Metabolic Effects Associated to the Highly Active Antiretroviral Therapy (HAART) in AIDS Patients

Hamilton Domingos[1], Rivaldo Venâncio da Cunha[1], Anamaria Mello Miranda Paniago[1], Diego Mira Martins[2], Eduardo Brandão Elkhoury[2] and Albert Schiaveto de Souza[3]

[1]Clinical Medic Department of Mato Grosso do Sul Federal University; [2] Medicine Academic of Mato Grosso do Sul Federal University; [3]Statistical Department of Mato Grosso do Sul Dom Bosco Catolic University

The aim of this study was to evaluate the metabolic abnormalities (dyslipidaemia and insulin resistance) associated with highly active antiretroviral therapy (HAART) in AIDS patients, treated in Campo Grande, Mato Grosso do Sul, Brazil. The patients were distributed in five different groups: Group 1, HIV-infected without antiretroviral therapy; Group 2, with Zidovudine, Lamivudine and Efavirenz or Nevirapine; Group 3, with Zidovudine, Lamivudine and Protease Inhibitor; Group 4, with Stavudine, Lamivudine and Efavirenz or Nevirapine; and Group 5, with Stavudine, Lamivudine and Protease Inhibitor. The lipid and glucose profile were determined and statistics comparison was made. The findings of this study showed significant statistics elevations of total cholesterol and triglycerides levels in patients of Groups 3, 4 and 5, when comparing to patients of Groups 1 and 2. Significant differences were not observed between the groups in the others parameters evaluated: Glucose, HDL cholesterol and LDL cholesterol. Comparing two drugs of same class (NNRTI) through the subgroups II-efavirenz and II-nevirapine, significant differences in the serum levels of total cholesterol, triglycerides and glucose favorable to the subgroup II-NVP were observed. These findings suggest that combinations including Protease Inhibitors and/or Stavudine could cause more adverse metabolic effects, and if possible, should be avoided in patients with others cardiovascular risk factors to prevent the precocious atherosclerosis in AIDS patients receiving HAART.

Key-Words: AIDS, HAART, metabolic effects, dyslipidaemia, insulin resistance.

Highly active antiretroviral therapy (HAART) has dramatically improved the life expectancy of patients with human immunodeficiency virus (HIV). Specific toxicities cited for HAART include elevations in serum levels of total cholesterol and triglycerides, reduction in high-density lipoprotein cholesterol (HDL chol.), alterations in the distribution of body fat, increase in insulin resistance and diabetes, which are major risk factors for cardiovascular disease (CVD). There is general consensus that the benefits of HAART far outweigh toxicity-related risks of the treatment with HAART. However prolonged survival among HIV-infected patients will likely need to use different antiretroviral regimens with potentially less cardiovascular toxicity in the future[1].

The clinical importance of these metabolic abnormalities is demonstrated by the increased prevalence of cardiovascular disease and diabetes in AIDS patients. In general, the available data do not define a single, definable etiology or mechanism explaining these clinical conditions. They suggest that these conditions are caused by a complex interaction potentially involving such things as the side effects of medications, alteration of immune function, and individual subject characteristics, such as body weight and baseline lipid level [2].

In accordance with the HAART regimen being used, changes are observed in body fat distribution (lipodystrophy). Lipodystrophy occurs in 25%-60% of patients receiving different HAART regimens containing IP after 1 - 2 years of therapy. However, these changes occur in significantly smaller frequency with HAART regimens containing non-nucleoside analog reverse transcriptase inhibitors (NNRTI) [3]. The changes body fat acquire several forms including the peripheral fat loss (lipoatrophy) in the face, limbs and buttocks, accompanied by central fat accumulation in the abdomen and breasts and over the dorso-cervical spine [4]. The increase of abdominal circumference occurs because of increase of the adiposity visceral. This increase is independent risk factor for several cardiovascular events in patients non HIV infected [5].

Hurwitz et al. found that, although it is likely that the greatest proportion of coronary heart disease risk in the HIV patients, may be accounted for by pathological conditions linked to HIV infection in interaction with mediating processes such as inflammation, central obesity and dyslipidaemia, which was greater than in controls, it appears that protease inhibitors medications may exacerbate oxidative stress and hypertriglyceridaemia to enhance this risk [6].

Both, protease inhibitors (PI) and nucleoside analog reverse transcriptase inhibitors (NRTI) appear to be involved, through direct metabolic effects and an indirect effect of PI and NRTI-related lipodystrophy [7].

Dyslipidaemia occurs in up 70%-80% of HIV- infected individuals receiving HAART and can be associated with all the available PI, although hypertriglyceridaemia appears to be more frequent in patients treated with ritonavir, saquinavir/ritonavir or lopinavir/ritonavir. The potential long-term consequences of HAART-associated hyperlipidaemia are not completely understood, but an increased risk of premature coronary artery disease has been reported in young HIV-positive persons receiving PI. Lipid lowering therapy is often required with statins or fibrates [8].

HAART itself causes in a high proportion of patients a metabolic syndrome, characterized by lipodystrophy,

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Address for correspondence: Dr. Hamilton Domingos. Jintoku Minei street, 179 – Ap. 2801. Zip code: 79021-450. Campo Grande, MS, Brazil. E-mail: hmdomingos@brturbo.com.br.

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dyslipidaemia and insulin resistance, that may be associated with an increase in coronary artery disease and stroke. Careful cardiovascular evaluation in course of HIV disease can identify cardiac complication enough to treat. All HIV- infected patients are candidates antiretroviral therapy and patients already under treatment should undergo an assessment that includes the evaluation the cardiovascular risk according to the available guideline [9].

This study had principal objective to evaluate in AIDS patients the incidence of adverse metabolic effects (dyslipidaemia and insulin resistance) HAART-associated, comparing the antiretroviral combinations more frequently used, establishing which combinations or specific drugs could be more associated with these adverse metabolic effects. This knowledge could contribute to the more rational choice of HAART regimen for AIDS patients. It is very important to have special attention to the others atherosclerosis risk factors added to the HAART metabolic effects because they can cause more premature atherosclerosis in AIDS patients.

Material and Methods

This study evaluated prospectively (n=235) or retrospectively (n=57) HIV infected and AIDS patients, attended in infectious diseases ambulatory of University Hospital and Infectious and Parasitic Diseases Center of Campo Grande, Mato Grosso do Sul state, Brazil, between March 2005 and July 2006.

The 292 patients chosen were adults with lipid profile and glucose dosed before and after HAART, distributed in five groups:

GROUP 1 (n=23): Control group - HIV infected without HAART;
GROUP 2 (n=92): Receiving AZT + 3TC or ddI + NVP or EFZ;
GROUP 3 (n=109): Receiving AZT + 3TC or ddI + PI*
GROUP 4 (n=15): Teceiving d4T + 3TC or ddI + NVP or EFZ
GROUP 5 (n=53): Receiving d4T + 3TC ou ddI + PI*

AZT= Zidovudine; 3TC= Lamivudine; ddI= Didanosine; NVP= Nevirapine; EFZ= Efavirenz; PI= Protease Inhibitor; d4T= Stavudine; *Protease Inhibitors used: LPV/r= Lopinavir/Ritonavir; NLV= Nelfinavir; IDV= Indinavir; ATV= Atazanavir.

To compare the metabolic effects between two drugs, NVP and EFZ, from the same class (non nucleosides reverse transcritpase inhibitors), the Group 2 was divided in two subgroups: 2-EFZ (n=73) and 2-NVP (n=19).

Averages between two or more consecutive measures of metabolic parameters (Fasting Total cholesterol, HDL cholesterol, LDL cholesterol, Triglycerides and Glucose) were obtained from these researched groups. These evaluated parameters were considered altered when the Total cholesterol up to 220 mg/dL, LDL cholesterol up to 130 mg/dL, Triglycerides up to 150 mg/dL and HDL cholesterol down to 40 mg/dL, in accordance with NCEP-ATP III [10], and Glucose up to 100 mg/dL, in accordance with American Diabetes Association [11].

Only the retrospectively evaluated patients with one dosage before and two dosages after HAART were included. The patients prospectively evaluated were submitted to one dosage before and three consecutive dosages after HAART, with minimum interval of thirty days between the dosages.

The lipodystrophy and obesity prevalences and the others risk factors cardiovascular disease including tobacco and systemic arterial hypertension were observed. The diagnosis of lipodystrophy was done through ectoscopy examination. The reduction of subcutaneous fat in face, limbs and buttocks was considered as lipoatrophy criteria. Lipohypertrophy was diagnosed when abdominal circumference was greater than 80 cm in women and greater than 94 cm in men, or still when accumulation of subcutaneous fat was observed in dorso-cervical region.

Patients with genetic dyslipidaemia, diabetes mellitus before of the HAART, drugs or alcohol usurious, with tireoide, kidney or hepatic diseases, in use of corticosteroids, androgenos, estrogenos, tiazidics diuretics or beta-blocks were excluded, because these situations are associated to alterations of lipid and glucose levels. The patients that interrupted or changed HAART regimen during the evaluation period were excluded too.

The comparison between the different HAART regimens, from the evaluated metabolic parameters, was made for the ANOVA test, and after Tukey test. To realize the statistical analysis, the data were transformed in $\log_{10}$, so that they could be more homogeneous in each group. The comparison between the HAART regimens, in relation to percentual of the cases, in each altered parameter, was made by the Z test. The comparison between the HAART regimens, to the variables age, body mass index (BMI) and time of treatment, was made by the Kruskal-Wallis test. The statistical analysis was made using the Sigma Stat Software, version 2.0, being considered significant differences when the p value was smaller than 0.05 [12].

The project of this study was approved by the Ethic in Research Committee of Mato Grosso do Sul Federal University (number 510/2005).

Results

Patient population descriptive data on gender, age, race and others epidemiological and clinics data were recorded (Table 1). The comparison between the groups didn't show significant differences in age (Kruskal-Wallis, p=0.172), in time of HAART (Kruskal-Wallis, p=0,127), and in the body mass indexes (Kruskal-Wallis, p=0.082).

Thirty nine patients were excluded of this study: the modification of the HAART, 10 cases; or the interruption, 6 cases; genetic dyslipidaemia, 6 cases; tireoide disfunction, 5 cases; diabetes mellitus, 5 cases; anti-hypertensive treatment with beta-blockade, 3 cases; with tiazidic diuretics, 2 cases; and, hormonal reposition therapy with estrogenio, 2 cases.

Among the patients receiving HAART, controlled immunological (CD4 lymphocytes > 200 cells/mm^3) and

Table 1. Epidemiologic and clinics aspects.

Variables	Freqüences
Gender (male/female)	175/117
Age (years) mean (range)	41,13 (18-75)
Race(white/mulatto/black)	101/170/21
Mean time of HIV infection (months)	46.6
Mean time of HAART (months)	40.4
Lipodystrophy patients, n (%)	47 (16.1%)
Overwheight or obesity patients (IMC>25), n (%)	98 (33.6%)
Smooking patients n (%)	45 (15.4%)
Hypertension patients n (%)	43 (14.7%)
Coronary artery disease patients n (%)	6 (2.1%)

Figure 1. Graphic ilustrating the serum level (mg/dL) of the parameters evaluated in groups. The columns represent mean values and the bars the standard error of mean. * Significative differences in relation to the Group 1 (G-1); ** Significative differences in relation to the Groups 1 e 2 (G-1 e G-2). *** Significative differences in relation to the Groups 1, 2 e 3 (G-1, G-2 e G-3). ANOVA of one way, and after-test of Tukey, p<0.05.

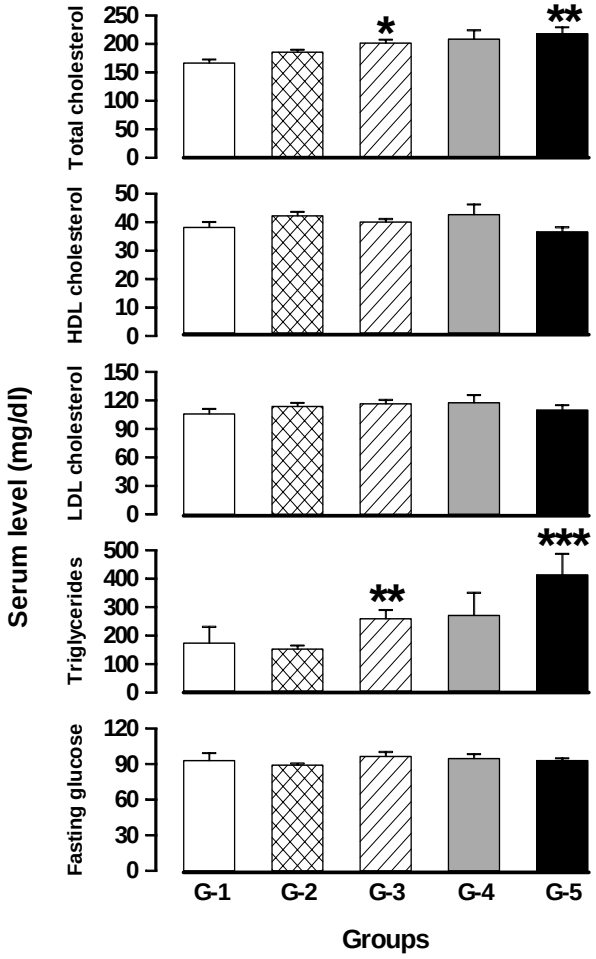
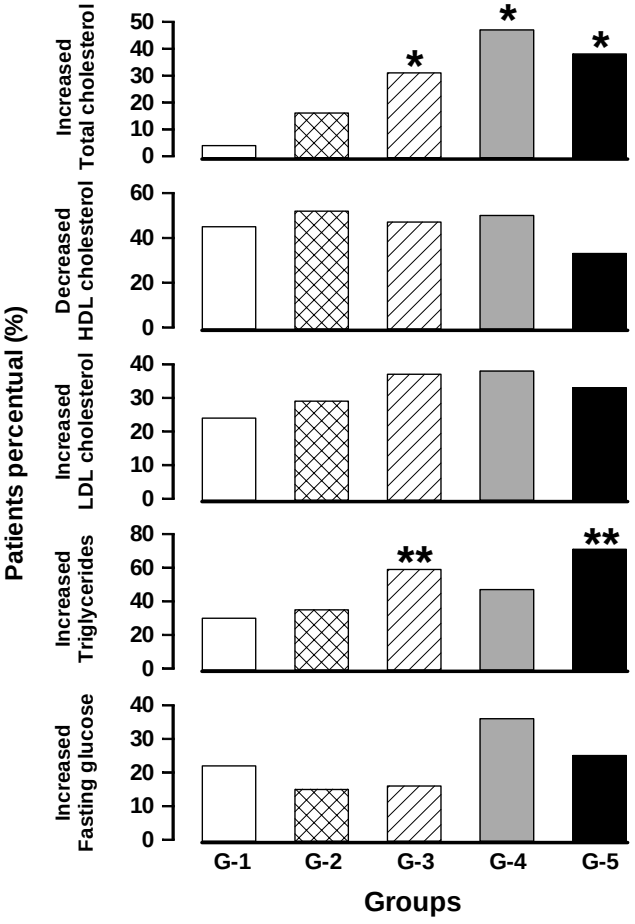


Figure 2. Graphic illustrating the percentual of patients with abnormal parameters in groups studied. The columns represent the percentual of patients. * Significant differences in relation to the Group 1 (G-1), to the same variable. ** Significant differences in relation to the Group 2 (G-2), to the same variable. (Z Test, p<0,05).



virological (viral load down to 80 copies/mL) were: 77(83,7%) of Group 2, 92 (84,4%) of Group 3, 13 (86,7%) of Group 4 and 45 (84,9%) of Group 5, without significant differences between the groups.

The average of metabolic parameters (total cholesterol, HDL and LDL cholesterol, triglycerides and fasting glucose in Groups 1, 2, 3, 4 and 5 were recorded (Table 2). The comparison between the groups showed significant differences between them (ANOVA of one way, p=0.004), being the total cholesterol level in Group 5 significantly greater than in Groups 1 and 2. Total cholesterol level in Group 3 was significantly greater than in Group 1 (Tukey test, p<0.05). In relation on triglycerides, the comparison between the groups showed significant differences between them (ANOVA of one way, p<0.001), being the triglycerides levels in Group 5 significantly greater than in Groups 1, 2 e 3. The triglycerides levels in Group 3 were significantly greater than in Groups 1

Table 2. Mean seric levels of metabolic parameters.

Parameters	Group 1 (n=23) (mean+std error)	Group 2 (n=92) (mean+std error)	Group 3 (n=109) (mean+std error)	Group 4 (n=15) (mean+std error)	Group 5 (n=53) (mean+std error)
Total Chol. (mg%)	166,39 +6,27	185,37 +4,14	201,54 +5,97	208,33 +15,63	217,87 +11,46
HDL chol. (mg%)	38,18 +1,86	42,22 +1,38	40,02 +1,11	42,64 +3,62	36,55 +1,72
LDL chol. (mg%)	105,67 +5,46	113,26 +3,65	116,53 +4,19	117,46 +8,48	109,84 +5,43
Triglycerides (mg%)	173,65 +57,24	152,26 +12,77	259,78 +30,01	270,80 +80,52	413,87 +74,11
Fasting Gluc. (mg%)	92,74 +6,61	89,06 +1,37	96,39 +3,93	94,79 +3,73	92,93 +2,10

Table 3. Percentual of cases to each variable in different groups of HAART.

Metabolic parameter	Classification	Percentual of cases to each group (%) (N)				
		G-1	G-2	G-3	G-4	G-5
Total cholesterol	Normal	96% (22)	84% (77)	69% (75)	53% (8)	62% (33)
	Increased	4% (1)	16% (15)	31%* (34)	47%* (7)	38%* (20)
HDL -cholesterol	Normal	55% (12)	48% (41)	53% (54)	50% (7)	67% (33)
	Decreased	45% (10)	52% (44)	47% (48)	50% (7)	33% (16)
LDL-cholesterol	Normal	76% (16)	71% (60)	63% (59)	62% (8)	67% (30)
	Increased	24% (05)	29% (24)	37% (34)	38% (5)	33% (15)
Triglycerides	Normal	70% (16)	65% (60)	41% (44)	53% (8)	29% (15)
	Increased	30% (7)	35% (32)	59%** (64)	47% (7)	71%** (37)
Fasting Glucose	Normal	78% (18)	85% (77)	84% (87)	64% (9)	75% (40)
	Increased	22% (5)	15% (14)	16% (17)	36% (5)	25% (13)
Lipodystrophy	Present	0% (0)	5% (5)	14% (15)	33% (5)	42% (22)
Overweight or Obesity	Present	39% (9)	29% (27)	40% (44)	13% (2)	30% (16)

* Significative difference in relation to the Group 1, to the same variable (Z test, p<0,05); **Significative difference in relation to the Group 2, to the same variable (Z test, p<0,05).

Table 4. Metabolic parameters and patients percentual with alterations in subgroups EFZ and NVP

Parameters	Tcol. mg/dL	Tcol> (%)	HDL mg/dL	HDL< (%)	LDL mg/dL	LDL> (%)	TG mg/dL	TG> (%)	Glu mg/dL	Glu> (%)
Subgroups										
EFZ (n=73)	189.0	39.7	41.2	52.2	116.0	25.8	162.9	39.7	90.5	19.4
NVP (n=19)	162.0	11.1	44.2	35.3	99.9	11.8	110.0	16.7	82.8	0.0
p	0.005	0.04	0.38	0.33	0.09	0.37	0.02	0.12	0.03	0.09

T col= total cholesterol; HDL= HDL cholesterol; nl= normal; mg/dL= milligram/decilitre; LDL= LDL cholesterol; TG= triglycerides; Glu= glucose.

and 2 (Tukey test, p< 0.05). HDL and LDL cholesterol and glucose didn't present significant differences in the comparison between the groups (Figure 1).

The percentual of the patients that presented increased total cholesterol, LDL cholesterol, triglycerides or glucose and decreased HDL cholesterol were recorded (Table 3). The percentual of the patients with increased total cholesterol in Groups 3, 4 and 5 was significantly greater than in Group 1 (Z test, p varying of 0.005 to 0.021). The percentual of the patients with triglycerides levels above to the normal limits in Groups 3 and 5 was significantly greater than in Group 2 (Z test, p varying of 0.006 to 0.045) (Figure 2).

The percentual of the patients with altered HDL and LDL cholesterol and glucose didn't present significant differences between the groups (Z test, p>0.05) (Figure 2).

Lipodystrophy was observed in 47 patients. The prevalence was significantly greater in Groups 4 and 5 (Table 3). It was observed: isolated lipoatrophy in 14 cases (29,8%), isolated lipoaccumulation in 3 cases (6,4%) and mixed form in 30 cases (63,8%).

The overweight or obesity prevalence was recorded (Table 3) and a significant difference between groups didn't occur.

When comparing two drugs from the same class (NNTRI) through the subgroups 2-EFZ and 2-NVP, significant differences in the serum levels of total cholesterol, triglycerides and glucose were observed. HDL and LDL cholesterol presented more changes in the subgroup 2-EFZ, but the differences were not significant statistically (Table 4).

Still in the comparison between the subgroups 2-EFZ and 2-NVP, considering the percentual of the patients that

presented altered metabolic parameters, only total cholesterol was significantly greater in the subgroup 2-EFZ, p=0.04. In relation to the others metabolic parameters evaluated, non significant statistical differences were found favorable to the subgroup 2-NVP (Table 4).

In synthesis, this study found significant statistically elevations of cholesterol total and triglycerides levels in Groups 3 (AZT + 3TC + PI) and 5 (d4T + 3TC + PI), when compared to the groups I (control group-HIV infected without HAART) and 2 (AZT + 3TC + EFZ or NVP). The same result was obtained in relation to the lipodystrophy prevalence, when comparing the five groups. There was not significant statistically differences between the others evaluated parameters: HDL-cholesterol, LDL-cholesterol and Glucose. The comparison between EFZ and NVP associated to AZT and 3TC showed advantages in using NVP.

Discussion

The Metabolic Syndrome is a complex disturbance represented for a whole of cardiovascular risk factors, usually associated to the central adiposity, dyslipidaemia and insulin resistance. It's important to detect the association of this syndrome with the cardiovascular disease, elevating the general mortality in approximately 1,5 times and the cardiovascular mortality in approximately 2,5 times [13]. The prevalence of this syndrome, considering the diagnosis criterions of NCEP / ATP III (National Cholesterol Education Program / Adult Treatment Panel III) [10], was estimated in 23,7 % of American adult population, affecting approximately 43% of the population with age above to 60 years old [14]. More recently, was found a prevalence of 32% in American adult population, demonstrating notorious increase in general population [15].

In this study, the data regarding to the total cholesterol levels in Groups 3, 4 and 5 were elevated in patients percentual in concordance with the literature data, reaching prevalence that ranges from 31% to 47%, when receiving HAART regimens including Protease Inhibitors (PIs) or Stavudine. The prevalence of hypertriglyceridaemia also was elevated, and ranged from 47% to 71 % in these patients (Figure 2). These data show a significative increase in prevalence of dyslipidaemia in patients in HAART, when compared to the general population, reaching almost the double of this prevalence.

Calza et al. found that in patients who receive a PI-containing antiretroviral regimen, the prevalence of hyperlipidaemia ranges from 28% to 80%, and it includes hypertriglyceridaemia in the majority of cases (40%-80%), followed by hypercholesterolaemia (10%-50%) [8].

Dubé et al. observed that use of PIs has been associated with hyperlipidaemia that is more common and more severe than what was observed before the advent of HAART. Sixty-two patients (47%) of 133 PI-recipients at one clinic had lipid abnormalities that met the 1994 NCEP intervention criteria [16].

In the Swiss HIV Cohort, hypercholesterolaemia and hypertriglyceridaemia were 1,7 - 2,3 times more common among individuals receiving HAART that contained a PI [17]. Hypercholesterolaemia (cholesterol level >240 mg/dL) and severe hypertriglyceridaemia (triglyceride level > 500 mg/dL) occurred in 60% and 75 % of subjects, respectively, receiving PIs at one center, with respective incident dyslipidaemia rate ratios of 2.8 and 6.1 attributable to use of these medications [18].

Several pathophysiologic models have been proposed to explain the development of dyslipidaemia in HIV-infected patients, involving several proposed interactions between the virus, antiretroviral therapies, and host factors. In one model, protease inhibitors, through various proposed actions, cause increased activity of sterol regulatory element-binding protein (SREBP), which alters adipocyte differentiation (contributing to lipodystrophy) and reduces leptin levels. In hepatocytes, SREBP induces lipogenic genes, which leads to increased hepatic very-low-density lipoprotein production. The increased lipid levels and reduced leptin levels, in turn, cause insulin resistance, which further activates SREBP, thus perpetuating the cycle [19].

A direct atherogenic effect of HIV infection itself or antiretroviral drugs is unlikely. Epidemiological studies suggested an increased risk for coronary artery disease in HIV infected persons; nevertheless, only long term follow-confirm this statement. Despite these uncertainties, it is reasonable to identify and manage cardiovascular risks of HIV infected patients [20].

Mondal et al. demonstrated that the oxidative stress can disrupt endothelial homeostasis by dysregulating the balance between pro and anti atherogenic factors. The chronic exposure to HAART results in endothelial oxidative stress and activation of mononuclear cells recruitment, an early event in atherosclerosis [21].

The results of this study, bigger prevalence of dyslipidaemia in Groups 4 and 5 suggest that the class of protease inhibitors and stavudine are the antiretroviral drugs more frequently associated to hypercholesterolaemia and hypertriglyceridaemia. Therefore, these drugs could be avoided or switched in AIDS patients with increased risk of cardiovascular disease.

In a prospective, randomized study reported in abstract form, antiretroviral-naïve subjects who initiated therapy with stavudine-lamivudine-nelfinavir had significant increases in total cholesterol. LDL-cholesterol and triglyceride levels, compared with subjects receiving zidovudine-lamivudine-nelfinavir [22]. Elevations in fasting triglyceride levels were more common in association with stavudine-didanosine-indinavir than with zidovudine-lamivudine-indinavir in a published randomized study [23]. The nucleoside reverse-transcriptase inhibitor (NRTI) tenofovir was associated with smaller increases in cholesterol and triglycerides levels than was stavudine, as published in a recent abstract [24]. Dubé et al. conclude that additional data are needed before any firm conclusions can be drawn regarding the relative tendencies

of individual nucleoside analogues to alter lipid profiles [16]. In relation to the lipid profiles observed in Group 2 of this study (patients received zidovudine, lamivudine, and nevirapina or efavirenz), also there was concordance with literature data, that show less repercussion on lipid profiles when compared with regimens containing PIs.

The nonnucleoside reverse-transcriptase inhibitors (NNRTIs) cause alterations in the lipid profiles, although generally to a lesser degree than has been observed with PIs. NNRTI use is associated with substantial increase in HDL- cholesterol levels to a degree not generally seen with PIs [25]. In a direct comparison between two NNRTIs reported in abstract form, nevirapine recipients had smaller increases in triglyceride levels, greater increases in HDL-cholesterol levels, and larger decreases in the ratio of total cholesterol to HDL-cholesterol than did efavirenz recipients, although the differences were relatively small in magnitude [26].

This study didn't find significant differences in HDL-cholesterol, LDL-cholesterol and glucose levels between the five groups, although these differences were reported in literature data. Maybe for the your smaller magnitude, these differences didn't have been detected in this sample of patients. However, statistical comparison, considering only patients of Group 2, divided in subgroups EFZ and NVP, showed favorable to NVP in relation to the adverse metabolic effects, being found lesser repercussion on lipid and glucose profiles, but these differences only were significant statistically to total cholesterol, triglycerides and fasting glucose. Although had been observed favorable differences to NVP also in the parameters HDL cholesterol and LDL cholesterol, these weren't significant statistically.

In relation on insulin resistance, the data obtained in this study didn't show significative differences between the groups, although prevalence of 36% had been observed in group IV (estavudine, lamivudine and NNRTI) compared with prevalence of 22% in Group 1 (sem HAART). Insulin resistance or diabete were more frequent in AIDS patients in HAART when associated to changes in body fat distribution, especially in patients with central obesity.

The insulin resistance occurs in approximately 30% of patients receiving HAART regimens based in IPs, and diabetes mellitus occurs in 4%-8 % [27,28]. Ritonavir has less probability to cause insulin resistance, therefore indinavir causes frequently; atazanavir is rarely associated to insulin resistance or dyslipidaemia [29].

Montessori et al. found that new-onset diabetes mellitus, clinically similar to type 2 diabetes, affects a small proportion (1% to 6%) of HIV infected patients treated with PI- based antiretroviral regimens. Many more patients receiving PI therapy have evidence of insulin resistance without frank diabetes. However, insulin resistance may also be associated with HIV infection itself in patients not receiving PI therapy, perhaps resulting from the direct effects of the HIV on pancreatic beta cell function and insulin secretion [30].

The lipodystrophy prevalence in this study was significantly greater in Group 5, having affected 42% of patients receiving HAART regimens including the association of PI and stavudine. These data also were concordance with literature data.

The study of Ena et al. showed that patients treated with protease inhibitor-containing regimens as well as patients treated with protease inhibitor-sparing agents showed high concentrations of cholesterol ($p<0.001$), triglycerides ($p=0.004$), glucose ($p=0.028$), and greater changes in body fat distribution- lipodystrophy - ($p=0.001$), than patients with no antiretroviral therapy [31].

Montessori et al. found that dyslipidaemia to levels associated with increased risk of cardiovascular disease occurs in about 70% of HIV- infected patients receiving antiretroviral therapy. The dyslipidaemia is more profound among those receiving PIs and in those with fat redistribution (lipoaccumulation or lipoatrophy) [30].

The follow-up of these AIDS patients in HAART, diagnosed 6 cases (prevalence of 2.1%) of coronary artery disease, all confirmed with cineangiocoronariography. Although this prevalence was low in relation to the general population, this study evaluated a sample of patients with mean age = 41 years, and the mean time of HAART was 40 month. These factors certainly affected this prevalence relatively low of coronary disease.

The D.A. D. study (Data Collection on Adverse Events of anti-HIV Drugs), multi cohort study, prospective including 23,468 patients from 11 previously established cohorts from December 1999 to April 2001 and collected follow-up data until February 2002 in Europe, observed over a period of 36,199 person-years, 126 patients had a myocardial infarction during follow-up (incidence, 3.5 events per 1,000 person-years). The incidence of myocardial infarction increased with longer exposure to combination antiretroviral therapy (adjusted relative rate per year of exposure, 1.26 [95 percent confidence interval, 1.12 to 1.41]; $p<0.001$. Although the absolute event rate was low, combination antiretroviral therapy was associated with a 26% relative increase in the rate of myocardial infarction per year of exposure during the first four to six years of use[32]. Therefore, the benefits of the currently available PIs should be balanced against the long- term risk of cardiovascular disease [33].

This study confirmed the adverse metabolic effects of HAART, especially with some specific classes or drugs, and so it's a contribution for the physicians to pay attention to a more rational choice of the HAART regimen, avoiding these adverse effects, and so making which HAART continues with your benefits greater than the risks.

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