Influence of immune activation and inflammatory response on cardiovascular risk associated with the human immunodeficiency virus

Luis M Beltrán1
Alfonso Rubio-Navarro2
Juan Manuel Amaro-Villalobos2
Jesús Egido2,4
Juan García-Puig1
Juan Antonio Moreno2

1Metabolic-Vascular Unit, Fundación IdiPAZ-Hospital Universitario La Paz, Madrid, Spain; 2Vascular, Renal, and Diabetes Research Lab, IIS-Fundación Jiménez Díaz, Madrid, Spain; 3Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Madrid, Spain; 4Fundación Renal Iñigo Álvarez de Toledo-Instituto Reina Sofía de Investigaciones Nefrológicas (FRIAT-IRSN), Madrid, Spain

Correspondence: Juan Antonio Moreno
Vascular, Renal, and Diabetes Research Lab, IIS-Fundación Jiménez Díaz, Madrid, Spain
Tel +34 915 504 800 ext 3168
Email jamoreno@fjd.es

Abstract: Patients infected with the human immunodeficiency virus (HIV) have an increased cardiovascular risk. Although initially this increased risk was attributed to metabolic alterations associated with antiretroviral treatment, in recent years, the attention has been focused on the HIV disease itself. Inflammation, immune system activation, and endothelial dysfunction facilitated by HIV infection have been identified as key factors in the development and progression of atherosclerosis. In this review, we describe the epidemiology and pathogenesis of cardiovascular disease in patients with HIV infection and summarize the latest knowledge on the relationship between traditional and novel inflammatory, immune activation, and endothelial dysfunction biomarkers on the cardiovascular risk associated with HIV infection.

Keywords: HIV, cardiovascular disease, immune activation, inflammation, antiretroviral therapy

Importance of cardiovascular disease in patients infected with the human immunodeficiency virus

In regions with universal access to care and antiretroviral therapy (ART), the prognosis of patients infected with the human immunodeficiency virus (HIV) has improved substantially.1-4 In the last 2 decades, the incidence and mortality of acquired immunodeficiency syndrome (AIDS)-defining illnesses (associated with severe immunosuppression in advanced stages of HIV infection) have been dramatically reduced, whereas the role of non-AIDS comorbidities has risen.5-9 A marked decrease in overall mortality due to AIDS-defining causes has been observed, while the proportion of deaths from other causes has increased, including those caused by cardiovascular disease (CVD).6-9 Similarly, hospitalizations due to AIDS-defining illnesses have decreased in European and North American populations, while admissions for non-AIDS diseases and CVD have increased.10,11

Patients with HIV infection have higher atherosclerotic CVD rates than the general population.12 HIV patients experience more clinical cardiovascular events (coronary heart disease13-15 and peripheral artery disease),16 and subclinical cardiovascular damage (elevation of intima–media thickness [IMT]),17 coronary calcification,18 abnormal ankle–brachial index,19 silent myocardial ischemia,20 or endothelial dysfunction).21 In addition, the incidence of ischemic stroke in the HIV-infected population is considerably high, particularly in young adults, although no studies have determined whether stroke risk is greater in this population.22,23

Besides atherosclerotic coronary heart disease, other cardiac abnormalities have been associated with HIV infection.24 Thus, in the pre-ART era, a high incidence of
dilated cardiomyopathy with left ventricular dysfunction related to viral myocarditis was reported, mainly during the AIDS stage. More recent studies, in settings with unrestricted access to ART, reported a low prevalence of dilated cardiomyopathy, but a high burden of subclinical myocardial disease (cardiac steatosis, myocardial fibrosis, and alterations in cardiac function) in HIV patients as compared to uninfected controls. Moreover, HIV patients may be at an increased risk of sudden arrhythmic death. The prevalence of prolonged corrected QT, a major risk for polymorphous ventricular tachycardia (Torsades de pointes) and sudden arrhythmic death, is also increased in HIV patients. In this regard, sudden cardiac death rate (due to atherosclerotic and/or arrhythmic causes) is 4.5-fold higher in HIV-infected patients than among those observed in the general population.

On the other hand, the mean age of the HIV population is increasing due to the effectiveness of ART and increased life expectancy, favoring the development of age-associated comorbidities, many of which are related to CVD, such as type 2 diabetes mellitus (T2DM), hypertension (HT), and chronic kidney disease (CKD). In the Swiss HIV Cohort Study, which gathered patient data from 1990–2010, the proportion of patients older than 50 years increased from less than 5% to just over 30%. It is expected that if this trend continues, in the next decade, 50% of patients in this cohort will be above 50 years.

In addition to chronological aging, it is believed that HIV patients experience accelerated biological aging, thus contributing to the early development of age-related comorbidities. Patients with HIV infection have a higher prevalence of noninfectious comorbidities commonly seen in the elderly (T2DM, CVD, osteoporosis, and CKD). An interesting case-control study in an Italian population found a prevalence of comorbidity in HIV patients equivalent to that observed in control individuals 10–15 years older. As seen in these studies, we are witnessing a change in the patterns of morbidity and mortality among the HIV-infected population, leading researchers to shift the focus to non-AIDS comorbidity, where CVD plays a central role.

**Etiopathogenesis of cardiovascular disease in patients with HIV infection**

The higher cardiovascular risk observed in patients with HIV infection is due to a combination of several determinants, including factors related to antiretroviral treatment, the inherent impact of the infection, a high prevalence of traditional cardiovascular risk factors among HIV-infected individuals, and the presence of other factors that occur more frequently in these patients: coinfection with hepatitis C virus (HCV), coinfection and the replication of herpes family viruses, or the development of CKD (Figure 1).

**Antiretroviral drugs**

Initially, the elevated cardiovascular risk observed in HIV patients was attributed to metabolic alterations associated with ART, due particularly to the effect of viral protease inhibitors (PI), whose introduction into clinical practice coincided with the first reported cases of ischemic heart disease in HIV patients. This relationship between CVD and ART was subsequently confirmed in epidemiological studies. The most representative study, the Data Collection on Adverse Events of Anti-HIV Drugs Study (DAD Study), showed a significant increase in acute myocardial infarction (AMI) incidence upon exposure to ART, with an increased AMI risk of 26% after 6 years of treatment. The increased cardiovascular risk associated with ART has been attributed to deleterious metabolic effects of these drugs, which favor the development of hypercholesterolemia and hypertriglyceridemia, insulin resistance, and T2DM. These alterations may occur either independently or as part of other disorders, such as metabolic syndrome or lipodystrophy. To a greater or lesser extent, the appearance of these entities has been reported in patients treated with PI drugs, nucleoside/nucleotide analog reverse transcriptase inhibitors (NRTIs) and non-nucleoside/nucleotide reverse transcriptase inhibitors. These alterations depend on the type of drug administered, and drugs belonging to the same family may have different effects. While these adverse effects have decreased with the new generation of antiretroviral drugs, the initiation of ART is usually associated with increased plasma lipids (triglycerides and total cholesterol with elevations in low-density lipoprotein [LDL] cholesterol [LDL-C] and, to a lesser extent, high-density lipoprotein cholesterol [HDL-C]) which, in part, could also be related to the weight gain observed after starting ART.

In addition to these metabolic effects, the use of some antiretroviral drugs may induce other proatherogenic effects. Studies conducted in vitro and in healthy volunteers have revealed that some antiretrovirals – mainly PIs, but also NRTIs – could impair endothelial function, and increase oxidative stress and inflammation, inducing the early onset of senescence markers in endothelial and mononuclear cells. However, the data of many clinical studies suggest that ART dampens inflammation, immune activation and endothelial dysfunction in HIV-infected patients, probably through the suppression of HIV replication, as we further discuss.
HIV infection

In recent years, the ART-dependent atherosclerosis hypothesis has been challenged. Evidence from experimental and observational studies, especially the findings of the Strategies for Management of Anti-Retroviral Therapy Study (SMART Study), has redirected attention from ART to the consequences of HIV infection itself. In this study, two different therapeutic strategies were compared. In the first group, ART was interrupted when a recovery of the immune system was achieved and CD4+ lymphocytes were above 350 cells/mL, whereas in the second group, ART was maintained continuously, regardless of CD4+ levels. Patients in whom the treatment was discontinued showed increased complications associated with immunosuppression and an increased risk of all-cause mortality. Moreover, patients assigned to discontinuous therapy exhibited an unexpected increase in cardiovascular outcomes in spite of less exposure to antiretroviral drugs. These results suggested that uncontrolled HIV infection might have a greater influence on CVD than ART.

HIV infection may increase cardiovascular risk by several mechanisms: 1) persistent inflammation and immune activation; 2) endothelial damage; 3) increased thrombotic activity; 4) higher oxidative stress; and 5) indirect metabolic disorders. HIV infection leads to the activation of several inflammatory pathways, causing the release of cytokines and endothelial adhesion molecule expression that facilitate adhesion and the transmigration of leukocytes. There is a close relationship between endothelial dysfunction and inflammation/immune activation. Various cytokines induce endothelial activation and alter its functionality. Additionally, HIV produces direct endothelial cell damage, increasing endothelial permeability, favoring apoptosis and increasing the expression of adhesion molecules (E-selectin, VCAM-1, and ICAM-1).

HIV infection is also accompanied by immune activation, as determined by the elevation of several activation markers on monocytes/macrophages (sCD163, sCD14, and CD14+/CD16+ monocyte expansion) and the increased proportion of activated CD8 T-lymphocytes human leukocyte antigen (HLA)-DR+CD38+. Monocytes/macrophages play a central role in the genesis and development of atherosclerosis. Thus, in atherosclerotic plaques, macrophages phagocytize modified lipoproteins, promote proinflammatory and chemotactic cytokine secretion, and mediate cholesterol efflux from the arterial wall. HIV infection increases the proportion of CD14+/CD16+ monocytes, as it exhibits an activated...
phenotype with increased secretion of proinflammatory cytokines.\textsuperscript{35,36} Furthermore, HIV blocks the adenosine triphosphate-binding cassette transporter A1 (ABCA-1) pathway, suppressing reverse cholesterol transport from arterial wall macrophages to HDL particles, and favoring the accumulation of foam macrophages within atherosclerotic plaques.\textsuperscript{62}

Inflammation and immune activation are also associated with increased thrombotic activity, with the elevation of biomarkers such as D-dimer (a fibrin degradation product that may be elevated in response to inflammatory stimuli and bacterial translocation), von Willebrand factor, and fibrinogen.\textsuperscript{63}

HIV also induces oxidative stress, impairing the mechanisms of DNA repair and promoting the accumulation of oxidative lesions.\textsuperscript{64} Furthermore, HIV promotes atherogenesis through its metabolic effects, mainly decreasing HDL-C and apoA1, decreasing LDL particle clearance, as well as increasing triglycerides and very LDL-C. This pattern is associated with a high prevalence of proatherogenic small and dense LDL particles.\textsuperscript{65–67} It has been proposed that circulating HDL particles in different proinflammatory conditions are functionally less active and are therefore less atheroprotective, reducing their ability to perform cholesterol efflux.\textsuperscript{68} However, this scenario has not been explored specifically in HIV infection.

Inflammation, immune activation, and prothrombotic state driven by HIV infection may participate not only in primary atherosclerosis, but also in occlusive complications after arterial revascularization procedures. It has been reported that HIV patients may have higher rates of stent restenosis and stent thrombosis after percutaneous coronary intervention.\textsuperscript{69–71} However, the results are not homogeneous and some studies report no differences in revascularization rates or major cardiac events after percutaneous coronary intervention in HIV-positive patients compared to age- and sex-matched HIV-negative subjects.\textsuperscript{72,73}

### Traditional cardiovascular risk factors

HIV patients show a high prevalence of certain traditional cardiovascular risk factors, such as smoking, dyslipidemia, and T2DM.\textsuperscript{12,74–76} The importance of these cardiovascular risk factors has been demonstrated in several cohort studies, highlighting a strong association between HIV and CVD, one that is even stronger than the link between ART and CVD. However, it is important to note that both ART and HIV infection may also induce dyslipidemia and diabetes.

### Lifestyle

Smoking is very common in HIV patients, more so than in the general population; between 35% and 72% of HIV-infected individuals smoke depending on the population analyzed.\textsuperscript{77–81} Dietary habits also appear to be worse in HIV patients. In a case-control study that included 356 HIV-infected patients and 162 healthy volunteers, it was found that infected patients had significantly higher trans-, saturated-, and total fat and cholesterol consumption.\textsuperscript{82} One potential explanation for this difference is that without appropriate dietary control, many HIV patients have a greater caloric intake in order to compensate for lipoatrophy. Interestingly, in HIV patients that started ART, the incidence of dyslipidemia was significantly lower in those subjects who initiated a hypocaloric and low saturated fat diet as compared with patients who did not undergo a dietary intervention.\textsuperscript{41}

### Metabolic cardiovascular risk factors

Patients with HIV infection share the same predisposing factors for the development of dyslipidemia, diabetes, or metabolic syndrome as the general population.\textsuperscript{79} However, in these individuals, other factors coexist such as the HIV infection itself, ART, and/or HCV coinfection, which could explain the higher prevalence of abnormal carbohydrate and lipid metabolism observed in this population. In the DAD study,\textsuperscript{76} the prevalence of dyslipidemia at baseline was 45.9%. It is expected that this prevalence would decrease with the use of lipid-lowering and antiretroviral drugs with a better metabolic profile. However, recent data from the Spanish cohort CoRIS\textsuperscript{81} showed that the prevalence remained elevated, as 27% of patients exhibited hypercholesterolemia, 36% low HDL cholesterol, and 19% hypertriglyceridemia. The frequency of abnormal carbohydrate metabolism has decreased in recent years, revealing a presence of diabetes of 17% in older cohorts,\textsuperscript{76} although a recent analysis found only 2.9% of the cohort to be diabetic.\textsuperscript{81} Patients with HIV infection also have a high prevalence of metabolic syndrome, around 25%.\textsuperscript{81,83,84}

### Hypertension

The prevalence of HT in patients with HIV infection does not appear to be greater than in non-HIV individuals.\textsuperscript{79} A recent meta-analysis showed lower levels of systolic and diastolic blood pressure in HIV-infected patients compared to HIV-negative individuals.\textsuperscript{85} Interestingly, it has been hypothesized that in spite of normal brachial blood pressure, HIV patients may have higher arterial stiffness than healthy controls.\textsuperscript{86,87} emerging as an early marker of vascular damage related to HT; however, the data remain conflicting.\textsuperscript{88}
Additional factors
In addition to the HIV infection itself, other factors may be involved in the increased vascular risk in patients with HIV infection, such as the presence of chronic coinfections (HCV or herpes family viruses) and CKD. HCV infection promotes inflammation, platelet activation, endothelial dysfunction, and increased production of reactive oxygen species. In the general population, HCV infection has been associated with a higher prevalence of subclinical atherosclerosis and overt CVD. Similarly, in HIV patients, HCV coinfection has been associated with a higher frequency of atherosclerotic plaques (carotid or femoral), stroke, and AMI when compared to non-HCV coinfected patients.

Latent infection with a virus of the herpes family has atherogenic effects and is associated with subclinical atherosclerosis. It has been hypothesized that herpes viruses may have more serious cardiovascular effects in HIV-infected patients, contributing to immune activation and inflammation. Cytomegalovirus (CMV) infection has been associated with atherosclerosis in HIV-infected patients. CMV-specific T-cell responses and CMV immunoglobulin G levels have been associated with increased carotid atherosclerosis. Moreover, other herpes viruses have been implicated. A case-control study that evaluated the association between subclinical coronary atherosclerosis and markers of CMV, herpes simplex virus 1 and 2, and human herpes virus type 8 in HIV patients, showed that herpes simplex virus 2 was independently associated with the presence of subclinical coronary atherosclerosis, supporting the proatherogenic role of the herpes virus in this population.

Finally, CKD is more frequent in HIV patients, and this factor is widely associated with CVD. This higher prevalence of renal disease can be explained by several factors, including a direct effect of HIV, the potential nephrotoxicity of some antiretroviral agents, the presence of traditional cardiovascular risk factors such as diabetes, and the development of atherosclerosis, which is bidirectionally associated with CKD. It is important to note that although some antiretroviral drugs may cause renal toxicity, many studies have shown that ART slows the decline of the estimated glomerular filtration rate, probably related to the effect of HIV viral suppression on glomerular function.

Inflammation, immune activation, and endothelial dysfunction in patients with HIV infection
Multiple biomarkers of inflammation, immune activation, and endothelial dysfunction associated with CVD in the general population have been studied in HIV patients (Table 1). Numerous inflammatory mediators and adhesion molecules are elevated in the HIV population, including high-sensitive C-reactive protein (hsCRP), interleukin (IL)-6, soluble receptors of tumor necrosis factor (sTNFR), soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1), or asymmetric dimethylarginine (ADMA).

Some of these biomarkers have been associated with the presence of subclinical vascular disease and/or cardiovascular events in HIV-infected patients. Thus, hsCRP predicts the risk of CVD and all-cause mortality in the HIV population. High levels of IL-6 are also associated with an increased risk of death from any cause and cardiovascular events. Moreover, sTNFR has been associated with non-AIDS-defining morbid events during ART, including CVD. In HIV patients, the levels of sVCAM-1 have been associated with carotid IMT and carotid plaques, whereas ADMA levels have been related with coronary calcium score, all of which are surrogate markers of atherosclerosis.

Immune activation markers are also elevated in the HIV population. Soluble markers such as sCD163 and sCD14, and the proportion of activated subsets of monocytes (CD14+/CD16+) and CD8 T-cells (HLA-DR+CD38+), are increased in HIV patients. Our group has recently reported that HIV patients also have lower levels of soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK), a multifunctional cytokine involved in various atherogenic processes through its interaction with Fn14 and CD163. sCD163 levels have been associated with the presence of subclinical atherosclerosis in patients with HIV infection. In 102 young HIV-infected men who were asymptomatic and had a low or undetectable viral load, sCD163 levels were independently associated with the percentage of noncalcified coronary plaques in both the overall analysis and in the 69 patients with undetectable viral RNA. These results were replicated in a study with 60 HIV-infected women that showed higher levels of sCD163 in those with noncalcified coronary plaques. Furthermore, in a similar scenario, sCD163 levels correlated positively with inflammation, as measured by aortic positron emission tomography. In both cases, neither the presence of coronary plaques nor vascular inflammation was associated with other biomarkers of CVD, such as hsCRP or D-dimer. sCD14 levels and CD14+/CD16+ monocytes have also been associated with coronary artery calcium score. These results suggest that monocyte–macrophage activation could play a central role in both coronary and aortic atherosclerosis in HIV patients on effective ART, independently of classical inflammatory
Table 1 Biomarkers of inflammation, immune activation, and endothelial dysfunction associated with CVD in the general population

<table>
<thead>
<tr>
<th></th>
<th>Association with CVD in non-HIV patients</th>
<th>Effect of HIV*</th>
<th>Effect of ART##</th>
<th>Association with CVD in HIV-infected patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsCRP</td>
<td>↑↑ in CVD patients and predicts incident CVD114–117</td>
<td>↑↑110</td>
<td>↓↓124,130</td>
<td>CVD115,116 (not seen in Ford et al118)</td>
</tr>
<tr>
<td>IL-6</td>
<td>↑↑ in CVD patients and predicts incident CVD118–122</td>
<td>↑↑110</td>
<td>↓↓121</td>
<td>CVD116–118</td>
</tr>
<tr>
<td>sTNFR I</td>
<td>↑↑ in LVH113</td>
<td>↑↑113,124</td>
<td>↓↓121,131</td>
<td>Subclinical atherosclerosis (IMT)132,133</td>
</tr>
<tr>
<td>Monocyte activation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sCD163</td>
<td>↑↑ in CAD, PAD, subclinical atherosclerosis177–179</td>
<td>↑↑18,19,121,124</td>
<td>↓↓121,124</td>
<td>Subclinical atherosclerosis (CoP)125–126</td>
</tr>
<tr>
<td></td>
<td>sCD14</td>
<td>Associated with subclinical atherosclerosis and incident CVD120</td>
<td>↑↑18,40</td>
<td>↓↓127,138</td>
</tr>
<tr>
<td></td>
<td>CD14+/CD16+ expansion</td>
<td>Associated with incident CVD183–185 (not seen in Jaipersad et al186 and Berg et al187)</td>
<td>↑↑18,59</td>
<td>↓↓121,134,b</td>
</tr>
<tr>
<td><strong>Endothelial disturbances</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sVCAM-1</td>
<td>↑↑ in CVD patients and predicts incident CVD188,190</td>
<td>↑↑11–113</td>
<td>↓↓130–133</td>
<td>Subclinical atherosclerosis (IMT, CoP180,191)</td>
</tr>
<tr>
<td>sICAM-1</td>
<td>↑↑ in CVD patients and predicts incident CVD184–185</td>
<td>↑↑11–113</td>
<td>↓↓130–133</td>
<td>No association with IMT in Hileman et al193</td>
</tr>
<tr>
<td>ADMA</td>
<td>↑↑ in CVD patients and predicts incident CVD192,193</td>
<td>↑↑14,124</td>
<td>↓↓134,135</td>
<td>Subclinical atherosclerosis (CAC122)</td>
</tr>
<tr>
<td>sTWEAK</td>
<td>↓↓ in CVD patients175,176</td>
<td>Low levels predict CV outcomes in PAD, HF, and CKD patients197–199</td>
<td>↓↓124</td>
<td>↓↓124</td>
</tr>
</tbody>
</table>

Notes: *Comparison of HIV-infected patients versus non-HIV-infected controls. ##Comparison of HIV-infected patients prior to and after initiating ART. *Nested case-control study; HIV-infected patients receiving ART presented with a lower proportion of CD16+ monocytes; no comparison prior to versus after ART.

Abbreviations: CVD, cardiovascular disease; HIV, human immunodeficiency virus; hsCRP, high sensitivity C-reactive protein; IL, interleukin; sTNFR, soluble receptors of tumor necrosis factor; LVH, left ventricular hypertrophy; HF, heart failure; IMT, intima-media thickness; CAD, coronary artery disease; PAD, peripheral artery disease; CoP, coronary plaques; AMI, acute myocardial infarction; CAC, coronary artery calcium; sVCAM-1, soluble vascular cell adhesion molecule-1; CoP, carotid plaques; sICAM-1, soluble intercellular adhesion molecule-1; ADMA, asymmetric dimethylarginine; PAH, pulmonary arterial hypertension; sTWEAK, soluble tumor necrosis factor-like weak inducer of apoptosis; CV, cardiovascular; CKD, chronic kidney disease; ART, antiretroviral therapy.

Biomarkers. In apparent contrast to these results, a study of 60 HIV-infected patients receiving ART with controlled viral replication found no association between carotid IMT and plaques with sCD14, sCD163, or proinflammatory monocyte subsets. However, the IMT was correlated with concentrations of fibrinogen and sTNFR-I, and subjects with carotid plaques had higher levels of sVCAM-1 and a higher percentage of CD38+HLA-DR+ CD8 T-cells. These results are not necessarily contradictory and may reflect the specific role of different immune responses in the genesis of different atherosclerotic lesions. Supporting this hypothesis, it has been recently reported that in HIV-treated patients, sCD14 was independently associated with coronary artery calcium, while T-cell activation and systemic inflammation biomarkers, but not sCD14, correlated with carotid IMT. To clarify this issue, more studies are needed to assess the relationship of these biomarkers with the incidence of different atherosclerotic lesions in different vascular territories.

**Role of ART in the control of inflammation, endothelial dysfunction, and immune activation**

Contrary to the initial perception, a number of data support the notion that ART has a net protective effect on CVD in HIV patients. It is hypothesized that this effect is mediated by ART’s ability to reduce inflammation, immune activation, and endothelial dysfunction by suppressing HIV replication (Table 1).

It has been reported that ART reduces inflammation and endothelial dysfunction biomarkers. A decrease in sVCAM-1, sICAM-1 and hsCRP was observed in 115 HIV-infected patients after 2 months and 14 months of antiretroviral treatment. In a further study, sTNFR-I,
sTNFR-II, sVCAM-1, sICAM-1, and IL-6 plasma levels were significantly decreased after 24 weeks and 96 weeks of ART.\textsuperscript{131} Additionally, ADMA levels also seem to be reduced after successful ART with suppression of viral replication.\textsuperscript{134,135}

A number of studies have also shown that immune activation decreases after ART. Data from two case-control studies suggest that sCD163 plasma levels decrease after ART.\textsuperscript{123,124} Moreover, ART-treated patients have a lower proportion of proinflammatory CD14+/CD16+ monocytes than patients who never received ART or those who discontinued this therapy.\textsuperscript{123,136} However, a reduction of sCD14 levels with ART has not been observed with similar concentrations before and after receiving treatment.\textsuperscript{137,138}

It is important to note that even in individuals with spontaneously suppressed viremia, the so-called “controllers”, ART reduced immune activation markers, specifically T-cell activation, and provoked a higher reduction of viremia.\textsuperscript{139} These patients showed higher subclinical CVD burden (coronary plaques or increased carotid IMT) than healthy individuals, in spite of maintaining suppressed viremia.\textsuperscript{140,141} Pereyra et al\textsuperscript{141} showed that controller HIV patients had a similar coronary disease burden as HIV patients on ART who exhibited suppressed viremia. In the study, controller HIV patients showed higher levels of sCD163, but no significant differences were observed in hsCRP plasma levels.\textsuperscript{141} These data support the key role of monocytes/macrophages in HIV-associated coronary atherosclerosis and the importance of ART in the reduction of activation of these cells, even in low viral replication situations.

However, it is important to note that ART did not completely reverse inflammation, immune activation, and endothelial dysfunction in HIV patients. In a study involving 781 patients from the SMART study and 8,500 HIV-seronegative control subjects from two large population-based studies (Multi-Ethnic Study of Atherosclerosis [MESA] study and Coronary Artery Development in Young Adults [CARDIA] study), the HIV patients had higher concentrations of hsCRP, IL-6, D-dimer, and C cystatin as compared with uninfected subjects, even when viral replication was suppressed with ART.\textsuperscript{148} Similar results were observed in a small case-control study, where ART reduced the concentrations of sVCAM-1, hsCRP, and sTNFR-II, although they remained elevated when compared with healthy subjects in spite of viral suppression.\textsuperscript{124} Also, sCD163 plasma levels decreased with ART but remained elevated as compared to healthy controls.\textsuperscript{123,124}

Altogether, these results support the claim that ART reduces immune activation, inflammation, and endothelial activation, explaining the favorable net effect on cardiovascular risk, in spite of the deleterious metabolic effects. Therefore, ART is a key factor in preventing CVD in patients with HIV. However, in spite of ART, these patients maintain a persistent state of immune activation, inflammation, and endothelial activation that could justify the increased frequency of CVD observed in HIV patients, even with stable suppression of viral replication.

Factors potentially involved in persistent inflammation and immune activation in HIV patients
Several factors could explain the persistent state of immune activation, inflammation, and endothelial activation in spite of the suppression of viral replication after ART (Figure 2).

Homeostatic drive and time to ART initiation
Sustained viral replication may promote an immune/inflammatory response that cannot be reversed after a certain point. Therefore, starting ART before reaching this immune/inflammatory set point may prevent the state of persistent inflammation and immune activation. Supporting this hypothesis, the results of several studies have demonstrated that starting ART with low CD4 counts and/or a lowest CD4 nadir was associated with worse immunologic outcomes, even if patients achieved effective viral suppression.\textsuperscript{142–144} Treating HIV infection in the acute phase significantly reduces the proportion of activated CD38+HLA-DR+ CD8 T-cells when compared to nontreated patients.\textsuperscript{145,146} In the Options Project,\textsuperscript{147} patients who started ART in the first 6 months after infection had a lower proportion of activated CD8 T-cells than those who initiated treatment 2 years or more after the infection. In another interesting study, Burdo et al\textsuperscript{123} showed that patients with chronic HIV infection experienced a decrease of sCD163 levels after 3 months of ART; however, the sCD163 plasma concentration remained elevated as compared with controls. By contrast, in patients with early HIV infection (<1 year postinfection), the sCD163 levels at 3 months of treatment were similar to those of controls.\textsuperscript{123} All together, these studies suggest that early ART could result in the decreased activation of CD8 T-cells and monocytes–macrophages, and they support the hypothesis that the activation of these cells could be reversed to normal levels with early ART.

Residual viral replication
Despite receiving effective ART, HIV patients may have residual viral replication below the detection limits of the
techniques commonly used, and/or they may have episodes of transient viral replication. It has been hypothesized that adding an additional antiretroviral drug could control this residual viral replication and reduce inflammation and immune activation, although the data are controversial. The results on the effect of ART intensification with maraviroc or raltegravir are contradictory, and the effect on the reduction of the inflammatory response, in any case, is modest.\(^ {148-152} \)

**ART-dependent effects**

Some antiretroviral drugs can induce endothelial dysfunction and oxidative stress and promote an inflammatory response. Drugs such as ritonavir, indinavir, lopinavir, zidovudine, and abacavir have been associated with these deleterious effects.\(^ {42-45} \) It has been suggested that other antiretroviral drugs, such as raltegravir, may have an additional beneficial effect on these processes, independently of the suppression of viral replication. Some studies have shown that substituting a PI or non-nucleoside/nucleotide reverse transcriptase inhibitors with raltegravir reduces the levels of circulating inflammatory markers such as IL-6, hsCRP, or D-dimer.\(^ {153-155} \)

**Coinfections**

Chronic coinfections with HCV or herpes viruses, very common in the HIV population, might activate inflammatory and immunological mechanisms, although HIV viral replication is suppressed.

**Bacterial translocation**

HIV causes damage in the intestinal mucosa, favoring the translocation of bacterial products that stimulate immune activation.\(^ {156-158} \) During acute infection phases, HIV severely damages the lymphoid tissue associated with the intestinal mucosa, with a massive depletion of T-cell lymphocytes. In patients with controlled chronic HIV infection, this lymphoid tissue cannot fully recover, and a predisposition to bacterial translocation persists in spite of ART.\(^ {159,160} \)

**Established atherosclerosis**

Atherosclerosis is, by itself, a process that is accompanied by persistent inflammation and immune activation.\(^ {161} \) The development of atherosclerotic lesions prior to the start of suppressive ART could be partially responsible for the persistent elevation of inflammation and immune activation biomarkers (intraplaque foam cells and endothelial dysfunction). In this
regard, the use of rosuvastatin in patients receiving ART has revealed reduced circulating levels of sCD14 and decreased CD14+/CD16+ monocytes, but it did not affect systemic inflammatory biomarkers.162,163

Conclusion

Patients with HIV infection are at increased cardiovascular risk due to the HIV infection itself, and due to other factors such as ART-associated metabolic abnormalities, lifestyle, or the coexistence of chronic infections. ART was initially proposed as the causal factor for CVD in these patients; however, there is growing evidence supporting a net beneficial effect on CVD risk, presumably through the control of viral replication and the subsequent reduction of inflammation and immune activation. Nevertheless, in spite of optimal treatment, HIV patients maintain a state of persistent inflammation and immune activation that facilitates the development of CVD. In this regard, strategies to control these processes, in addition to ART and the treatment of traditional cardiovascular risk factors, may be useful in CVD prevention for HIV patients.

Acknowledgments

We thank Isabel Martin (Hospital Quirón San Camilo, Madrid) for her assistance in the design and preparation of the figures. We thank Oliver Shawn (Instituto de Investigaciones Sanitarias Fundación Jiménez Díaz [IIS-FJD]) for his editorial assistance. This work has been supported by grants from FIS (Programa Miguel Servet: CP10/00479, PI13/00802 and PI14/00883) and Spanish Society of Nephrology to Juan Antonio Moreno.

Disclosure

The authors report no conflicts of interest in this work.

References


