

Effect of non-nucleoside reverse transcriptase inhibitors and protease inhibitors on serum levels of myeloperoxidase and C-reactive protein in HIV-infected individuals

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It remains unclear whether increased inflammatory and cardiovascular risk biomarkers differ depending on the class of antiretroviral that is used. This study evaluated the plasma levels of inflammatory and cardiovascular risk biomarkers, such as MPO, hs-CRP, glucose, lipid profile, ALT (GPT), AST (GOT), urea and creatinine, as well as the blood count, of all the 164 participants in the study, either infected or un-infected with HIV. Thirty of the 104 HIV-infected individuals did not receive any antiretroviral; twenty-four of them were treated with non-nucleoside reverse transcriptase inhibitor class; and fifty took protease inhibitors. The control group consisted of sixty non-HIV infected individuals. In the case of the HIV-infected volunteers, the CD4+ T lymphocyte counts and viral load were also analyzed. Regardless of the hematological and biochemical changes resulting from the antiretroviral therapy (ART), the MPO and hs-CRP values significantly increased for the HIV-infected individuals (treated or untreated), irrespective of the class of ART that was used. This is important because these biomarkers are designed to be predictors of the risk of cardiovascular disease. The results of this study provide supporting evidence for the hypothesis that HIV-infected individuals are at increased risk of developing cardiovascular disease related to chronic inflammations, despite virological control with ART, and regardless of the class of ART that is used.

Keywords: MPO. Hs-CRP. Inflammatory. Cardiovascular risk; HIV-infected. Drug class.

INTRODUCTION

The complex interactions that exist between traditional cardiovascular risk factors, HIV infection itself, and the cumulative exposure to antiretroviral therapy (ART) increase the incidence of cardiovascular diseases in individuals infected with HIV (Ballocca *et al.*, 2017).

The toxicity of ART may contribute either indirectly, favoring traditional cardiovascular risk factors, i.e. hypertension, dyslipidemia, insulin resistance and central adiposity, or directly by acting on the endothelium (Calza *et al.*, 2010); these changes may diversify according to the specific class of antiretrovirals that are used (Currier *et al.*, 2008).

Among ART drugs, protease inhibitors may play an important role in the progression of cardiovascular diseases (Reyskens, Essop, 2014). Moreover, this class of antiretrovirals is associated with increased levels of plasma transaminases, renal complications, hematological disorders and classic cardiovascular

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risk factors such as hyperglycemia and dyslipidemia (Bonfanti *et al.*, 2000; Duval *et al.*, 2004).

It should be emphasized that persistent inflammation in HIV-infected individuals, even with viral suppression sustained by the use of ART, seems to strongly predict cardiovascular events (Hsue *et al.*, 2012). Therefore, the use of inflammatory biomarkers is important in order to predict cardiovascular risk in this population (Baker, Duprez, 2010).

C-reactive protein (hs-CRP) is ultrasensitive; it is the most extensively used inflammation and cardiovascular risk biomarker and is well established in clinical medicine (Zakynthinos, Pappa, 2009). In addition, several studies have recommended the use of myeloperoxidase (MPO; 1.11.1.7) as a preventive measure for assessing cardiovascular risk (Meuwese *et al.*, 2007; Schindhelm *et al.*, 2009; Teng *et al.*, 2017).

MPO is a potent heme peroxidase, which is predominantly found in neutrophil and monocytes, with multiple atherogenic effects (Nicholls, Hazen, 2009). It has been shown that MPO, which plays a central role in inflammation, is involved in the initiation and progression of atherosclerosis (Karakas, Koenig, 2012).

Previous studies have investigated inflammation and cardiovascular risk biomarkers in individuals either treated or untreated with ART (Borato *et al.*, 2012; Neuhaus *et al.*, 2010). However, it remains unclear whether the increased plasma levels of these biomarkers differ depending on the class of antiretrovirals that is used, more specifically, in view of the hematologic and biochemical changes related to their use.

Therefore, the aim of this study was to analyze the plasma levels of MPO and hs-CRP, as well as biochemical and hematological parameters, in HIV-infected individuals exposed to different classes of antiretrovirals.

MATERIAL AND METHODS

Study participants

The study included 164 individuals; 104 were HIV-infected and sixty were uninfected. The HIV-infected volunteers were patients receiving follow-up at the Counseling and Testing Center/Specialized Care Service (CTA/SAE) in Ponta Grossa, Paraná, Brazil. The uninfected individuals were recruited from the University Laboratory of Clinical Analyses. All the participants were individually informed about the survey and they

freely signed and dated a consent form. The protocol was approved by the Ethics in Research Committee of the State University of Ponta Grossa (N. 0443710-21) and was conducted in accordance with the Helsinki Declaration.

The clinical characteristics of all the volunteers, such as age, gender and the use of drugs, were obtained on the day of blood collection. The medical records of the HIV-infected volunteers were reviewed regarding the use of antiretroviral drugs, the class of antiretroviral therapy, and the start date of that therapy.

The volunteers were divided into the following four groups: thirty patients who were untreated with ART (Not-ART); twenty-four treated with ART, including the class of non-nucleoside reverse transcriptase inhibitors (ART-NNRTIs); fifty treated with ART including the class of protease inhibitors (ART-PIs); and sixty non-HIV-infected participants who made up the control group (CON).

The ART-NNRTIs group presented as a therapeutic regimen two nucleoside reverse transcriptase inhibitors (NRTIs) with another drug from the non-nucleoside reverse transcriptase inhibitors (NNRTI) class. The ART-PIs group presented two drugs from the NRTI class combined with another drug from the protease inhibitors (PIs) class.

The inclusion criteria for all the groups were to be aged over eighteen years and to have fasted for twelve hours. The exclusion criteria were as follows: i) for all groups, to have used medications that could affect the laboratory results (biochemical, hematological and inflammatory); ii) for the ART-NNRTIs and ART-PIs groups, to have been exposed to ART for less than three months; iii) and for the Not-ART group, previous exposure to ART.

Immunologic and virologic analysis

The immunological parameter of absolute CD4+ T count was performed in the HIV-infected groups by immunophenotyping. The standard protocol, BD Multitest[®] CD3/CD4/CD8/CD45, was used in a FACSCalibur[®] flow cytometer (Becton-Dickinson Biosciences, San Jose, California, USA).

The virological analysis was performed by the quantification of viral RNA (viral load) using an automated System 340[®] analyzer (Siemens Healthcare Diagnostics Inc., Tarrytown, New York, USA), bDNA 3.0 technique, using the HIV 3.0 RNA kit.

Biochemical analysis

A BT 3000 PLUS[®] biochemical analyzer (Wiener Lab[®], Rosario, Argentina) was used to determine the following: levels of glucose, triglycerides and total cholesterol (Enzyme-Trinder method); glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) (kinetic method UV-IFCC - International Federation of Clinical Chemistry); creatinine (Jaffe reaction); urea (colorimetric method); and high-density lipoprotein cholesterol (HDL-C) (colorimetric method without precipitate). The cholesterol low-density lipoproteins (LDL) were determined by the Friedewald equation ($LDL-C = [total\ cholesterol] - [HDL-C] - [triglycerides/5]$) for triglyceride levels below 400 mg/dL, and non-HDL cholesterol was calculated by the formula ($CT - [HDL-C]$).

Hematological analysis

The following hematological data: erythrocytes; hemoglobin; hematocrit; mean cell volume (MCV); mean corpuscular hemoglobin (MCH); corpuscular hemoglobin concentration (MCHC); total leukocytes; lymphocytes; neutrophils and platelets were obtained using the Cell-Dyn 3700[®] hematology system (Abbot[®], Quebec, Canada). The hemoglobin levels were also evaluated for anemia in compliance with the recommendations of the World Health Organization (WHO), which are less than 12 g/dL in women and less than 13 g/dL in men (WHO, 2011).

Inflammatory and cardiovascular risk biomarkers

The MPO levels in serum were determined by an enzyme immunoassay technique (ELISA, enzyme-linked immunosorbent assay) in the sandwich format according to the manufacturer's instructions (Consultants Immunology Laboratory, USA).

The hs-CRP levels were determined by a turbidimetric kit (CRP U-hs, DiaSys, Germany) using an automated BT 3000 PLUS[®] analyzer (Wiener Lab[®], Rosario, Argentina).

The analyses of these biomarkers were considered as the cutoff point for increased cardiovascular risk: values above 350 µg/L for MPO (Baldus *et al.*, 2003), and above 3 mg/L for hs-CRP (Ridker, 2003).

Statistical analysis

The Kolmogorov-Smirnov test was performed to verify the normality of the clinical and laboratory

parameters. The clinical parameters presented normal distribution and were presented as mean \pm standard deviation for the continuous variables, and as absolute and relative (%) frequencies for the categorical variables. Possible differences between the groups were found using analysis of variance (ANOVA) followed by Tukey's post-test for the continuous variables, and the chi-square test (χ^2) for the categorical variables. The treatment time (years) was compared for the ART-NNRTIs and ART-PIs groups using Student's t-test for independent samples. However, the results of some of the laboratory parameters did not present a normal distribution (glucose, HDL-C, urea, hemoglobin, hematocrit and MCH) and were presented as median and interquartile range. Possible differences between the groups were found using the Kruskal-Wallis test. In all the tests, the level of significance was pre-set at $p < 0.05$. The data were analyzed using the STATISTICA 7 (Statsoft, USA) statistical program.

RESULTS AND DISCUSSION

The study population consisted of 164 individuals: 104 (63%) were HIV-infected, of whom thirty (28.8%) patients were untreated with ART; twenty-four (23.1%) were treated with ART including the class of NNRTIs; fifty (48.1%) were treated with ART including the class of PIs; and sixty (37%) were non-infected individuals. The clinical characteristics of the study participants are shown in Table I. There was no statistical difference in age and gender between the groups, which confirmed the homogeneity of the study population. The results for absolute CD4⁺ T lymphocytes and viral load showed a similar immunological and virological profile between all the HIV groups included in this study (Table I).

ART regimens containing a combination of atazanavir and ritonavir were most commonly prescribed for all those who were receiving PIs; lamivudine and zidovudine were most frequently used for the class of NRTIs and efavirenz had the highest usage in the NNRTI class, as shown in Table I.

Table II shows the biochemical parameters. The most evident changes in the biochemical assays were observed in relation to the ART-PIs group, which exhibited significant increase in triglyceride levels ($p < 0.005$) compared to all the other groups (Table II).

TABLE I – Characterization of studied groups

Characteristics	CON (n=60)	Not-ART (n=30)	ART-NNRTIs (n=24)	ART-PIs (n=50)	p-value
Age (years)*	38 ± 15	37 ± 10	40 ± 7	41 ± 12	0.707
Gender**					
Male, n (%)	20(33)	14(47)	14(58)	19(38)	0.169
Female, n (%)	40(67)	16(53)	10(42)	31(62)	0.169
CD4+ (cells/mL)*	-	535 ± 339	524 ± 252	458 ± 247	0.132
V.L.(<50copies/mL)**	-	21(70)	20(83)	39(78)	0.497
Treatment (years)†	-	-	6.3 ± 2.9	6.4 ± 4.0	0.935
Antiretroviral‡					
<i>PIs prescribed, n (%)</i>					
Lopinavir+Ritonavir (LPV-r)	-	-	-	19(38)	-
Atazanavir+Ritonavir (ATV-r)	-	-	-	31(62)	-
<i>NRTIs prescribed, n (%)</i>					
Zidovudina (AZT)	-	-	23(96)	30(60)	-
Lamivudina (3TC)	-	-	23(96)	49(98)	-
Didanosina (ddI)	-	-	1(4)	3(6)	-
Estavudina (d4T)	-	-	0(0)	5(10)	-
Tenofovir (TDF)	-	-	1(4)	13(26)	-
<i>NNRTIs prescribed, n (%)</i>					
Efavirenz (EFV)	-	-	22(92)	0(0)	-
Nevirapina (NVP)	-	-	2(8)	0(0)	-

Values are mean ± SD or absolute and relative (%) frequencies.

*ANOVA and Tukey's post hoc test.

† Student's t-test.

** χ^2

‡Descriptive statistics only.

- not applicable.

V.L., viral load.

PIs, protease inhibitors.

NRTIs, nucleotide reverse transcriptase inhibitors.

NNRTIs, non-nucleotide reverse transcriptase inhibitors.

CON, control group.

Not-ART, untreated with ART group.

ART-NNRTIs, treated with antiretroviral therapy including the class of non-nucleoside reverse transcriptase inhibitors group.

ART-PIs, treated with antiretroviral therapy including the class of protease inhibitors group.

TABLE II – Biochemical analysis for the study groups

Biochemical Parameters	CON (n=60)	Not-ART (n=30)	ART-NNRTIs (n=24)	ART-PIs (n=50)
Glucose (mg/dL)	82 (78-88)	95 (81-101)*	94 (90-103)*	92 (85-101)*
Cholesterol (mg/dL)	159 (143-183)	171 (120-186)	191 (167-203)*†	195 (163-233)*†
Triglycerides (mg/dL)	94 (66-125)	113 (77-155)	111 (71-161)	265 (115-249)*†‡
HDL-C (mg/dL)	52 (42-60)	37 (29-46)*	45 (38-54)*†	42 (34-49)*
non-HDL-C (mg/dL)	107 (93-129)	130 (87-146)	145 (119-157)*	161 (125-188)*†
LDL-C (mg/dL)	88 (73-103)	94 (73-116)	120 (97-129)*†	121 (93-145)*†
GOT (UI/L)	19 (17-24)	17 (14-22)	19 (15-23)	20 (16-24)
GPT (UI/L)	10 (8-13)	13 (10-20)	16 (13-25)*	17 (12-27)*
Urea (mg/dL)	28 (22-34)	27 (21-33)	28 (22-33)	30 (26-36)
Creatinine (mg/dL)	0.97 (0.87-1.10)	0.90 (0.80-1.10)	0.80 (0.70-1.10)	0.90 (0.75-1.05)

Values are median and interquartile range.

*Significant difference from the control group.

†Significant difference from the Not-ART group.

‡Significant difference from the ART-NNRTIs group.

Kruskal-Wallis, $p < 0.05$.

CON, control group.

Not-ART, untreated with ART group.

ART-NNRTIs, treated with antiretroviral therapy including the class of non-nucleoside reverse transcriptase inhibitors group.

ART-PIs, treated with antiretroviral therapy including the class of protease inhibitors group.

The Not-ART group was significantly different from the CON group regarding glucose ($p=0.034$) and HDL-C ($p<0.001$). Whereas, the ART-NNRTIs and ART-PIs groups showed significant differences ($p<0.001$) compared to the CON group regarding glucose, total cholesterol, HDL-C, non-HDL-C, LDL-C and GPT (Table II).

Compared to the Not-ART group, the ART-NNRTIs group presented a significant increase in total cholesterol ($p=0.019$), HDL-C ($p=0.015$) and LDL-C ($p=0.025$). Whereas, the total cholesterol ($p<0.001$), non-HDL-C ($p<0.001$) and LDL-C ($p=0.002$) levels were significantly increased in the ART-PIs group compared to the Not-ART group (Table II). No statistical differences between the groups were observed regarding urea ($p=0.108$), creatinine ($p=0.110$) and AST ($p=0.081$) (Table II).

The lipid profile results were in agreement with other studies that have reported the presence of dyslipidemia in individuals using NNRTIs and PIs. Individuals treated with NNRTIs exhibited increased plasma concentrations for total cholesterol, non-HDL-C and LDL-C (Pereira *et al.*, 2006). Furthermore, in addition to the above-mentioned parameters, HIV-infected individuals receiving PIs in the therapeutic regimen, also presented hypertriglyceridemia, particularly in regimens containing a combination of lopinavir and ritonavir (Walmsley *et al.*, 2002). In the present study, significant decreases were observed in HDL-C levels in both treated and untreated individuals compared to non-HIV infected individuals.

Decreasing HDL-C levels could be explained as a change in metabolism, characterized by an increase in the activity of the cholesterol ester transfer protein,

which transfers cholesterol from HDL-C to Apo-B-containing proteins, resulting in a decrease in HDL-C (Rose *et al.*, 2008). However, when treatment regimens include the NNRTIs efavirenz or nevirapine, individuals may experience an increase in HDL-C levels (Van Leth *et al.*, 2004), which lowers the risk factors related to cardiovascular disease. As noted in the present study, the individuals exposed to NNRTIs had higher HDL-C levels than those with HIV- infected individuals who were not receiving ART.

Lipid metabolism changes can be linked to type I cytoplasmatic retinoic-acid binding proteins (CRABP-1) and LDL-receptor-related protein (LRP), to which protease inhibitors bind (Carr *et al.*, 1998). Thus, protease inhibitors inhibit the action of CRABP-1 protein, which is critical for the maturation, proliferation and apoptosis of adipocytes. Similarly, the LRP site is occupied by a hepatic cell receptor, which cleaves off the fatty acid, resulting in a lower uptake of triglycerides, with consequent hypertriglyceridemia (Carr *et al.*, 1998).

In addition to changes in the lipid profile, in the present study the HIV-infected individuals also showed changes in glucose metabolism. These results corroborated previous information regarding the presence of hyperglycemia related to HIV infection (Dubé, 2000) or ART (Brown *et al.*, 2005).

Hyperglycemia associated with HIV infection may be directly caused by the virus infecting the pancreatic beta cells (Dubé, 2000). Changes in glucose homeostasis in HIV-infected patients exposed to ART are characterized by complex and interrelated changes in adipocyte function, peripheral glucose disposal, hepatic insulin resistance, and insulin secretion impaired by pancreatic beta cells (Hruz, 2011).

A major change to the glucose metabolism caused by PIs is the inhibition of the main GLUT4 glucose transporter protein in response to insulin (Hresko *et al.*, 2014). Furthermore, the induction of hyperglycemia via NRTIs is mediated by mitochondrial toxicity (Hruz, 2011). On the other hand, previous research found that the use of efavirenz and nevirapine reduced resistance to insulin in HIV-infected individuals (Martínez *et al.*, 2000, 1999).

Table III shows the hematologic parameters. Compared to the CON group, the Not-ART group showed statistical significance regarding erythrocytes and MCV ($p<0.001$). The results for the ART-NNRTIs and ART-PIs groups were significantly different from the CON group regarding erythrocytes ($p<0.001$), hemoglobin in female

participants ($p=0.015$), MCV ($p<0.001$), MCH ($p<0.001$), MCHC ($p=0.007$) and lymphocytes ($p<0.001$) (Table III).

Significant differences were found in the ART-NNRTIs group compared to the Not-ART group regarding erythrocytes ($p<0.001$), hemoglobin in female participants ($p=0.015$), MCV ($p=0.001$) and MCH ($p=0.001$). Similarly, the ART-PIs group was significantly different from the Not-ART group regarding erythrocytes ($p=0.003$), MCV ($p=0.043$) and MCH ($p=0.011$). The values for MCV ($p=0.033$) and MCH ($p=0.039$) in the ART-PIs group were significantly decreased compared to ART-NNRTIs group (Table III).

No statistical differences between the groups were observed regarding hemoglobin in male participants ($p=0.127$), hematocrit ($p=0.331$), MCHC ($p=0.421$), total leukocytes ($p=0.081$) and neutrophils ($p=0.129$) (Table III). All the participants showed platelets within normal ranges (data not shown).

The presence of anemia (according to the WHO criteria) was observed, for 4% and 6% of males in the ART-NNRTIs and ART-PIs groups, respectively. In addition, in both the ART-NNRTIs and ART-PIs groups 12% of females had anemia, which was in accordance with previous studies that found an increased incidence of anemia in HIV-infected women (Semba, Shah, Vlahov, 2002).

The hematological analysis evidenced cytopenias and agreed with previous studies that reported decreased erythrocytes (treated or untreated HIV-infected individuals) and lymphocytes (HIV-infected individuals on therapy, regardless of the class of antiretrovirals used) (Sloand, 2005).

In addition, higher values for MCV and MCH were observed. These data characterize the occurrence of macrocytosis, either due to bone marrow infiltration by HIV infection or due to the use of myelosuppressive drugs such as zidovudine (Volberding *et al.*, 2004); 96% of the population in the present study was exposed to zidovudine in the ART-NNRTIs group and 60% in the ART-PIs group.

Figure 1 shows a comparison between the groups regarding the results for inflammation and cardiovascular risk biomarkers (i.e. MPO and hs-CRP). MPO was significantly increased ($p<0.001$) in the Not-ART, ART-NNRTIs and ART-PIs groups compared to the control group (Figure 1A). The hs-CRP biomarker increased significantly for the Not-ART ($p=0.026$), ART-NNRTIs ($p<0.001$) and ART-PIs ($p<0.001$) groups compared to the control group (Figure 1 B).

TABLE III – Hematological analysis for the study groups

Hematological Parameters	CON (n=60)	Not-ART (n=30)	ART-NNRTIs (n=24)	ART-PIs (n=50)
Erythrocytes (millions/ μ L)	4.78 (4.46-5.08)	4.55 (4.22-4.94)*	3.97 (3.45-4.15)*†	4.02 (3.67-4.63)*†
Hemoglobin (g/dL)				
Male	15.6 (14.9-16.3)	15.0 (13.8-15.8)	15.0 (14.5-15.5)	14.9 (13.1-16.0)
Female	13.4 (12.8-14.2)	13.5 (12.7-14.1)	12.3 (11.8-12.7)*†	12.8 (12.1-13.7)*
Hematocrit (%)	41.5 (39.2-45.1)	43.1 (39.7-44.7)	41.2 (36.9-45.4)	40.5 (37.6-44.7)
MCV (fL)	88 (85-90)	91 (87-95)*	111 (104-113)*†	102 (90-109)*†‡
MCH (pg)	30 (28-30)	30 (28-31)	37 (33-39)*†	33 (31-36)*†‡
MCHC (%)	34 (33-34)	33 (32-34)	33 (32-34)	33 (32-34)
White cell count (10^3 cell/mL)	5.7 (4.75-6.90)	5.36 (4.09-6.10)	4.69 (4.05-6.45)	5.09 (4.41-5.69)
Lymphocytes (10^3 cell/mL)	2.11 (1.74-2.37)	1.92 (1.69-2.52)	1.40 (1.10-1.61)*	1.72 (1.25-2.20)*
Neutrophils (10^3 cell/mL)	3.12 (2.69-3.68)	2.60 (1.87-3.26)	2.95 (2.45-3.49)	3.03 (2.55-3.79)

Values are median and interquartile range.

*Significant difference from the control group.

†Significant difference from the Not-ART group.

‡Significant difference from the ART-NNRTIs group.

Kruskal-Wallis, $p < 0.05$

CON, control group.

Not-ART, untreated with ART group.

ART-NNRTIs, treated with antiretroviral therapy including the class of non-nucleoside reverse transcriptase inhibitors group.

ART-PIs, treated with antiretroviral therapy including the class of protease inhibitors group.

No individuals in the CON group presented MPO levels above 350 μ g/L, which is considered to be the cutoff point for high cardiovascular risk (Baldus *et al.*, 2003), while 27%, 37% and 36% of individuals presented MPO levels above this cutoff point for the Not-ART, ART-NNRTIs and ART-PIs groups, respectively. With regard to hs-CRP, values above 3 mg/L are associated with future cardiovascular events (Ridker, 2003) and levels above this value were observed in up to 3% of the CON group, 30% of the Not-ART group, 58% of the ART-NNRTIs group and 42% of the ART-PIs group.

These results agree with previous data showing significant increases in MPO and hs-CRP levels for HIV-

infected individuals (Ross *et al.*, 2009). In addition, the aforementioned study also demonstrated an association between these biomarkers, endothelium activation and carotid intima-media thickness, demonstrating an interrelationship between inflammation, endothelial activation and cardiovascular disease in HIV-infected individuals (Ross *et al.*, 2009).

Similarly, another study observed significant MPO increases in HIV-infected individuals either treated or untreated with ART; however, that study demonstrated increased hs-CRP levels only for individuals exposed to ART (Borato *et al.*, 2012).

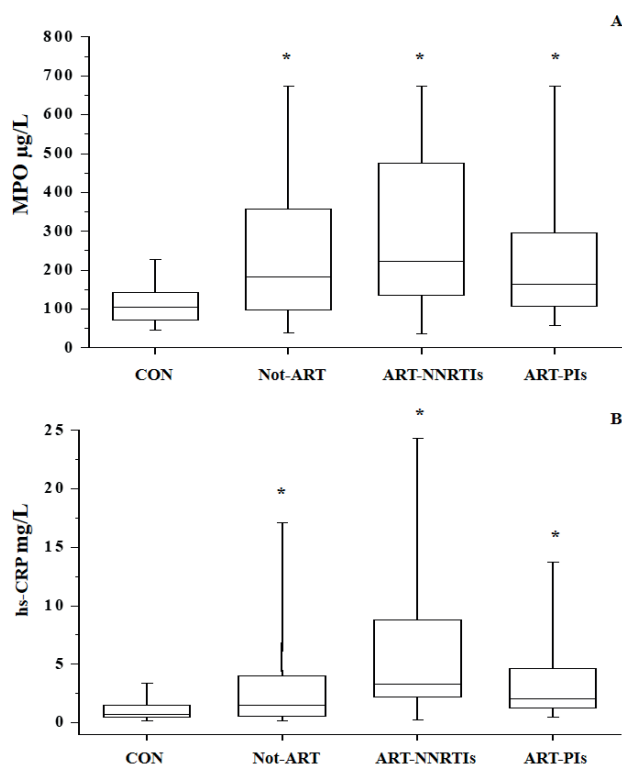


FIGURE 1 - Inflammatory and cardiovascular risk biomarkers: MPO (A) and hs-CRP (B); CON (control), Not-ART (untreated group), ART-NNRTIs (NNRTIs-treated group) and ART-PIs (PIs-treated group). *Significant difference from the control group.

With regard to the different ART classes, Neuhaus *et al* (2010) demonstrated increased hs-CRP levels for individuals taking NNRTI drugs compared to individuals receiving PIs. In a regression model that was adjusted for baseline covariables, an increase of 48% in hs-CRP levels was observed for individuals taking NNRTIs (with or without a PI) compared to those taking PIs alone (Neuhaus *et al.*, 2010). Kristoffersen *et al.* (2009) found increased levels of MPO and hs-CRP biomarkers, only for individuals on an NNRTI-containing ART regimen, following a change from zidovudine or estavudina to abacavir. MPO levels increased after three and twelve months exposure to abacavir. The levels of hs-CRP 1 increased after three months exposure to abacavir but returned to the starting point after twelve months of treatment, indicating an increased cardiovascular risk in viral load-suppressed HIV-1-infected individuals switching to abacavir (Kristoffersen *et al.*, 2009).

In the present study, higher levels of MPO and hs-CRP were found in the HIV-infected individuals regardless of the hematologic and biochemical changes induced by ART, or the class of ART that was used. This

is important because these biomarkers are designed to be predictors of cardiovascular disease. These study results provide evidence to support the hypothesis that HIV-infected individuals are at risk of developing cardiovascular disease, which is directly linked to the presence of inflammation, independently of virological control with ART and the specific class of antiretrovirals that is used.

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