, GPT and CPK after 30, 60 and 90 days from the beginning of the lipid-lowering agents.

The clinical data regarding tolerability of the patients to the agents used were obtained at the control consultations every month during the outpatient follow-up, when patients were asked about digestive symptoms (dyspepsia, nausea, vomiting, epigastralgia, diarrhea, dry mouth and flatulence) and musculoskeletal symptoms (myalgia or muscular weakness).

The exclusion criteria were as follows:

- Use of other agents that could interfere with the lipid profile: corticosteroids; thiazide diuretics; beta-blockers; estrogens; androgens
- Thyroid or suprarenal hormone dysfunction or diabetes mellitus
- Need to change the HAART during the assessment
- Hepatitis prior to the use of the lipid-lowering agent
- Renal failure with glomerular filtration rate (GFR) below normal, assessed according to the Modification of Diet in Renal Disease (MDRD) study equation, where $GFR = 186 \times [\text{serum creatinine (mg/dL)}]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ if female}] \times [1.21 \text{ if the patient is black}]$

The results of the comparison between the groups of this study were assessed by use of nonparametric statistical tests, because the samples of the variables measured in this study were not normally distributed according to the Kolmogorov-Smirnov test. The correlation of sex and ethnicity with the experimental group was assessed by use of the chi-square test.

The lipid levels before and after treatment were compared by using the Wilcoxon test. The comparison between the experimental groups regarding the variables age and percentage of lipid reduction/elevation was performed by using the Kruskal-Wallis test followed by Dunn's post test.

The Mann-Whitney test was used to compare sexes regarding lipid levels.

The results of the comparison between the parameters used to monitor liver or muscle toxicity due to the use of lipid-lowering agents were analyzed by use of nonparametric statistical tests, because the samples of the variables measured in this study were not normally distributed according to the Kolmogorov-Smirnov test.

The comparison between the experimental groups regarding the variables GOT, GPT and CPK was performed by using the Kruskal-Wallis test followed by Dunn's post test. The relationship between the GOT, GPT and CPK levels in the experimental groups was assessed by use of the chi-square test. The comparison between the experimental groups regarding the percentage of patients with high GOT, GPT and CPK levels was performed by use of the Z-test of distribution.

The other results of the variables assessed were shown as descriptive statistics or as tables and graphs. The statistical analysis was performed by using the SigmaStat software, version 2.0, and the relationships, correlations and differences were considered significant when "p" value was lower than 0.05¹¹.

Results

Of the 648 patients with AIDS and on HAART assessed, 346 had dyslipidemia refractory to changes in lifestyle and were divided into those three groups as follows: Group I, comprising 200 patients with hypertriglyceridemia treated with ciprofibrate; Group II, comprising 79 patients with hypercholesterolemia treated with rosuvastatin; and Group III, comprising 67 patients with hypertriglyceridemia and hypercholesterolemia treated with ciprofibrate associated with rosuvastatin.

No significant difference between the groups regarding age, sex and ethnicity was observed as shown in Table 1.

Regarding HAART regimens, the three groups showed a predominance of patients on HAART containing PI, distributed as follows: Group I, 62.0% (n = 124) on PI and 38.0% (n = 76) on non-nucleoside reverse transcriptase inhibitor (NNRTI); Group II, 64.6% (n = 51) on PI and 35.4% (n = 28) on NNRTI; and Group III, 70.1% (n = 49) on PI and 29.9% (n = 20) on NNRTI.

The results regarding the lipid measurements before and after lipid-lowering treatment for the Groups I, II and III are shown in Table 2 and Figure 1.

The percentages of lipid reduction or elevation before and after lipid-lowering treatment are shown in Table 3 and Figure 2. Only Goup II showed a difference between the sexes, specifically regarding HDL-cholesterol (Mann-Whitney test, p = 0.023), in which female patients showed a reduction in that variable with treatment (3.98 ± 2.11%), while male patients showed an elevation in HDL-cholesterol (2.71 ± 2.16%) with treatment, as shown in Table 4.

The comparison between the groups showed a difference regarding GOT levels (Kruskal-Wallis test, p = 0.002), which were significantly higher in Groups I and III as compared with those in Group II (Dunn's post test, p < 0.05). Regarding GPT levels, no difference between the groups was evidenced

Table 1 – Distribution of patients (relative and absolute frequency) according to sex, ethnicity and age

Variables	Groups				p
	Total	I	II	III	
Sex - % (n)					0.344
Male	71.1 (n = 246)	73.0 (n = 146)	64.6 (n = 51)	73.1 (n = 49)	
Female	28.9 (n = 100)	27.0 (n = 54)	35.4 (n = 28)	26.9 (n = 18)	
Age (years) - mean ± standard error of the mean	0.387				
	44.44 ± 0.57	43.56 ± 0.72	45.58 ± 1.18	45.72 ± 1.43	
Ethnicity - % (n)					0.517
White	33.8 (n = 117)	36.0 (n = 72)	30.4 (n = 24)	31.3 (n = 21)	
Mixed	58.4 (n = 202)	55.5 (n = 111)	62.0 (n = 49)	62.7 (n = 42)	
Black	7.8 (n = 27)	8.5 (n = 17)	7.6 (n = 6)	6.0 (n = 4)	

Table 2 – Lipid profile before and after lipid-lowering treatment

Triglycerides (mg%)			
Groups	Lipid-lowering treatment		p
	Before*	After*	
Group I	630.74 ± 33.62	248.88 ± 8.95	< 0.001
Group II	206.67 ± 9.89	184.04 ± 7.53	0.002
Group III	892.87 ± 84.85	242.82 ± 16.60	< 0.001
Total cholesterol (mg%)			
Groups	Lipid-lowering treatment		p
	Before*	After*	
Group I	238.12 ± 4.87	217.18 ± 3.68	< 0.001
Group II	272.17 ± 4.08	206.99 ± 2.74	< 0.001
Group III	325.15 ± 9.37	211.66 ± 4.63	< 0.001
HDL-cholesterol (mg%)			
Groups	Lipid-lowering treatment		p
	Before*	After*	
Group I	33.87 ± 0.56	38.89 ± 0.65	< 0.001
Group II	46.63 ± 1.50	46.09 ± 1.42	0.531
Group III	38.57 ± 1.41	42.87 ± 1.13	0.002
LDL-cholesterol (mg%)			
Groups	Lipid-lowering treatment		p
	Before*	After*	
Group I	126.70 ± 2.88	131.47 ± 3.01	0.164
Group II	184.10 ± 3.18	123.91 ± 2.58	< 0.001
Group III	213.60 ± 7.95	125.39 ± 3.54	< 0.001

*Results shown as mean ± standard error of the mean.

(Kruskal-Wallis test, $p = 0.172$). Regarding CPK levels, the comparison between the groups showed a difference (Kruskal-Wallis test, $p = 0.032$); in post test, however, pairwise comparison of the groups showed no significant difference between them (Dunn's post test, $p > 0.05$) as shown in Table 5.

Considering the different HAART regimens, no significant difference in lipid-lowering responses was observed between the agents assessed.

None of the patients showed GOT or GPT levels greater than three times the upper limit of normality, or CPK levels greater than ten times the upper limit of normality.

Discussion

The increase in cardiovascular risk became an important problem after the introduction of HAART in 1996 for AIDS treatment, because of the potentially atherogenic metabolic complications associated with that therapy (dyslipidemia and insulin resistance).

Several studies have reported the association between antiretroviral therapy and the risk for cardiovascular events. Baum et al.¹² have reported a 4.8 ± 1.7 risk for cardiovascular events

in ten years according to the Framingham score in HIV-positive patients on antiretroviral therapy. Bergensen et al.¹³ have reported a 11.9% prevalence of cardiovascular risk over 20% (high risk) among patients on HAART, while for the control group, that prevalence was 5.3%. In addition, in that same group, a 5.2% increase in the prevalence of angina pectoris was observed in patients on HAART as compared with those of the control group¹³.

The DAD study has reported a 0.3% increase in the incidence of acute myocardial infarction, passing to 1.07% in HIV-positive patients on HAART. In addition, a 1.26% increase in the risk for cerebrovascular disease after using antiretroviral therapy was identified^{14,15}.

The use of antiretroviral therapy has intensified the tendency towards an increase in triglyceride levels and a reduction in HDL-cholesterol, which already occurred in patients with HIV. Triglycerides, when affected, can reach levels over 1,000 mg/dL, in association with an increased risk for pancreatitis and atherosclerosis. This study identified a mean 130.15-mg/dL increase in triglyceride levels.

According to the literature, total cholesterol and LDL-cholesterol levels increase, on average, 30 mg/dL, but a significant individual variation exists. Kumar et al. have

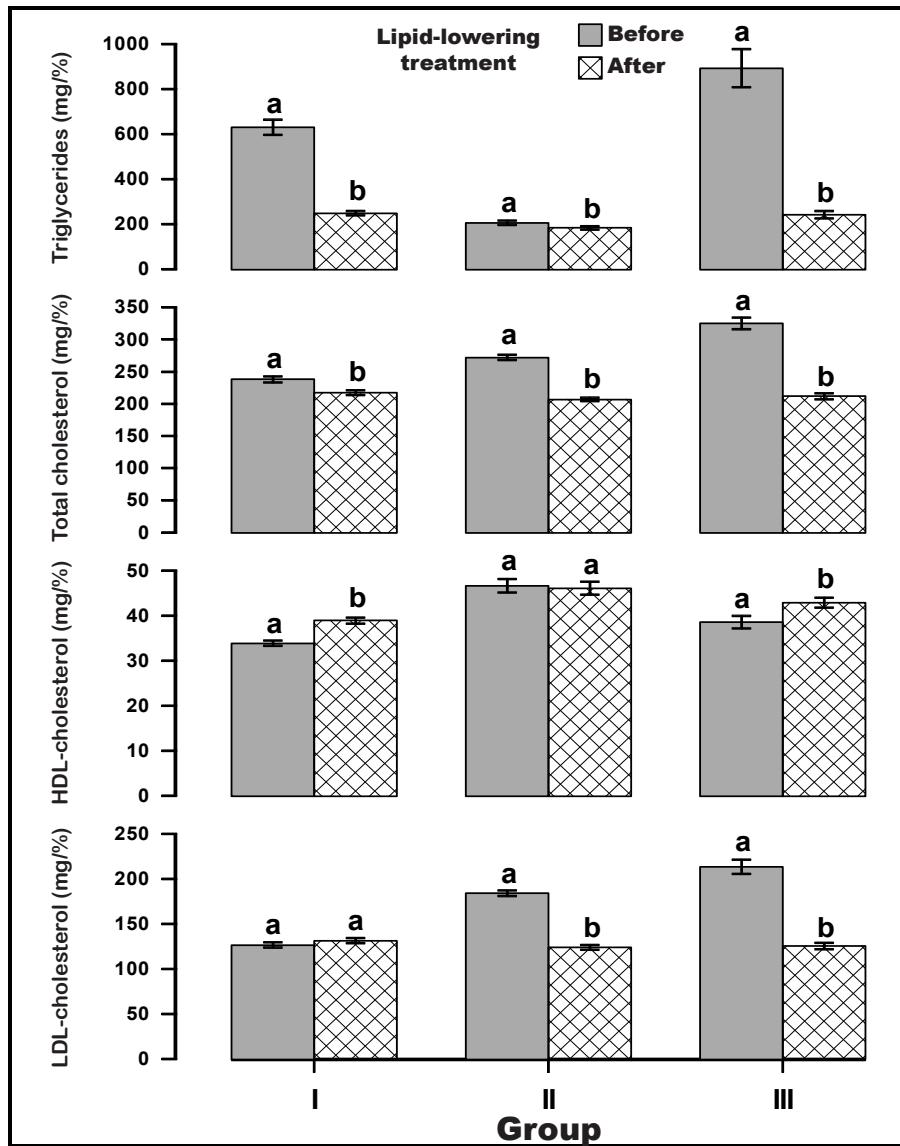


Figure 1 – Levels of triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol before and after lipid-lowering treatment. Each column represents the mean, and the bar represents the standard error of the mean. Different letters indicate a significant difference between the time points of analysis (Wilcoxon test, p ranging from < 0.001 to 0.002)

reported an increase of 28% for total cholesterol and of 96% for triglycerides¹⁶. In this study, a 33-mg/dL increase was observed in total cholesterol levels, but only a 16.29-mg/dL increase in LDL-cholesterol levels.

Domingos et al. have assessed the prevalence of some cardiovascular risk factors, such as smoking, hypertension, and family history of early atherosclerosis. The prevalence of smoking was 15.4% and of systemic arterial hypertension, 14.7%. The prevalence of hypercholesterolemia ranged from 31% to 47%, and that of hypertriglyceridemia, from 47% to 71%; that variation depended on the HAART regimen used, affecting mainly the users of HAART containing PI¹⁷.

HIV-infected patients showed significant changes in serum lipid concentrations. Those changes are more intense when patients are on HAART, especially if the regimen includes a PI. Initially, a reduction in HDL-cholesterol levels and elevation in triglyceride levels have been described, probably translating an unspecific inflammatory response¹⁸. After the introduction of the HAART containing PI, a marked elevation in triglyceride and total cholesterol levels was observed, as well as an intensification of the reduction in HDL-cholesterol levels¹⁹. The mechanisms that explain those results seem to relate to changes in the lipid metabolism²⁰.

Table 3 – Percentages of reduction or elevation in lipid levels before and after lipid-lowering treatment

Triglycerides		
Groups	Reduction with treatment (%)*	p
Group I	54.85 ± 1.05	< 0.001
Group II	4.98 ± 3.14	
Group III	64.96 ± 2.01	
Total cholesterol		
Groups	Reduction with treatment (%)*	p
Group I	6.46 ± 1.22	< 0.001
Group II	23.39 ± 0.93	
Group III	33.23 ± 1.43	
DL-cholesterol		
Groups	Elevation with treatment (%)*	p
Group I	17.95 ± 2.03	< 0.001
Group II	0.34 ± 1.61	
Group III	18.82 ± 4.93	
LDL-cholesterol		
Groups	Reduction with treatment (%)*	p
Group I	-9.36 ± 2.59	< 0.001
Group II	32.19 ± 1.29	
Group III	38.66 ± 1.83	

*Results shown as mean ± standard error of the mean.

The binding site of PI to HIV has a molecular structure similar to that of some proteins involved in lipid metabolism. That similarity allows partial or total inhibition of those proteins by PI, affecting the lipid metabolism, probably depending on the gene expression of the receptors involved¹⁹.

Carr et al. have proposed a theory based on the structural similarity between the catalytic region of HIV protease and two important human proteins that regulate lipid metabolism: cytoplasmic retinoic-acid binding protein type 1 (CRABP-1) and low density lipoprotein-receptor-related protein (LRP). The antiretroviral agents of the PI class would also inhibit important steps of the human metabolism. Occasionally, the PIs would interrupt the metabolism of retinoic acid and would reduce the activity of the peroxisome proliferator activated receptor gamma (PPAR- σ), which plays a key role in the differentiation of adipocytes and their apoptosis, in addition to improving peripheral sensitivity to insulin. The final results of those effects would be increased lipid release in the circulation and hypertriglyceridemia. On the other hand, LRP inhibition would result in lower hepatic uptake of triglycerides and in reduced cleavage of triglycerides into fatty acids and glycerol, which would occur due to the endothelial LRP-lipoprotein lipase complex (LRP-LPL) activity. Hypertriglyceridemia would account for the elevated insulin resistance, which, in susceptible individuals could cause type 2 diabetes mellitus. Inhibition of cytochrome P450 3A, a common step of the metabolism of PIs and retinoic acid inhibitors, would also contribute to that metabolic dyscrasia²⁰.

An alternative mechanism that has been proposed is based on the molecular similarity of PIs, which would compete for the binding site of the liver receptors of remaining chylomicrons. Thus, a balanced increase in the levels of total cholesterol and triglycerides related to the permanence of the remaining chylomicrons in plasma would occur. In parallel, those changes would increase insulin resistance, and, consequently, would increase the prevalence of type 2 diabetes mellitus and systemic arterial hypertension in those patients²⁰.

The high prevalence of risk factors for atherosclerotic disease observed in this study evidences the importance of taking preventive measures in that specific population. The prevalence of dyslipidemia aggravated by HAART, present in 64.5% of the patients, almost doubled as compared with that observed in the general population (32.4%)^{21,22}.

Multiple scientific studies have evidenced the correlation between risk factors for atherosclerosis alone or as part of the metabolic syndrome. A genetically predisposed individual with AIDS and undergoing antiretroviral therapy, who has that syndrome aggravated by the adverse effect of agents and at a young age, is at potential risk for atherothrombotic events, especially when considering a second mechanism also present, the elevation in inflammatory mediators associated with HIV and metabolic syndrome.

Since the introduction of HAART in 1996, several studies have been conducted, aiming at establishing a correlation between AIDS, HAART and cardiovascular morbidity and mortality.

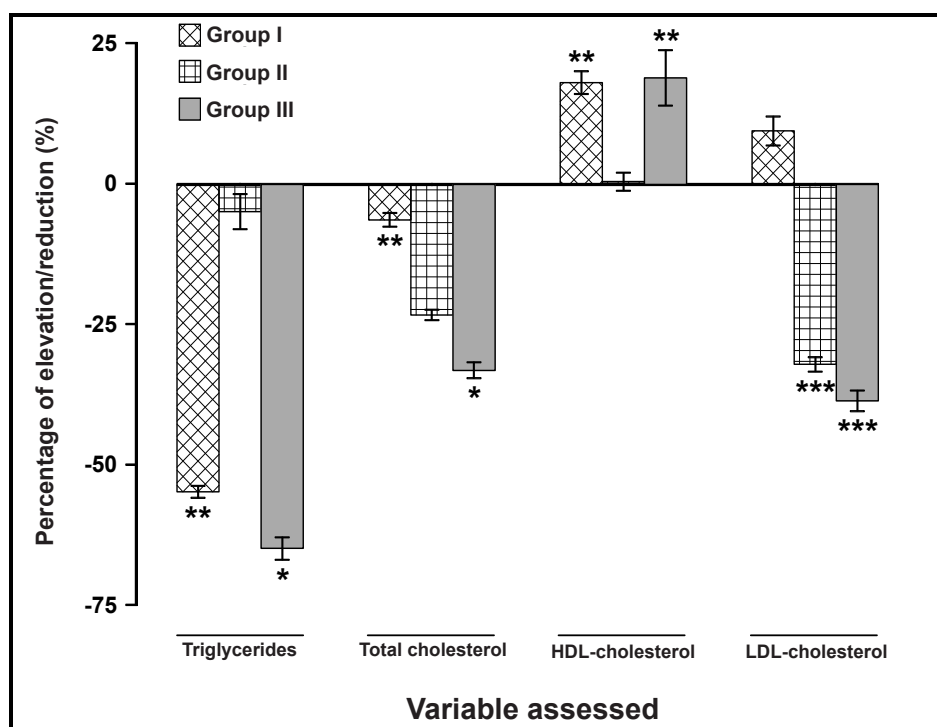


Figure 2 – Percentage of elevation/reduction in the levels of triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol before and after lipid-lowering treatment. Each column represents the mean percentage, and the bar represents the standard error of the mean.

* Significant difference regarding Groups I and II;

** Significant difference regarding Group II;

*** Significant difference regarding Group I (Kruskal-Wallis test, $p < 0.050$, followed by Dunn's post test, $p < 0.050$)

Bozzette et al.²³, assessing coronary and cerebrovascular disease retrospectively from 1996 to 2001 with a case series including 15,296 patients on HAART, have reported a 7.9% prevalence. Friis-Moller et al.¹⁵, in the DAD cohort study carried out with data obtained from 1999 to 2002, including 23,468 patients, have reported 126 coronary events and a 1.26 increase in the relative risk per year of exposure to HAART¹⁵. Moore et al.²⁴, assessing the occurrence of myocardial infarction or unstable angina in 2,671 patients on HAART for eight years, have reported an incidence of 5.9 events/1,000 patient/years in the group exposed to HAART versus 2.0/1,000 patient/years in the analysis of the control group of patients without AIDS²⁴.

Disorders of the lipid metabolism increase by two to three fold the cardiovascular risk of HIV-infected patients. New strategies aimed at preventing and treating those emerging disorders are necessary²⁵.

In the few prospective studies approaching dyslipidemia in that specific group of patients, only some lipid-lowering agents, especially those more easily accessed, have been assessed, and such agents are not always the best regarding efficacy and tolerability.

It is worth noting at least two important aspects that need to be discussed regarding the indication and choice of lipid-

lowering agents for those patients. The first aspect relates to the worsening and severity of dyslipidemia observed in those cases, requiring potent agents, aimed at achieving the goals recommended by the NCEP/ATP. The second aspect, also characteristic of that group, relates to the association of multiple medications of continuous use, not only for the underlying disease (AIDS), but also for its comorbidities.

The use of either ciprofibrate or rosuvastatin or their combination proved to be effective, safe and well tolerated in HIV-infected individuals on HAART. However, the fact that this study was not randomized should be considered as a possible bias in data analysis. Regarding safety, it is worth noting that the short follow-up is a limiting factor in the analysis of the results of the present study.

Lipid-lowering drugs should be more carefully administered to patients on HAART, compared with the general population, aiming at obtaining efficacy at lower doses to avoid the potential elevation of toxicity, especially hepatic and renal, associated with antiretroviral agents.

Kannel and Giordano²⁶ have reported 30% and 60% reductions in total cholesterol and triglycerides, respectively, in patients on atorvastatin associated with gemfibrozil. Calza et al.²⁷ have shown 40.7% and 21.9% reductions in triglycerides and total cholesterol, respectively, in 69 patients treated with fibrates.

Table 4 – Percentages of reduction or elevation in lipid levels before and after lipid-lowering treatment, according to sex

Group I	Variation (%)*			p
	Sex			
Variable	Female	Male		
Triglycerides	54.16 ± 2.15	55.11 ± 1.20		0.927
Total cholesterol	9.11 ± 2.20	5.49 ± 1.45		0.244
HDL-cholesterol	-12.55 ± 3.58	-19.95 ± 2.43		0.182
LDL-cholesterol	-2.97 ± 4.12	-11.72 ± 3.19		0.141
Group II	Sex			
Variable	Female	Male		p
Triglycerides	6.11 ± 4.09	4.36 ± 4.34		0.996
Total cholesterol	22.74 ± 1.32	23.74 ± 1.26		0.894
HDL-cholesterol	3.98 ± 2.11	-2.71 ± 2.16		0.023
LDL-cholesterol	30.60 ± 2.08	33.06 ± 1.64		0.445
Group III	Sex			
Variable	Female	Male		p
Triglycerides	59.83 ± 4.22	66.84 ± 2.24		0.115
Total cholesterol	34.74 ± 2.61	32.67 ± 1.71		0.484
HDL-cholesterol	-10.34 ± 7.38	-21.94 ± 6.15		0.777
LDL-cholesterol	39.74 ± 3.63	38.26 ± 2.13		0.777

* Results shown as mean ± standard error of the mean.

Stein et al.²⁸ have shown in a double-blind placebo-controlled study a 20.8% reduction in LDL-cholesterol with pravastatin.

Rosuvastatin, the newest and most potent agent among statins, with no known interaction with PIs (it does not use the cytochrome P450 pathway, differently from pravastatin and fluvastatin), seems to be promising in the treatment of dyslipidemia in HIV-infected individuals²⁹. Studies showing the safety and efficacy of rosuvastatin are expected in coming years. It is worth noting that several PIs interact with the cytochrome P450 system and can affect the toxic potential of other drugs³⁰.

Palacios et al.³¹ have demonstrated a significant reduction of 27% in total cholesterol and of 37% in LDL-cholesterol with atorvastatin (10 mg/day), but that statin is also metabolized via the cytochrome P450 pathway, and, thus, its use should be avoided in patients on HAART regimens containing PI³¹.

Statins and fibrates have a high potential for liver and muscle toxicity. Patients on those lipid-lowering agents should be monitored with laboratory tests, which comprise measuring GOT, GPT and CPK levels at baseline and four to six weeks later³⁰.

Regarding tolerability to the agents used in the three groups assessed, isolated reports of myalgia (three cases) occurred in Group II (rosuvastatin), but none of them was associated with CPK elevation, not characterizing rhabdomyolysis. Dyspepsia was reported by only five patients, three in Group I (ciprofibrate) and two in Group III (ciprofibrate and rosuvastatin). Regarding the potential for liver and muscle

toxicities, enzyme elevations in a significant number of cases were not observed. When elevations in transaminases and CPK occurred, they did not exceed the maximum limits of tolerance recommended by the NCEP/ATP.

This study showed that ciprofibrate and rosuvastatin have adequate pharmacological profiles regarding efficacy, safety and tolerability, and can be considered effective to control dyslipidemia secondary to HAART.

Reports of dyslipidemia and cardiovascular events associated with HAART are increasingly frequent. If the treatment is able to control those complications, it will reduce cardiovascular morbidity and mortality, improving the quality of life and increasing the survival of patients with AIDS.

Conclusions

For the treatment of dyslipidemia, ciprofibrate and rosuvastatin in isolation or combined proved to be effective, safe and well tolerated in a group of patients with HIV undergoing HAART. Percentages of lipid level reduction and HDL-cholesterol level elevation similar to those observed in the general population were observed.

In addition to increasing the efficacy in reducing the levels of triglycerides and cholesterol with concomitant elevation in HDL-cholesterol levels, the necessary association of statins and fibrates in the mixed dyslipidemia group aggravated by

Table 5 – Mean GOT, GPT and CPK levels after lipid-lowering treatment

GOT *		
Groups	(U/L)	p
Group I	34.37 ± 0.94	0.002
Group II	29.21 ± 0.90	
Group III	36.60 ± 1.74	
GPT *		
Groups	(U/L)	p
Group I	49.46 ± 1.24	0.172
Group II	46.91 ± 1.69	
Group III	52.25 ± 2.36	
CPK *		
Groups	(U/L)	p
Group I	159.70 ± 6.17	0.032
Group II	132.41 ± 6.09	
Group III	174.49 ± 13.49	

* Results shown as mean ± standard error of the mean.

antiretroviral agents was also useful to deconstruct the myth prevailing among specialists in cardiology and metabolism about the potential toxicity and risk of that association. As there is a real risk for hepatotoxicity and myotoxicity, despite their very low prevalence, clinical and laboratory monitoring of patients on lipid-lowering treatment, especially in the presence of concomitant HAART, is mandatory.

In addition to pharmacological therapy, changes in lifestyle, such as smoking cessation, adequate diet and aerobic physical activity, are critical points of great impact to achieve lipid level goals in atherosclerosis prevention. Switching therapy or changing the HAART regimen by replacing one or more agents can be considered an option to control the adverse metabolic effects, although maintaining viral control should be the major objective of the treatment³². The pharmacological treatment of dyslipidemia (usually with statins and/or fibrates) and of impaired glucose tolerance (with insulin sensitizers) are indicated when changes in lifestyle and switching therapy are ineffective or not applicable.

Despite the lack of definitive epidemiological studies, there is sufficient indirect evidence to suppose that the population studied is at a greater risk for cardiovascular disease. Thus, further studies are necessary to define whether the goals of lipid levels, glycemia and blood pressure aimed at atherosclerosis prevention currently adopted for the general population would apply for the population studied.

Potential Conflict of Interest

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

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Study Association

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