Atherosclerosis in HIV Patients: a New Face for an Old Disease?

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Abstract

As we have become more familiar with the pathogenesis of atheroma, it has become recognized atherogenesis is mainly an inflammatory disease. Therefore, it is not surprising that a body of evidence demonstrates that endothelium injury is associated with the progression and severity of HIV infection. Another important question is: do antiretroviral drugs increase or reduce endothelial injury? Various studies support the hypothesis that HAART does induce activation of endothelial function. Thus, HIV virus as well as immune reconstitution and HAART itself promote premature endothelial activation. Such a prominent role played by inflammatory events could affect the structure of the arterial lesions in HIV patients that could present different characteristics with respect to the classical atheroma. In fact, in two HIV patients with severe stenosis of the carotid, histology revealed extensive inflammatory infiltration of the vascular wall. The characteristics of these lesions were similar to those of arteritis. Another study evidenced that the ultrasonographic structure of the lesions in HIV patients substantially differ from those found in atherosclerosis, sharing similar characteristics with arteritis.

We hypothesize that the atherosclerotic lesions in HIV patients develop in two distinct phases: the first one characterized by an inflammation of the vascular wall, and subsequently, the lesions could evolve towards the classic feature of the atheroma. The lesions in the first phase are probably determined by immunodeficiency, immune reconstitution, and the same effect of HAART. In the second phase they could be maintained by the classic risk factors. **(AIDS Reviews 2006;8:204-9)**

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Key words

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Introduction

Development of atheroma has been attributed for many years to a process whereby blood-borne cholesterol and inflammatory cells work together to incorporate lipids into the vascular wall, resulting in the formation of plaques that obstruct blood flow. As we have become more familiar with disease process, it has become recognized that atherogenesis is mainly an inflammatory disease. Factors that induce and promote inflammation participate in all stages of atherosclerosis, from the early lesion to the final events that culminate in acute thrombotic complications.

Experimental and human studies of atherosclerosis demonstrate that inflammatory molecules are expressed early in the process of lipid accumulation in the artery wall. Injury to the endothelium increases its adhesiveness and permeability to leukocytes and platelets. The initial injury to the endothelium not only facilitates leukocyte adhesion, but also promotes elaboration of vasoactive and chemo-attractive molecules, inflammatory cytokines, and a variety of growth factors. Continued inflammatory stimuli result in recruitment of macrophages and lymphocytes, which can induce further damage and eventually lead to focal areas of necrosis[1,2].

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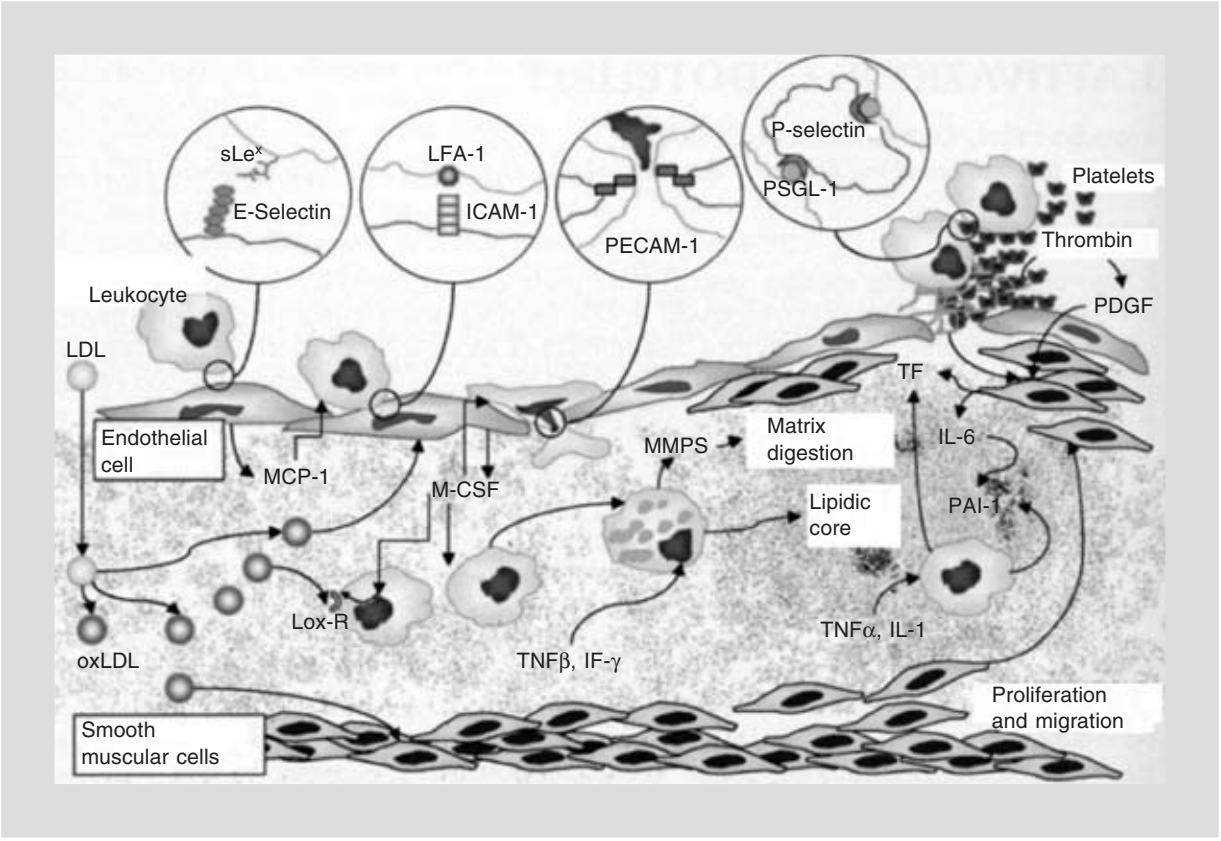

Figure 1. *The role of inflammation in the pathogenesis of the atherosclerosis. 1) Inflammation of the endothelium stimulates the production of adhesion molecules (E-Selectin, ICAM-1, PECAM-1). 2) Chemotactic cytokines (MCP-1 and M-CSF) lead the migration of monocytes and macrophages. 3) Leukocytes turn into macrophages and activate the receptor for the oxidized LDL cholesterol. 4) TNFβ and TNFα are produced by lymphocytes. Metalloproteases are responsible for local necrosis. 5) IL-6 induces the production of tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1), that activate the coagulation and inhibit the fibrinolysis.*

The traditional cardiovascular risk factors, such as hypercholesterolemia and modified lipids and lipoproteins, elevated blood pressure, high plasma homocysteine concentrations, glycation end products of hyperglycemia and insulin resistance nowadays are seen as factors associated with increased inflammation[3-5]. The adhesion to and subsequent transmigration of leucocytes across the endothelium are very early inflammatory events, and are mediated by endothelial cellular adhesion molecules (CAM) and other molecules present on leukocytes and other blood cells[6-14].

Adhesion molecules involved in firm adhesion and subsequent transmigration are intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), both belonging to the immunoglobulin superfamily[15]. E-selectin seems to be the most specific endothelial CAM, while both VCAM-1 and ICAM-1 are also produced by other cell types such as lymphocytes, epithelial cells, monocytes, and smooth muscle cells. P-selectin is also contained in the platelet α-granules[16].

Many other molecules are involved in the processes of endothelial damage such as tissue factor, von Willebrand factor (vWF), thrombomodulin, tissue plasminogen activator (TPA), plasminogen activator inhibitor-1 (PAI-1), nitric oxide (NO) and, most importantly, C-reactive protein (CRP). A significant association between increasing concentrations of soluble ICAM-1, VCAM-1, P-selectin and E-selectin, and cardiovascular events have been described[6,17-19,20-24].

The role of inflammation in the pathogenesis of atherosclerosis is summarized in figure 1.

HIV and endothelial damage

Given the role of inflammation at all stages of atherosclerosis, it is not surprising that HIV infection could represent *per se* a risk factor for the development of endothelial damage. In fact, various studies evidenced that the HIV virus can activate the endothelium either directly or by a leukocyte-mediated inflammatory cascade[25-29]. This is particularly true during the advanced stages of the disease: Lafeuillade compared HIV-positive patients with HIV-negative controls, showing increased concentrations of vWF in association with

Table 1. Studies evaluating the changes of the markers of endothelial activation in HIV-positive patients

Author and year of publication	N.º of HIV patients	Endothelial marker	Results	Association with disease progression
Lafeuillade, 1992	125	vWF, TPA	Increased vWF and TPA	yes
Most, 1993	76	ICAM-1	Increased ICAM-1	no
Diez-Ruiz, 1993	27	ICAM-1	Increased ICAM-1	no
Puppo, 1993	66	ICAM-1	Increased ICAM-1	yes
Sipsas, 1994	60	ICAM-1	Increased ICAM-1	yes
Zangerle, 1994	47	ICAM-1	–	no
Sfikakis, 1995	72	E-selectin	Increased E-selectin	yes
Nordøy, 1996	65	E-selectin, VCAM-1, ICAM-1	Increased VCAM-1 and ICAM-1	yes VCAM-1 and ICAM-1
Zietz, 1996	32	VCAM-1, E-selectin	Increased VCAM-1 and E-selectin	–
Galea, 1997	132	ICAM-1,-2,-3 VCAM-1	Increased ICAM-1,-2,-3 and VCAM-1	yes ICAM-1
Seigneur, 1997	90	vWF, thrombomodulin E-selectin	Increased vWF, hrombomodulin E-selectin	yes
Holme, 1998	20	P-selectin	Increased P-selectin	–
Hadigan, 2001	86	TPA, PAI-1	Increased TPA and PAI-1	–
de Larrañaga, 2003	92	vWF, TPA	Increased vWF	–

vWF: von Willebrand factor; TPA: tissue plasminogen activator; ICAM: intercellular adhesion molecule; VCAM: vascular cell adhesion molecule; PAI: plasminogen activator inhibitor

disease progression[30]. Increased soluble ICAM-1 concentrations in HIV-positive patients were also demonstrated[31] On the other hand, higher concentrations of soluble ICAM-1 were seen in AIDS patients with acute opportunistic infections when compared with HIV-positive patients without infections, both values being higher than that of HIV-negative patients[32]. A correlation between ICAM-1 concentrations and the progression of disease as well as the reduction of CD4+ cell count was also reported. Increased leukocyte adherence to aortic endothelium of HIV-positive patients and increased VCAM-1 and E-selectin plasma concentrations from these patients adds further experimental evidence of endothelial-cell involvement in AIDS disease[33]. In a small group of HIV-infected patients, ICAM-1/ICAM-2 ratio rather than individual CAM rates correlated with a decrease in CD4+ cell count[34].

In table 1 we outline the mayor studies evaluating the changes of the markers of endothelial activation in HIV-positive patients.

In summary, it is clear that endothelium injury is associated with the progression and severity of HIV infection.

The role of HAART

The introduction of HAART raised an important question: do antiretroviral drugs increase or reduce endothelial injury due to the activation of adhesion molecules?

Antiretrovirals, by reducing viral load and thus inflammation, might be expected to downregulate endothelial inflammatory components. However, since these drugs also induce proinflammatory alterations of lipid profile, they might paradoxically promote atherosclerosis.

In a small group of HIV-positive patients with a CD4+ cell count < 500/µl who were given a protease inhibitor (PI)-based HAART, plasma L-selectin concentrations were progressively normalized in almost all patients and VCAM-1 concentrations were partly reduced, while no changes in E-selectin or ICAM-1 levels were seen during the nine months of therapy[35]. Comparing concentrations of different CAM and other endothelial biomarkers in two groups of patients receiving different antiretroviral regimens – including PI or nonnucleoside reverse transcriptase inhibitors (NNRTI) – all the parameters measured seemed to be substantially decreased but not normalized by either HAART regimen,

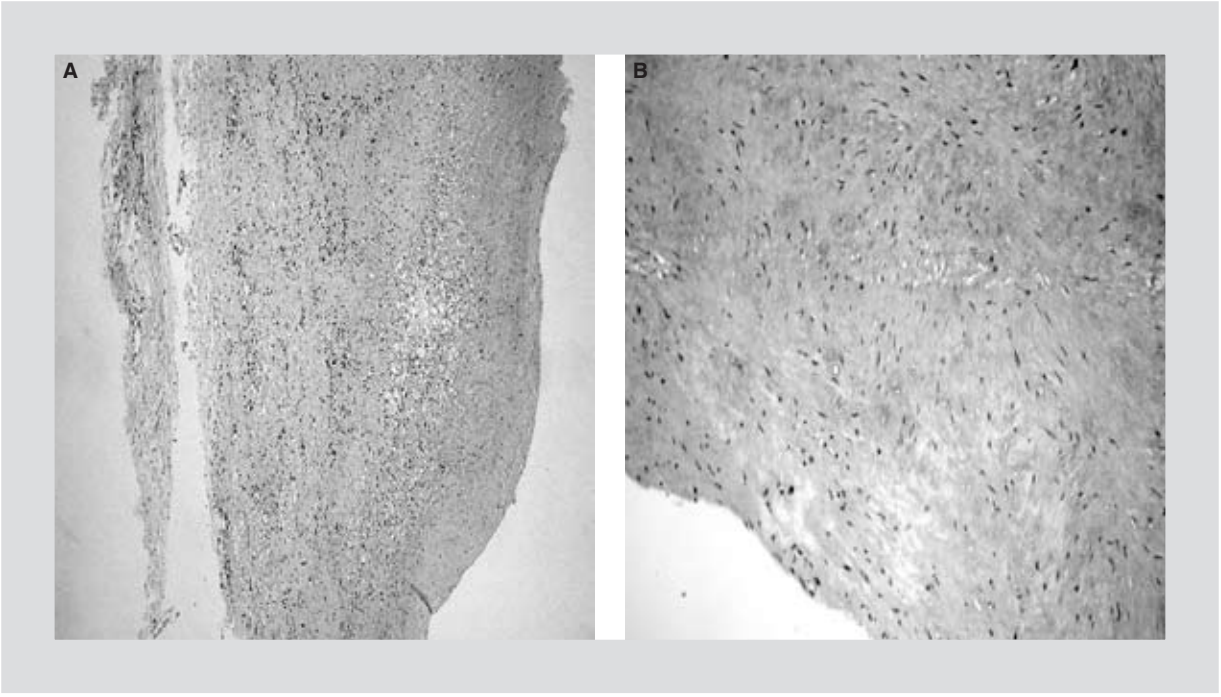

Figure 2. A: *Patient 1. Histology of the carotid plaque revealed: Intimal lesion with fragmentation of the internal elastic lamina, atrophy and fragmentation of the elastic fibers of the media with fibrosis and scars; fibrosis of the adventitia. Wide phlogistic infiltration, with lymphomonocytes and plasma cells along all the thickness of the wall and around the vasa vasorum (Reference 42).* **B:** *Patient 2. Arterial fragment consisting of intima and part of the media with marked fibrotic component and phlogistic infiltration, with lymphomonocytes and plasma cells involving both the intima and the media (Reference 42).*

suggesting that the reported reversion of endothelial activation by HAART is mediated by control of viral replication rather than by specific mechanisms associated with drug class[36].

Other studies support the hypothesis that HAART does induce activation of endothelial function: de Gaetano Donati, et al.[37] measured ICAM-1 and P-selectin concentrations (as well as TPA and PAI-1) in a group of patients undergoing either PI or NNRTI therapy and compared them with naive HIV-positive patients. P-selectin, TPA, and PAI-1 levels were all significantly higher in both HAART subgroups, while ICAM-1 concentrations did not differ significantly from those measured in the naive group.

Increased levels of soluble adhesion molecules could be the consequence of autoreactive cell destruction by an improved autoimmune system and/or of the efficacy of a therapy in destroying the most active or sensitive cells. However, the possibility that HAART directly induces endothelial activation was recently documented. Zhong, et al.[38] for the first time showed that ritonavir, at concentrations comparable with those attainable *in vivo*, was able to directly cause endothelial mitochondrial DNA damage and cell death. Other convincing evidence was provided by an experiment in healthy volunteers given indinavir for four weeks: a significant endothelial dysfunction was measured by invasive monitoring of arterial blood flow, possibly mediated by nitric oxide. Such a result was independent of lipid profiles[39].

In a recent publication[40], Jiang, et al. treated male Sprague-Dawley rats with clinically relevant doses of zidovudine, indinavir, or zidovudine plus indinavir. They found that zidovudine and zidovudine plus indinavir treatments dramatically reduced endothelium-dependent vessel relaxation. However, zidovudine treatment did not significantly alter plasma levels of cholesterol or triglyceride. In addition, plasma endothelin-1 levels were elevated in rats treated with zidovudine plus indinavir. Indinavir treatment alone increased plasma cholesterol levels, but had no effect on endothelial function.

In summary, it is plausible that HIV virus, as well as immune reconstitution induced by HAART itself, promotes premature endothelial lesions mediated by a massive activation of inflammatory molecules and cells. Metabolic disturbances attributed to antiretrovirals should also be taken into account, but as an indirect means to promote atherosclerosis and, possibly, in a second phase of the vascular disease. An exhaustive review of these arguments is provided by de Gaetano Donati, et al.[41].

Vascular lesions in HIV: atherosclerosis or arteritis?

For all these reasons, one could hypothesize that the prominent role played by the inflammatory events involving the endothelium could affect the structure and histologic compo-

sition of the arterial lesions in HIV-positive patients, and that these could present different characteristics with respect to those found in classical atheromatous lesions.

In fact, two cases of HIV-1-positive patients with asymptomatic, hemodynamically significant stenosis of the internal carotid arteries have been recently described[42]. In both patients, the first 1.5 cm of the internal carotid arteries was resected with re-implantation of the remaining artery on the external carotid artery. Histology revealed extensive inflammatory infiltration of the vascular wall, fragmentation of the internal elastic lamina and the elastic fibers of the media, and fibrosis of the adventitia (Figs. 2a, 2b). The characteristics of these lesions, which were more similar to those of arteritis rather than classical atherosclerosis, could shed new light on the pathogenesis of vascular risk in HIV-1-positive patients. This unexpected pattern of carotid damage prompted the authors to perform a more accurate investigation of the characteristics of carotid plaques in a group of HIV-positive patients[43]. The results were compared with those obtained from young patients affected by atherosclerosis of the epi-aortic vessels and patients with arteritis. The patients underwent ultrasonography of the epi-aortic vessels using a latest generation power color-Doppler with 7.5 MHz probes. The study population included 61 HIV-positive patients and 47 HIV-negative patients (37 atherosclerotic patients and 10 with arteritis). Compared with HIV-negative, atherosclerotic hypoechogenic lesions (81.8 *vs.* 29%) were homogeneous both in their parietal and endoluminal portions (96.7 *vs.* 21.6% and 88.5 *vs.* 54.0%, respectively), with a smooth or slightly irregular surface (99.0 *vs.* 56.7%) ($p = 0.001$ for all differences). No statistically significant differences were seen between HIV-positive and arteritis patients. The study evidenced that the ultrasonographic structure of the epi-aortic lesions in HIV-positive patients substantially differ from those of the plaques in atherosclerotic patients, while they share similar characteristics with patients affected by arteritis.

The hypothesis of a two-step lesion

In synthesis, in the light of these evidences, we hypothesize that the atherosclerotic lesions in HIV-positive patients could develop in two distinct phases: the first one being characterized by a florid inflammation of the vascular wall, while in a second phase, the lesions could evolve towards the more classic feature of the atheromatous plaques. The lesions in the first phase are probably determined by different factors such as immunodeficiency and consequent opportunistic events involving the arteries, immune reconstitution, and the same effect of PI. They seem to be very premature, with the characteristics of an arteritis, not prone to emboli detachment and, consequently, reversible. It is reasonable to suspect that such a severe inflammation could subsequently determine a more evolutive, severe, and extensive atheromatous lesion. The lesions in this second phase could be maintained by the classic risk factors, like hypercholesterolemia, hypertriglyceridemia and insulin resistance, due to the same effect of PI.

Conclusions

Such a feature of arterial lesions in HIV-positive patients opens several perspectives for their prevention: in fact, if in the first phase avoiding opportunistic events involving the endothelium or an abrupt immune reconstitution could prevent the inflammatory lesions, in the second phase the attention could be moved toward the classic risk factors for the atherosclerosis such as metabolic disturbances, hypertension, or cigarette smoking.

References

1. Badr K, Wainwright C. Inflammation in the cardiovascular system: here, there and everywhere. Current Op Pharmacol 2004;4:107-9.
2. Rohde L, Lee R. Pathophysiology of atherosclerotic plaque development and rupture: an overview. Semin Vascular Med 2003;3:347-54.
3. Davies M, Gordon J, Pigott R, Woolf F, Katz D, Kyriakopulos A. The expression of the adhesion molecules ICAM-1, VCAM-1, PECAM, and E-selectin in human atherosclerosis. J Pathol 1993;171:223-9.
4. Libby P, Ridker P, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135-43.
5. Rohde L, Hennekens C, Ridker P. Survey of C-reactive protein and cardiovascular risk factors in apparently healthy men. Am J Cardiol 1999;84:1018-22.
6. Blankemberg S, Rupprecht H, Bickel C, et al. Circulating cell adhesion molecules and death in patients with coronary artery disease. Circulation 2001;104:1336-42.
7. Ridker P, Burning J, Rifai N. Soluble P-selectin and the risk of future cardiovascular events. Circulation 2001;103:491-5.
8. Davies M, Gordon J, Gearing A, et al. The expression of the adhesion molecules ICAM-1, VCAM-1, PECAM and E-selectin in human atherosclerosis. J Pathol 1993;171:223-9.
9. Frijns C, Kappelle L. Inflammatory cell adhesion molecules in ischemic cerebrovascular disease. Stroke 2002;33:2115-22.
10. Ridker P, Hennekens C, Roitman-Johnson B, Stampfer M, Allen J. Plasma concentration of soluble ICAM-1 and risks of future myocardial infarction in apparently healthy men. Lancet 1998;351:88-92.
11. Kuijper P, Gallardo Tores H, Lammers J, et al. Platelet-associated fibrinogen and ICAM-2 induce firm adhesion of neutrophils under flow conditions. Thromb Haemost 1998;80:443-8.
12. Diacovo T, de Fougerolles A, Bainton D, Springer T. A functional integrin ligand on the surface of platelets: ICAM-2, J Clin Invest 1994;94:1243-51.
13. Freedman J. CD40 ligand – assessing risk instead of damage? N Engl J Med 2003;348:1163-5.
14. Inwald D, McDowall A, Peters M, Callard R, Klein N. CD40 is constitutively expressed on platelets and provides a novel mechanism for platelet activation. Circ Res 2003;92:1041-8.
15. Cerletti C, Evangelista V, de Gaetano G. P-selectin–beta 2-integrin cross-talk: a molecular mechanism for polymorphonuclear leukocyte recruitment at the site of vascular damage, Thromb Haemost 1999;82:787-93.
16. Davì G, Romano M, Mezzetti A, et al. Increased levels of soluble P-Selectin in hypercholesterolemic patients. Circulation 1998;97: 953-7.
17. Ridker P, Hennekens C, Buring J, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836-43.

18. Hwang P, Ballantyne C, Sharrett A, et al. Circulating adhesion molecules VCAM-1, ICAM-1, and E-selectin in carotid atherosclerosis and incident coronary heart disease cases: the Atherosclerosis Risk In Communities (ARIC) study. Circulation 1997;96:4219-25.
19. Mulvihill N, Foley J, Murphy R, et al. Evidence of prolonged inflammation in unstable angina and non-Q wave myocardial infarction. J Am Coll Cardiol 2000;36:423-6.
20. Lip G, Blann A, Zarifis J, et al. Soluble adhesion molecules P-selectin and endothelial dysfunction in essential hypertension: implications for atherogenesis? A preliminary report. J Hypertens 1995;13:1674-8.
21. Blann A, Dobrotova M, Kubisz P, et al. Von Willebrand factor, soluble P-selectin, tissue plasminogen activator and plasminogen activator inhibitor in atherosclerosis. Thromb Haemost 1995;74:626-30.
22. Ikeda H, Takajo Y, Ichiki K, et al. Increased soluble form of P-selectin in patients with unstable angina. Circulation 1995;92: 1693-6.
23. Sakurai S, Inoue A, Koh C, et al. Soluble form of selectins in blood of patients with acute myocardial infarction and coronary intervention. Vasc Med 1997;2:163-8.
24. Shimomura H, Ogawa H, Arai H, et al. Serial changes in plasma levels of soluble P-selectin in patients with acute myocardial infarction. Am J Cardiol 1998;81:397-400.
25. Krishnaswamy G, Smith J, Mukkamala R, Hall K, Joyner W, Chi D. Multifunctional cytokine expression by human coronary endothelium and regulation by monokines and glucocorticoids. Microvasc Res 1998;55:189-200.
26. Horbein G, Koshav S, Collin M, Montaner L, Gordon S. HIV induces TNF and IL-1 gene expression in primary human macrophages independent of productive infection. Clin Exp Immunol 1994;95:442-9.
27. Lifson J, Reyes G, McGrath M, Stein B, Engleman E. AIDS retrovirus induced cytopathology: giant cell formation and involvement of CD4 antigen. Science 1986;232:1123-7.
28. Stefano G, Salzet M, Bilfinger T. Long-term exposure of human blood vessels to HIV gp120 morphine and anandamide increases endothelial adhesion of monocytes: uncoupling of nitric oxide release. J Cardiovasc Pharmacol 1998;31:862-8.
29. Ren Z, Yao Q, Chen C. HIV-1 envelope gp120 increases ICAM-1 expression by human endothelial cells. Lab Invest 2002;82:245-55.
30. Lafeuillade A, Alessi M, Poizot-Martin I, et al. Endothelial cell dysfunction in HIV infection. J Acquir Immune Defic Syndr 1992;5:127-31.
31. Puppo F, Brenci S, Scudeletti M, Lanza L, Bosco O, Indiveri F. Elevated serum levels of circulating ICAM-1 in HIV infection. AIDS 1993;7:593-4.
32. Sipsas N, Sfikakis PP, Sfikakis P, Choremi H, Kordossis T. Serum concentrations of soluble ICAM-1 and progress towards disease in patients infected with HIV. J Infect 1994;29:271-82.
33. Zietz C, Hotz B, Sturzl M, Rauch E, Penning R, Lohrs U. Aortic endothelium in HIV-1 infection: chronic injury, activation and increased leukocyte adherence. Am J Pathol 1996;149:1887-98.
34. Galea P, Vermot-Desroches C, Le Contel C, Wijdenes J, Chermann J. Circulating cell adhesion molecules in HIV-1 infected patients as indicator markers for AIDS progression. Res Immunol 1997;148:109-17.
35. Mastroianni C, Lichtner M, Mengoni F, et al. Changes in circulating levels of soluble cell adhesion molecules following highly active antiretroviral treatment of HIV-1-infected patients. Clin Immunol 2000;95:212-7.
36. Wolf K, Tsakiris D, Weber R, Erb P, Battegay M. Antiretroviral therapy reduces markers of endothelial and coagulation activation in patients infected with HIV-1. J Infect Dis 2002;185:456-62.
37. De Gaetano Donati K, Rabagliati R, Tumbarello M, et al. Increased soluble markers of endothelial dysfunction in HIV-positive patients under HAART. AIDS 2003;17:765-8.
38. Zong D, Lu X, Conklin B, et al. HIV protease inhibitor ritonavir induces cytotoxicity of human endothelial cells. Arterioscler Thromb Vasc Biol 2002;22:1560-6.
39. Shankar S, Dube M, Gorski J, et al. Indinavir impairs endothelial function in healthy HIV-negative men. Am Heart J 2005;15:933.
40. Jiang B, Hebert V, Zavecz J, Dugas T. Antiretrovirals induce direct endothelial dysfunction *in vivo*. J Acquir Immune Defic Syndr 2006;42:391-5.
41. De Gaetano Donati K, Rabagliati R, Iacoviello L, et al. HIV infection, HAART, and endothelial adhesion molecules: current perspectives. Lancet Infect Dis 2004;4:213-22.
42. Regina G, Impedovo G, Angiletta D, et al. Surgical experience with carotid stenosis in young HIV-1 positive patients under antiretroviral therapy: an emerging problem? Eur J Vasc Endovasc Surg 2005;29:167.
43. Maggi P, Perilli F, Lillo A, et al. An ultrasound-based comparative study on carotid plaques in HIV-positive patients *vs.* atherosclerotic and arteritis patients: atherosclerotic or inflammatory lesions? Coronary Artery Disease [in press].