Endothelial function in HIV-infected patients with low or mild cardiovascular risk

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Background: Highly active antiretroviral therapy for HIV-infected patients is associated with metabolic side effects, which could cause an increased cardiovascular risk in these patients. Non-invasive study of endothelial function by brachial artery ultrasound can detect subclinical atherosclerosis. Several studies have assessed endothelial function in HIV-infected patients with associated cardiovascular risk factors.

Objectives: The aim of this study is to determine endothelial function in HIV-infected patients under antiretroviral therapy with low or mild coronary risk and lipid levels within the normal range.

Methods: Transversal study including 28 HIV-infected adults (15 receiving antiretroviral therapy and 13 naive) with low or mild cardiovascular risk and 12 healthy controls. Subjects with diabetes mellitus, hypertension, cardiovascular disease, obesity, high cholesterol or high triglyceride levels were excluded. Endothelial function was determined with flow-mediated dilation (FMD) of the brachial artery by ultrasound study.

Results: Treated HIV-infected patients had significantly lower FMD (5.93 ± 3.56) than healthy controls (10.64 ± 3.08, P = 0.008). Naive patients had an intermediate FMD, but this was not statistically significant.

Conclusions: HIV-infected patients receiving antiretroviral therapy who have low or mild cardiovascular risk and lipid levels within the normal range have endothelial dysfunction compared with healthy controls.

Keywords: atherosclerosis, risk factors, antiretroviral therapy

Introduction

Highly active antiretroviral therapy (HAART) has improved the prognosis of patients infected with human immunodeficiency virus (HIV) by means of decreasing the incidence of opportunistic infections, hospitalizations and mortality. However, HAART has metabolic side effects, including hypertriglyceridaemia, increased levels of low-density lipoprotein cholesterol (LDL-C), decreased levels of high-density lipoprotein cholesterol (HDL-C), insulin resistance and lipodystrophy. The clinical importance of these cardiovascular risk factors in patients receiving HAART still remains controversial. Several studies have suggested a higher incidence of cardiovascular events in patients with HAART, but the long-term consequences of these pro-atherogenic metabolic side effects are still unknown. HIV-infected patients treated with HAART also have a higher prevalence of other cardiovascular risk factors such as smoking compared with the general population, and several risk-factor modification strategies have been proposed including lifestyle and dietary changes (especially cessation of smoking), lipid-lowering drugs or the use of antiretroviral agents with less metabolic side effects.

Endothelial dysfunction (ED) is an early event in the development of atherosclerotic lesions and it is associated with major cardiovascular risk factors such as arterial hypertension, dyslipidaemia and diabetes mellitus. Endothelial function

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can be easily measured with ultrasound by assessing brachial artery flow-mediated dilation (FMD) after upper-arm occlusion. This non-invasive technique has already been used in patients with HIV infection. Stein et al. found ED in HIV-infected patients who were receiving protease inhibitors (PI) and had hypertriglyceridaemia compared with HIV-infected patients who were not receiving PI.17 On the other hand, Nolan et al. compared HIV-infected patients with dyslipidaemia who were being treated with PI and healthy controls, and he did not find any differences in endothelial function between the two groups.18 Bonnet et al. found ED in HIV-infected children without any other cardiovascular risk factors.19 It is still not clear whether HIV infection or antiretroviral therapy can cause ED independently of other cardiovascular risk factors.

The aim of this study is to assess endothelial function by non-invasive brachial artery ultrasound in HIV-infected patients, naive and receiving HAART, who have low or mild coronary risk. We compare brachial artery FMD in three groups: naive HIV-infected patients, HIV-infected patients receiving HAART and healthy controls.

Methods

Design and patients

This cross-sectional study was performed in La Paz University Hospital in Madrid, Spain, a tertiary hospital with a 650,000 population area, from January to July 2003. The Department of Internal Medicine covers around 1200 HIV-infected outpatients per year.

Patients were selected among all HIV-infected patients over 18 years of age attending the Department of Internal Medicine as outpatients. Twelve healthy volunteers over 18 years of age were included as a control group.

Inclusion criteria: evidence of HIV infection and informed consent. Patients with HIV infection were divided into two groups: first, naive patients, and second, patients receiving HAART with only one combination of antiretroviral drugs for at least 6 months.

Exclusion criteria: presence of opportunistic infection or neoplasms; personal history of diabetes mellitus, coronary heart disease, cerebrovascular disease or peripheral arterial occlusive disease; body mass index over 30; arterial hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg);20 plasma creatinine > 159.12 μmol/L, total cholesterol > 6.21 mmol/L, triglycerides > 1.98 mmol/L; treatment with statins, antioxidants or oestrogen replacement therapy; moderate, high or very high coronary risk as determined by the Second Joint Task Force of European and other Societies on Coronary Prevention coronary risk chart;21 use of illicit drugs during the last year; alcohol intake > 20 g/day (women) or > 40 g/day (men). Patients on methadone maintenance programmes were also excluded.

Variables

Data were obtained from the clinical history of the subjects and included age, sex, weight (kg), body mass index (kg/m²), smoking, date of the diagnosis of HIV infection, risk factor (intravenous drug use, heterosexual, homosexual, receipt of transfusion of blood or blood components; or other risk factor) and stage of HIV infection according to the CDC criteria.22 Blood pressure was determined following the recommendations of the Joint National Committee VI.23 For patients receiving HAART we recorded each antiretroviral drug, duration of antiretroviral therapy and existence of lipodystrophy. A patient was considered to have lipodystrophy when it was described by the patient’s usual physician and the patient himself had a subjective perception of having lipodystrophy.

Blood samples were obtained in the morning after an 8 h overnight fast for the determination of glycaemia, insulinaemia, total cholesterol level, HDL-C, triglycerides, creatinine and homocysteine. Glycaemia, total cholesterol, HDL-C, triglycerides and creatinine were determined using a Modular PPP HITACHI Analyzer. Insulinaemia was determined by immunoradiometric assay using a double monocolonal antibody. Homocysteinaemia was determined using high resolution liquid chromatography. LDL-C was calculated using Friedewald’s formula.23 Insulin resistance was calculated using the HOMA (Homeostasis Model Assessment): fasting insulin (mU/mL) × fasting glucose (mmol/L)/22.5; values ≥3.8 were considered as insulin resistance. CD4+ cell count was determined by direct immunofluorescence and plasma viral load was determined using PCR with Cobas Roche Amplicor HIV-1 Monitor 1.5, Ultra-sensitive, <50 copies/mL limit of detection. Serology of hepatitis C virus (HCV) was determined using a second-generation ELISA.

Coronary risk was calculated for each subject using the Second Joint Task Force of European and other Societies on Coronary Prevention coronary risk chart.24

Ultrasound studies

Vascular ultrasound scans were performed according to the method described by Celermajer et al.22 for non-invasive determination of ED and the recent guidelines developed by the International Brachial Artery Reactivity Task Force.24 All studies were performed around 8:30 a.m. after the subjects had been lying supine for 15 min in a quiet room. Patients were indicated not to smoke or eat during the previous 8 h. The radiologist performing the ultrasound study was unaware of the patient’s clinical details. Images were obtained with an SSH-140 HG Toshiba ultrasound machine provided with a 7.0 MHz transducer. Flow increase was induced by inflation of a pneumatic tourniquet placed around the forearm to 300 mm Hg for 4 min. Images of the brachial artery were recorded on videotape VHS AG 5700 at baseline and 60–90 s after cuff deflation. Video images were analysed separately by two radiologists unaware of the patients’ clinical details. Brachial artery diameter was determined at baseline and 60 s after cuff deflation in end-diastole. FMD was expressed as the percentage change of brachial artery diameter 60 s after cuff deflation relative to the average baseline scan. Inter-assay variability was <2%.

Ethical issues

The study protocol (code HULP PI-212) was approved by the Ethics Committee in Clinical Research on August 5, 2002. All subjects in the study signed informed consent.

Statistical analysis

Data were analysed using the statistical program SPSS version 9.0. All quantitative variables in the text are expressed as means ± SD. Univariate analysis of quantitative variables was performed by use of ANOVA or non-parametric tests depending on whether the variables had a normal distribution and homogeneous variances tested with Shapiro-Wilk and Levene test, respectively. The variables that showed significant differences with the ANOVA test were compared afterward between each group by use of Bonferroni test for multiple comparisons. The variables that showed significant differences with the non-parametric test were compared afterward between each group by use of a *post hoc* non-parametric test. Qualitative variables were tested by use of χ² test. The correlations between variables
**Endothelial function in HIV patients**

Table 1. Demographic, clinical and laboratory data for the three groups

<table>
<thead>
<tr>
<th>Clinical and demographic variables</th>
<th>Control group (n = 12)</th>
<th>Naive HIV (n = 13)</th>
<th>HIV receiving HAART (n = 15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (years)</td>
<td>34.4 ± 10.2</td>
<td>34.7 ± 4.4</td>
<td>42.1 ± 8.2</td>
<td>0.015*</td>
</tr>
<tr>
<td>sex (male/female, n)</td>
<td>9/3</td>
<td>13/0</td>
<td>9/6</td>
<td>0.034‡</td>
</tr>
<tr>
<td>smokers/non-smokers (n)</td>
<td>4/8</td>
<td>5/8</td>
<td>10/5</td>
<td>0.165</td>
</tr>
<tr>
<td>systolic blood pressure (mm Hg)</td>
<td>113.7 ± 12.5</td>
<td>106.5 ± 11.3</td>
<td>115.3 ± 11.9</td>
<td>0.168</td>
</tr>
<tr>
<td>diastolic blood pressure (mm Hg)</td>
<td>71.7 ± 12.3</td>
<td>69.7 ± 8.3</td>
<td>76.7 ± 7.9</td>
<td>0.146</td>
</tr>
<tr>
<td>waist-to-hip ratio</td>
<td>0.84 ± 0.07</td>
<td>0.86 ± 0.04</td>
<td>0.88 ± 0.05</td>
<td>0.099</td>
</tr>
<tr>
<td>body mass index (kg/m²)</td>
<td>23.2 ± 3.5</td>
<td>23.9 ± 2.1</td>
<td>23.5 ± 2.1</td>
<td>0.663</td>
</tr>
<tr>
<td>lipidostrophy (n)</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>0.018</td>
</tr>
<tr>
<td>time since HIV diagnosis (months)</td>
<td>–</td>
<td>63.3 ± 48.6</td>
<td>89.9 ± 53.6</td>
<td>0.183</td>
</tr>
<tr>
<td>CDC classification (n)</td>
<td>A</td>
<td>12</td>
<td>7</td>
<td>0.133‡</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0</td>
<td>6</td>
<td>0.001*</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1</td>
<td>2</td>
<td>0.027‡</td>
</tr>
</tbody>
</table>

| Laboratory variables              |                       |                    |                             |    |
| total cholesterol (mmol/L)        | 4.6 ± 0.58            | 4.23 ± 0.87        | 5.10 ± 0.7                 | 0.013* |
| triglycerides (mmol/L)            | 0.72 ± 0.20           | 0.97 ± 0.30        | 1.21 ± 0.34                | 0.001* |
| HDL-C (mmol/L)                    | 1.56 ± 0.29           | 1.24 ± 0.28        | 1.28 ± 0.34                | 0.027‡ |
| LDL-C (mmol/L)                    | 2.71 ± 0.68           | 2.54 ± 0.76        | 3.27 ± 0.69                | 0.025‡ |
| VLDL-C (mmol/L)                   | 0.33 ± 0.09           | 0.44 ± 0.14        | 0.55 ± 0.16                | 0.001* |
| basal insulinaemia (μU/mL)        | 7.3 ± 5.2             | 7.8 ± 3.7          | 13.8 ± 17.2                | 0.292 |
| basal glycaemia (mmol/L)          | 4.83 ± 0.61           | 4.87 ± 0.5         | 4.78 ± 1.27                | 0.431 |
| HOMA                              | 1.6 ± 1.1             | 1.8 ± 0.9          | 3.2 ± 4.3                  | 0.788 |
| homocystine (μmol/L)              | 10.3 ± 3              | 9.3 ± 3.9          | 8.8 ± 4.7                  | 0.225 |
| CD4+ cell count (×10⁹/L)          | 464.7 ± 219.1         | 600.2 ± 228.1      | 600.2 ± 228.1              | 0.607 |
| viral load (HIV RNA copies/mL)    | 61815 ± 78.053        | 232.5 ± 439.4      | 0.001                      |

Values are means ± SD.

CDC, Centers for Disease Control and Prevention; HOMA, Homeostasis Model Assessment; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol.

*Significant difference between control group and HIV receiving HAART.
†Significant difference between naive HIV and HIV receiving HAART.
‡Significant difference between control group and naive HIV.

were determined by use of Pearson’s or Spearman’s correlation coefficient, depending on the distribution of the variables.

Another analysis was performed adjusting the values of FMD independently for each of the baseline variables that showed significant differences between the three groups.

Multivariable regression analysis was performed with FMD as the outcome variable and the study group as the predictive variable, adjusting for potential confounders. The control group was considered as baseline. A second multivariable analysis was performed including only the HIV-infected subjects, adjusting for potential confounders and considering the naive group as baseline. P < 0.05 was considered statistically significant.

**Results**

**Demographic, clinical and laboratory parameters**

After application of inclusion and exclusion criteria, 28 HIV-infected patients were included: 13 patients were naive and 15 patients were receiving antiretroviral therapy. Demographic and clinical baseline variables are shown in Table 1. There were no significant differences between the three groups in the values of blood pressure, BMI or waist-to-hip ratio. Six patients in the group receiving HAART had lipodystrophy.

Mean total cholesterol and LDL-C levels were higher in the group under antiretroviral treatment, showing significant differences with the naïve HIV-infected patients. Both triglyceridaemia and very-low-density lipoprotein cholesterol (VLDL-C) levels were also higher in the group under antiretroviral treatment, showing significant differences with the control group. Mean HDL-C was higher in the control group. Homocysteine levels showed no significant differences among the three groups. Only four patients had insulin resistance: three in the group under antiretroviral therapy (only one of them had metabolic syndrome) and one in the control group.

Risk factors for HIV infection were distributed similarly in both HIV-infected groups. In the naïve HIV-infected group, four patients had been intravenous drug users, six had had homosexual contacts, two had had heterosexual contacts and one had received blood components. Among HIV-infected patients receiving HAART, four had been intravenous drug users, six had had homosexual contacts and five had had heterosexual contacts. Neither the time since diagnosis of HIV infection nor CD4+ cell counts showed significant differences between both groups. As expected, viral load was lower in the group under
antiretroviral treatment and the control group persisted after adjusting independently by each of these baseline variables.

Among HIV-infected patients, FMD did not show any linear relationship with CD4+ cell count, viral load or time since diagnosis of HIV infection. The values of FMD were not significantly different between patients with or without lipodystrophy. Neither did FMD differ significantly between patients receiving PI and those receiving NNRTI.

A univariable linear regression model was adjusted with FMD as the outcome variable and the study group as the predictive variable. Taking the control group as the baseline, the naive group had an FMD that was 2.46% lower than the control group (95% CI: –6.48%, 0.83%, \( P = 0.124 \)).

A multivariable regression model was adjusted with FMD as the outcome variable and HAART as the predictive variable, adjusting for the same potential founders as the previous model (age, sex, smoking, total cholesterol, pulse pressure and basal brachial artery diameter). Taking the control group as the baseline, the naive group had an FMD that was 2.82% lower than the naive group (95% CI: –6.48%, 0.83%, \( P = 0.124 \)).

A second analysis was performed including only HIV-infected individuals (both naive and HAART-treated, \( n = 28 \)). The univariable regression model was adjusted with FMD as the outcome variable and HAART as the predictive variable, taking the naive group as the baseline. Compared with the naive group, the HAART-treated group had an FMD that was 4.30% lower than the control group (95% CI: –8.77%, 0.17%, \( P = 0.059 \)).

A multivariable regression model was adjusted with FMD as the outcome variable and HAART as the predictive variable, adjusting for the same potential founders as the previous model (age, sex, smoking, total cholesterol, pulse pressure and basal brachial artery diameter), and also CD4-cell count. After adjusting for these variables, the HAART-treated group had an FMD that was 4.74% lower than the naive group (95% CI: –11.47%, 2.0%, \( P = 0.157 \)).

**Discussion**

This study shows that HIV-infected patients who have been receiving HAART for at least 6 months have ED (and therefore an early marker of atherosclerosis) compared with non-infected controls. The main contribution of these results to previous work is that our subjects did not have hypercholesterolaemia or hypertriglyceridaemia and their coronary risk was only low or mild.

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**Figure 1.** Flow-mediated vasodilation (FMD). Outliers (case numbers 30 and 33) are indicated for the control group, and an extreme outlier (case number 26) is indicated for the group of HIV-infected patients receiving antiretroviral therapy.

**Table 2.** Brachial artery basal diameters, post-ischaemic diameters and flow-mediated dilation

<table>
<thead>
<tr>
<th></th>
<th>Control group (( n = 12 ))</th>
<th>Naive HIV (( n = 13 ))</th>
<th>HIV receiving HAART (( n = 15 ))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal diameter (mm)</td>
<td>3.49 ± 0.67</td>
<td>3.45 ± 0.44</td>
<td>3.66 ± 0.57</td>
<td>0.57</td>
</tr>
<tr>
<td>Post-ischaemic diameter (mm)</td>
<td>3.86 ± 0.75</td>
<td>3.75 ± 0.45</td>
<td>3.88 ± 0.39</td>
<td>0.83</td>
</tr>
<tr>
<td>FMD (%)</td>
<td>10.64 ± 3.08</td>
<td>8.76 ± 5.72</td>
<td>5.93 ± 3.56</td>
<td>0.008*</td>
</tr>
</tbody>
</table>

Values are means ± SD.

*FMD, flow-mediated dilation.

Significant difference between control group and HIV receiving HAART.
Our subjects did not have any other cardiovascular risk factor that could cause ED except smoking. Owing to the high prevalence of smoking in our population we could not select a sufficient number of non-smoking patients; however, there were no significant differences in smoking habit between the three groups.

Previous works have studied endothelial function in HIV-infected patients by brachial artery FMD, which is correlated with the risk of coronary disease.25-26 This ultrasound technique is non-invasive, accurate and reproducible.27 Most of the studies of endothelial function compare FMD in groups with cardiovascular risk factors or cardiovascular disease and healthy controls. However, the absolute values of FMD vary across studies: FMD varies between different populations, and only a small part of this variability can be explained by technical variations of the FMD assessment method, such as the location and duration of the occlusion.28 A reference value for FMD to be used as an indicator of cardiovascular risk has not yet been established due to this variability of FMD values across different populations.28

Stein et al.17 studied endothelial function in 37 HIV-infected patients under antiretroviral therapy and found that 22 patients receiving PI had ED compared with 15 who received other antiretroviral treatments other than PI. However, patients receiving PI had mild hypercholesterolemia and intermediate-density lipoprotein cholesterol and VLDL-C levels above the normal range: these dyslipidaemias cause ED independently from other risk factors.24,29 On the other hand, Nolan et al.18 did not find any differences in endothelial function when comparing brachial artery FMD in 24 HIV-infected patients treated with PI and 24 non-infected controls. In this study, among HIV-infected patients an explanatory multivariable linear regression model showed significant associations between FMD and baseline artery diameter, pulse pressure, CD4 cell count and age, whereas there was no significant association with smoking status, body mass index, total cholesterol and HOMA index. More recently Bonnet et al.19 studied endothelial function in 49 HIV-infected children (among which 34 received antiretroviral therapy) without any cardiovascular risk factors, compared with 24 healthy controls. They found that HIV-infected children had a significantly lower FMD than controls. There were no significant differences in endothelial function between treated and non-treated patients, even though there were 15 patients with increased cholesterol and/or triglyceride levels among those receiving PI.

One of the major limitations of our study is the small sample size. This is due to the strict inclusion criteria, because we intended to study patients without any major cardiovascular risk factors (except smoking) and with low or mild cardiovascular risk. Other studies of endothelial function in HIV-infected patients have included a similar number of subjects, such as the one performed by Stein et al.17 which included 37 patients. Although our sample size was enough to find significant differences in FMD between the HAART-treated group and the controls, our study was probably underpowered to detect a smaller difference between the HAART-treated and the naive group.

HIV-infected patients under antiretroviral therapy in our study showed a significantly lower FMD than healthy controls. Non-treated HIV-infected patients showed intermediate values of FMD compared with the other two groups, although this was not statistically significant. Given that our patients did not have other major cardiovascular risk factors (except smoking, which was evenly distributed among the three groups), these differences could be attributed to the combination of HIV infection and antiretroviral therapy. On average, HIV-infected patients treated with HAART had FMD that was 4.71% lower than controls (P = 0.007). This effect of HIV infection and HAART on FMD decreased slightly to 4.3% after adjusting for potential confounders (basal artery diameter, age, sex, smoking, pulse pressure and total cholesterol). After adjusting for these variables there was still evidence of there being an effect of the combination of HIV and HAART on endothelial function (P = 0.039). Some studies have found ED in patients over 40 years of age,30 and even in patients between 30 and 39 years of age.31 However, other studies find significant ED only in patients over 65 years compared with younger subjects.32,33 In our study, age was significantly higher in the group of treated HIV-infected patients. However, the effect of age on FMD was small and not statistically significant after adjusting for other variables in the multivariable analysis. This could be due to the fact that the subjects in this group were all under 64 years, and even if there could be a possible influence of age on endothelial function, it might not be as strong in patients under 65 years of age as in older patients, and therefore it would not be clinically evident.

Although all subjects had cholesterol and triglyceride levels within the normal range, treated patients had higher levels of total cholesterol and LDL-C. Naive patients had lower levels of HDL-C than the control group. The lipid profiles found in our patients are consistent with previous studies that show that HIV-infected, non-treated patients have substantial decreases in total cholesterol, HDL-C and LDL-C, and that initiating HAART afterwards is associated with increased levels of total cholesterol and LDL-C, with little increase in HDL-C.34 None of these variables showed correlation with FMD, and the differences in FMD between HAART-treated patients and controls remained significant after adjusting independently for each of these variables. Since cholesterol levels were within the normal range, we would expect the effect of lipid profiles on FMD to be small. Although previous studies have found an association of ED with dyslipidaemia,14 Nolan et al.18 did not find significant correlations between FMD and triglyceride, LDL-C, HDL-C or total cholesterol levels. Stein et al.17 did not find any correlations between FMD and any lipid parameter; however, among patients receiving PI, the levels of several lipoproteins predicted FMD.

The proportion of women differed among the groups. Given that ED is more frequent in men than in pre-menopausal women of similar age,30 the different proportions of women among the group has to be taken into account. However, the values of FMD did not show statistically significant differences between men and women.

The distribution of hepatitis C infection also differed among the groups, reflecting the high prevalence of hepatitis C in HIV-infected patients compared with the general population.32 To date, an effect of HCV on FMD has not been demonstrated. One study has evaluated the influence of hepatitis C infection on brachial artery FMD in 67 HIV-infected patients, and there were no differences in FMD between patients infected and not infected by HCV.36 In our study, FMD did not show statistically significant differences when comparing subjects infected with HCV and those who were not infected. Also, the differences in FMD found between the group treated with HAART and the control group remained statistically significant after adjusting for hepatitis C infection.
Lipodystrophy and insulin resistance are associated with PI and could account for an increased cardiovascular risk in HIV-infected patients.37 Although only four of our subjects had insulin resistance, three of them were in the group of treated patients: this fact could have had an influence in the lower FMD observed in this group, but the low number of cases does not allow us to draw conclusions. We could not find any influence of lipodystrophy on FMD.

Endothelial function in naive HIV-infected patients did not show significant differences with treated patients or healthy controls. However, FMD in this group was lower than that of controls and higher than that of treated patients, although these results did not show statistical significance. The hypothesis of endothelial damage being induced by HIV infection has been suggested by previous studies that demonstrated that HIV-infected patients had increased plasma levels of endothelial procoagulant and proinflammatory mediators, which are markers of ED.38–40 This is also congruent with autopsy series published before the advent of HAART, which showed atherosclerotic lesions in HIV-infected patients without any other major cardiovascular risk factors.41 However, our results of FMD only showed statistical significance when comparing the HIV-infected, HAART-treated group with the control group; these results support that it is the combination of HIV infection and HAART what is associated with ED.

As other studies have suggested,42 we would expect a lower FMD in patients treated with PI compared with patients treated with other antiretroviral drugs, but we did not find any differences in endothelial function between these two subgroups. We did not find any association between CD4+ cell count or viral load with FMD; this is consistent with the results found by Stein et al.17

The major contribution of our study is the evaluation of the effect of HIV infection and its treatment on endothelial function among patients without any other major cardiovascular risk factors and with low or moderate cardiovascular risk and normal cholesterol and triglyceride levels. Previous studies have not specifically evaluated this group of patients. In conclusion, our study shows that ED is present in HIV-infected patients treated with HAART who have low or mild coronary risk. ED is an early marker of atherosclerosis, and these results are congruent with recent epidemiological studies that showed a higher risk of myocardial infarction in HIV-infected patients receiving HAART.11 HIV-infected patients treated with HAART might be considered as having additional cardiovascular risk even in the absence of other traditional cardiovascular risk factors, and effort should be made to prevent cardiovascular disease and treat other modifiable cardiovascular risk factors in this population. More studies are needed to determine the role and indications of pharmacological therapies such as statins, which not only reduce lipid levels but also revert ED.43

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Transparency declarations

None of the authors has any conflict of interest.

References

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