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Metabolic changes associated with antiretroviral therapy in HIV-positive patients

Alterações metabólicas associadas à terapia anti-retroviral em pacientes HIV-positivos

ABSTRACT

OBJECTIVE: To evaluate metabolic changes associated with highly active antiretroviral therapy (HAART) in HIV-positive patients, and to identify risk factors associated.

METHODS: Retrospective study that included 110 HIV-positive patients who where on HAART in the city of Porto Alegre (Southern Brazil) between January 2003 and March 2004. Data on demographic variables, cigarette smoking, diabetes mellitus, cholesterol and triglyceride levels, stage of HIV infection, antiretroviral therapy and HCV coinfection were collected. General linear models procedure for repeated measures was used to test the interaction between HAART and HCV coinfection or protease inhibitor treatment.

RESULTS: Total cholesterol, triglycerides, and glucose levels significantly increased after receiving HAART ($p<0.001$ for all variables), but no interaction with protease inhibitors was seen for total cholesterol, glucose and triglyceride levels (interaction treatment*protease inhibitors $p=0.741$, $p=0.784$, and $p=0.081$, respectively). An association between total cholesterol levels and HCV coinfection was found both at baseline and follow-up (effect of HCV coinfection, $p=0.011$). Glucose levels were increased by HAART (treatment effect, $p=0.036$), but the effect was associated to HCV coinfection (treatment*HCV effect, $p=0.018$). Gender, smoking habit, intravenous drug use and age were not significantly associated with cholesterol, triglyceride and glucose changes.

CONCLUSIONS: HCV-infected patients at baseline were significantly less likely to develop hypercholesterolemia. The results provide further evidence of the role of HAART for the development of metabolic disturbances.

DESCRIPTORS: HIV Infections, prevention & control. Anti-HIV Agents, adverse effects. Comorbidity. Hepatitis C. Lipid Metabolism. Cholesterol, blood. Epidemiologic Studies.

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RESUMO

OBJETIVO: Avaliar as alterações metabólicas associadas à terapia anti-retroviral potente em pacientes HIV-positivos e identificar fatores de risco associados.

MÉTODOS: Estudo retrospectivo com 110 pacientes HIV-positivos que estavam sob terapia anti-retroviral potente (HAART) na cidade de Porto Alegre (RS), entre janeiro de 2003 e março de 2004. Os dados coletados incluem variáveis demográficas, tabagismo, diabetes mellitus, níveis de colesterol e triglicerídeos, estágio da infecção viral, terapia anti-retroviral e co-infecção com hepatite C. A análise multivariada para medidas repetidas *(General Linear Model procedure for Repeated Measures)* foi utilizada para testar a interação entre o efeito do uso de HAART e o uso de inibidores de protease ou co-infecção por hepatite C.

RESULTADOS: Foram observados aumentos significativos nos níveis de colesterol total, triglicerídeos e glicose após o tratamento com HAART ($p<0.001$, para todas as variáveis). No entanto, nenhuma interação do tratamento com inibidores de protease foi observada para colesterol total, glicose e triglicerídeos (interação tratamento*inibidores de protease $p=0.741$, $p=0.784$ e $p=0.081$, respectivamente). Uma associação entre os níveis de colesterol total e co-infecção por HCV foi observada tanto antes como após o tratamento (efeito da co-infecção por hepatite C, $p=0.011$). Os níveis de glicose foram aumentados pelo uso da HAART (efeito do tratamento, $p=0.036$), sendo este dependente da co-infecção por hepatite C (efeito interação tratamento*hepatite C = 0.018). Gênero, tabagismo, uso de drogas intravenosas e idade não influenciaram significativamente os níveis de colesterol total, triglicerídeos e glicose durante o tratamento.

CONCLUSÕES: Pacientes infectados pelo vírus da hepatite C no início do tratamento tiveram aumento menos significativo nos níveis de colesterol total. Os resultados reforçam as evidências do papel da HAART no desenvolvimento de desordens metabólicas.

DESCRITORES: Infecções por HIV, prevenção & controle. Agentes Anti-HIV, efeitos adversos. Comorbidade. Hepatite C. Metabolismo dos Lipídeos. Colesterol, sangue. Estudos Epidemiológicos.

INTRODUCTION

Adverse drug reactions are one of the important factors associated with reduced quality of life among HIV-infected patients taking highly active antiretroviral therapy (HAART).[18] Abnormalities in lipid metabolism make HIV-positive patients subject to high risk for the development of coronary heart disease.[2] The mechanisms responsible for metabolic changes of anti-HIV drugs are not fully understood. Increases in serum triglycerides, low-density lipoproteins (LDL), and total cholesterol have been reported as well as the development of insulin resistance.[5]

Lipid disturbances in HIV patients receiving protease inhibitor (PI) treatment are more evident.[13] Deeks et al[7] (1997), in a 32-week study, identified persistent elevations in cholesterol of 30%–40% from baseline and in triglycerides of 200%–300% from baseline. It has been reported that ritonavir increases the production of very low-density lipoprotein cholesterol (VLDL), triglycerides, and apolipoprotein (apo) B in HIV-negative subjects indicating that treatment with this protease inhibitor in the absence of HIV infection can cause dyslipidemia.[19] These observations have motivated researchers to investigate whether it is safe to switch patients with a PI-based regimen and optimal viral suppression to a simplified maintenance therapy (SMT) to reduce side effects and metabolic disturbances.[4]

The objective of the present study was to describe both metabolic changes associated with HAART and risk factors associated in HIV-positive patients.

METHODS

A retrospective cohort study was conducted including 110 HIV-positive subjects who were on HAART at a reference laboratory in the city of Porto Alegre,

Southern Brazil. Of all 200 subjects, we selected all subjects with at least one follow-up lipid profile between January 2003 and March 2004. Data (drug treatments, symptoms, HAART duration, time of HIV exposure or HIV diagnosis, laboratory results, and patient demographics) were collected through local database search. Data for hepatitis C virus (HCV) and tuberculosis coinfection were identified by laboratory testing. The diagnoses of diabetes and hypertension were defined as specific guidelines.[20,21] Further exclusion criteria were secondary hyperlipidemia due to renal, hepatic or thyroid disease, and diabetes or fasting blood glucose levels above 110 mg/dL. Individuals that were on lipid-lowering medications were also excluded. Disease classification was based on the National Sexually Transmitted Diseases (STD) and AIDS Program of the Brazilian Ministry of Health.[a]

Continuous variables were expressed as mean (standard deviation, SD) or median (interquartile range) when no normal distribution was assumed. A general linear models procedure for repeated measures using type III sums of squares statistics was used to test the interaction between HAART and HCV coinfection or PI treatment. This sum of squares applies to unbalanced study designs and measures the effect of an independent variable (HCV coinfection or PI treatment) after adjustment for all other covariables included in the model. To test the interaction between HAART and HCV coinfection or PI treatment two different multivariate models were applied. Age, gender, CD4 levels, HIV-RNA measurements, HAART duration were included in both models as covariables. HCV coinfection was included as a covariable to test the interaction between HAART and PI treatment and PI treatment was included as a covariable to test the interaction between HAART and HCV coinfection. A 5% significance level was set. All statistical analyses were performed using the SPSS package v. 13.0.

The study was approved by the Ethics Committee of Fundação Estadual de Produção e Pesquisa em Saúde (nº 2004-373H). Written informed consent was obtained from all subjects.

RESULTS

Table 1 shows the demographic characteristics, concomitant diseases and lipid, glucose, CD4 and HIV-RNA measurements of HIV-positive subjects taking non-nucleoside reverse transcriptase inhibitors

Table 1. Baseline characteristics of subjects treated with highly active antiretroviral therapy (HAART). Porto Alegre, Southern Brazil, 2003–2004.

Characteristic	Overall n(%)[a]	NNRTI n(%)[a]	PI n(%)[a]
Number of subjects	110	86	24
Time of HIV exposure (months) [median (IQR)]	28 (25-32)	26 (24-31)	29 (27-32)
Follow-up duration (months) [median (IQR)]	14 (2-16)	13 (4-16)	14 (2-16)
Female sex	55 (49.5)	40 (46.5)	14 (58.3)
Age (years) [mean (SD)]	37.2 (9.5)	37.7 (10.0)	34.8 (7.3)
Source of HIV exposure			
Intravenous drug use	28 (25.2)	21 (24.4)	7 (29.2)
Homosexual	15 (13.5)	10 (11.6)	5 (20.9)
Heterosexual	59 (53.2)	46 (53.5)	12 (50.0)
Transfusion	5 (4.5)	5 (5.8)	0 (0.0)
Other	4 (3.6)	4 (4.7)	0 (0.0)
CD4 cells/mm^3 [median (IQR)]	225 (164-289)	225 (174-289)	225 (136-301)
HIV-RNA log10 copies/mL [median (IQR)]	4.3 (3.7-4.8)	4.2 (3.7-4.7)	4.5 (3.9-4.9)
Current smoker	59 (54.1)	43 (51.2)	15 (62.5)
Hypertension	3 (3.5)	2 (3.0)	1 (5.6)
Diabetes mellitus	2 (2.4)	2 (3.0)	0 (0.0)
Tuberculosis	15 (13.5)	13 (15.1)	2 (8.3)
Hepatitis C	19 (22.4)	15 (22.4)	4 (22.2)

[a] Except where indicated otherwise.
NNRTI: non-nucleoside reverse transcriptase; PI: protease inhibitors; IQR: interquartile range; SD: Standard deviation

[a] Ministério da Saúde. National Sexually Transmitted Diseases (STD) and AIDS Programme.[cited 2007 Mar 03]. Brasília; Available from: http://www.aids.gov.br, 2007

Table 2. Non-nucleoside reverse transcriptase and protease inhibitor-containing regimens used in the study. Porto Alegre, Southern Brazil, 2003–2004.

HAART	Regimen	n (%)
NNRTI (n=86)	EFV + 3TC + AZT	54 (62.8%)
	EFV + 3TC + d4T	17 (19.8%)
	NVP + AZT + 3TC	13 (15.1%)
	EFV + 3TC + TNF	1 (1.2%)
	NVP + 3TC + d4T	1 (1.2%)
PI (n=24)	NFV + AZT + 3TC	10 (41.7%)
	LPV + RTV + AZT + 3TC	7 (29.2%)
	ATV + AZT + 3TC	3 (12.5%)
	NFV + d4T + 3TC	2 (8.3%)
	LPV + RTV +TC + ABC	2 (8.3%)

NNRTI: non-nucleoside reverse transcriptase; AZT: zidovudine; ATV: atazanavir; EFV: efavirenz; NVP: nevirapine; 3TC: lamivudine; d4T: estavudine; TNF: tenofovir; NFV: nelfinavir, LPV: lopinavir; RTV: ritonavir; ABC: abacavir; PI: protease inhibitors

(NNRTI group) and protease inhibitors (PI group). The median follow-up was 14 months (interquartile range 2-16 months). Overall, 54 subjects (49%) were female and mean age was 37 years (SD =10 years, median = 36 years). The therapy group receiving NNRTI-containing HAART included 86 subjects, while the group receiving PI treatment consisted of 24 subjects. Mean CD4 cell count was 225/mm^3 in both groups. The most frequent concomitant diseases were: hypertension (3.5%), diabetes mellitus (2.4%), tuberculosis (13.5%), and hepatitis C (22.4%). None of the variables differed between NNRTI group and PI group (p>0.05 for all comparisons).

Details on the antiretroviral drugs used in the study are given in Table 2. The NNRTI-containing regimen including zidovudine, lamivudine and efavirenz was the most frequently prescribed (62.8%). For PI-containing regimens, the most common combination was zidovudine, lamivudine, and nelfinavir (41.7%).

Total cholesterol >200 mg/dL was seen only in 7.2% of subjects at baseline, and in 25.5% of subjects on HAART. Similar results were found for triglyceride and glucose levels. Triglyceride levels >150 mg/dL were seen in 20.9% of subjects at baseline and in 32.7% during follow-up. Eight percent and 20.0% of subjects were hyperglycemic (glucose >110 mg/dL) at baseline and during follow-up, respectively. There were no risk differences between PI and NNRTI treatments for the development of hypercholesterolemia (RR=0.78, 95% CI = 0.33;1.83), hyperglycemia (RR=1.05, 95% CI = 0.43;2.56) or hypertriglyceridemia (RR=1.37, 95% CI = 0.78;2.44) during follow-up. Similar results were found for HCV coinfection (Table 3).

Table 4 and the Figure provide adjusted lipid and glucose levels at baseline and follow-up for PI treatment and HCV coinfection. There were significant increases in total cholesterol, triglyceride and glucose levels after receiving HAART (effect of treatment, p<0.001 for all variables), but no interaction with PI treatment was seen for total cholesterol (interaction treatment*PI p=0.741, Figure 1A), glucose (interaction treatment*PI p=0.784, Figure 1B) or triglyceride levels (interaction treatment*PI p=0.081, Figure 1C).

Table 3. Incidence and relative risk for total cholesterol >200 mg/dL, glucose >110 mg/dL and triglyceride >150 mg/dL. Porto Alegre, Southern Brazil, 2003–2004.

Variable	n	TC >200 mg/dL	Glucose >110 mg/dL	TG >150 mg/dL
Overall	110			
Baseline		8 (7.2%)	9 (8.1%)	23 (20.9%)
Follow-up		28 (25.5%)	22 (20.0%)	36 (32.7%)
Follow-up				
PI treatment				
No	86	23 (26.7%)	17 (19.8%)	26 (30.2%)
Yes	24	5 (20.8%)	5 (20.8%)	10 (41.7%)
RR (95% CI)[a]		0.78 (0.33;1.83)	1.05 (0.43;2.56)	1.37 (0.78;2.44)
HCV coinfection				
No	92	26 (28.3%)	20 (21.7%)	32 (34.8%)
Yes	18	2 (11.1%)	2 (11.1%)	5 (27.8%)
RR (95% CI)[a]		0.39 (0.10;1.52)	0.51 (0.13;1.99)	0.79 (0.36;1.77)

[a] Relative risk (95% confidence interval)
TC: total cholesterol
TG: triglycerides
PI: protease inhibitor
HCV: hepatitis C virus

Table 4. Estimated marginal means for total cholesterol, glucose and triglyceride levels analyzed by general linear models procedure for repeated measures. Porto Alegre, Southern Brazil, 2003–2004.

Variable	Category	Mean (SD)	n	Effect	p-value
Protease inhibitor					
TC					
No	Baseline	153.4 (37.0)	86	Treatment	<0.001
	Follow-up	177.3 (37.4)		PI	0.558
Yes	Baseline	156.3 (38.3)	24	Treatment*PI	0.741*
	Follow-up	183.3 (43.6)			
Glucose					
No	Baseline	92.5 (17.9)	86	Treatment	<0.001
	Follow-up	100.6 (14.4)		PI	0.631
Yes	Baseline	91.7 (8.1)	24	Treatment*PI	0.784*
	Follow-up	98.7 (11.2)			
TG					
No	Baseline	122.4 (62.4)	86	Treatment	<0.001
	Follow-up	147.4 (125.9)		PI	0.776
Yes	Baseline	109.6 (42.4)	24	Treatment*PI	0.081*
	Follow-up	164.5 (141.4)			
HCV coinfection		TC			
TC					
No	Baseline	156.6 (37.4)	92	Treatment	<0.001
	Follow-up	183.0 (38.5)		HCV	0.011
Yes	Baseline	141.7 (33.2)	18	Treatment*HCV	0.292*
	Follow-up	157.3 (31.8)			
Glucose					
No	Baseline	91.4 (15.3)	92	Treatment	0.036
	Follow-up	100.9 (13.9)		HCV	0.790
Yes	Baseline	97.3 (19.8)	18	Treatment*HCV	0.018*
	Follow-up	96.7 (12.1)			
TG					
No	Baseline	120.8 (61.8)	92	Treatment	0.029
	Follow-up	156.6 (139.2)		HCV	0.732
Yes	Baseline	114.5 (39.2)	18	Treatment*HCV	0.397*
	Follow-up	124.9 (43.2)			

* Statistically significant
TC: total cholesterol
TG: triglycerides
PI: protease inhibitor
HCV: hepatitis C virus

These results show a HAART effect on metabolic changes regardless of the antiretroviral regimen used. The same approaches were applied to investigate the effects of HCV coinfection on lipid and glucose parameters. For HCV coinfection, after controlling for age, gender, CD4 levels, HIV-RNA measurements, HAART duration and PI treatment, significant increases in total cholesterol, triglyceride and glucose levels after receiving HAART (effect of treatment, $p<0.001$ for total cholesterol levels and $p<0.05$ for glucose and triglyceride levels) were evidenced. An association between total cholesterol levels and HCV coinfection was seen both at baseline and follow-up (effect of HCV coinfection $p=0.011$). At baseline, HCV-positive subjects had lower total cholesterol levels (141.7±33.2 mg/dL) than HCV-negative subjects (156.6±37.4 mg/dL). The same results were found during follow-up (157.3 ± 31.8 mg/dL and 183.0±38.5

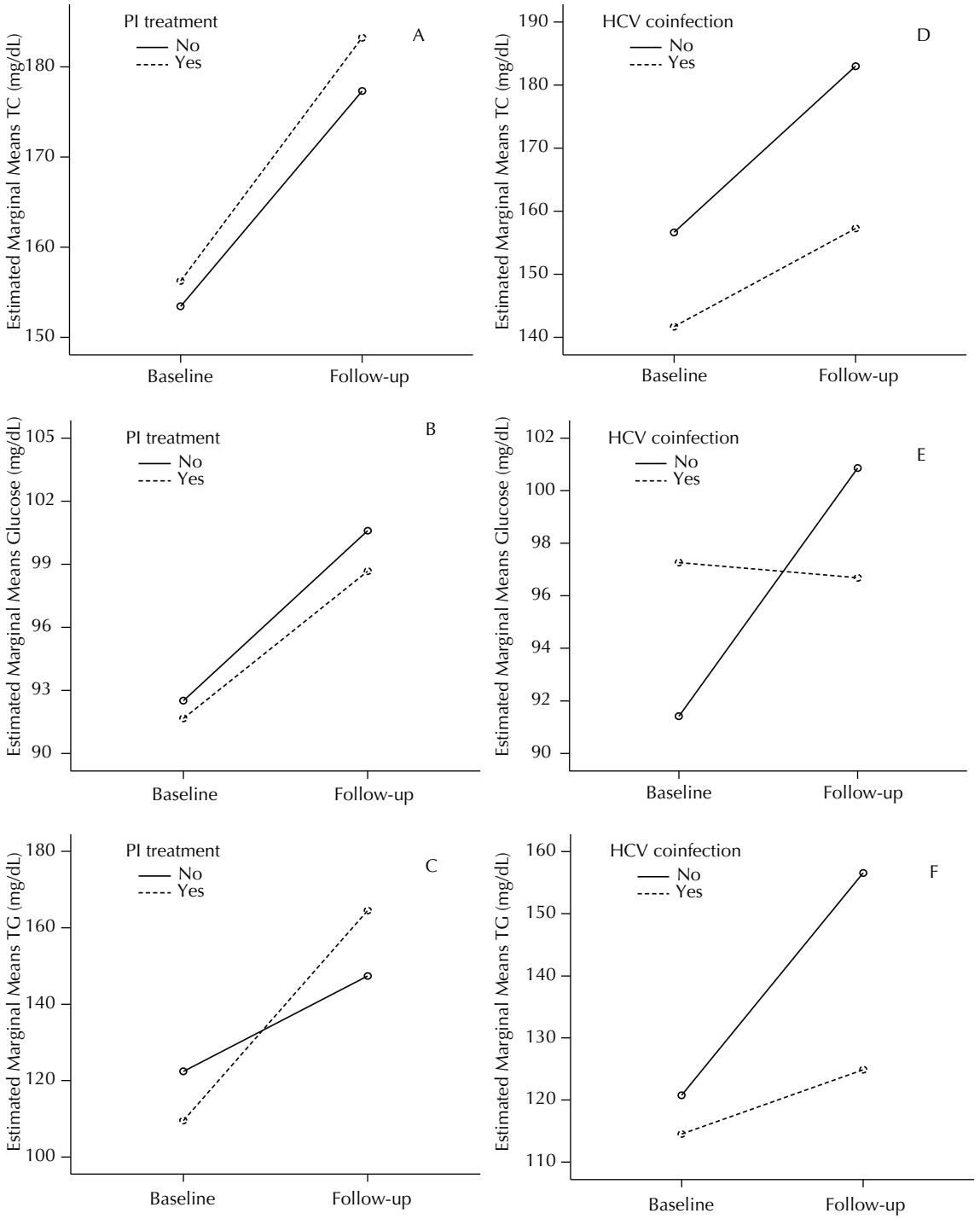

Figure. Adjusted marginal means for total cholesterol, glucose, and triglyceride levels (mg/dL) in antiretroviral-naïve subjects treated with HAART by PI treatment (A, B and C) and HCV coinfection (D, E and F). Porto Alegre, Southern Brazil, 2003–2004.

mg/dL, respectively), showing an effect of HCV coinfection on total cholesterol levels regardless of HAART (Figure 1D). Glucose levels were increased by HAART (treatment effect p=0.036), but the effect was associated to HCV coinfection. HCV-negative subjects showed an increase of 10.4% in glucose levels, whereas HCV-positive subjects had similar glucose levels regardless of HAART (effect of HCV coinfection*treatment = 0.018, Figure 1E). No effect of HCV coinfection was seen for triglyceride levels (effect of HCV coinfection = 0.732, effect of HCV coinfection*treatment = 0.397, Figure 1F).

DISCUSSION

Data about the effect of HAART on metabolic changes in Brazilian HIV-positive patients are scarce. Data for other populations showed that multidrug antiretroviral therapy, including the use of protease inhibitors, is associated with dyslipidemia,[2-12,15] a well-recognized risk factor for the development of coronary artery disease.[10] Previous studies have indicated a broad variation in hypercholesterolemia and hypertriglyceridemia rates among HIV-positive patients on diverse highly-active antiretroviral therapy regimens. Lipid disorders are frequently associated with protease inhibitor treatment.[11] However, emerging evidences indicated an association between NNRTI-containing regimens and dyslipidemia and other metabolic changes.[11] Hypercholesterolemia has been seen in almost 30% of PI-treated subjects and 23% of NNRTI users, while hypertriglyceridemia has been seen in 40% and 32% of patients, respectively. In our study both PI-containing and NNRTI-containing HAART increased total cholesterol, triglyceride and glucose levels compared to baseline, regardless of PI-containing HAART. In our study nelfinavir was the most frequent PI used (50% of PI-containing regimens). A recent clinical trial comparing atazanavir with nelfinavir showed that the latter was more strongly associated to increases in total cholesterol, LDL-cholesterol and triglycerides.[16]

The role of HCV coinfection in the development of metabolic complications or in the response to antiretroviral treatment in HIV-positive patients remains incompletely understood. In our data, total cholesterol levels were significantly lower in HIV-HCV coinfected patients on antiretroviral therapy. Previous investigations reported that patients infected with hepatitis C at baseline were significantly less likely to develop hyperlipidemia.[6,5,17] Interestingly, the presence of HCV coinfection during HIV treatment was also associated to higher insulin resistance, activated platelets, endothelial perturbation[8] and lipodystrophy.[6,9] Moreover, HCV coinfection was associated to treatment discontinuation and interruption.[1,3,14] The mechanism underlying the protective effect of hepatitis C in the risk of developing hyperlipidemia is not known, but might reflect an impaired total cholesterol synthesis in the liver or total cholesterol hypercatabolism.

The limitations of our study include the retrospective cohort design (with high rates of missing data), disproportionately smaller number of patients in the PI-group, and absence of HIV-negative controls. In addition, data concerning other risk factors for coronary heart disease were not obtained in our study, including genetic factors, body mass index, plasma HDL and LDL levels, physical activity, and diet. To elucidate how antiretroviral therapy is associated to metabolic disturbances and could contribute to premature cardiovascular disease is of major importance. Therefore further research with larger sample size and detailed information regarding additional risk factors for coronary heart disease are necessary to better understand the effects of HAART.

In conclusion, our results provide further evidence of the role of HAART in lipid disorder development and emphasize the importance of analyzing the effect of antiretroviral therapy in different populations. In Brazil, the treatment of HIV-infected patients is provided by the government. Thus evidences found in our study may be useful to propose new guidelines for managing the metabolic changes during antiretroviral therapy. Moreover, our study found a significant relationship between HIV-HCV coinfection and HAART effects on total cholesterol and glucose levels. In this regard, further studies are needed to clarify the exact role of HCV infection in the induction of such abnormalities.

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