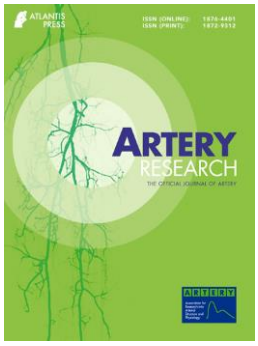

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REVIEW

Atherosclerotic vascular disorders in HIV infected patients

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Abstract Individuals infected with human immunodeficiency virus (HIV) frequently demonstrate a metabolic syndrome associated with atherosclerosis and cardiovascular disease. Extensive functional and structural arterial wall changes have been observed in these individuals. It is documented that these vascular changes are closely related to highly active antiretroviral therapy (HAART) -induced disorders of metabolic parameters such as serum glucose, cholesterol, triglycerides and arterial blood pressure. In addition, characteristics of the HIV infection itself such as immunodeficiency, viral load, duration of the disease, appear to influence the pathogenesis of these vascular changes. Intensive treatment of vascular dysfunction might be helpful in preventing or retarding the atherosclerotic process in HIV patients.

Introduction

Treatment with highly active antiretroviral therapy (HAART) in patients infected with human immunodeficiency virus (HIV) has been documented to significantly increase longevity.[1] The HAART includes a combination of protease inhibitors (PI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and nucleoside reverse transcriptase inhibitors (NRTI). However, adverse metabolic effects like dyslipidemia, increased blood pressure and insulin resistance have been attributed to HAART.[2,3] Therefore, the use of HAART raises concerns regarding the acceleration of the atherosclerotic disease in HIV-infected patients who now present an extended life expectancy because of HAART. An increase of approximately 26% of the risk for myocardial infarction has been reported in patients on HAART.[4] The detrimental effect of HAART on arterial wall properties[5–7] and atherosclerotic plaque formation[8] was proposed as a potential mechanism for the above finding. It is also documented that HIV infection itself may promote atherosclerosis through various mechanisms involving immunodeficiency, chronic inflammation progress, viral load, endothelial cell dysfunction, either directly or

Abbreviations: HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; PI, protease inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitor.

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indirectly via metabolic risk factors.[9–13] In this review we aimed to describe the vascular changes in HIV-infected patients, the available non invasive methods for the assessment of these changes as well as the current therapeutic strategies for preventing atherosclerosis in these patients.

Vascular changes in HIV patients

A few studies support direct deleterious effect of HIV infection on vascular properties through immunodepression.[9,11] Autopsy studies performed during the pre-HAART era reported the presence of atherosclerotic lesions in HIV-infected patients, even in the absence of traditional risk factors.[14] In a study by Coll et al.[9] the role of immunity and inflammation in the progression of atherosclerosis in 305 HIV-infected patients was studied. Measurements included plasma total cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, serum HIV-1 RNA and blood lymphocyte T CD4+ cell count. Age and total cholesterol were positively associated with IMT progression. CD4 cell count, SDF1-3′A, and the CX3CR-1249 I mutated alleles were associated with lesser IMT progression. Investigators concluded that the course of atherosclerosis in patients with HIV infection is influenced by polymorphisms in the SDF1 and CX3CR1 genes, by metabolic variables and the CD4 cell count.

Kaplan et al.[11] investigated the association of HIV infection, HIV disease parameters and antiretroviral medication use with subclinical carotid artery atherosclerosis among participants in The Women's Interagency HIV Study and Multicenter AIDS Cohort Study. Among HIV-infected individuals, a low CD4+ T-cell count was independently associated with an increased prevalence of carotid lesions. The investigators concluded that low CD4+ T-cell count is the most robust risk factor for increased subclinical carotid atherosclerosis in HIV-infected women and men.

A study by Francisci et al.[12] tried to assess whether patients with chronic HIV infection present endothelial dysfunction and whether this is the consequence of the infection or the HAART. Fifty-six HIV-infected patients were studied before and after starting HAART. Soluble P-selectin, soluble vascular cell adhesion molecule-1, monocyte chemoattractant protein-1 and von Willebrand factor were significantly higher in HIV-infected patients than in healthy controls, whereas soluble CD40 ligand and tissue type plasminogen activator were within normal range. During follow-up, soluble vascular cell adhesion molecule-1, monocyte chemoattractant protein-1 and von Willebrand factor but not soluble P-selectin decreased progressively, without significant differences between protease inhibitors and non-nucleoside reverse transcriptase inhibitors treatment. The authors suggested that chronic HIV infection, and not its pharmacological treatment, induces alterations of markers of endothelial function.

A study by Zangerle et al.[15] investigated 63 individuals with HIV infection, 34 of whom were asymptomatic for plasma lipids, soluble tumor necrosis factor receptor 75 (sTNF-R75) and other immune activation markers, namely urinary neopterin, beta 2-microglobulin, and the CD4+ T-cell count. The frequency and the extent of the decrease of HDL and LDL cholesterol and the increase in triglyceride levels were greater in HIV-infected patients with a CD4+ T-cell count below the median when comparing HIV infected individuals with CD4+ T-cell counts above and below 500 × 10(6)/L. Plasma levels of triglycerides correlated significantly however weakly with serum concentrations of sTNF-R75 but not at all with urinary neopterin or serum beta 2-microglobulin. HDL cholesterol correlated inversely with sTNF-R75 and to a lesser extent with urinary neopterin and beta 2-microglobulin. Thus, lipid-metabolic changes in patients with untreated HIV infection are closely related to chronic immune activation.

Increased levels of neopterin, a proinflammatory protein, are found in HIV-infected patients despite HAART treatment.[16] Neopterin is related to endothelial dysfunction and smooth muscle cell apoptosis through increased production of iNOS.[17] Endothelial dysfunction and smooth muscle cell apoptosis may alter microvascular permeability.[18] In a recent study[19] investigators noticed decreased forearm blood flow during reactive hyperemia in HIV-infected patients under HAART compared to patients naive to treatment. The investigators suggested that this microcirculatory dysfunction may be directly associated to a) HAART -induced cytotoxicity and dyslipidemia or b) to disease-induced endothelial dysfunction, mitochondrial toxicity on vascular cells and enhanced inflammatory process. Immune activation markers such as C-reactive protein and macrophage product neopterin have been shown to correlate with the extent and activity of coronary artery disease, and higher levels strongly predict unfavourable outcomes in addition to the traditional risk factors for cardiovascular disease.[20] The above immune activation markers are elevated in HIV-infected patients.[16]

Higher neopterin concentrations are well established to significantly predict the future course of HIV infection according to a study by Mildvan et al.[21] in 152 HIV-infected patients watched for a period of 344 days. Authors concluded that soluble markers of immune activation add prognostic information to CD4 counts and viral load for risk of disease progression in advanced HIV-1 infection.

The data derived from another study by Zangerle et al.[22] underscore the fact that both neopterin production and tryptophan degradation are triggered by immune activation. Tryptophan degradation is increased in HIV infection and partially reversed under HAART. Increased neopterin production indicates the presence of activated macrophages by proinflammatory cytokines, such as interferon. The antiproliferative activity of the proinflammatory cytokines leads to the withdrawal of important nutrients such as tryptophan, iron, and also lipids and incorporation in macrophages. When HAART reduces virus production, immune activation is reduced. Consequently, neopterin levels decrease, tryptophan levels increase, and iron and lipids are redistributed. According to Zangerle et al.[15,16] this transient increase of lipids could contribute to vascular changes and cardiovascular events in HIV-infected patients.

Furthermore increased carotid intima-media thickness was associated with the depletion of circulating myeloid dendritic cells in HIV-infected patients.[23] The depletion of dendritic cells in peripheral blood correlated with accelerated atherosclerosis in HIV-infected patients in spite of

a suppressive HAART regimen. Dendritic cells are immune cells that form part of the mammalian immune system. Their main function is to process antigen material and present it on the surface to other cells of the immune system, thus functioning as antigen-presenting cells.

In a cross-sectional study by Guaraldi et al,[24] 400 HIV-infected patients underwent cardiac computed tomography imaging to identify coronary artery calcium (CAC). Increased vascular age was observed in 162 patients (40.5%), with an average increase of 15 years over the chronological age. Chronological age, male sex, systolic blood pressure, duration of ART, fasting glucose level, fasting serum triglyceride level, total cholesterol level, low-density and high-density lipoprotein cholesterol levels, hypertension, and the presence of the metabolic syndrome were associated with increased vascular age while current CD4+ cell count was the only predictor of increased vascular age. The authors concluded that increased vascular age is frequent among HIV-infected patients and appears to be associated with CD4+ cell count.

According to Maggi et al[25] the ultrasonographic structure of the epi-aortic lesions in HIV-positive patients substantially differ from those of the plaques in atherosclerotic patients, although they share similar characteristics with patients affected by arteritis suggesting an extensive inflammatory infiltration of the vascular wall leading to vascular changes in HIV-infected patients. There seems to be a significant role of immune reconstitution in the onset of subclinical atheromatic lesions in these patients.[26]

In general, several studies have demonstrated that HAART is associated with vascular disorders in HIV patients. From the available antiretroviral medications, protease inhibitors have been associated with endothelial dysfunction and subclinical atherosclerosis despite a recent systematic review suggesting the opposite.[27]

Methods evaluating vascular disorders in HIV patients

Several non invasive methods have been used to evaluate vascular dysfunction in HIV infected individuals and therefore, to predict future cardiovascular risk. These methods include measurements of pulse wave velocity (PWV), augmentation index, AI (HR) a marker of wave reflections, reactive hyperemia parameters, endothelial dependent flow-mediated dilatation (FMD) of the brachial artery and carotid artery intima-media thickness (IMT) all of which are considered surrogate markers of atherosclerosis and prognostic markers of cardiovascular risk.[28–30]

Arterial stiffness in HIV patients

PWV is a direct estimate of arterial stiffness with a documented prognostic value for cardiovascular disease.[31] PWV is assessed by measuring the pulse transit time and the distance travelled between the two recording sites (pulse wave velocity [m/sec] = travel distance [m]/transit time [sec]). A simultaneous recording is performed by two pressure-sensitive transducers of two different pulse waves, usually, at the right base of the neck for the common carotid artery and over the right femoral artery. Measurement of the distance between the transducers over the body surface allow to obtain PWV (m/sec). An increase in arterial stiffness as assessed by measuring PWV in 'HIV-infected' patients compared to normal controls (Table 4) has been repeatedly documented.[32–34]

In a case–control study, Lekakis et al.[32] compared measurements of pulse wave velocity (PWV), arterial blood pressure, and markers of metabolic profile in 56 HIV-infected patients to 28 age- and sex-matched newly diagnosed untreated patients with hypertension and 28 healthy individuals. HIV-infected patients had higher PWV than healthy controls but lower PWV than hypertensives; however, patients on HAART had similar PWV with hypertensives. Patients on HAART had higher PWV than patients without (Fig. 1). In multivariate analysis, the independent determinants of increased PWV were HAART duration, serum cholesterol and mean or diastolic blood pressure. It appears to be an independent association between duration of antiretroviral therapy with increased arterial stiffness in HIV-infected patients.

According to a study by Schillaci et al.[33] aortic stiffness was increased in HIV-positive individuals receiving antiretroviral therapy including a protease inhibitor compared

Table 1 Studies concerning carotid atherosclerosis in HIV patients.

	Study population	Features studied	Endpoints
Lekakis et al. (Clin Sci. 2008)	71 HIV pts 29 CAD pts 25 healthy	IMT Metabolic parameters	Increased IMT is related to protease-inhibitor-related change of metabolic parameters
Hsue et al. (AIDS 2009)	368 HIV pts 93 healthy 33 HIV controls	IMT Infection/immune parameters	Chronic inflammation may account for early atherosclerosis
PERI study (Coron Artery Dis. 2008)	83 HIV pts 83 healthy	IMT CVD factors	HIV infection is associated with increased IMT and elevated prevalence of CVD factors
Lorenz et al. (Atherosclerosis 2008)	292 HIV pts 1168 healthy	IMT Infection and treatment parameters	HIV infection and HAART are independent risk factors for early carotid atherosclerosis
Jerico et al. (Stroke 2006)	68 HIV pts 68 HIV pts with CVD risk factors	HAART	HAART is an independent predictor for subclinical atherosclerosis

Table 2 Studies concerning endothelial dysfunction in HIV patients.

	Study population	Features studied	Endpoints
Charakida et al. (Circulation 2005)	83 HIV pts 59 healthy	FMD HAART Infection parameters	HIV infection in childhood is associated with adverse vascular changes
Lekakis et al. (Clin Sci. 2008)	71 HIV pts 25 healthy 29 CAD pts	FMD HAART Metabolic parameters	HAART induced lipid disorders lead to endothelial dysfunction
Solages et al. (Clin. Infect. Dis. 2006)	75 HIV pts 223 healthy	FMD HAART Metabolic parameters	HAART induced metabolic disorders lead to endothelial dysfunction

to normal controls. Furthermore, the investigators showed that pulse wave velocity was increased in parallel with longer exposure to protease inhibitors. In the same study, central aortic pressures, aortic augmentation index and aortic pulse wave velocity were compared between 32 HIV-infected patients treated with protease inhibitors and 32 HIV-uninfected control subjects. HIV-infected patients had a higher aortic pulse wave velocity and aortic augmentation than control subjects. Age and HIV infection independently predicted aortic pulse wave velocity after adjustment for several cardiovascular risk factors.

The above investigators[34] examined whether aortic stiffness is increased in HIV-infected patients who were not under antiretroviral treatment. Aortic pulse wave velocity (PWV), was determined in 39 untreated HIV-infected patients and 78 HIV-uninfected controls. The authors found that HIV-infected patients not receiving HAART had a higher aortic PWV than control subjects. Prevalence of the metabolic syndrome was higher in HIV patients than in age and sex-matched controls. Age, mean arterial pressure as a measure of distending pressure, and HIV infection independently predicted aortic PWV after adjustment for a consistent number of cardiovascular risk factors. In conclusion, aortic stiffness was increased in HIV-infected individuals who have never received antiretroviral therapy supporting the hypothesis that HIV infection is a risk factor for atherosclerosis.

A cross-sectional study by Sevastianova et al.[35] investigated the impact of antiretroviral therapy and the HAART-associated lipodystrophy on arterial stiffness in 42 HAART-treated lipodystrophic and 17 non-lipodystrophic patients. Pulse wave analysis and augmentation index were used to evaluate arterial wave reflection. There was no significant difference between the study groups in peripheral or aortic blood pressures and augmentation index. The investigators found that age, duration of antiretroviral therapy, lamivudine therapy and ritonavir therapy as well as cumulative exposure to protease inhibitors were significant determinants of augmentation index. Duration of antiretroviral therapy, cumulative exposure to nucleoside reverse transcriptase inhibitors and to protease inhibitors were identified as independent factors predicting an abnormal augmentation index.

Additionally, Van Vonderen et al.[36] evaluated the arterial stiffness in 77 HIV-infected men and 52 healthy controls. The investigators concluded that all patients with HIV infection had increased arterial stiffness compared to healthy controls. Furthermore, the use of HAART was associated with increased arterial stiffness.

Finally, Vlachopoulos et al.[37] studied the impact of HIV infection on arterial stiffness and wave reflections in the early disease stages. The authors provided evidence of decreased wave reflections and similar aortic stiffness, as assessed by PWV, in the early stages of HIV infection in treatment-naive patients compared to controls suggesting that subclinical inflammation and resultant peripheral vasodilatation constitute potential mediators of the pathophysiological process in the arterial wall.

In summary, there is substantial evidence that exposure to highly active antiretroviral therapy is a contributing factor for increased arterial stiffness in HIV-infected patients and that HAART may be linked to an increased PWV (32,33, 35).

Endothelial dysfunction in HIV patients

Assessment of endothelial function is a valuable tool for the prediction of acute coronary events in various clinical settings.[38–40] Several studies (Table 2) have shown that endothelial function, as assessed by flow mediated dilation of the brachial artery, is abnormal in HIV patients compared to normal controls.[5,7,41–43]

Table 3 Studies concerning microcirculation disorders in HIV patients.

	Study population	Features studied	Endpoints
Palios et al. (Microcirc. 2010)	60 HIV pts	HAART Reactive hyperemia	HIV pts under HAART present microcirculation disorders
Rui-Juan Xiu et al. (Microvasc. Res. 1991)	11 HIV pts 11 healthy	Infection parameters Microcirculation	HIV pts present microcirculation disorders
Monsuez et al. (J AIDS 2000)	29 HIV pts 19 healthy	Infection parameters Reactive hyperemia	HIV pts present reduced reactive hyperemia

Table 4 Studies concerning arterial stiffness in HIV patients.

	Study population	Features studied	Endpoints
Lekakis et al. (Am J Hypertens. 2009)	56 HIV 28 hypertensives 28 healthy	PWV Metabolic parameters	HIV patients on HAART had similar PWV with hypertensives. Patients on HAART had higher PWV than patients without. There is an independent association between duration of antiretroviral therapy with increased arterial stiffness
Schillaci et al. (Arterioscer Thromb Vasc Biol. 2005)	32HIV 32 healthy	PWV Infection parameters	HIV infection and age predict higher PWV values
Van Vonderen et al. (J AIDS. 2009)	77 HIV 52 healthy	Arterial stiffness HIV infection	HIV infection was associated with increased arterial stiffness
Schillaci et al. (Hypertension. 2008)	39 HIV 78 healthy	Arterial stiffness HIV infection	HIV infection is an independent risk factor for worse arterial stiffness
Sevastianova et al. (Antivir Ther. 2005)	59 HIV	Arterial Stiffness HAART	The use of protease inhibitors predicts abnormal arterial stiffness
Vlachopoulos et al. (Artery research 2009). Bottom of Form	51 HIV	Arterial Stiffness HIV infection	Decreased wave reflections and similar to normal aortic stiffness was found in the early stages of HIV infection

Charakida et al.[5] studied 83 HIV-infected children and a control group of 59 healthy children. Carotid intima-media thickness (IMT) and brachial artery flow-mediated dilatation (FMD) were measured. FMD was significantly reduced in the HIV-infected children compared with control subjects. The investigators concluded that HIV infection in childhood is associated with adverse structural and functional vascular changes that are most pronounced in children exposed to PI therapy.

Other investigators[7] compared measurements of brachial artery FMD between a group of 71 HIV-positive individuals, a group of 25 age- and sex-matched controls with similar risk factors and a group of 29 patients with established CAD. The authors found that the HIV-infected patients had higher FMD than patients with CAD but lower FMD than the matched healthy controls. In the above study, HIV-infected patients taking protease inhibitors had higher blood pressure, cholesterol and triglycerides than those not taking protease inhibitors. In multiple regression analysis reduced FMD was independently associated with elevated serum triglycerides. The authors concluded that HAART-induced hypertriglyceremia may be one of the mechanisms explaining impairment of endothelial function in HIV infected individuals.

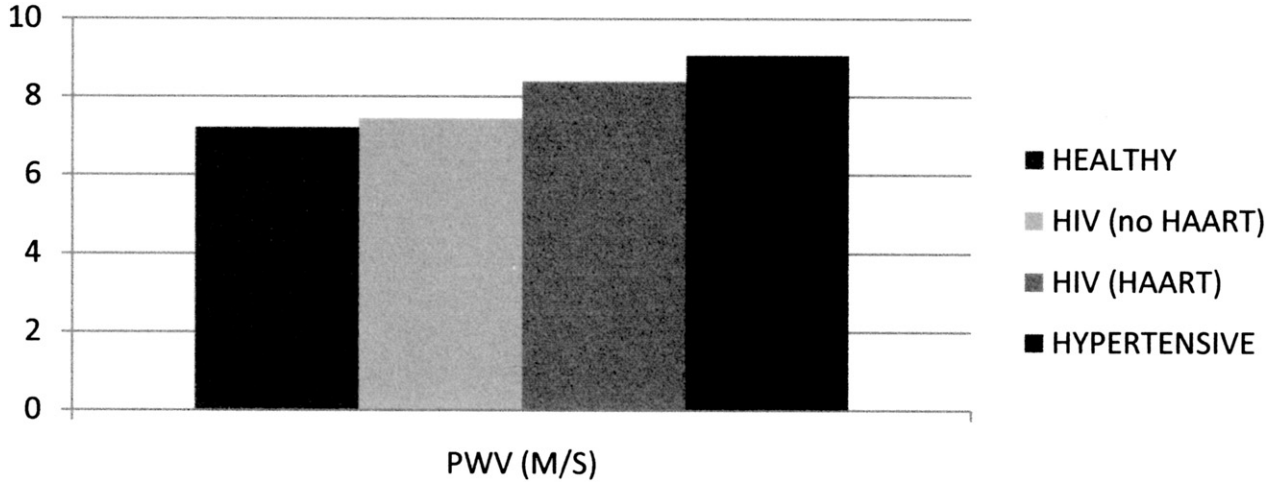

Figure 1 HIV infected patients appear with higher PWV than healthy controls and lower PWV than individuals with hypertension. HIV patients on HAART present higher PWV than HIV patients without therapy (modified from Lekakis J, Ikonomidis I, Palios J, Tsiodras S, Karatzis E, Poulakou G, et al. *Am J Hypertens*. 2009).

In a study by Solages et al.[41] endothelial function, as assessed by FMD, was compared between 75 HIV-infected patients and 223 healthy control subjects. HIV-infected patients had significantly impaired FMD, compared with control subjects. The difference in FMD values between the 2 groups remained statistically significant after adjustments for smoking status, sex, and body mass index. In multivariate analysis, lower alpha-high-density lipoprotein triglyceride level were significantly associated with FMD.

According to a study by Jiang B. et al.[42] HIV antiretroviral drug combination may induce endothelial mitochondrial dysfunction and reactive oxygen species production, but not apoptosis.

Furthermore, in a study by Flammer AJ et al.,[43] 39 HIV-infected individuals with suppressed viral replication on PI-containing regimens and high fasting low-density lipoprotein (LDL)-cholesterol were randomly assigned to continue the current PI or change to atazanavir. Atazanavir is a PI causing milder increases in blood lipids than other PI's. Twenty four weeks after initiation of atazanavir FMD was assessed. The switch from a PI regimen other than atazanavir to atazanavir therapy did not result in improvement of endothelial function despite significantly improved serum lipids in treatment-experienced patients. The investigators concluded that some HAART regimens may affect vascular function through a combination of atherogenic lipid profiles and direct detrimental effects on endothelium while other regimens including atazanavir may exert mainly direct detrimental effects on vascular function.

In summary, studies indicate that endothelial dysfunction is present in HIV patients[5,7,12,41–43] and is associated with the use of the antiretroviral agents as well as the inflammatory processes of HIV infection itself.

Carotid atherosclerosis in HIV patients

Carotid intima-media thickness (IMT) is a surrogate marker of atherosclerosis; it is associated with the extent of coronary atherosclerosis as well the occurrence of cardiovascular events in the general population.[44]

Several studies (Table 1) have reported that HIV-infected patients present abnormal values of IMT revealing subclinical atherosclerosis.[7,13,45]

Lekakis et al.[7] compared carotid artery IMT in HIV-positive individuals with age- and sex-matched controls with similar risk factors and patients with established CAD. Seventy-one HIV patients were compared with 29 CAD patients and 25 controls. The authors found that the HIV-infected patients had similar IMT values with patients with CAD patients and higher IMT than the matched healthy controls (Fig. 2). Blood pressure, glucose, cholesterol, duration of HIV disease, increased viral load, and use of protease inhibitors were the most important determinants of IMT respectively. The investigators suggested that increased IMT was closely related to protease-inhibitor-related changes of metabolic parameters in HIV —infected patients.

A previous study by Hsue et al.[13] evaluated the factors leading to HIV-associated atherosclerosis, by assessing carotid artery intima-media thickness in a diverse cohort of HIV-negative and positive adults. The investigators examined a unique group of HIV-infected patients who were untreated, had undetectable viral loads, preserved CD4 T-cell counts and were defined as "HIV controllers". Carotid intima-media thickness was measured in 494 participants, including 33 ''HIV controllers'', 368 HIV infected individuals and 93 HIV-negative controls. "HIV controllers" had higher intima-media thickness than HIV-negative controls even after adjustment for traditional risk factors. Intima-media thickness in HIV controllers was similar to antiretroviral-untreated HIV patients with detectable viremia.

Among all participants, intima-media thickness was strongly associated with the presence of HIV disease rather than viral load or CD4 T-cell count. Antiretroviral drug exposure was also associated with higher intima-media thickness. Thus, increased atherosclerosis with HIV infection can occur in the absence of antiretroviral therapy, detectable viremia, or overt immunodeficiency. The investigators concluded that chronic inflammation as reflected by elevated CRP levels in all HIV-infected patients, may account for early atherosclerosis in these patients.

PERI study[45] examined 83 HIV-infected and 83 healthy children and adolescents in order to compare carotid intima-media thickness (cIMT) of children and adolescents with and without HIV infection and to determine associations among independent socio-demographic, clinical or cardiovascular variables and cIMT. The cIMT was higher in HIV-infected

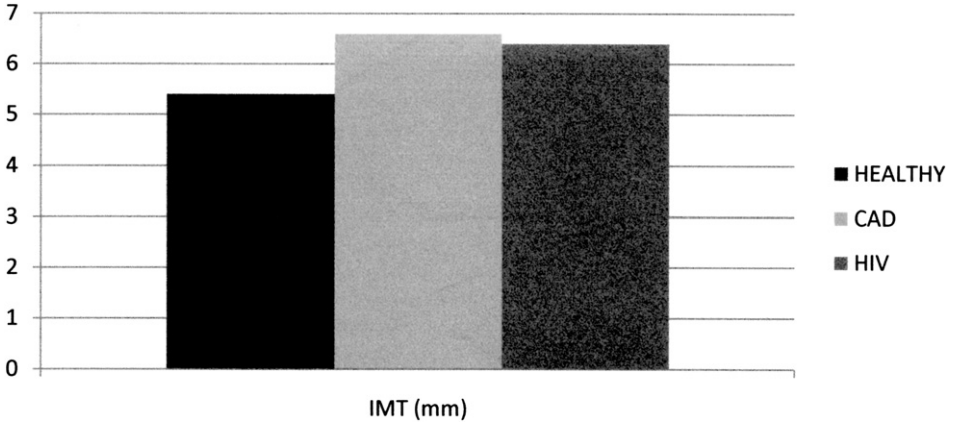

Figure 2 HIV infected patients appear with higher IMT than healthy controls and similar IMT to coronary artery disease patients (modified from Lekakis J, Tsiodras S, Ikonomidis I, Palios J, Poulakou G, Rallidis L, et al. *Clin Sci*. 2008).

individuals compared with controls Increased cIMT was positively associated with stavudine use, left atrial/aorta index, CD8 lymphocyte count and CD4 T-lymphocyte count. cIMT increment was negatively associated with total cholesterol and with CD8 zenith. In conclusion, HIV infection was associated with increased cIMT and elevated prevalence of cardiovascular risk factors.

Similarly, a case—control study by Lorenz et al.[46] emphasized the independent role of the duration of HIV infection as well as exposure to HAART in the development of higher IMT values. 292 HIV-positive subjects and 1168 age- and sex-matched controls were included. The investigators explored the effects of HIV status and antiretroviral medication on IMT using multivariate regression models. The IMT value of the common carotid artery (CCA) was higher in HIV-positive individuals than controls after adjustment for multiple risk factors. Thus, the investigators demonstrated that HIV infection and HAART were independent risk factors for early carotid atherosclerosis. Assuming a risk ratio similar to that in large population-based cohorts, the observed IMT elevation suggested that vascular risk is 4—14% greater and the "vascular age" 4—5 years higher in HIV-positive subjects compared to healthy controls.

Finally, a study by Jerico et al.[47] aimed to confirm the relationship between HAART therapy and subclinical carotid atherosclerosis among different grades of cardiovascular risk defined by the prevalence of traditional atherosclerotic risk factor. Sixty-eight HIV-infected patients with $<$ or $=$ 1 cardiovascular risk factors and 64 with $>$ or $=$ 2 risk factors completed the study protocol. Among the 132 enrolled patients, 93 were on HAART and 39 had never been on antiretroviral therapy.

Subclinical carotid atherosclerosis was found in 26.6% of the very low-risk group, 35.3% of the low-risk group and 76.5% of the moderate/high-risk group. Thus, 55 (41.7%) of the 132 HIV-infected patients had subclinical carotid atherosclerosis. The independent variables associated with carotid atherosclerosis were HAART exposure and 10-year coronary risk $>$ or $=$ 10%. In very low coronary risk HIV-infected patients, age, systolic blood pressure and HAART exposure were independently associated with subclinical carotid atherosclerosis. The authors concluded that HAART should be considered a strong, independent predictor for the development of subclinical atherosclerosis in HIV-infected patients, regardless of known major cardiovascular risk factors and atherogenic metabolic abnormalities induced by this therapy.

In summary, HIV-infected patients present abnormal values of IMT indicating subclinical atherosclerosis.[7,13,45—47] Measurement of IMT in HIV-infected patients may be useful in evaluating cardiovascular risk as increased IMT is associated with the extent of coronary atherosclerosis and predicts adverse cardiovascular event.

Microcirculatory vascular dysfunction in HIV patients

Investigators have demonstrated that reactive hyperemic blood flow in HIV-infected patients is decreased suggesting the presence of impaired vascular microcirculatory function.[19,48,49]

A recent study[19] investigated whether HIV- infected patients receiving HAART and patients who had never been treated with antiretroviral medication had differences in their vascular microcirculatory function. Forty HIV-infected male patients receiving HAART were compared to twenty male patients,who had never received HAART. Investigators assessed the forearm blood flow using venous occlusion strain gauge plethysmography. Patients on HAART had similar baseline forearm blood flow but lower maximal and percent (%) change in forearm blood flow during reactive hyperemia than patients who had never received HAART. Additionally, patients receiving HAART had higher total cholesterol levels than untreated patients. In a multivariable model including viral load, markers of HIV disease activity, duration of disease and metabolic factors, HAART was independently related with the (%) change in the forearm blood flow during hyperemia. Thus, HIV-infected patients receiving HAART presented abnormalities of vascular microcirculation in comparison with patients who had never received HAART.

In another study,[48] close d-circuit television microscopic observation of the microcirculation in the nail fold was compared between 11 HIV-infected patients and 11 healthy controls. There were severe microvascular disturbances in HIV-infected patients consisting of a) a suppression of the spontaneous, rhythmic adjustments of capillary blood perfusion, and b) damage to the endothelium of the capillary wall. In this study all patients were under HAART treatment.

Finally,in a study by Monsuez et al.[49] vascular reactivity was assessed noninvasively using finger-skin blood-flow monitoring by laser-Doppler flow in 29 HIV-infected patients. The investigators examined a group of 10 HIV-infected-patients with cardiac symptoms and/or HIV -related protease inhibitor-induced hyperlipidemia, a group of 19 HIV-infected patients free of cardiac disease, hyperlipidemia, and previous opportunistic infections and a control group of 19 healthy subjects. Laser-Doppler flow was measured at baseline and during post occlusive hyperemic response following transient interruption of brachial blood flow (reactive hyperemia). During reactive hyperemia, the absolute increase in flow was found to be lower in asymptomatic HIV-infected patients than in healthy controls. This abnormality was more pronounced in symptomatic patients. There was also a reduced peak/baseline flow ratio and a reduced hyperemic response. Thus, post ischemic reactive hyperemia was reduced in HIV-infected patients compared to healthy controls.

In conclusion, patients with HIV infection present abnormalities of arterial microcirculation (Table 3) as assessed by the reactive hyperemia parameters.

Prevention of vascular disorders in HIV patients

Cardiovascular prevention is required in more than one half of HIV-infected/treated patients to reduce the cardiovascular risk and thus to achieve a reliable effectiveness of modern antiretroviral therapy. As the prognosis of HIV patients improves continuously, this rate is also likely to increase in the future.[50]

A study by Schuster et al.[51] investigated the usefulness of systematic non invasive screening in HIV-infected patients. This study evaluated noninvasively cardiac morphologic characteristics and function in HIV-positive men receiving HAART for > or = 2 years with no clinical evidence of cardiovascular disease. A higher prevalence of LV diastolic dysfunction was revealed in HIV-infected patients while LV systolic function indexes were significantly lower. Pulmonary artery pressure was higher in HIV-infected patients compared with controls. Finally, exercise testing showed decreased exercise tolerance in HIV-infected patients, with no case of myocardial ischemia.

Another study by Lima et al.[52] analyzed the effect of a prevention program on the estimated cardiovascular risk calculated by three risk scores. Investigators prospectively evaluated 87 HIV-infected patients with elevated cardiovascular risk. Framingham (FRS), PROCAM and National Cholesterol Education Program (ATP-III) were used to estimate cardiovascular risk. Cardiovascular risk was defined as elevated if >10%. All patients received non-pharmacological (diet, exercise, smoking cessation) and, when appropriate, pharmacological therapy. All patients were under HAART and 56.3% were receiving protease inhibitors (PI). After 6-month follow up, intervention was associated to significant changes on triglycerides, total cholesterol and LDL-cholesterol. The authors concluded that an intervention program focused on reduction of traditional risk factors was able to decrease the frequency of HIV-infected patients with elevated cardiovascular risk estimation.

An ongoing study by De Lorenzo et al.[53] is aiming to assess whether rosuvastatin therapy could i) slow the progression of the carotid intima-media thickness over 2 years in HIV-infected patients, ii) reduce highly sensitive C-reactive protein (hs-CRP) inflammatory marker that is increased in HIV-infected patients iii) affect serum lipid levels (total cholesterol [TC], low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol and triglycerides [TG]) and apolipoproteins and finally to assess the safety of Rosuvastatin. For the first time, this study will investigate anti-inflammatory and anti-atherogenic effects of a pharmacological lipid-lowering agent in HIV-infected patients that may lead to the reduction of CVD.

Studies suggest that both HIV disease and its treatment may cause dyslipidemia similar to that seen with the metabolic syndrome. The most notable effects are elevated triglyceride levels and decreased high-density lipoprotein cholesterol levels, with or without elevated low-density lipoprotein cholesterol (LDL-C) levels. Current recommendations by the National Cholesterol Education Program for HIV-infected persons focus on LDL-C as the primary target of therapy. The LDL-cholesterol goal is <160 mg/dL for persons with 0–1 cardiovascular risk factors, <130 mg/dL for persons with multiple (2+) risk factors and <100 mg/dL for persons with established CHD or CHD risk equivalents. After lifestyle modifications, statins should be used to lower LDL-C levels. Therapy with fibrates is recommended to lower triglyceride levels. However, omega-3 fatty acids can be an effective means of lowering triglyceride levels as well, particularly in patients with markedly elevated triglyceride levels.[54] The efficacy of statins in HIV-infected persons appears to be lower than expected, although adherence to statin therapy has not been well assessed. Statins combining high potency and minor interactions with antiretroviral therapy (pravastatin, fluvastatin, atorvastatin and rosuvastatin) should be preferred as initial therapy, though comparative studies in HIV-infected persons are scarce. A combination of a statin at medium doses with either ezetimibe or a fibrate may result in more satisfactory results than higher doses of statin monotherapy.[55]

Adequate choice and dosing of lipid-lowering drugs, given as isolated agents or in combination therapy, and care for good drug compliance in HIV-infected patients at moderate or high cardiovascular risk should help maximize their long-term health. Sixty eight HIV-infected patients with viral suppression because of effective antiretroviral therapy, and two or more cardiovascular risk factors or a Framingham risk score > or = 10% were examined in randomized pilot clinical trial[56] In this study an intensive intervention targeting low-density lipoprotein (LDL)-cholesterol <100 mg/dl, using antiplatelet therapy, and switching protease inhibitor (PI) therapy, was compared with the standard intervention aiming for LDL-cholesterol <130 mg/dL.

The primary endpoint was progression of atherosclerosis measured by the IMT. Secondary endpoints were efficacy in achieving the LDL-cholesterol goal, changes in inflammatory biomarkers, and feasibility and safety of each intervention. Thirty-two and 36 patients were assigned to the intensive and the standard interventions, respectively. After 12 months, the median proportion of change in the IMT was similar among the intensive intervention and the standard group. LDL-cholesterol and Framingham score showed larger reductions in the intensive intervention group compared to the standard intervention group. No significant changes in levels of C-reactive protein, interleukin-6 and tumor necrosis factor-alpha were found. No significant adverse events were reported and no virological failures occurred during the study. Thus an aggressive intervention targeting LDL-cholesterol in HIV-infected patients was safe and capable of attaining very stringent target levels in adherent patients.

Conclusions

Patients with HIV infection present functional and structural arterial changes resembling those found in patients with atherosclerotic cardiovascular disease. Adverse metabolic effects like dyslipidemia, increased blood pressure and insulin resistance have been attributed to HAART. Therefore, the use of HAART raises concerns regarding the acceleration of the atherosclerotic disease in HIV-infected patients who present an extended life expectancy because of HAART. Characteristics of the HIV infection itself such as viral load, duration of the disease, treatment with protease inhibitors as well as parameters of the metabolic syndrome (serum glucose, cholesterol and triglyceride values and blood pressure measurements) appear to influence the pathogenesis of these vascular changes. From the available antiretroviral medications, specific protease inhibitors have been associated with endothelial dysfunction and subclinical atherosclerosis. Several non invasive techniques have been employed to estimate various aspects of vascular dysfunction including endothelial dysfunction, increased

arterial stiffness, carotid atherosclerosis and microcirculation disorders in HIV-infected patients in an effort to predict future cardiovascular risk.

Intensive treatment of metabolic disorders in HIV-infected patients might be helpful in preventing or retarding the atherosclerotic process in HIV patients. The usefulness of systematic non invasive screening in these patients should be considered. Adequate choice and dosing of lipid-lowering drugs at moderate or high cardiovascular risk should help maximize their long-term health.

Conflict of interest

None declared.

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None declared.

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