Giuseppe Barbaro • Franck Boccara (Eds)

Cardiovascular Disease in AIDS

Foreword by W. Rozenbaum

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Foreword

Never in the history of humanity has knowledge progressed as quickly as in the field of AIDS. Over a period of 15 years, successive discoveries of the disease, its viral origin, the virus responsible, its physiopathology and highly effective therapies have led to spectacular improvement in life expectancy and in the quality of life of people who have access to these treatments.

However, this progress in therapy has been accompanied by initially unforeseeable anomalies, such as abnormalities in lipid and glucose metabolism and modifications in fat distribution, particularly in perivisceral and trunkal accumulation as well as pseudo-obesity usually accompanied by peripheral atrophy.

Several of these anomalies constitute risk factors for cardiovascular diseases and may be predictors of these diseases. Over time, most investigators have come to accept that HIV-infected patients are at an increased risk for cardiovascular complications.

However, several issues remain unclear:

- Does the increased risk merely reflect modification of the usual factors: metabolic disorders, tobacco consumption, infectious context related to HIV infection or opportunistic infections, inappropriate immune and cytokine response, or genetic background?
- The physiopathology of disorders in glucose or lipid metabolism remains to be clarified. It is unclear whether they result from treatment, use of a specific medication, use of a therapeutic class of medication, or an association of treatments. Here, too, genetic background may well be a factor, along with the history of the individual's HIV infection.

It is particularly difficult to devise a therapeutic strategy under these conditions, especially since the efficacy of the usual lipid- or glucose-modifying medication is not established, and the benefit of any eventual correction of such biological anomalies in this population is unclear. The issue is further complicated by the many drug interactions between antiretroviral medications and medications likely to act on the lipid metabolism, which renders their usage complex.

In this atmosphere of uncertainty, the simple measure of diminishing tobacco usage is itself difficult, and overconsumption of tobacco is regularly observed in this population.

The medical management of HIV-infected patients is mostly carried out by infectious disease specialists, and the field of cardiovascular diseases is not usually familiar to them.

The history of AIDS has taught us that phenomena are most quickly and effectively understood when light is cast on them from a variety of angles, using a variety of tools. The dynamism which has always characterized AIDS research will doubtless benefit from greater comprehension of the mechanisms of these poorly understood metabolic disorders.

The present volume contributes to disseminating knowledge in the field so that the various actors can pool their expertise towards a successful management of cardiovascular disease in HIV-infected patients.

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Evolution and Pathogenesis of the Involvement of the Cardiovascular System in HIV Infection

G. Barbaro

Introduction

Cardiac illness related to human immunodeficiency virus (HIV) infection tends to occur late in the disease course and is therefore becoming more prevalent as therapy of the viral infection and longevity improve. Autopsy series and retrospective analyses performed before the introduction of highly active antiretroviral therapy (HAART) regimens suggest that cardiac lesions are present in 25%–75% of patients with acquired immunodeficiency syndrome (AIDS) [1]. HAART regimens have significantly modified the course of HIV disease, with longer survival rates and improvement of life quality in HIV-infected subjects expected. However, early data raised concerns about HAART being associated with an increase in both peripheral and coronary arterial diseases. HAART is only available to a minority of HIV-infected individuals worldwide, and studies prior to HAART therapy remain globally applicable. As 36.1 million adults and children are estimated to be living with HIV/AIDS and 5.3 million adults and children are estimated to have been newly infected with HIV during the year 2000 [2], HIV-associated symptomatic heart failure may become one of the leading causes of heart failure worldwide. A variety of potential etiologies have been postulated for HIV-related heart disease, including myocardial infection with HIV itself, opportunistic infections, viral infections, autoimmune response to viral infection, drug-related cardiotoxicity, nutritional deficiencies, and prolonged immunosuppression (Table 1).

Congenital Cardiovascular Malformations in HIV-Infected Children

Most pediatric patients with HIV are infected in the perinatal period [3]. In a prospective, longitudinal, multicenter study, diagnostic echocardiograms were performed at 4- to 6-month intervals on two cohorts of children exposed to maternal HIV-1 infection: (a) a neonatal cohort of 90 HIV-infected, 449 HIV-uninfected, and 19 HIV-indeterminate children; and (b) an older HIV-infected cohort of 201 children with vertically transmitted HIV-1 infection recruited after 28 days of age [3]. In the neonatal cohort, 36 lesions were seen in 36 patients, yielding an overall congenital cardiovascular malformation prevalence of 6.5% (36/558), with an 8.9% (8/90) prevalence in HIV-infected children and a 5.6% (25/449) prevalence in HIV-uninfected children [3]. Two children (2/558, 0.4%) had cyanotic lesions. In the older HIV-infected cohort, there was a congenital cardiovascular malformation prevalence of 7.5% (15/201). The distribution of lesions did not differ significantly between the groups. There was no statistically significant difference in congenital cardiovascular malformation prevalence in the HIV-infected compared to the HIV-uninfected children born to HIV-infected women. With the use of early screening echocardiography, rates of congenital cardiovascular malformations in both the HIV-infected and HIV-uninfected children were five- to tenfold higher than rates reported in population-based epidemiologic studies, but not higher than in normal populations similarly screened [3].

Dilated Cardiomyopathy

The estimated annual incidence of dilated cardiomyopathy with HIV infection before introduction of HAART was 15.9 in 1,000 cases [4]. Symptoms of heart failure may be masked in HIV-infected patients by concomitant illnesses such as diarrhea or malnutrition, or may be disguised by bron-

Table 1. Principal HIV-associated cardiovascular abnormalities [6]

Type	Possible etiologies and associations	Incidence
Dilated cardiomyopathy	Infectious: HIV, *Toxoplasma gondii,* Coxsackievirus group B, Epstein-Barr virus, *Cytomegalovirus, Adenovirus* Autoimmune response to infection Drug-related Cocaine, possibly nucleoside analogs IL-2, doxorubicin, interferon Metabolic/endocrine Nutritional deficiency/wasting Selenium, B_{12}, carnitine Thyroid hormone, growth hormone Adrenal insufficiency, hyperinsulinemia Cytokines TNF-α, nitric oxide, TGF-β, endothelin-1 Hypothermia Hyperthermia Autonomic insufficiency Encephalopathy Acquired immunodeficiency HIV viral load, length of immunosuppression	15.9 patients/1,000 asymptomatic HIV- infected persons before the introduction of HAART [4]
Coronary heart disease	Protease-inhibitor-induced metabolic and coagulative disorders. Arteritis	Studies on the risk of coronary heart disease among HIV-infected individuals receiving protease inhibitor-including HAART have not shown a consistent association [44–51]
Systemic arterial hypertension	HIV-induced endothelial dysfunction. Vasculitis in small, medium, and large vessels in the form of leukocytoclastic vasculitis; atherosclerosis secondaryto HAART; aneurysms of the large vessels such as the carotid, femoral, and abdominal aorta with impairment of flow to the renal arteries; PI-induced insulin resistance with increased sympathetic activity and sodium retention	20%–25% of HIV-infected persons before the introduction of HAART [52] Up to 74% in HIV-infected persons with HAART-related metabolic syndrome [53]
Pericardial effusion	Bacteria: *Staphylococcus, Streptococcus, Proteus, Nocardia, Pseudomonas, Klebsiella, Enterococcus, Listeria* Mycobacteria (*Mycobacterium tuberculosis*, *Mycobacterium avium intracellulare, Mycobacterium kansaii*) Viral pathogens HIV, herpes simplex virus, herpes simplex virus type 2, cytomegalovirus Other pathogens *Cryptococcus, Toxoplasma, Histoplasma* Malignancy Kaposi's sarcoma Malignant lymphoma Capillary leak/wasting/malnutrition Hypothyroidism Prolonged acquired immunodeficiency	11%/year in asymptomatic AIDS patients before the introduction of HAART [24]

cont. →

Table 1. *cont.*

HIV-associated pulmonary hypertension	Recurrent bronchopulmonary infections, pulmonary arteritis, microvascular pulmonary emboli due to thrombus or drug injection. Plexogenic pulmonary arteriopathy. Mediator release from endothelium	1/200 of HIV-infected persons before the introduction of HAART [35]
AIDS-related tumors	Kaposi's sarcoma	12%–28% of AIDS patients before the introduction of HAART [12, 35]
	Non-Hodgkin's lymphomas	Mostly limited to case reports before the introduction of HAART

chopulmonary infections. The gross and microscopic findings for HIV-associated dilated cardiomyopathy are similar to those for idiopathic dilated cardiomyopathy in immunocompetent persons, with four-chamber dilation and patchy myocardial fibrosis. Additional echocardiographic findings include diffuse left ventricular hypokinesis and decreased fractional shortening. The echocardiographic classification of HIV-associated cardiomyopathy with related clinical implications is reported in Fig. 1.

Compared to patients with idiopathic dilated cardiomyopathy, those with HIV infection and dilated cardiomyopathy have markedly reduced survival rates (hazard ratio for death from congestive heart failuire: 5.86) [5] (Fig. 2). The median survival to AIDS-related death is 101 days in patients with left ventricular dysfunction and 472 days in patients with a normal heart at a similar stage of HIV infection [6]. Although there is no evidence from prospective studies to suggest that HAART has a beneficial effect on HIV-associated

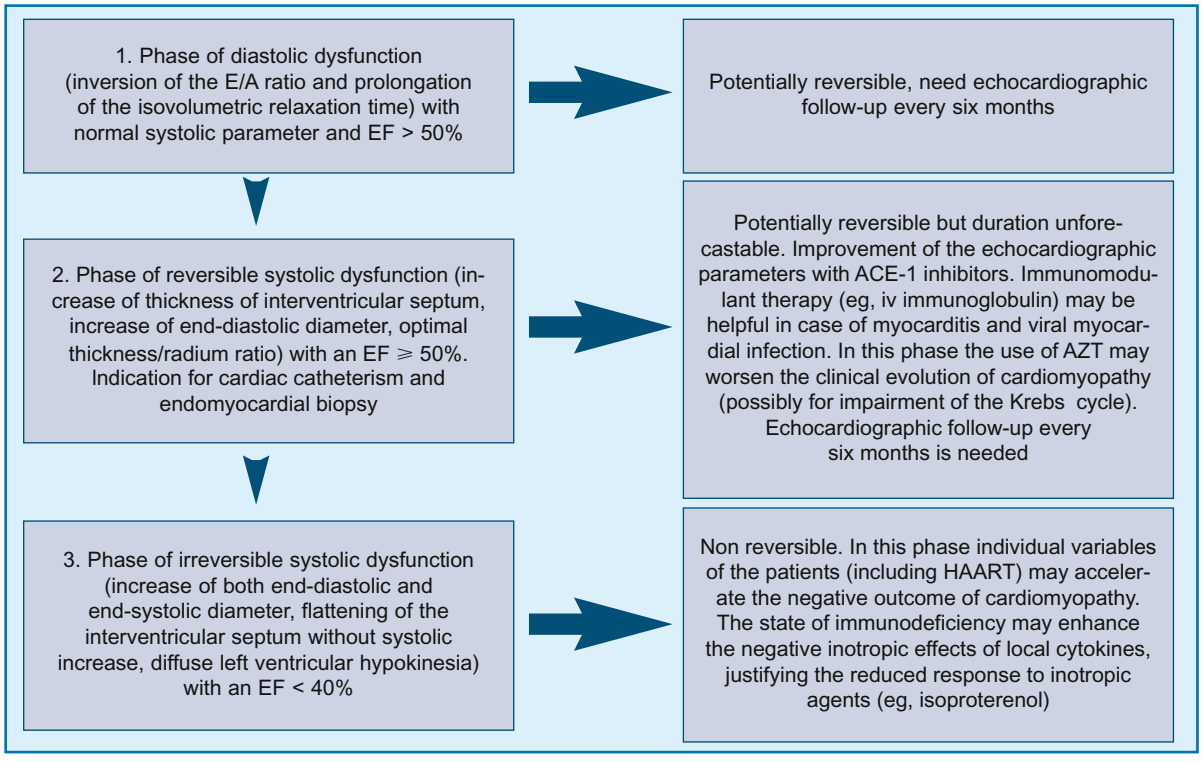


Fig. 1. Echocardiographic classification of HIV-associated cardiomyopathy with related clinical implications

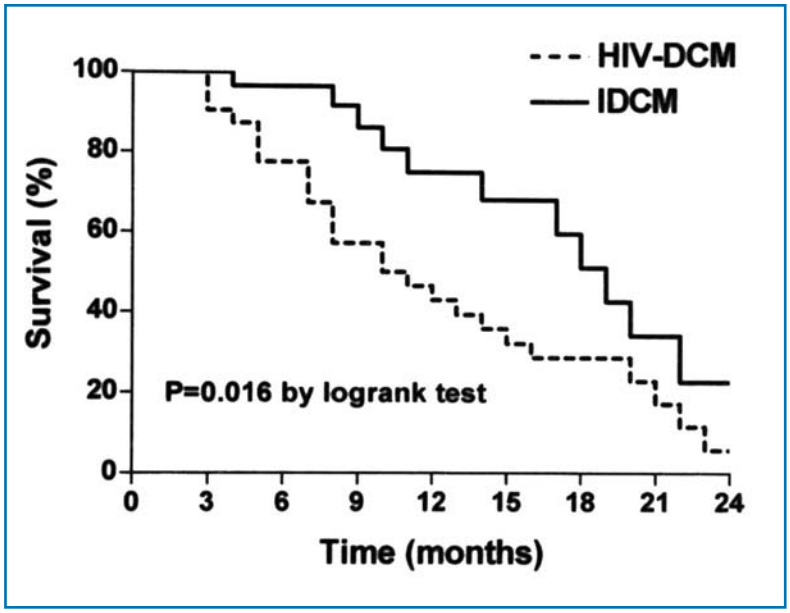


Fig. 2. Kaplan–Meier curves comparing the survival rate during follow-up between patients with HIV-associated cardiomyopathy and patients with idiopathic dilated cardiomyopathy. (From [5] with permission)

cardiomyopathy and on HIV-associated pericardial effusion, some retrospective studies suggest that by preventing opportunistic infections and reducing the incidence of myocarditis, HAART might reduce the incidence of cardiomyopathy by about 33% (Fig. 3) and improve its course [7, 8]. However, the median incidence of HIV-associated cardiomyopathy is increasing in developing countries (about 32%), where the availability of HAART is limited and the pathogenetic impact of nutritional factors is greater [9].

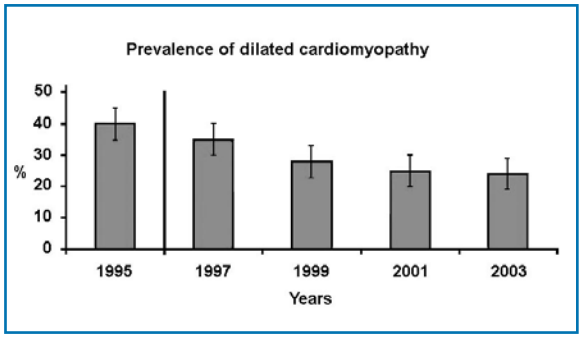


Fig. 3. Prevalence of HIV-associated dilated cardiomyopathy in the years 1995–2003. The *vertical line* indicates the introduction of HAART in the treatment of HIV infection

Animal Models

Simian immunodeficiency virus (SIV) infection in rhesus macaques is valuable for understanding the pathogenesis of cardiac injury associated with retroviral infection in a relevant nonhuman primate model of AIDS [10]. Chronic SIV infection resulted in depressed left ventricular systolic function and an extensive coronary arteriopathy suggestive of injury due to cell-mediated immune response [10]. Two-thirds of chronically infected macaques that died of SIV had related myocardial effects. Lymphocytic myocarditis was seen in 9 of 15 macaques and coronary arteriopathy in 9 of 15 (6 alone and 3 in combination with myocarditis) upon necropsy. In infected macaques, coronary arteriopathy was extensive, with evidence of vessel occlusion and recanalization and related regions of myocardial necrosis in four macaques. At necropsy, two animals had marantic endocarditis and one had a left ventricular mural thrombus. Macaques with cardiac pathology were emaciated to a greater extent than macaques with SIV and similar periods of infection who did not experience cardiac pathology [8, 10].

Myocarditis and Viral Myocardial Infection as Causes of Cardiomyopathy

Myocarditis and myocardial infection with HIV are the best-studied causes of dilated cardiomyopathy in HIV disease [11]. HIV-1 virions appear to infect myocardial cells in a patchy distribution with no direct association between the presence of the virus and myocyte dysfunction [11]. The myocardial fiber necrosis is usually minimal, with accompanying mild to moderate lymphocytic infiltrates. It is unclear how HIV-1 enters myocytes, which do not have CD4 receptors, although dendritic reservoir cells may play a role by activating multifunctional cytokines that contribute to progressive and late tissue damage, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-10 (IL-10) [5]. Coinfection with other viruses (usually coxsackievirus B3 and cytomegalovirus) may also play an important pathogenetic role [5, 12].

Autoimmunity as a Contributor to Cardiomyopathy

Cardiac-specific autoantibodies (anti-alpha-myosin autoantibodies) are more common in HIV-infected patients with dilated cardiomyopathy than in HIV-infected patients with healthy hearts. Currie et al. reported that HIV-infected patients were more likely to have specific cardiac autoantibodies than were HIV-negative control subjects [13]. Those with echocardiographic evidence of left ventricular dysfunction were particularly likely to have cardiac autoantibodies, supporting the theory that cardiac autoimmunity plays a role in the pathogenesis of HIV-related heart disease and suggesting that cardiac autoantibodies could be used as markers of left ventricular dysfunction in HIV-positive patients with previously normal echocardiographic findings [13].

In addition, monthly intravenous administration of immunoglobulin in HIV-infected pediatric patients minimizes left ventricular dysfunction, increases left ventricular wall thickness, and reduces peak left ventricular wall stress, suggesting that both impaired myocardial growth and left ventricular dysfunction may be immunologically mediated [14]. These effects may be the result of immunoglobulins inhibiting cardiac autoantibodies by competing for Fc receptors, or they could be the result of immunoglobulins dampening the secretion or effects of cytokines and cellular growth factors [14]. These findings suggest that immunomodulatory therapy might be helpful in adults and children with declining left ventricular function, although further study of this possible therapy is needed.

Myocardial Cytokine Expression as a Factor in Cardiomyopathy

Cytokines play a role in the development of HIV-related cardiomyopathy [5]. Myocarditis and dilated cardiomyopathy are associated with markedly elevated cytokine production, but the elevations may be highly localized within the myocardium, making peripheral cytokine levels uninformative [5].

When myocardial biopsy samples from patients with HIV-associated cardiomyopathy are compared to samples from patients with idiopathic dilated cardiomyopathy, the former stain more intensely for both TNF-α and inducible nitric oxide synthase (iNOS) (Fig. 4). Staining is particularly intense in samples from patients with a myocardial viral infection and is correlated with CD4 count, independent of antiretroviral treatment [5] (Fig. 5). Staining is also more intense in samples from patients with HIV-associated cardiomyopathy coinfected with coxsackievirus B3, cytomegalovirus, or other viruses [5]. Moreover, staining for iNOS is more intense in samples from patients coinfected with HIV-1 and coxsackievirus B3 or cytomegalovirus than in samples from patients with idiopathic dilated cardiomyopathy and myocardial infection with coxackievirus B3 or those who had adenovirus infection alone [5].

In patients with HIV-associated dilated cardiomyopathy and more intense iNOS staining, the survival rate was significantly lower: those whose samples stained more than 1 optical density unit had a hazard ratio of mortality of 2.57 (95% confidence interval: 1.11–5.43). Survival in HIV-infected patients with less intense staining was not significantly different from survival in patients with idiopathic dilated cardiomyopathy [5].

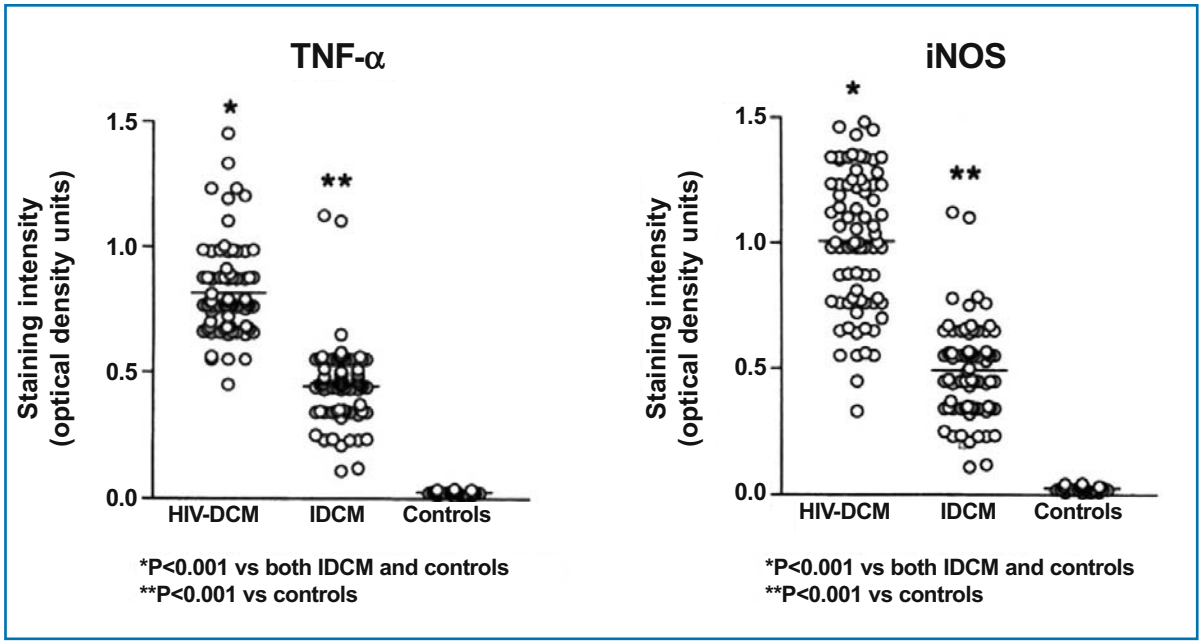


Fig. 4. Mean optical density of staining of TNF-α and iNOS in patients with HIV-associated cardiomyopathy (*HIV-DCM*), with idiopatic dilated cardiomyopathy (*IDCM*), and control subjects. *Horizontal bars* represent mean values. (From [5] with permission)

The inflammatory response may be enhanced by HIV-1 myocardial infection, by the interaction between HIV-1 and cardiotropic viruses, and by immunodeficiency. These factors may increase both the expression and the cytotoxic activity of specific cytokines such as TNF-α and iNOS and blunt the expected increase of anti-inflammatory cytokines such as IL-10 [15].

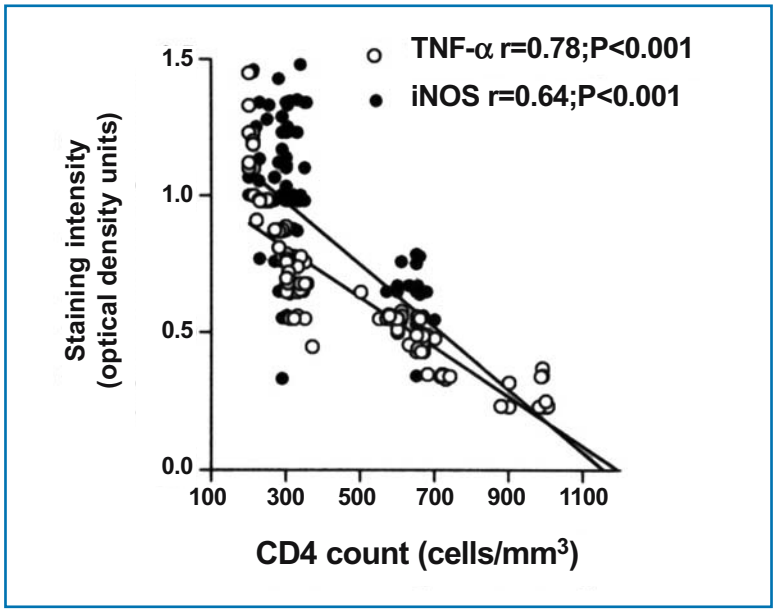


Fig. 5. Correlation between myocardial optical density units of TNF-α and iNOS and CD4 count. (From [5] with permission)

Relationship Between HIV-Associated Cardiomyopathy and Encephalopathy

HIV-infected patients with encephalopathy are more likely to die of congestive heart failure than are those without encephalopathy (hazard ratio: 3.4) [16, 17]. Cardiomyopathy and encephalopathy may both be traceable to the effects of HIV reservoir cells in the myocardium and the cerebral cortex. These cells may hold HIV-1 on their surfaces for extended time periods even after antiretroviral treatment, and they may chronically release cytotoxic cytokines (TNF-α, IL-6, and endothelin-1), which contribute to progressive and late tissue damage in both systems (Fig. 6). Because the reservoir cells are not affected by treatment, the effect is independent of whether the patient receives HAART.

Nutritional Deficiencies as a Factor in Left Ventricular Dysfunction

Nutritional deficiencies are common in HIV infection and may contribute to ventricular dysfunction independently of HAART. Malabsorption and diarrhea can both lead to trace element deficiencies,

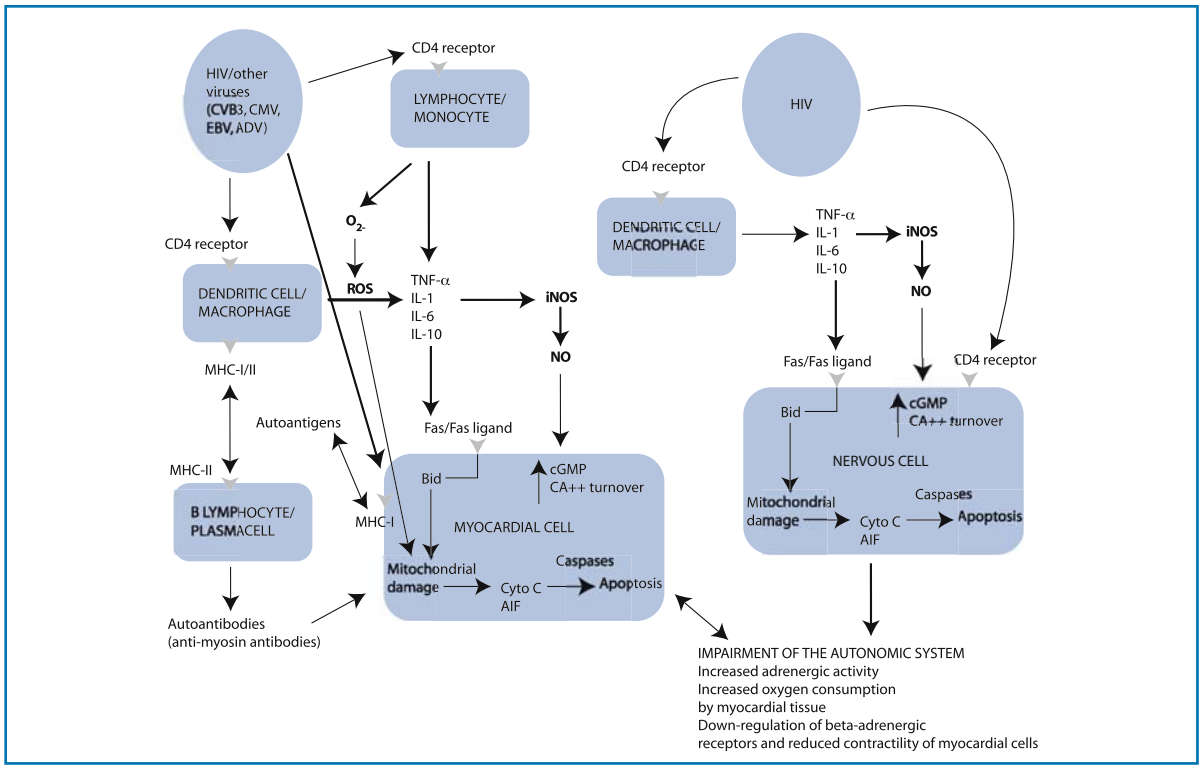


Fig. 6. The possible pathogenic mechanisms involved in the development of HIV-associated cardiomyopathy and encephalopathy and their relationship. The infection of dendritic cells, of CD4 lymphocytes, and of myocardial or neuronal cells by HIV-1 or by other viruses may be responsible for the release of specific cytokines (TNF-α, IL-1, IL-6, IL-10) that activate the inducible form of nitric oxide synhase (*iNOS*). The interaction between cytotoxic T lymphocytes and the receptoral complex *Fas/Fas ligand* located on the surface of the target cell may cause mitochondrial damage with release of mitochondrial pro-apoptosis factors [cytochrome c, apoptosis inducing factor (*AIF*)]. Similar mitochondrial damage may be caused by reactive oxygen species (*ROS*) released by activated lympho-monocytes. The interaction between autoantigens and major histocompatibility complex (*MHC*) molecules on the surface of dendritic cells/macrophages, of myocardial cells (*MHC-I*), and of B lymphocytes (*MHC-II*) determines the production of autoantibodies (e.g., alpha-antimyosin) that are responsible for direct cellular damage. The neuronal damage, specifically the impairment of the autonomic system, may enhance the functional damage to myocardial cells because of increased adrenergic activity and down-regulation of beta-adrenergic receptors. *CVB3*, coxsackievirus B3; *CMV*, cytomegalovirus; *EBV*, Epstein-Barr virus; *ADV*, adenovirus; *Ca++*, calcium; *cGMP*, cyclic guanine monophosphate; *Bid*, a protein of the bcl 2 family involved in apoptosis. (From [35])

which have been directly or indirectly associated with cardiomyopathy [18–20]. Selenium replacement may reverse cardiomyopathy and restore left ventricular function in selenium-deficient patients [18–20]. HIV infection may also be associated with altered levels of vitamin B_{12}, carnitine, growth hormone, and thyroid hormone, all of which have been associated with left ventricular dysfunction [20].

Left Ventricular Dysfunction Caused by Drug Cardiotoxicity

Studies of transgenic mice suggest that zidovudine is associated with diffuse destruction of cardiac mitochondrial ultrastructure and inhibition of mitochondrial DNA replication [21, 22]. This mitochondrial dysfunction may result in lactic acidosis, which could also contribute to myocardial cell dysfunction. However, in a study of infants born to HIV-positive mothers followed up from birth to age 5, perinatal exposure to zidovudine was not found to be associated with acute or chronic abnormalities in left ventricular structure or function [23]. Other nucleoside reverse transcriptase inhibitors, such as didanosine and zalcitabine, do not seem to either promote or prevent dilated cardiomyopathy.

Pericardial Effusion

Before the introduction of HAART, the prevalence of pericardial effusion in asymptomatic AIDS patients was estimated at 11% per year [24]. Although prospective data are lacking, retrospective data suggest that HAART has reduced the overall incidence of pericardial effusion in HIV disease by about 30% [7] (Fig. 7). AIDS patients with pericardial effusion survive a median of 6 months, significantly shorter than do AIDS patients without effusion. Survival is independent of CD4 count and albumin levels [24].

A 5-year prospective evaluation of cardiac involvement in AIDS found 16 of 231 patients had or developed pericardial effusions [24]. Three subjects had an effusion on enrollment, and 13 developed effusions during follow-up (12/13 with AIDS at enrollment). Pericardial effusions were generally small (80%) and asymptomatic (87%). The calculated incidence of pericardial effusion among those with AIDS was 11% per year. The prevalence of effusion in AIDS patients may rise over time, reaching an estimated mean of 22% after 25 months of follow-up in asymptomatic patients [24].

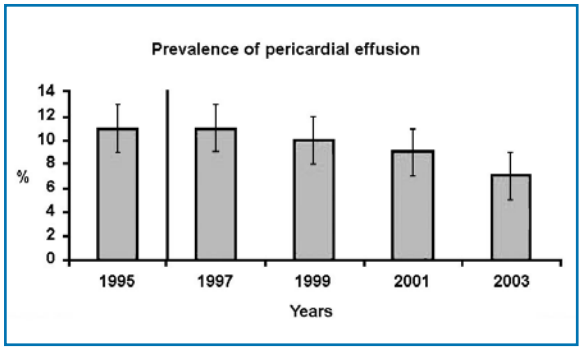


Fig. 7. Prevalence of HIV-associated pericardial effusion in the years 1995–2003. The *vertical line* indicates the introduction of HAART in the treatment of HIV infection

Among subjects with AIDS and pericardial effusion, 36% were alive after 6 months of follow-up, whereas 93% of those without effusion were alive at 6 months [24]. Two patients developed pericardial tamponade as assessed by clinical and echocardiographic criteria [24]. Several studies have suggested spontaneous resolution of pericardial effusion over time in 13%–42% of affected patients [24]. However, mortality remains markedly increased in patients who had developed an effusion, whether or not the effusion resolved [24].

Endocardial Involvement

The prevalence of infective endocarditis in HIV-infected patients is similar to that of patients in other risk groups, such as intravenous drug users [25]. Estimates of endocarditis prevalence vary from 6.3% to 34% of HIV-infected patients who use intravenous drugs independently of HAART regimens [12]. Right-sided valves are predominantly affected and the most frequent agents are *Staphylococcus aureus* (>75% of cases), *Streptococcus pneumoniae* (15%–20% of cases), *Haemophilus influenzae* (10% of cases), *Candida albicans*, and *Aspergillus fumigatus*

[12, 26]. Patients with HIV generally have similar presentations and survival (85% vs. 93%) from infective endocarditis as those without HIV [26] (Figs. 8–11). However, patients with late-stage HIV disease have a mortality rate, from infective endocarditis, of about 30% higher than do asymptomatic HIV-infected patients, related to the state of immunodeficiency [26]. Nonbacterial thrombotic endocarditis – which was described with a prevalence of 3%–5% in AIDS patients before the introduction of HAART, and mostly in patients with HIV wasting syndrome – is now more frequently observed in developing countries with a high incidence (about 10%–15%) and mortality rate for systemic embolization [9]. Death from marantic endocarditis is rare in HIV-infected patients receiving HAART.

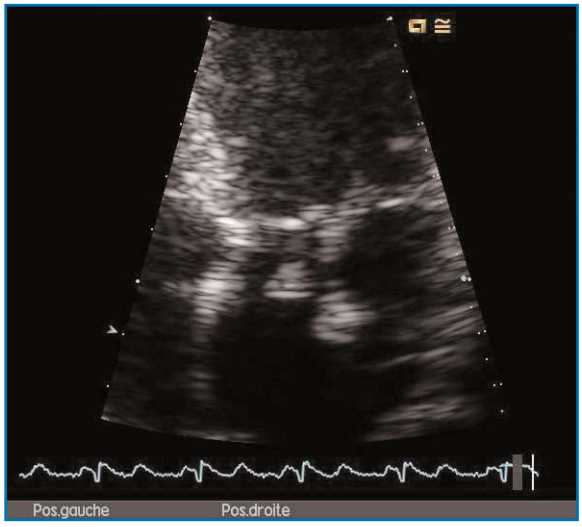


Fig. 8. Voluminous mobile vegetation on the anterior and posterior mitral leaflet in an HIV-infected patient, detected by transthoracic echocardiography (apical four-chamber view)

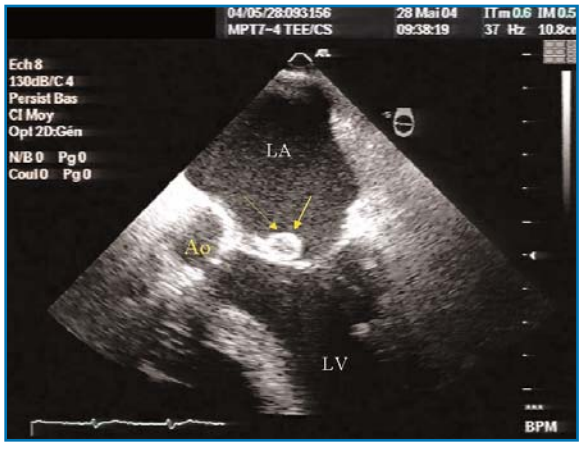


Fig. 9. Large anterior mitral vegetation in an HIV-infected patient, detected by transesophageal echocardiography

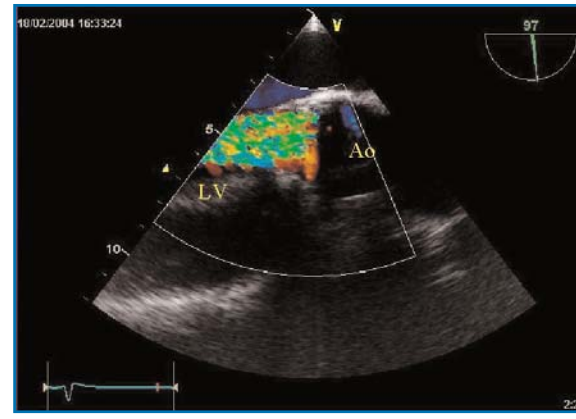


Fig. 10. Significant aortic regurgitation (grade IV) in an HIV-infected patient, detected by color Doppler transesophageal echocardiography

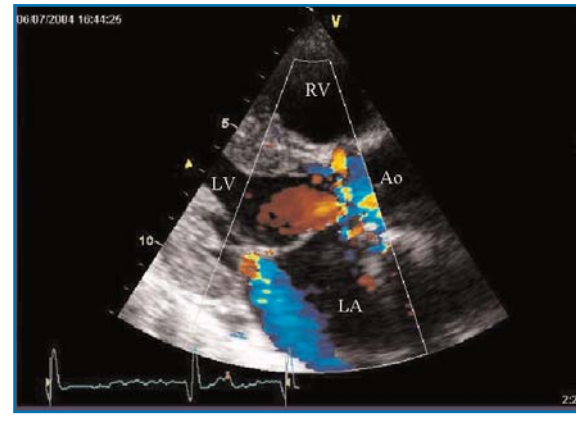


Fig. 11. Significant mitral regurgitation in HIV-infected patients with endocarditis, detected by color Doppler transthoracic echocardiography (parasternal long-axis view)

HIV Infection, Opportunistic Infections, and Vascular Disease

A wide range of inflammatory vascular diseases including polyarteritis nodosa, Henoch-Schönlein purpura, and drug-induced hypersensitivity vasculitis may develop in HIV-infected individuals. Kawasaki-like syndrome [27] and Takayasu's arteri-

tis [28] have also been described. The course of vascular disease may be accelerated in HIV-infected patients because of atherogenesis stimulated by HIV-infected monocyte-macrophages, possibly via altered leukocyte adhesion or arteritis [29].

Some patients with AIDS have a clinical presentation resembling systemic lupus erythematosus (SLE) including vasculitis, arthralgias, myalgias, and autoimmune phenomena with a low-titer positive antinuclear antibody, coagulopathy with lupus anticoagulant, hemolytic anemia, and thrombocytopenic purpura. Hypergammaglobulinemia from polyclonal B-cell activation may be present, but often diminishes in the late stages of AIDS. Specific autoantibodies to double-stranded DNA, Sm antigen, RNP antigen, SSA, SSB and other histones may be found in a majority of HIV-infected persons, but their significance is unclear [29].

Endothelial Dysfunction

Endothelial dysfunction and injury have been described in HIV infection [30]. Circulating markers of endothelial activation, such as soluble adhesion molecules and procoagulant proteins, are elaborated in HIV infection. HIV may enter the endothelium via CD4 or galactosylceramide receptors [30]. Other possible mechanisms of entry include chemokine receptors [31]. Endothelium isolated from the brain of HIV-infected subjects strongly expresses both CCR3 and CXCR4 HIV-1 coreceptors, whereas coronary endothelium strongly expresses CXCR4 and CCCR2A coreceptors [31]. CCR5 is expressed at a lower level in both types of endothelium. The fact that CCR3 is more common in brain endothelium than in coronary endothelium could be significant in light of the different susceptibilities of the heart and brain to HIV-1 invasion. Endothelial activation in HIV infection may also be caused by cytokines (e.g., TNF-α) secreted in response to mononuclear or adventitial cell activation by the virus, or may be a direct effect of the secreted HIV-associated proteins gp 120 (envelope glycoprotein) and tat (transactivator of viral replication) on endothelium with the possible induction of an apoptosis process [32]. Opportunistic agents, such as cytomegalovirus, frequently coinfect HIV-infected patients and may contribute to the development of endothelial damage. It has also been hypothesized that human herpes virus-8 (a virus that is found in all forms of Kaposi's sarcoma) may trigger or accelerate the development of atheroma in the presence of HAART-related hyperlipidemia [33]. In spite of all these observations, the clinical consequences of HIV-1 and opportunistic agents on endothelial function have not been elucidated yet.

HIV Infection and Coronary Arteries

The association between viral infection (cytomegalovirus or HIV-1 itself) and coronary artery lesions is not clear. HIV-1 sequences have been detected by in situ hybridization in the coronary vessels of an HIV-infected patient who died of acute myocardial infarction [34]. Potential mechanisms through which HIV-1 may damage coronary arteries include activation of cytokines and cell-adhesion molecules and alteration of major histocompatibility complex class I molecules on the surface of smooth muscle cells [34]. It is also possible that HIV-1-associated protein gp 120 may induce smooth muscle cell apoptosis through a mitochondrion-controlled pathway by activation of inflammatory cytokines (e.g., TNF-α) [32].

Opportunistic Infections

Toxoplasma gondii can produce a gross pattern of patchy irregular white infiltrates in myocardium, similar to non-Hodgkin's lymphoma. Microscopically, the myocardium shows scattered mixed inflammatory cell infiltrates with polymorphonuclear leukocytes, macrophages, and lymphocytes. True *T. gondii* cysts or pseudocysts containing bradyzoites are often hard to find, even if inflammation is extensive. Immunohistochemical staining may reveal free tachyzoites, otherwise difficult to distinguish, within the areas of inflammation. *T. gondii* myocarditis can produce focal myocardial fiber necrosis and heart failure can ensue [25].

Other opportunistic infections of the heart are infrequent. They are often incidental findings at

autopsy, and cardiac involvement is probably the result of widespread dissemination, as exemplified by *Candida* and by the dimorphic fungi *Cryptococcus neoformans*, *Coccidioides immitis*, and *Histoplasma capsulatum*. Patients living in endemic areas for *Trypanosoma cruzi* may rarely develop a pronounced myocarditis and dilated cardiomyopathy [25].

Commom HIV Therapies and the Heart

In AIDS patients with Kaposi's sarcoma, reversible cardiac dysfunction was associated with prolonged, high-dose therapy with interferon alpha [35]. Doxorubicin (Adriamycin) used to treat AIDS-related Kaposi's sarcoma and non-Hodgkin's lymphoma has a dose-related effect on dilated cardiomyopathy, as does foscarnet sodium used to treat cytomegalovirus esophagitis [35]. Cardiac arrhythmias have been described with the administration of amphotericin B [36], ganciclovir [37], trimethoprim-sulfamethoxazole [38], and pentamidine [39]. The principal cardiovascular actions/interactions of common HIV therapies are reported in Table 2.

Table 2. Cardiovascular actions/interactions of common HIV therapies [6]

Class	Drugs	Cardiac drug interactions	Cardiac side effects
A) Antiretroviral A. Nucleoside reverse transcriptase inhibitors (RTI)	Abacavir (Ziagen), zidovudine (AZT, Retrovir)	Dipyridamole	Lactic acidosis (rare), hypotension, skeletal muscle myopathy (mitochondrial dysfunction hypothesized, but not seen clinically)
B. Nucleotide RTI	Tenofovir (Viread)		
B) Non-nucleoside RTI	Delavirdine (Rescriptor), efavirenz (Sustiva), nevirapine (Viramune)	Warfarin (class interaction), calcium channel blockers, beta blockers, quinidine, steroids, theophylline	Delavirdine can cause serious toxic effects if given with antiarrythmic drugs and myocardial ischemia if given with vasoconstrictors
C) Protease inhibitors	Amprenavir (Agenerase), indinavir (Crixivan), nelfinavir (Viracept), ritonavir (Norvir), saquinavir (Invirase, Fortovase), atazanavir (Reyataz)	All are metabolized by cytochrome p-450 and interact with: sildenafil, amiodarone, lidocaine, quinadine, warfarin, statins Calcium channel blockers, beta-blockers (1.5–3 x increase), prednisone, quinine, theophylline (decrease concentrations)	Implicated in premature atherosclerosis, dyslipidemia, insulin resistance, and lipodystrophy/lipoatrophy
Anti-infective A) Antibiotics	Erythromycin, clarithromycin	Cytochrome p-450 metabolism and drug interactions	Orthostatic hypotension, ventricular tachycardia, bradycardia, QT prolongation
	Rifampicin	Reduces therapeutic effect of digoxin by induction of intestinal P-glycoprotein	
	Trimethoprim/sulfamethoxazole (Bactrim)	Increases warfarin effects	Orthostatic hypotension, QT prolongation

cont. →

Table 2. *cont.*

Class	Drugs	Cardiac drug interactions	Cardiac side effects
B) Antifungal agents	Amphotericin B	Digoxin toxicity	Hypertension, renal failure, hypokalemia, thrombophlebitis
	Ketoconazole, itraconazole	Cytochrome p-450 metabolism and drug interactions- increases levels of sildenafil, warfarin, "statins", nifedipine, digoxin	Angioedema, dilated cardiomyopathy, arrhythmias
C) Antiviral agents	Foscarnet, ganciclovir	Zidovudine	Reversible cardiac failure (dose-related effect), electrolyte abnormalities, ventricular tachycardia (QT prolongation), hypotension
D) Antiparasitic	Pentamidine (intravenous)		Hypotension, arrhythmias (torsade de pointes, ventricular tachycardia), hyperglycemia, hypoglycemia, sudden death Note: Contraindicated if baseline QTc>0.48

Cardiovascular Malignancy

Cardiac Kaposi's sarcoma in AIDS may cause visceral and parietal pericardial lesions and, less frequently, myocardial lesions. The prevalence has ranged from 12% to 28% in retrospective autopsy studies performed before the introduction of HAART [12]. Cardiac Kaposi's sarcoma is not usually obstructive or associated with clinical cardiac dysfunction, morbidity, or mortality [25].

Malignant lymphoma involving the heart is infrequent in AIDS [12]. Lymphomatous infiltration may be diffuse or may result in discrete isolated lesions, which are usually derived from the Burkitt or immunoblastic type B cells [25]. The lesions are usually nodular or polypoid masses, and they predominantly involve the pericardium, with variable myocardial infiltration. The prognosis of patients with HIV-associated cardiac lymphoma is generally poor, although clinical remission has been observed with combination chemotherapy. The introduction of HAART led to an approximately 50% reduction in the overall incidence of cardiac involvement by Kaposi's sarcoma and non-Hodgkin's lymphomas (Fig. 12).

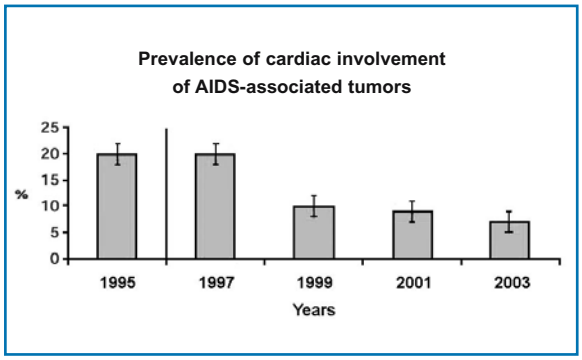


Fig. 12. Prevalence of cardiac involvement of AIDS-associated tumors (Kaposi's sarcoma and non-Hodgkin's lymphoma) in the years 1995-2003. The vertical line indicates the introduction of HAART in the treatment of HIV infection

The fall may be attributable to the improved immunologic state of the patients and the prevention of opportunistic infections (human herpes virus-8 and Epstein-Barr virus) known to play an etiologic role in these neoplasms [40].

Antiretroviral Therapy and Metabolic Disorders

The introduction of HAART in recent years has significantly modified the course of HIV disease, prolonging survival and improving patients' quality of life. However, early data have raised concern that HAART regimens, especially those including protease inhibitors (PIs), are associated with an increased incidence of metabolic (hyperlipidemia, insulin resistance) and somatic (lipodistrophy/lipoatrophy) changes that in the general population are associated with an increased risk for cardiovascular disease (coronary and peripheral artery disease and stroke), producing an intriguing clinical scenario [41].

HIV-associated lipodystrophy/lipoatrophy, first described in 1998 [42], is characterized by prominence of the dorsocervical fat pad ("*buffalo hump*"), increased abdominal girth and breast size, lipoatrophy of subcutaneous fat of the face, buttocks, and limbs, and prominence of the veins on the limbs [42]. The overall prevalence of at least one physical abnormality is about 50% in otherwise healthy outpatients. The differences between these prevalence rates (which ranged from 18% to 83%) may also have been confounded by patient sex and age, the type and duration of antiretroviral therapy, and the lack of an objective and validated case definition. Metabolic features significantly associated with lipodystrophy include dyslipidemia (about 70% of patients), insulin resistance (elevated C-peptide and insulin), type 2 diabetes mellitus (8% to 10% of the patients), lactic acidemia, and elevated hepatic transaminases (non-alcoholic steatohepatitis) [43]. These metabolic abnormalities are more profound in those with more severe physician-assessed lipodystrophy and are associated with an increased risk in cardiovascular events (about 1.4 cardiac events per 1,000 years of therapy according to the Framingham score) [43].

A detailed description of HAART-associated metabolic syndrome and coagulation disorders, and of HAART-associated coronary and peripheral artery disease and stroke is provided by J. Capeau, L. Drouet, F. Boccara, P. Mercié, and A. Moulignier in separate chapters in this volume.

References

1. Barbaro G, Di Lorenzo G, Grisorio B, Barbarini G and the Gruppo Italiano per lo Studio Cardiologico dei pazienti affetti da AIDS Investigators (1998) Cardiac involvement in the acquired immunodeficiency syndrome: a multicenter clinical-pathological study. AIDS Res Hum Retroviruses 14:1071-1077
2. Temesgen Z (1999) Overview of HIV infection. Ann Allergy Asthma Immunol 83:1-5
3. Lai WW, Lipshultz SE, Easley KA et al (1998) Prevalence of congenital cardiovascular malformations in children of human immunodeficiency virus-infected women: the prospective P2C2 HIV Multicenter Study. P2C2 HIV Study Group, National Heart, Lung, and Blood Institute, Bethesda, Maryland. J Am Coll Cardiol 32:1749-1755
4. Barbarini G, Barbaro G (2003) Incidence of the involvement of the cardiovascular system in HIV infection. AIDS 17:S46-S50
5. Barbaro G, Di Lorenzo G, Soldini M et al (1999) Intensity of myocardial expression of inducible nitric oxide synthase influences the clinical course of human immunodeficiency virus-associated cardiomyopathy. Circulation 100:933-939
6. Barbaro G (2002) Cardiovascular manifestations of HIV infection. Circulation 106:1420-1425
7. Pugliese A, Isnardi D, Saini A, Scarabelli T, Raddino R, Torre D (2000) Impact of highly active antiretroviral therapy in HIV-positive patients with cardiac involvement. J Infect 40:282-284
8. Bijl M, Dieleman JP, Simoons M, Van Der Ende ME (2001) Low prevalence of cardiac abnormalities in an HIV-seropositive population on antiretroviral combination therapy. J AIDS 27:318-320
9. Nzuobontane D, Blackett KN, Kuaban C (2002) Cardiac involvement in HIV-infected people in Yaounde, Cameroon. Postgrad Med J 78:678-681
10. Shannon RP, Simon MA, Mathier MA et al (2000) Dilated cardiomyopathy associated with simian AIDS in nonhuman primates. Circulation 101:185-193
11. Barbaro G (2003) Pathogenesis of HIV-associated heart disease. AIDS 17:S12-S20

12. Barbaro G, Di Lorenzo G, Grisorio B, Barbarini G and the Gruppo Italiano per lo Studio Cardiologico dei pazienti affetti da AIDS investigators (1998) Cardiac involvement in the acquired immunodeficiency syndrome. A multicenter clinical-pathological study. AIDS Res Hum Retroviruses 14:1071-1077
13. Currie PF, Goldman JH, Caforio AL et al (1998) Cardiac autoimmunity in HIV-related heart muscle disease. Heart 79:599-604
14. Lipshultz SE, Easley KA, Orav EJ et al (2000) Cardiac dysfunction and mortality in HIV-infected children. The Prospective P2C2 HIV Multicenter Study. Circulation 102:1542-1548
15. Freeman GL, Colston JT, Zabalgoitia M, Chandrasekar B (1998) Contractile depression and expression of proinflammatory cytokines and iNOS in viral myocarditis. Am J Physiol 274:249-258
16. Lipshultz SE, Easley KA, Orav EJ et al (1998) Left ventricular structure and function in children infected with human immunodeficiency virus. The prospective P2C2 HIV multicenter study. Circulation 97:1246-1256
17. Cooper ER, Hanson C, Diaz C et al (1998) Encephalopathy and progression of human immunodeficiency virus disease in a cohort of children with perinatally acquired human immunodeficiency virus infection. J Pediatr 132:808-812
18. Miller TL, Orav EJ, Colan SD, Lipshultz SE (1997) Nutritional status and cardiac mass and function in children infected with the human immunodeficiency virus. Am J Clin Nutr 66:660-664
19. Miller TL (1998) Cardiac complications of nutritional disorders. In: Lipshultz SE (ed) Cardiology in AIDS. Chapman & Hall, New York, pp 307-316
20. Hoffman M, Lipshultz SE, Miller TL (1999) Malnutrition and cardiac abnormalities in the HIV-infected patients. In: Miller TL, Gorbach S (eds) Nutritional aspects of HIV infection. Arnold, London, pp 33-39
21. Lewis W, Simpson JF, Meyer RR (1994) Cardiac mitochondrial DNA polymerase gamma is inhibited competitively and noncompetitively by phosphorylated zidovudine. Circ Res 74:344-348
22. Lewis W, Grupp IL, Grupp G et al (2000) Cardiac dysfunction in the HIV-1 transgenic mouse treated with zidovudine. Lab Invest 80:187-197
23. Lipshultz SE, Easley KA, Orav EJ et al (2000) Absence of cardiac toxicity of zidovudine in infants. N Engl J Med 343:759-766
24. Heidenreich PA, Eisenberg MJ, Kee LL et al (1995) Pericardial effusion in AIDS. Incidence and survival. Circulation 92:3229-3234
25. Barbaro G, Klatt EC (2002) HIV infection and the cardiovascular system. AIDS Rev 4:93-103
26. Nahass RG, Weinstein MP, Bartels J, Gocke DJ (1990) Infective endocarditis in intravenous drug users: a comparison of human immunodeficiency virus type 1-negative and -positive patients. J Infect Dis 162:967-970
27. Johnson RM, Little JR, Storch GA (2001) Kawasaki-like syndromes associated with human immonodeficiency virus infection. Clin Infect Dis 32:1628-1634
28. Shingadia D, Das L, Klein-Gitelman M, Chadwick E (1999) Takayasu's arteritis in a human immunodeficiency virus-infected adolescent. Clin Infect Dis 29:458-459
29. Gisselbrecht M (1999) [Vasculitis during human acquired immunodeficiency virus infection]. Pathol Biol (Paris) 47:245-247
30. Chi D, Henry J, Kelley J, Thorpe R, Smith JK, Krishnaswamy G (2000) The effects of HIV infection on endothelial function. Endothelium 7:223-242
31. Berger O, Gan X, Gujuluva C et al (1999) CXC and CC chemokine receptors on coronary and brain endothelia. Mol Med 5:795-805
32. Twu C, Liu QN, Popik W et al (2002) Cardiomyocytes undergo apoptosis in human immunodeficiency virus cardiomyopathy through mitochondrion and death receptor-controlled pathways. Proc Natl Acad Sci USA 99:14386-14391
33. Grahame-Clarke C, Alber DG, Lucas SB, Miller R, Vallance P (2001) Association between Kaposi's sarcoma and atherosclerosis: implications for gammaherpesviruses and vascular disease. AIDS 15:1902-1905
34. Barbaro G, Barbarini G, Pellicelli AM (2001) HIV-associated coronary arteritis in a patient with fatal myocardial infarction. N Engl J Med 344:1799-1800
35. Barbaro G, Fisher SD, Lipshultz SE (2001) Pathogenesis of HIV-associated cardiovascular complications. Lancet Infectious Diseases 1:115-124
36. Arsura EL, Ismail Y, Freeman S, Karunakav AR (1994) Amphotericin B-induced dilated cardiomyopathy. Am J Med 97:560-562
37. Cohen AJ, Weiser B, Afzal Q, Fuhrer J (1990) Ventricular tachycardia in two patients with AIDS receiving ganciclovir (DHPG). AIDS 4:807-809
38. Lopez JA, Harold JG, Rosenthal MC, Oseran DS, Schapira JN, Peter T (1987) QT prolongation and torsade de pointes after administration of thrimethoprim-sulfamethoxazole. Am J Cardiol 59:376-377
39. Stein KM, Haronian H, Mensah GA, Acosta A, Jacobs J, Klingfield P (1990) Ventricular tachycardia and torsades de pointes complicating pentamidine therapy of *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. Am J Cardiol 66:888-889

40. Dal Maso L, Serraino D, Franceschi S (2001) Epidemiology of HIV-associated malignancies. Cancer Treat Res 104:1-18
41. Barbaro G, Klatt EC (2003) Highly active antiretroviral therapy and cardiovascular complications in HIV-infected patients. Curr Pharm Des 9:1475-1481
42. Carr A, Samaras K, Burton S et al (1998) A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 12:F51-F58
43. Carr A (2003) HIV lipodystrophy: risk factors, pathogenesis, diagnosis and management. AIDS 17:S141-S148
44. Holmberg SD, Moorman AC, Williamson JM et al (2002) Protease inhibitors and cardiovascular outcomes in patients with HIV-1. Lancet 360:1747-1748
45. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA (2003) Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. N Engl J Med 348:702-710
46. Friis-Moller N, Weber R, Reiss P et al (2003) Cardiovascular risk factors in HIV patients – association with antiretroviral therapy. Results from DAD study. AIDS 17:1179-1193
47. Klein D, Hurley LB, Quesenberry Jr CP, Sidney S (2002) Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? J AIDS 30:471-477
48. Coplan PM, Nikas A, Japour A et al (2003) Incidence of myocardial infarction in randomized trials of protease inhibitor-based antiretroviral therapy: an analysis of four different protease inhibitors. AIDS Res Hum Retroviruses 19:449-455
49. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D and the Clinical Epidemiology Group from the French Hospital Database (2003) Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. AIDS 17:2479-2486
50. Barbaro G, Di Lorenzo G, Cirelli A et al (2003) An open-label, prospective, observational study of the incidence of coronary artery disease in patients with HIV receiving highly active antiretroviral therapy. Clin Ther 25:2405-2418
51. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group (2003) Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med 349:1993-2003
52. Aoun S, Ramos E (2000) Hypertension in the HIV-infected patient. Curr Hypertens Rep 2:478-481
53. Sattler FR, Qian D, Louie S et al (2001) Elevated blood pressure in subjects with lipodystrophy. AIDS 15:2001-2010

Pathogenesis of HAART-Associated Metabolic Syndrome

J. Capeau

Highly active antiretroviral therapy (HAART) with protease inhibitors (PIs) and nucleoside analog inhibitors of viral reverse transcriptase (NRTI) allowed a major reduction in the severity and morbidity of HIV infection; however, they were associated with the occurrence of secondary effects collectively termed "HAART-related lipodystrophy or metabolic syndrome." This syndrome is associated with alterations in body fat repartition with peripheral fat loss and/or central fat accumulation together with metabolic disorders such as hypertriglyceridemia (hyper-TG), hypercholesterolemia, and insulin resistance sometimes with altered glucose tolerance. This set of abnormalities is close to that reported to be present in the very common metabolic or insulin resistance syndrome and some of the pathophysiological mechanisms are probably the same. In addition, the HAART-related metabolic syndrome probably results from alterations directly related to the treatment of, and to the context of, altered immunity and modified cytokine profile, which most likely enhances its severity and could be responsible for its specific features.

Definition of Metabolic Syndrome in Non-HIV-Infected Patients

Metabolic syndrome – also called syndrome X, insulin resistance syndrome, or dysmetabolic syndrome – was defined, according to the WHO [1], by the presence of:

1. Impaired glucose regulation (either impaired fasting glucose or glucose intolerance or diabetes) or insulin resistance (the HOMA values being in the top quartile)
2. With at least two of the following criteria: triglycerides (TG)>1.7 mmol/l (1.5 g/l), high-density lipoprotein (HDL)<0.9 mmol/l (0.35 g/l) for men or <1.0 mmol/l (0.39 g/l) for women, SBP/DBP>140/90 mmHg, body mass index (BMI)>30 kg/m^2 or waist-to-hip ratio (WHR) >0.9 for men and 0.85 for women, albumin/creatinine ratio≥30 mg/g.

A simplified definition was proposed by the NCEP ATP-III guidelines in 2001 [1]. The diagnosis requires at least three of the following criteria: fasting glycemia>6.1 mmol/l (1.1 g/l), fasting TG>1.7 mmol/l (1.5 g/l), HDL<1 mmol/l (men) or 1.3 mmol/l (women; 0.6 and 0.5 g/l), SBP/DBP>130/85 mmHg, waist circumference>102 cm (men) or 88 cm (women). In France, the prevalence of metabolic syndrome in the population is about 9% and 6% of adult men and women, respectively, while in the USA it is up to 24% of adults [2].

This syndrome is also associated with increased small dense LDL particles, increased uric acid, and plasminogen activator inhibitor (PAI)-1 levels together with insulin resistance, which appears to play a central role [3]. The accumulation of fat in the abdomen, at the visceral level, results in visceral obesity. The major risks concern the liver, with the occurrence of NASH (non-alcoholic steato-hepatitis) and the possible evolution towards cirrhosis, and the cardiovascular system, with the development of atherosclerosis and the occurrence of cardiovascular complications.

Physiology of Insulin Signaling and Adipose Tissue

Insulin acts on glucose and lipid metabolism, favoring the storage of energy after meals. At the clinical level, insulin resistance is defined as the inability or decreased ability of insulin to control

glycemia, which means that a high level of insulin is required to maintain normoglycemia or that, when glycemia is increased, the levels of insulinemia are disproportionately elevated. To evaluate insulin resistance, the index most used is HOMA (homeostasis model assessment), which is calculated from fasting glycemia levels (mmol/l) multiplied by fasting insulin levels (μU/ml) divided by 22.5. This index, or its derivatives (FIRI, QUICKY), is closely correlated with the evaluation of insulin sensitivity given by the gold standard test, i.e., the euglycemic hyperinsulinemic clamp [4]. The measurement of fasting glycemia and insulinemia mainly relies on the effect of insulin on the liver, where insulin inhibits hepatic glucose production by inhibiting glycogenolysis and gluconeogenesis. During the clamp test, or when a post-prandial measurement is performed, the presence of elevated levels of glycemia and insulin is mainly due to the defective entry and utilization of glucose at the muscle level.

At the cellular level, the mechanisms whereby insulin transduces its signal have been studied for a long time, as have the mechanisms responsible for insulin resistance. In addition to the liver and muscles, adipose tissue is an important target tissue of insulin (Fig. 1). Insulin signals inside the cell by activating its receptor, which possesses a tyrosine kinase activity, and after insulin binding phosphorylates its intracellular domain, therefore allowing cytosol substrate proteins to associate with the receptor. The insulin receptor substrate (IRS) class of proteins transduces the signal towards different intracellular pathways: briefly, the metabolic signals are mainly transduced through the phosphatidylinositol 3 kinase (PI3K) pathway, while the mitogenic signals are mainly transmitted through the mitogen-activated protein (MAP) kinase pathway, which can use the IRS and SHC classes of proteins as receptor substrates. At the level of the liver, insulin acts on glycogen synthesis and increases lipogenesis, in particular from glucose. It inhibits hepatic glucose production by impairing glycogenolysis and gluconeogenesis. In muscle cells, insulin recruits the glucose transporters GLUT4 to the plasma membrane and activates glucose entry together with its storage as glycogen and its oxidation. In adipocytes, insulin

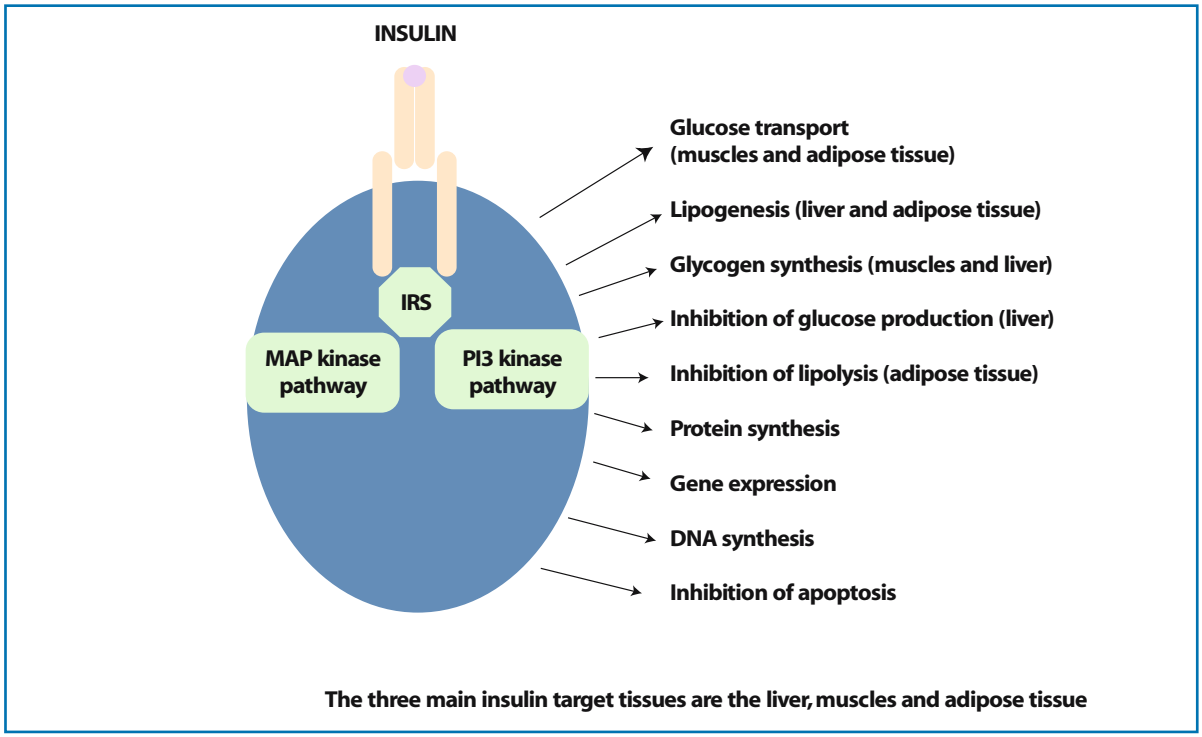


Fig. 1. Insulin signal leads to the activation of major anabolic pathways. *MAP kinase*, mitogen activated kinase; *PI3 kinase*, phosphatidyl inositol 3 kinase

plays a strong metabolic role by increasing TG storage through the activation of lipoprotein lipase and glucose entry and by decreasing TG hydrolysis through the inhibition of the hormone-sensitive lipase involved in lipolysis [5], a pathway stimulated by catecholamines in humans.

In 1963, Randle [6] described the glucose–fatty acid cycle and its role in physiology and pathology. He showed that free fatty acids (FFA) are used in preference to glucose by the heart and diaphragm muscles, leading to decreased glucose utilization. This concept has recently been revisited by G. Shulman and his group [7]. By performing both human and animal studies in vivo, they revealed that FFA entering the muscle cell are transformed into acyl-CoA derivatives and they activate the PKCθ isoform and IKKβ, which in turn activate IRS phosphorylation on serine residues. This serine phosphorylation has been shown by numerous groups to stop insulin signaling and to impede the activation of the downstream steps, including the recruitment of GLUT4 transporters from their intracellular location to the plasma membrane. In that situation, muscle and liver cells use FFA to produce the energy required for their metabolism.

In addition to its metabolic function, adipose tissue now appears to play an important endocrine role: it can release a number of hormones, proteins, and cytokines acting through endocrine or autocrine/paracrine mechanisms (Fig. 2) [8, 9].

Leptin

Leptin is a 16-kDa protein mainly produced by subcutaneous adipose tissue, and it acts as an endocrine factor at the hypothalamic level to reduce food intake and to regulate energy production and utilization. In addition, leptin exerts pleiotropic actions and plays a role in peripheral energy and bone metabolism, reproduction, and immunity. Leptin receptors located on muscle cells have been shown to activate AMP kinase (AMPK) and thereby to favor FFA oxidation (see below).

Adiponectin

Adiponectin or adipoQ or ACRP30 is secreted at high levels by adipose tissue, and circulating levels are between 5 and 10 μg/ml in human plasma. They are negatively correlated with BMI and with the content in visceral fat [10] and are decreased in diabetic and obese patients. It has been reported in numerous studies that the level of circulating adiponectin is inversely related to insulin resistance. Adiponectin is also decreased in patients with ischemic heart disease.

The mechanisms whereby adiponectin acts are now starting to be understood. Two receptors have recently been cloned, but the transduction pathway is still unknown. Interestingly, it has been found

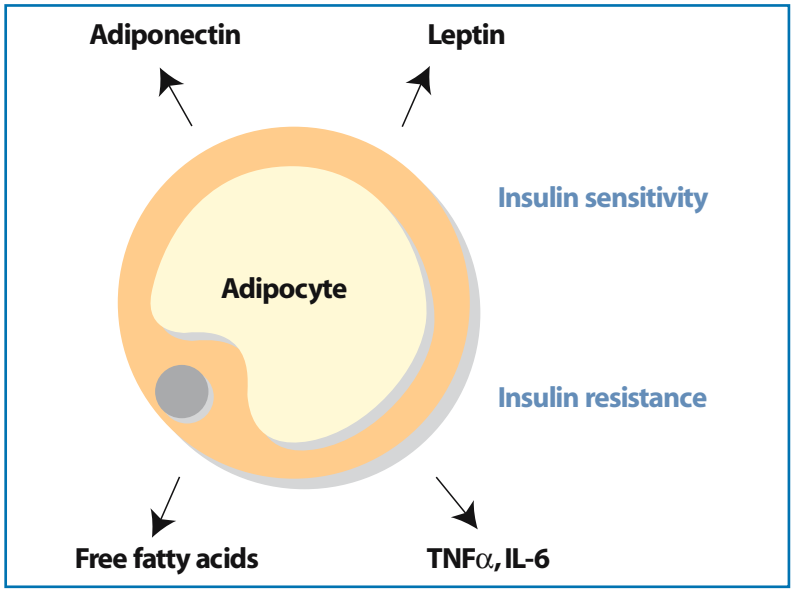


Fig. 2. Adipocytes secrete a range of adipocytokines which control insulin sensitivity

that adiponectin is able to activate AMPK in the liver and muscles. There has been a major interest recently in the role of this enzyme in cell metabolism. AMPK is activated by AMP, the level of which is increased when ATP has been hydrolysed. AMPK now appears as an energy level-detecting enzyme, which plays a key role in redirecting the energy-synthesizing pathways of glucose and lipid metabolism. First, activated AMPK is able to activate indirectly the entry of acyl-CoA into the mitochondria to be degraded by the β-oxidation pathway in the liver and muscles and to be converted into energy. In liver cells, AMPK is also able to inhibit the expression of the gluconeogenic enzymes required for hepatic glucose production. In muscle cells, AMPK can recruit glucose transporters GLUT4 to the membrane, even in the absence of insulin, allowing glucose entry and utilization [8]. In addition to its insulin-sensitizing effect, adiponectin can act at the level of the arterial wall. Atherosclerotic cellular changes include monocyte adhesion to endothelial cells due to the expression of adhesion molecules, uptake of oxidized LDL by macrophages through scavenger receptors, and proliferation of vascular smooth muscle cells in response to PDGF. Adiponectin has been found to inhibit tumor necrosis factor (TNF)-α production and TNF-α-induced adverse effects on the vascular wall, therefore inhibiting all these atherogenic processes [10, 11]. Thus, it probably has a potent anti-atherogenic role and could protect injured vessels against the development of atherogenic lesions. The expression of adiponectin has been found to be inhibited in vitro by TNF-α and interleukin (IL)-6.

Tumor Necrosis Factor-α

TNF-α is synthesized as a 26-kDa plasma membrane-bound monomer. A secreted trimer is formed by proteolysis of the precursor giving rise to a 17-kDa cytokine, which binds to two receptors, type I and II, and activates the classic inflammatory NFκB pathway [12]. In physiological conditions, adipose tissue production is very low. However, its production has been found to be increased in pathological conditions, even if the reason for this increased production remains unclear. Animal studies have revealed that in cases of obesity and insulin resistance, the secretion of TNF-α was increased and could be involved in insulin resistance. In particular, TNF-α has been found to act at the local level on adipocytes and to inhibit insulin signal transduction through the inhibitory phosphorylation of the IRS1 protein together with a decreased expression of GLUT4 [8]. In human studies, the deleterious role of TNF-α has been questioned. Several studies reported that the circulating levels of TNF-α were related with obesity and insulin resistance. However, systemic inhibition of TNF-α in type 2 diabetic patients was not able to decrease insulin resistance. It could be proposed that TNF-α acts mainly at the local and not the systemic level and that it induces adipose tissue resistance: this results in increased lipolysis and FFA fluxes (Fig. 3). In addition TNF-α acts on adipocytes by decreasing adiponectin and increasing IL-6 expression. These latter cytokines, which act at a distance from adipose tissue, probably play a major role in insulin sensitivity and indirectly trigger the insulin-resistant effect of TNF-α.

In addition, in patients with HIV-related metabolic syndrome, several studies consistently revealed increased levels of TNF-α, pointing to a major role for this cytokine in this condition (next section).

Interleukin-6

IL-6 is a proinflammatory cytokine produced by several tissues and cells and, in particular, by adipose tissue: 10%–30% of circulating IL-6 could be produced by adipose tissue. IL-6 may exert its effects at the central level on the hypothalamus. At the liver level, IL-6 induces the production of acute-phase proteins and in particular of C-reactive protein (CRP). The levels of circulating IL-6 were shown to be increased in obesity and were related to insulin resistance. IL-6 also acts by paracrine/autocrine mechanisms on adipocytes and induces insulin resistance and altered differentiation in particular by inducing the expression of SOCS3 [13].

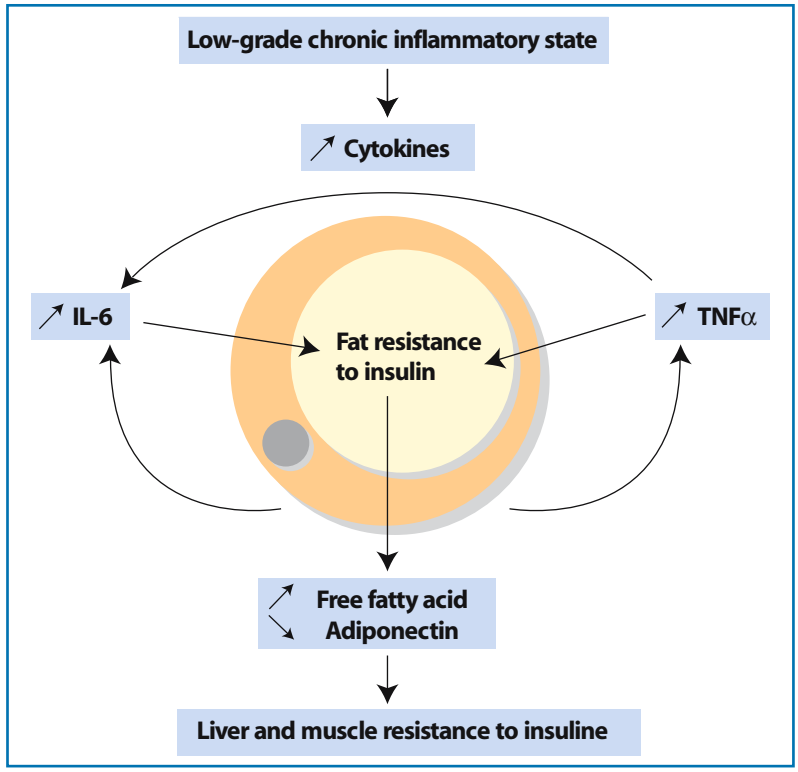


Fig. 3. Proinflammatory cytokines induce insulin resistance

Plasminogen Activator Inhibitor-1

PAI-1 is a protein involved in thrombosis, which compromises the clearance of fibrin. Its level is increased in obesity, type 2 diabetes, and metabolic syndrome. In addition, it is strongly associated with vascular disease including myocardial infarction and venous thrombosis [9].

Regional Differences in Fat Distribution and Physiology

The visceral fat depot is contained within the body cavity surrounding the internal organs and is composed of mesenteric and omental depots. Visceral fat represents about 20% and 6% of total body fat in men and women, respectively. The subcutaneous fat depot is located under the skin, particularly in the abdominal region. In the lower body, all adipose depots are subcutaneous and the largest sites of storage are the gluteal and femoral regions [14]. Visceral and subcutaneous fat express and secrete various amounts of different cytokines. Leptin is mainly secreted by peripheral fat, while adiponectin and IL-6 are secreted in higher quantities by visceral fat. For TNF-α the results are less clear. In addition, visceral fat is more sensitive to catecholamines, and therefore to lipolysis, and more resistant to insulin than subcutaneous fat [15].

It has long been known that glucocorticoids act on adipose tissue and can inhibit proliferation but enhance lipid storage leading to fat hypertrophy. Visceral adipocytes, which contain higher levels of glucocorticoid receptors, are more sensitive to the effect of this hormone. Accordingly, in Cushing's syndrome with hypercorticism, visceral fat is increased particularly. More recently, profound differences have been demonstrated in the level of the enzyme that can convert inactive cortisone to active cortisol, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), with very high activity in visceral fat and barely detectable activity in subcutaneous fat [14, 16]. Therefore, visceral fat is able to produce cortisol locally, which could act inside adipocytes and increase lipid accumulation. Interestingly, this enzyme is activated by TNF-α (Fig. 4).

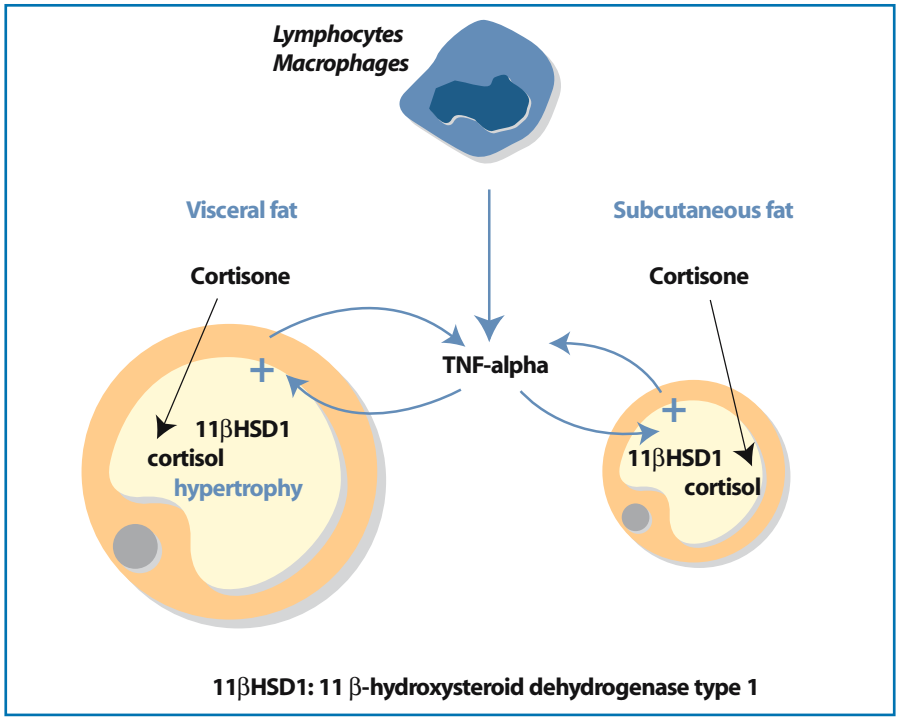


Fig. 4. Pathophysiology of visceral fat hypertrophy: hypothetical mechanisms

Pathology of Insulin Signaling and Adipose Tissue

When adipose tissue is hypertrophic and resistant to insulin, as seen for visceral fat in metabolic syndrome, lipolysis is increased, resulting in increased levels of circulating free fatty acids (FFA). An increased level of FFA plays a detrimental role on glucose utilization in the liver and muscles and leads to insulin resistance. The mechanisms responsible for this resistance to insulin can be hypothesized from the studies performed by Shulman's group [7] and are related to the inhibition of the insulin signaling pathway induced by acyl-CoA derivatives as indicated above. In addition, this excess of acyl-CoA inside the cytosol, exceeding the capacities of degradation in the mitochondria and peroxysomes, leads to accumulation of TG in hepatocytes and muscle cells. Such an accumulation has been reported in numerous studies of patients with insulin resistance, metabolic syndrome, obesity, and diabetes. Moreover, it has been consistently reported that the extent of fat accumulation in the liver is related to the amount of visceral fat and also to insulin resistance evaluated by HOMA or clamp tests [17]. Similarly, the amount of intramyocellular fat has been related to insulin resistance in obese and diabetic patients [18]. This set of alterations has been named lipotoxicity [19]. The location of adipose tissue is probably important: visceral fat, which is highly sensitive to catecholamines and resistant to insulin, is prone to release large amounts of FFA in the portal system which will be driven mainly to the liver. Subcutaneous fat, which is more resistant to lipolysis, would release lower levels of FFA, particularly towards peripheral tissues such as muscles.

Metabolic syndrome, type 2 diabetes, and obesity are now considered as low-grade chronic inflammatory states, like atherosclerosis, leading to coronary heart disease. Hyperinsulinemia and insulin resistance are considered as common preceding factors of hypertension, decreased HDL concentrations, hyper-TG, and altered glucose tolerance (Fig. 5). Part of the features of insulin resistance syndrome can be explained by the altered secretion of products from adipose tissue (and in particular from expanded visceral fat) with increased levels of proinflammatory cytokines, TNF-α and IL-6, responsible for this inflammatory profile. Interestingly, it has recently been shown in animal models of obesity and in human subcuta-

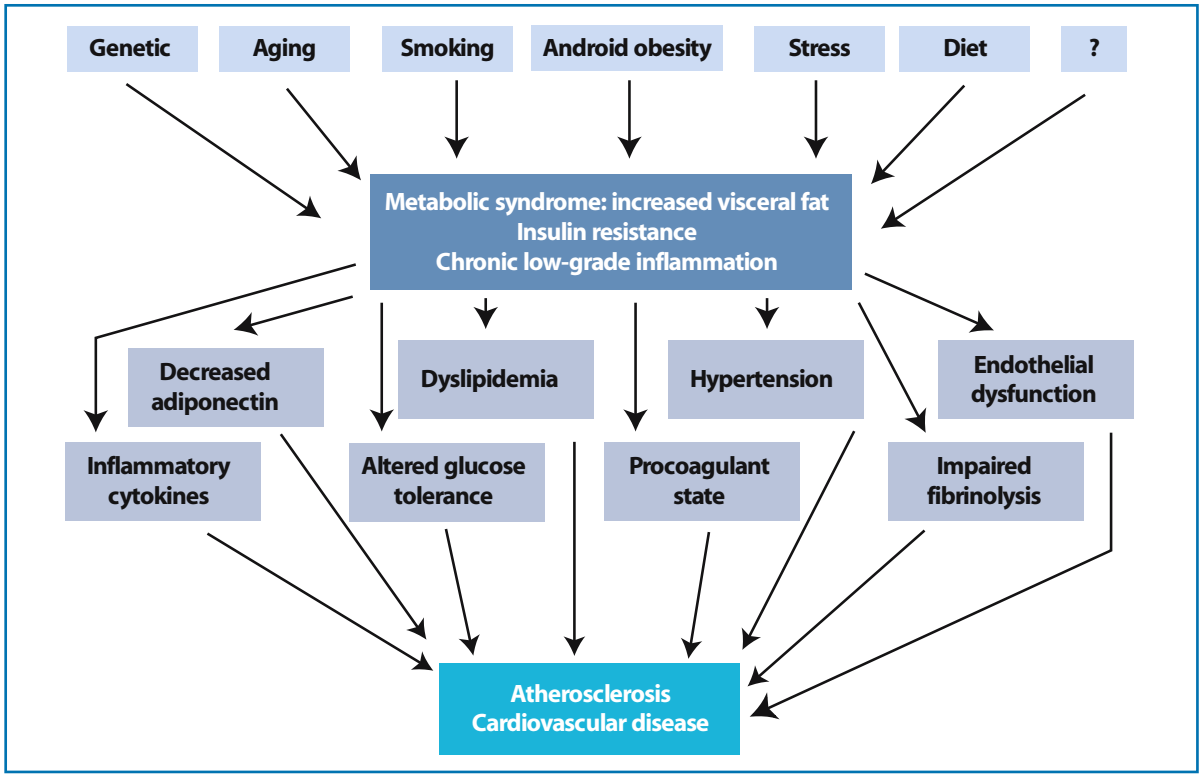


Fig. 5. Pathophysiology of metabolic syndrome

neous fat that white adipose tissue presents macrophage accumulation, which is responsible for increased TNF-α expression [20–22]. Increased endogenous production of cortisol increases insulin resistance participating in a vicious cycle (Fig. 6). Even if visceral fat is more difficult to study than subcutaneous fat in patients, it is highly probable that visceral fat is prone to release higher amounts of FFA and IL-6 and decreased amounts of adiponectin. They are released in the portal system and reach the liver first. This will result in increased production of acute inflammation proteins, such as CRP, and in increased glucose production and very-low-density lipoprotein (VLDL) synthesis resulting in hyper-TG [14].

Subcutaneous abdominal fat, if insulin-resistant, will produce increased FFA used by muscles, resulting in reduced glucose utilization at that level.

The causes for this altered adipocyte function remain speculative: insulin can alter TNF-α and IL-6 secretion and therefore, in the case of insulin resistance, these cytokines could be increased. Otherwise, insulin resistance could be a consequence of TNF-α and IL-6 oversecretion (Fig. 6).

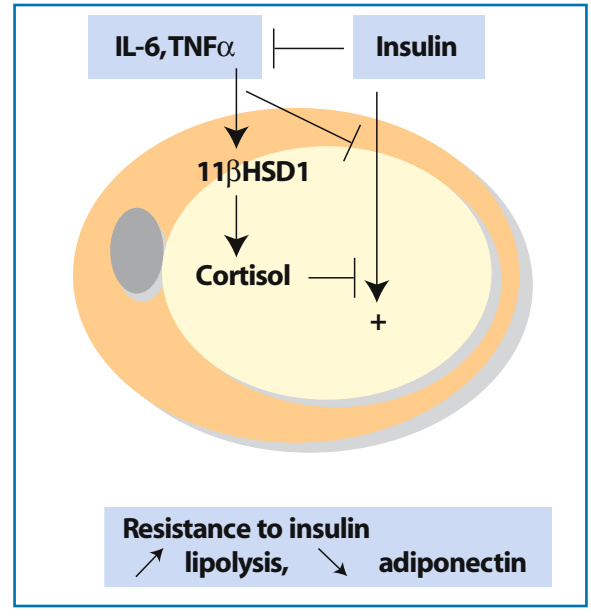


Fig. 6. Cytokines, cortisol, and insulin vicious cycle resulting in insulin resistance

Increased levels of these cytokines at the level of the arterial wall lead to inflammatory lesions of atherosclerosis. Factors such as aging, smoking, and obesity can be responsible for increased proinflammatory cytokines [23]. This set of alterations will create a vicious cycle resulting in metabolic and vascular changes, ultimately leading to atherosclerosis and cardiovascular disease.

Description and Pathophysiology of the HAART-Related Metabolic Alterations

Dyslipidemia

Increased levels of TG and cholesterol together with decreased HDL and increased LDL cholesterol have been described in HIV patients undergoing HAART [24].

Those alterations probably have multiple origins. The HIV infection itself has been shown to be associated with increased levels of TG, decreased levels of HDL and, in patients with AIDS, of LDL cholesterol [24]. These alterations could result from the high level of proinflammatory cytokines (TNF-α, IL-6, IL-1) observed in these patients with an active infection, due to their increased secretion by activated monocytes and macrophages. TNF-α and IL-6 can decrease the expression and activity of lipoprotein lipase, which is involved in TG clearance from circulation lipoproteins. Moreover, acute-phase proteins can bind to HDL particles, promoting their uptake by macrophages and therefore increasing their clearance rate. These phenomena are seen in infection with severe inflammation whatever its origin [25].

After the introduction of HAART, increased levels of lipids were constantly reported. Regarding the NRTIs, stavudine was associated with increased levels of TG [26]. However, the major contributor to dyslipidemia was the class of PIs. Studies performed in non-HIV-infected control subjects revealed that RTV was able, after a few days, to alter lipid parameters with hyper-TG and increased cholesterol levels [27]. Similarly, boosting concentrations of RTV in association with LPV increased TG levels. NNRTIs are also able to modify lipid parameters: NVP increases total and HDL cholesterol levels but not TG [28]. EFV has a similar effect but induces a more marked hypercholesterolemia. Various phenotypes of dyslipidemia were reported in patients undergoing HAART with PIs, but the major alterations are increased levels of TG, decreased levels of HDL, and increased content in small dense LDLs, the profile of which is very similar to that seen in classic metabolic syndrome. The prevalence of lipid alterations is important in PI-treated patients: in an Australian cohort, 14 months after initiating treatment with PIs, 50% of the patients had TG levels above 2 mmol/l and 60% had cholesterol levels above 5.5 mmol/l, whereas these values were 22% and 11%, respectively, in patients under NRTI treatment without PIs [29]. In the French cohort APROCO-TM, after 1 and 3 years of PI treatment, respectively, the prevalence of hyper-TG increased from 26% to 36% in men and from 20% to 25% in women. The prevalence of hypercholesterolemia was elevated between 55% and 60% in both groups [26].

These alterations could result from a direct effect of the drugs, particularly at the liver level, resulting in modified lipid metabolism (Fig. 7). The synthesis and secretion of Apo-B, the major VLDL-linked apoprotein, are partly regulated by the balance between the association to lipids and the degradation in the proteasome system involved in overall cellular protein degradation. Thus, it has been shown, in in vitro models of hepatic cells, that RTV and SQV could inhibit the degradation of ApoB by inhibiting the proteasome, which results in increased VLDL secretion [30]. When animals were fed a high-fat diet, an increased synthesis of TG on VLDL was observed [31]. Moreover, RTV is able to increase VLDL secretion in mice through the activation of the lipogenic transcription factor SREBP-1 in the liver [32]. Regarding VLDL catabolism, B. Perret's group presented interesting data [33] indicating that, in PI-treated patients, there was an accumulation of lipoparticles containing apo C-III and apo-E in association with apo-B. These complex particles would represent persistent potentially atherogenic cholesterol-rich remnant particles derived from TG-rich lipoproteins. The observed excess in apo-CIII on lipoproteins might be a major determinant of a slower catabolism of TG-rich lipoproteins, since apoC-III is an

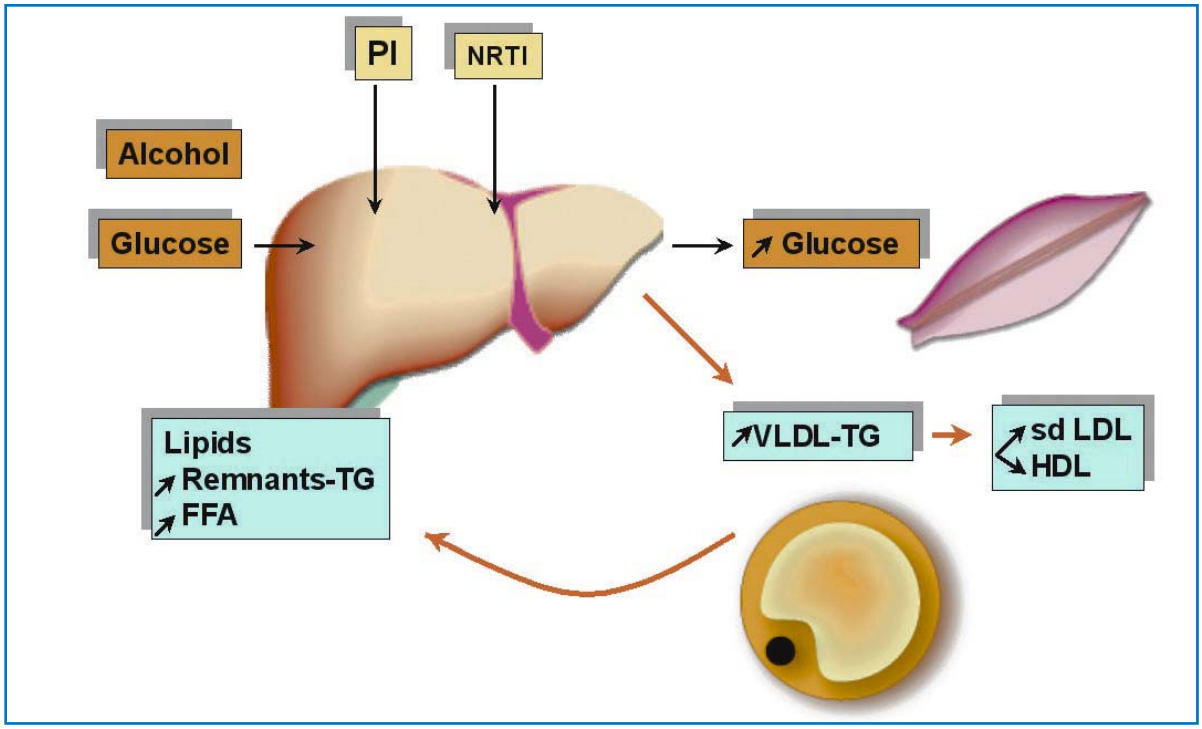


Fig. 7. Adverse effects of antiretroviral treatment on lipid and glucose metabolism. *sdLDL*, small dense LDL

inhibitor of lipoprotein lipase activity and it also impairs the interaction of apoB and apo-E with the LDL-receptor and LRP [25]. This will result in an increased level of remnant lipoprotein returning to the liver.

In addition to a direct effect of some PIs on lipid metabolism, the altered repartition of body fat is probably also involved in lipid alterations. As explained above for metabolic syndrome, increased content in visceral fat as well as decreased peripheral adipose tissue are associated with an increased level of lipolysis and of FFA fluxes together with altered adipocytokine production: increased levels of TNF-α, IL-1, and IL-6 and decreased levels of adiponectin. Thus, even after the introduction of HAART, the severity of the inflammatory syndrome is markedly decreased as compared to the state of active infection. Patients with HAART-related metabolic syndrome still present a state of low-grade inflammation with increased cytokines and acute-phase proteins such as CRP, which could contribute to the dyslipidemia observed in these patients.

Altered Glucose Tolerance and Insulin Resistance

The presence of altered glucose tolerance concerns only a minority of PI-treated patients, but its prevalence is increasing. In the APROCO-TM French cohort, increased glycemia (either fasting hyperglycemia or glucose intolerance) increased from 17% to 27% in men after 1 and 3 years of treatment, respectively, while diabetes increased from 4% to 9%. In women, alterations in glucose tolerance remained stable at 25% but the prevalence of diabetes increased from 2% to 11%. These data suggest that the prevalence and the severity of glucose alterations tend to increase with the duration of PI treatment. Insulin resistance, which can be evaluated by the simple HOMA test, is highly prevalent in these patients [26].

The type and prevalence of theses alterations are linked to the individual molecules in the PI class. Studies performed with non-HIV-infected control subjects revealed that IDV was able to induce insulin resistance and to modify glycemia after a few days [34]. After a single dose, IDV was

able to decrease glucose uptake during a clamp test, indicating insulin resistance, which was rapid and reversible [35]. It is hypothesized that this effect could be due to inhibition of the insulin-sensitive glucose transporter GLUT4 that has been evidenced in in vitro studies [36]. Similarly, LPV boosted by RTV induced an increased glycemia and insulinemia after 4 weeks in normal volunteers.

The prevalence of glucose alterations and insulin resistance has been consistently found to be higher in patients with lipodystrophy than in patients without lipodystrophy. A role for adipose tissue in insulin resistance resulting from altered cytokine production and increased lipolysis can be easily hypothesized, which would accentuate the metabolic disorders. As explained below, lipodystrophic adipose tissue presents an altered profile of secreted cytokines with increased TNF-α and IL-6. These cytokines are responsible for insulin resistance at the adipocyte level resulting in increased lipolysis and FFA fluxes, which in turn induce insulin resistance at the level of the liver and muscles. In addition, lipodystrophic adipose tissue has a decreased secretion of adiponectin, which could result in decreased lipid oxidation and glucose intake in the muscles, and in decreased lipid oxidation and increased glucose production in the liver as explained above.

Therefore, the drug-induced alterations in glucose metabolism and in insulin sensitivity are aggravated by the altered adipose tissue function due to lipodystrophy.

Description and Pathophysiology of the HAART-Related Abnormal Fat Distribution

Description

Different forms of abnormal fat distribution or lipodystrophies are seen in HIV-infected patients undergoing HAART. Lipoatrophy mainly concerns peripheral fat, at the level of the limbs, buttocks, face, and abdomen and could be clinically evaluated by the reduced skin-fold due to the decrease in subcutaneous fat. Central lipoatrophy, inside the abdomen, can only be diagnosed by imaging technologies such as MRI or CT scans. In addition, fat is increased in some regions located primarily in the visceral area but also in the chest and neck, giving an aspect of a buffalo hump. When lipoatrophy and lipohypertrophy are associated, a phenotype of mixed lipodystrophy is present, which is very typical of HAART-related lipodystrophy. This syndrome resembles the typical metabolic syndrome but is more striking since both the loss of the peripheral fat and the increase in visceral fat can be very marked in the same patient.

In fact, two lipodystrophy syndromes are depicted in HIV-infected patients. After several years of treatment, 30% of patients undergoing NRTI therapy without PIs can present a phenotype of mainly peripheral lipoatrophy with minor metabolic alterations, but sometimes with signs in favor of mitochondrial dysfunction such as an increased lactate level. This lipodystrophy is observed with a higher frequency in patients treated with stavudine or to a lesser extent with zidovudine than with other NRTIs [37].

In patients undergoing HAART with PIs and NRTIs, there is a higher prevalence of lipodystrophy, about 60% (but this value is highly variable according to the study and the definition, from 20% to 80%), and metabolic alterations are generally involved [37].

The pathophysiology of these lipodystrophies remains poorly understood due to their multifactorial origin. Among the numerous factors found to be concerned, drugs play an important role, but other factors linked to the disease and to the patients themselves also have to be considered. Studies performed with cohorts of patients have outlined the importance of the severity of HIV infection, of the quality of immune restoration, as well as of age, sex, and BMI in the prevalence, type, and severity of lipodystrophy. NRTIs were found to be linked primarily to peripheral lipoatrophy and PIs to visceral fat accumulation. Their association increases their prevalence and severity [38]. However, individual molecules of these two classes have different effects.

In Vitro Studies

To better understand the pathophysiology of fat alterations, studies were performed first in vitro, so as to decipher the precise role of each drug on adipocyte functions. Most of the studies concerned PIs, since lipodystrophies were diagnosed shortly after their introduction. Several studies reported that in the short term, PIs were able to inhibit the insulin-activated glucose transporter GLUT4, thereby rapidly inducing insulin resistance, which was reversible when the PI concentration was lowered [36]. In the long term (several days), most of the studies reported that some PIs, but not all, were able to greatly alter adipocyte functions by decreasing adipocyte differentiation and by inducing insulin resistance [39]. Our group and others have reported that the step of the adipogenic transcription factor SREBP-1 was specifically targeted by some but not all PIs, with a decreased level of the protein and a decreased activation of the downstream pathways. We have recently shown that some PIs were able to impair the nuclear location of SREBP-1 and to alter the structure and stability of the nuclear lamina, possibly by impairing the maturation of prelamin A to lamin A [40, 41]. Lamin A and lamin C are encoded by the same gene and they can combine with lamin B to form a meshwork of filamentous proteins that lines the inner nuclear membrane called lamina. Lamina interacts with the nuclear membrane and with chromatin. In particular, the C-terminal globular domain of lamin A/C can bind DNA and also SREBP-1 [42, 43]. Interestingly, mutations in this domain are responsible for a genetic form of partial lipodystrophy, Dunnigan's syndrome or FPLD, with peripheral lipoatrophy, accumulation of fat at the level of the face and neck, and major metabolic alterations with hyper-TG, diabetes, and insulin resistance. The mutations responsible for FPLD reduced the interactions of lamin with DNA and SREBP-1, which could explain the altered adipose tissue differentiation observed in these patients. The cells from these patients present nuclear alterations and altered lamina stability, similar to the alterations induced in cultured adipocytes by some PIs [44]. Thus, we can hypothesize that some PIs could alter lamina structure by comparing lamin A maturation and thereby altering the SREBP-1 normal location inside the nucleus [41]. This could impair adipocyte differentiation and induce insulin resistance. In addition, some PIs have been shown to alter the expression of adipocytokines in cultured adipocytes [45, 46]: they increased the expression of TNF-α and IL-6, the proinflammatory cytokines that could play a role in adipose tissue insulin resistance and apoptosis. They were also shown to decrease the expression of adiponectin, which could explain, at least in part, the resistance to insulin.

As regards NRTIs, only a few in vitro studies have been presented. We have observed that the thymidine analogs, stavudine and AZT, but not the other NRTIs, were able to mildly decrease lipid content in adipocytes without major alteration of the differentiation onset and of insulin sensitivity. In addition, they increased apoptosis and induced mitochondrial dysfunction at concentrations close to their C_{max} in patients [47]. In addition, thymidine analogs also altered the expression of adipocytokines in vitro [46].

Taken as a whole, in the two classes of ART, some drugs modified adipocyte function. PIs altered differentiation and insulin sensitivity possibly through their effect on SREBP-1 and adipocytokines, while NRTIs altered lipid content and increased apoptosis possibly through their effect on mitochondria and adipocytokines. Therefore, when present together, a synergistic effect could be hypothesized (Fig. 8).

Ex Vivo and In Vivo Studies

To go further, different groups performed studies on subcutaneous adipose tissue from lipodystrophic patients, which was compared with fat from control subjects or from non-lipodystrophic patients undergoing HAART.

The level of mitochondrial DNA was evaluated by several groups and consistently found to be decreased in fat from HAART-treated patients: this

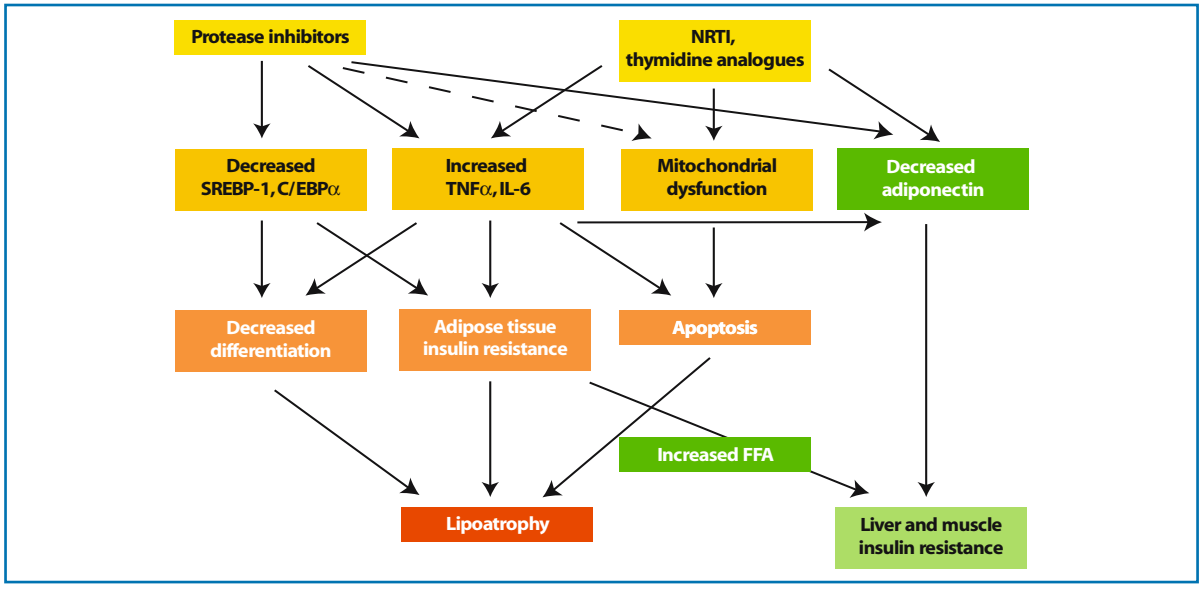


Fig. 8. Hypothetical scheme of the mechanisms responsible for lipoatrophy and insulin resistance in HAART-related lipodystrophy

decrease was seen in patients undergoing stavudine treatment and to a lesser extent with AZT, in accordance with the hypothesis that these NRTIs can alter mitochondrial function. However, the extent of the decrease was not different in fat from lipodystrophic or non-lipodystrophic HAART-treated patients [48]. Morphological studies revealed important morphological alterations in patients' lipoatrophic fat with adipocytes of reduced size, increased apoptosis, increased fibrosis, and mitochondria numbers [48–52].

The expression of the transcription factors SREBP-1, PPARγ, and C/EBPα was found to be decreased in fat from lipodystrophic as compared to non-lipodystrophic and control subjects, indicating a state of altered differentiation and insulin resistance [49, 52, 53]. In addition, the expression of the adipocytokines was deeply altered in fat from lipodystrophic patients as compared to control or non-lipodystrophic patients: TNF-α and IL-6 expression was increased, while that of leptin and adiponectin was decreased [49, 52, 53]. Accordingly, the circulating levels of these cytokines were altered [54]. These alterations are seen in patients undergoing HAART including PIs. It could be postulated from the in vitro studies that the two classes of drugs act in synergy to induce lipoatrophy.

Clinical data on the effects of individual molecules on lipodystrophy are now becoming available. A role for thymidine analogs, stavudine in particular, in peripheral lipoatrophy has been revealed by different studies, which found a strong correlation between the presence of peripheral lipoatrophy and the use of these molecules [48]. In addition, in the MITOX study, when lipoatrophic patients were switched from thymidine analogs to abacavir, peripheral fat was increased by 1.26±2.02 kg [55], arguing again for the implication of thymidine analogs in lipoatrophy.

Increased apoptosis was reported in fat from patients undergoing treatment with PIs and NRTIs. Domingo [56] found that when the patients were switched from PIs to nevirapine, fat cell apoptosis persisted. Otherwise, when patients were switched from stavudine to ABC, they recovered about 20% of peripheral fat after 1 year. However, increased mDNA level remained two times lower than that of control fat and even if apoptosis was reduced, it remained higher than that observed in control fat [57]. This adipose tissue toxicity could result from the ability of these molecules to induce mitochondrial dysfunction and alter adipocytokine secretion. In addition, the fact that apoptosis was only partly reverted argues in favor of a role for other ART, including PIs, in lipoatrophy (Fig. 8).

Pathophysiology of Increased Visceral Fat in HAART-Related Lipodystrophy

While the mechanisms responsible for peripheral lipoatrophy begin to be understood, as fat biopsies can be performed to analyze adipose tissue alterations, only speculative mechanisms can be proposed for visceral fat hypertrophy, since to date no results have been presented on fat from this location. One working hypothesis could refer to the presence of 11β-HSD1 in greater amounts in visceral than in subcutaneous fat, which will result in an increased synthesis of cortisol from cortisone and an endogenous activation of fat hypertrophy. Such a mechanism has been postulated in the classic metabolic syndrome.

In addition, TNF-α has been shown to activate this enzyme. If we hypothesize that TNF-α production is increased in HAART-treated patients due to the effect of therapeutic molecules, this could lead to an even greater activation of the enzyme. Moreover, Gougeon's group has shown that CD4 and CD8 lymphocytes in HAART-treated patients produced TNF-α and were resistant to TNF-α-induced apoptosis [58], which would further increase TNF-α levels. Otherwise, in subcutaneous fat, we observed the presence of activated macrophages that probably release TNF-α [52]. This could be also the case in visceral fat as found in animal models of obesity [21, 22]. Therefore, it could be proposed that increased TNF-α could hyperactivate 11β-HSD 1 and result in an increased synthesis of cortisol inside the adipocytes, thereby favoring their hypertrophy. In addition, other hormones could modulate this enzyme: growth hormone (GH) and testosterone were found to inactivate the enzyme. It is interesting to note that HIV-infected patients with lipodystrophy often present a relative decrease in GH [59] and testosterone levels. Moreover, when patients with visceral fat hypertrophy were treated with GH, a reduction in the amount of visceral fat was consistently reported [60].

Conclusion

Taken as a whole, HAART-related metabolic syndrome could result from the combination of factors found in the metabolic syndrome observed in the general population and it could also result from factors related to the treatment, the infection, and the immune status specific to HIV infection. These factors will favor a proinflammatory, procoagulant, and proatherogenic state, which will worsen the situation (Fig. 9). Even if the occurrence of cardiovascular complications remains uncommon

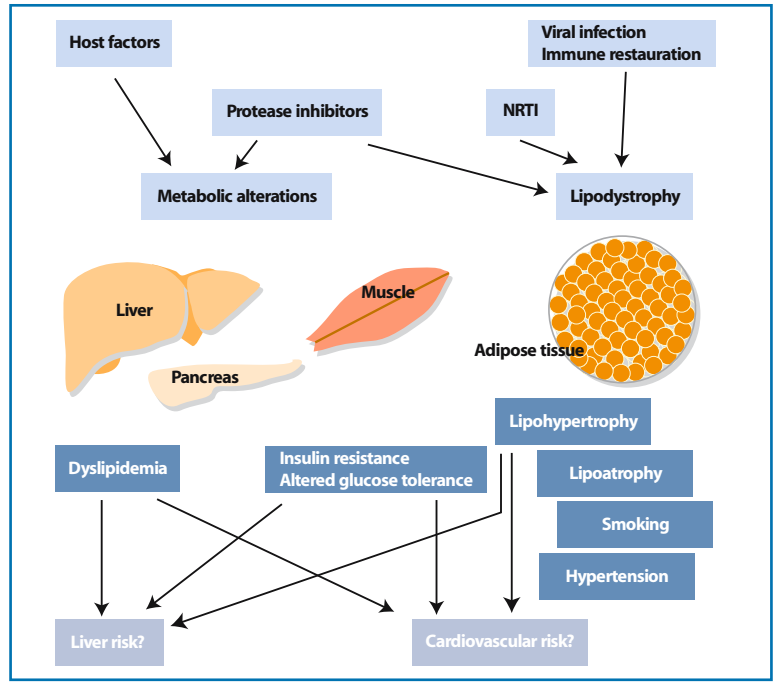


Fig. 9. Pathophysiology of HAART-related metabolic syndrome

in this population exposed for only a few years to this deleterious situation, it could be predicted that the above-mentioned factors will probably rapidly lead to cardiovascular complications. This is a major concern in these patients who require continuous antiretroviral treatment to control viral infection and who can now expect prolonged life duration.

References

1. Hanley AJ, Wagenknecht LE, D'Agostino RB Jr, Zinman B, Haffner SM (2003) Identification of subjects with insulin resistance and beta-cell dysfunction using alternative definitions of the metabolic syndrome. Diabetes 52:2740-2747
2. Balkau B, Vernay M, Mhamdi L et al (2003) The incidence and persistence of the NCEP (National Cholesterol Education Program) metabolic syndrome. The French D.E.S.I.R. study. Diabetes Metab 29: 526-532
3. Ginsberg HN (2000) Insulin resistance and cardiovascular disease. J Clin Invest 106:453-458
4. Leow MK, Addy CL, Mantzoros CS (2003) Clinical review 159: Human immunodeficiency virus/highly active antiretroviral therapy-associated metabolic syndrome: clinical presentation, pathophysiology, and therapeutic strategies. J Clin Endocrinol Metab 88:1961-1976
5. Saltiel AR, Kahn CR (2001) Insulin signalling and the regulation of glucose and lipid metabolism. Nature 414:799-806
6. Randle PJ, Garland PB, Hales CN, Newsholme EA (1963) The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1:785-789
7. Perseghin G, Petersen K, Shulman GI (2003) Cellular mechanism of insulin resistance: potential links with inflammation. Int J Obes Relat Metab Disord 27[Suppl 3]: S6-11
8. Fasshauer M, Paschke R (2003) Regulation of adipocytokines and insulin resistance. Diabetologia 46:1594-1603
9. Mattison RE, Jensen M (2003) The adipocyte as an endocrine cell. Curr Opin Endocrinol Diabetes 10317-10321
10. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I (2004) Adiponectin and metabolic syndrome. Arterioscler Thromb Vasc Biol 24:29-33
11. Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, Walsh K (2003) Obesity, adiponectin and vascular inflammatory disease. Curr Opin Lipidol 14:561-566
12. Ruan H, Lodish HF (2003) Insulin resistance in adipose tissue: direct and indirect effects of tumor necrosis factor-alpha. Cytokine Growth Factor Rev 14:447-455
13. Lagathu C, Bastard JP, Auclair M, Maachi M, Capeau J, Caron M (2003) Chronic interleukin-6 (IL-6) treatment increased IL-6 secretion and induced insulin resistance in adipocyte: prevention by rosiglitazone. Biochem Biophys Res Commun 311:372-379
14. Montague CT, O'Rahilly S (2000) The perils of portliness: causes and consequences of visceral adiposity. Diabetes 49:883-888
15. Lafontan M, Berlan M (2003) Do regional differences in adipocyte biology provide new pathophysiological insights? Trends Pharmacol Sci 24:276-283
16. Stulnig TM, Waldhausl W (2004) 11beta-Hydroxysteroid dehydrogenase type 1 in obesity and type 2 diabetes. Diabetologia 47:1-11
17. Lewis GF, Carpentier A, Adeli K, Giacca A (2002) Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. Endocr Rev 23:201-229
18. Gan SK, Kriketos AD, Poynten AM et al (2003) Insulin action, regional fat, and myocyte lipid: altered relationships with increased adiposity. Obes Res 11:1295-1305
19. Schaffer JE (2003) Lipotoxicity: when tissues overeat. Curr Opin Lipidol 14:281-287
20. Wellen KE, Hotamisligil GS (2003) Obesity-induced inflammatory changes in adipose tissue. J Clin Invest 112:1785-1788
21. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. (2003) Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 112:1796-1808
22. Xu H, Barnes GT, Yang Q et al (2003) Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 112:1821-1830
23. Fernandez-Real JM, Ricart W (2003) Insulin resistance and chronic cardiovascular inflammatory syndrome. Endocr Rev 24:278-301
24. Jain RG, Furfine ES, Pedneault L, White AJ, Lenhard JM (2001) Metabolic complications associated with antiretroviral therapy. Antiviral Res 51:151-177
25. Perret B, Ferrand C, Bonnet E, Tercé F, Collet X (2003) Lipoprotein metabolism in HIV-positive patients. Eur J Med Res 8:[Suppl II]:6
26. Savès M, Raffi F, Capeau J et al (2002) Factors related to lipodystrophy and metabolic alterations in patients with human immunodeficiency virus infec-

tion receiving highly active antiretroviral therapy. Clin Infect Dis 34:1396-1405
27. Purnell JQ, Zambon A, Knopp RH et al (2000) Effect of ritonavir on lipids and post-heparin lipase activities in normal subjects. AIDS 14:51-57
28. Van der Valk M, Kastelein JJ, Murphy RL et al (2001) Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an anti-atherogenic lipid profile. AIDS 15:2407-2414
29. Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA (1999) Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. Lancet 353:2093-2099
30. Liang JS, Distler O, Cooper DA, et al (2001) HIV protease inhibitors protect apolipoprotein B from degradation by the proteasome: a potential mechanism for protease inhibitor-induced hyperlipidemia. Nat Med 7:1327-1331
31. Lenhard JM, Croom DK, Weiel JE, Winegar DA (2000) HIV protease inhibitors stimulate hepatic triglyceride synthesis. Arterioscler Thromb Vasc Biol 20:2625-2629
32. Riddle TM, Kuhel DG, Woollett LA, Fichtenbaum CJ, Hui DY (2001) HIV protease inhibitor induces fatty acid and sterol biosynthesis in liver and adipose tissues due to the accumulation of activated sterol regulatory element-binding proteins in the nucleus. J Biol Chem 276:37514-37519
33. Bonnet E, Ruidavets JB, Tuech J et al (2001) Apoprotein c-III and E-containing lipoparticles are markedly increased in HIV-infected patients treated with protease inhibitors: association with the development of lipodystrophy. J Clin Endocrinol Metab 86:296-302
34. Noor MA, Lo JC, Mulligan K et al (2001) Metabolic effects of indinavir in healthy HIV-seronegative men. AIDS 15:F11-18
35. Noor MA, Seneviratne T, Aweeka FT et al (2002) Indinavir acutely inhibits insulin-stimulated glucose disposal in humans: a randomized, placebo-controlled study. AIDS 29:F1-8
36. Murata H, Hruz PW, Mueckler M (2002) Investigating the cellular targets of HIV protease inhibitors: implications for metabolic disorders and improvements in drug therapy. Curr Drug Targets Infect Disord 2:1-8
37. Miller J, Carr A, Emery S et al (2003) HIV lipodystrophy: prevalence, severity and correlates of risk in Australia. HIV Med 4:293-301
38. Mallal SA, John M, Moore CB, James IR, McKinnon EJ (2000) Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. AIDS 14:1309-1316
39. Gougeon M-L, Pénicaud L, Fromenty B, Leclercq P, Viard J-P, Capeau J (2004) Adipocytes targets and actors in the pathogenesis of HIV-associated lipodystrophy and metabolic alterations. Antivir Ther 9:161-177
40. Caron M, Auclair M, Vigouroux C, Glorian M, Forest C, Capeau J (2001) The HIV protease inhibitor indinavir impairs sterol regulatory element-binding protein-1 intranuclear localization, inhibits preadipocyte differentiation, and induces insulin resistance. Diabetes 50:1378-1388
41. Caron M, Auclair M, Sterlingot H, Kornprobst M, Capeau J (2003) Some HIV protease inhibitors alter lamin A/C maturation and stability, SREBP-1 nuclear localization and adipocyte differentiation. AIDS 17:2437-2444
42. Krimm I, Ostlund C, Gilquin B, et al (2002) The Ig-like structure of the C-terminal domain of lamin A/C, mutated in muscular dystrophies, cardiomyopathy, and partial lipodystrophy. Structure (Camb) 10:811-823
43. Lloyd DJ, Trembath RC, Shackleton S (2002) A novel interaction between lamin A and SREBP1: implications for partial lipodystrophy and other laminopathies. Hum Mol Genet 11:769-777
44. Vigouroux C, Auclair M, Dubosclard E et al (2001) Nuclear envelope disorganization in fibroblasts from lipodystrophic patients with heterozygous R482Q/W mutations in the lamin A/C gene. J Cell Sci 114:4459-4468
45. Jones SP, Janneh O, Back DJ, Pirmohamed M (2003) Altered adipocytokine gene expression in murine 3T3-F442A adipocytes treated with protease inhibitors and nucleoside reverse transcriptase inhibitors. Antivir Ther 8:L11
46. Lagathu C, Bastard JP, Auclair M et al (2004) HIV-1 protease inhibitors and nucleoside analogue reverse transcriptase inhibitors alter the expression and secretion of proinflammatory cytokines and adiponectin in cultured adipocytes. Antivir Ther (in press)
47. Caron M, Auclair M, Lagathu C et al (2004) Thymidine analogues contrary to other HIV-1 reverse transcriptase inhibitors, alter adipocyte functions in vitro. AIDS (in press)
48. Nolan D, Moore C, Castley A et al (2003) Tumour necrosis factor-alpha gene -238G/A promoter polymorphism associated with a more rapid onset of lipodystrophy. AIDS 17:121-123
49. Bastard JP, Caron M, Vidal H et al (2002) Association between altered expression of adipogenic factor

SREBP1 in lipoatrophic adipose tissue from HIV-1-infected patients and abnormal adipocyte differentiation and insulin resistance. Lancet 359:1026-1031

50. Domingo P, Matias-Guiu X, Pujol RM et al (1999) Subcutaneous adipocyte apoptosis in HIV-1 protease inhibitor-associated lipodystrophy. AIDS 13:2261-2267
51. Lloreta J, Domingo P, Pujol RM et al (2002) Ultrastructural features of highly active antiretroviral therapy-associated partial lipodystrophy. Virchows Arch 441:599-604
52. Jan V, Cervera P, Maachi M et al (2004) Altered fat differentiation and adipocytokine expression are interrelated and linked to morphological changes and insulin resistance in HIV-1-infected lipodystrophic patients. Antivir Ther 9:555-564
53. Sutinen J, Korsheninnikova E, Funahashi T, Matsuzawa Y, Nyman T, Yki-Jarvinen H (2003) Circulating concentration of adiponectin and its expression in subcutaneous adipose tissue in patients with highly active antiretroviral therapy-associated lipodystrophy. J Clin Endocrinol Metab 88:1907-1910
54. Vigouroux C, Maachi M, Nguyen TH et al (2003) Serum adipocytokines are related to lipodystrophy and metabolic disorders in HIV-infected men under antiretroviral therapy. AIDS 17:1503-1511
55. Martin A, Smith DE, Carr A et al (2004) Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. AIDS 18:1029-1036
56. Domingo P, Matias-Guiu X, Pujol RM et al (2001) Switching to nevirapine decreases insulin levels but does not improve subcutaneous adipocyte apoptosis in patients with highly active antiretroviral therapy-associated lipodystrophy. J Infect Dis 184:1197-1201
57. Thomson K, McComsey, Paulsen D et al (2003) Improvements in body fat and mitochondrial DNA levels are accompanied by decreased adipose tissue cell apoptosis after replacement of stavudine therapy with either abacavir or zidovudine. 10th Conference on Retroviruses and Opportunistic Infections, Boston, 2003, p 728
58. Ledru E, Christeff N, Patey O, de Truchis P, Melchior JC, Gougeon ML (2000) Alteration of tumor necrosis factor-alpha T-cell homeostasis following potent antiretroviral therapy: contribution to the development of human immunodeficiency virus-associated lipodystrophy syndrome. Blood 95:3191-3198
59. Rietschel P, Hadigan C, Corcoran C et al (2001) Assessment of growth hormone dynamics in human immunodeficiency virus-related lipodystrophy. J Clin Endocrinol Metab 86:504-510
60. Lo JC, Mulligan K, Noor MA et al (2001) The effects of recombinant human growth hormone on body composition and glucose metabolism in HIV-infected patients with fat accumulation. J Clin Endocrinol Metab 86:3480-3487

Pathology of Cardiac Complications in HIV Infection

G. Barbaro

Pathology of the Myocardium

The prevalence of myocardial abnormalities in HIV-infected patients ranges from 25% to 75% [1]. This wide range probably reflects differences in methodology, patients' risk factors, disease stage, and environmental factors, such as drug addiction or therapeutic agents. Myocardial involvement in HIV-infected patients includes dilated cardiomyopathy, myocarditis, ischemic heart disease, and neoplastic invasion from HIV-associated malignancies (e.g., non-Hodgkin's lymphoma or Kaposi's sarcoma). In addition, the right ventricle can be involved as a consequence of AIDS-related pulmonary disease.

Dilated Cardiomyopathy

The reported prevalence of this heart condition ranges between 5% and 23% of autopsy studies [1–3].

Pathologic Features

Pathologic features of AIDS-related cardiomyopathy are similar to those observed in seronegative patients. At autopsy, the heart shape is modified, because of ventricular dilation and apical rounding. Heart weight is generally increased, owing to fibrosis and myocyte hypertrophy [1]. On average, long-term survivors have significantly heavier hearts than those dying after a brief disease course. The epicardium is usually normal and coronary arteries do not show significant atherosclerosis. The myocardium is rather flabby and the ventricular wall usually collapses on section [1].

On the cut surface, the ventricles show an *eccentric hypertrophy*, that is, a mass increase with chamber volume enlargement. Although hypertrophy is demonstrated by the increase in cardiac weight, this is not always grossly evident owing to ventricular dilation; the free wall width may be normal, or even thinner than normal, as happens in short-term survivors. Endocardial fibrosis is a common finding, as well as mural thrombi, mainly located at the apex. Dilated cardiomyopathy can be associated with pericardial effusion or infective endocarditis, especially in intravenous drug abusers [1].

On histology, myocytes show variable degrees of hypertrophy and degenerative changes, such as myofibril loss, causing hydropic changes within the myocyte. An increase in interstitial and endocardial fibrillar collagen is a constant feature in this cardiomyopathy [1–3].

Myocarditis

Myocarditis is documented at autopsy in up to 50% of AIDS patients who died from non-cardiac causes [2] and in 31%–83% of patients with clinical signs of congestive heart failure [1]. It can be part of a disseminated infection, resulting from opportunistic microorganisms, such as *Candida albicans, Cryptococcus neoformans*, and *Toxoplasma gondii*. It most often shows histological features of lymphocytic myocarditis, suggestive of a viral etiology. In fact, the presence of coxsackievirus B3, cytomegalovirus, and Epstein-Barr virus has been reported from autopsy samples from HIV-infected patients [1]. In addition, HIV-1 nucleic acid sequences have been detected by in situ hybridization in autopsy samples of patients with left ventricular dysfunction [1]. Most of them had active myocarditis on histology.

Pathologic Findings

On gross examination, a marked dilation of the cardiac chambers is almost always present. In most cases, owing to the focal distribution of inflammation and myocyte necrosis, the myocardium is not flabby as it is in hearts with a diffuse inflammatory response. Heart weight is within normal limits. According to the Dallas criteria [4], active myocarditis is characterized by multifocal or diffuse interstitial inflammatory infiltrates associated with degenerative changes or frank myocyte necrosis (Fig. 1). Histological findings in HIV-infected patients with myocarditis do not substantially differ from those observed in seronegative patients. However, the degree of inflammatory infiltrate is generally milder. This is believed to result from the impaired efficiency of cell-mediated immunity [2]. In addition, the inflammatory infiltrate is mainly made by $CD8^+$ lymphocytes, and aberrant expression of class II human leukocyte antigens (HLA) by cardiac myocytes is much rarer than in HIV-negative myocarditis [5]. The severity of clinical symptoms is not always related to the degree of myocardial inflammation and damage. Autopsy studies of AIDS patients who died of acute left ventricular dysfunction almost invariably show a marked inflammatory infiltrate [2]. However, mild and focal mononuclear infiltrates are frequently observed in hearts of AIDS patients, irrespective of the presence of cardiac symptoms.

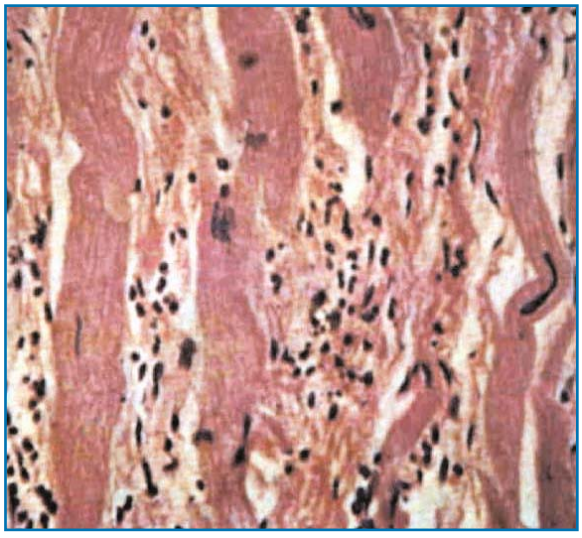


Fig. 1. AIDS-related active lymphocytic myocarditis. There is a marked interstitial lymphocytic infiltrate and myocyte necrosis. H&E, x20

Histology and immunohistochemistry rarely detect the presence of viruses in the myocardium. However, in situ hybridization or polymerase chain reaction studies reveal a high frequency of either cytomegalovirus or HIV-1, or both, in AIDS patients with lymphocytic myocarditis and severe left ventricular dysfunction [1, 6] (Fig. 2). These data support the hypothesis that, at least in a subset of patients, HIV-1 has a pathogenic action and possibly influences the clinical evolution towards dilated cardiomyopathy [2, 3].

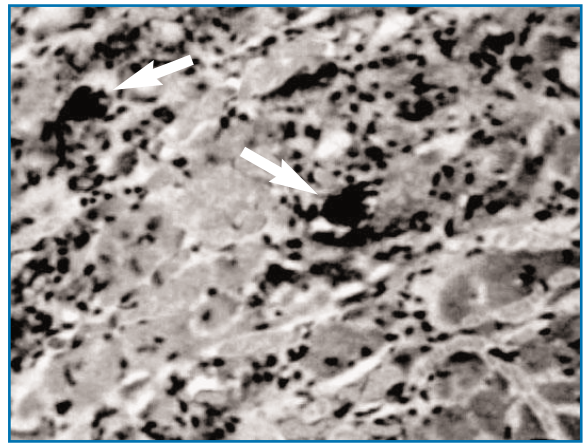


Fig. 2. In situ hybridization from an endomyocardial biopsy sample in an HIV-infected subject with echocardiographic diagnosis of dilated cardiomyopathy (left ventricular ejection fraction: 28%) and histologic diagnosis of active myocarditis. It is possible to observe two myocytes showing a positive signal for nucleic sequences of HIV-1 (*arrows*). H&E, x20

Opportunistic myocardial infection is generally part of systemic infections. Fungal lesions are visible on gross examination as multiple, small, rounded plaques of whitish color, often hemorrhagic. On histology, the pathogens most frequently observed are protozoa, such as *Toxoplasma gondii*, or fungi, such as *Candida albicans*, *Cryptococcus neoformans*, and *Aspergillus* spp. [2, 3]. Myocardial and cerebral toxoplasmosis are often associated; histological examination shows "*pseudocysts*" packed

with the protozoa within cardiac myocytes [2, 3]. Bacterial myocarditis is not infrequent in HIV-infected drug addicts with infective endocarditis. It is a consequence of coronary embolization from valve vegetations [2].

Ischemic Heart Disease

The association between viral infection (cytomegalovirus or HIV-1 itself) and coronary artery lesions is not clear. HIV-1 sequences have recently been detected by in situ hybridization in the coronary vessels of an HIV-infected patient who died from acute myocardial infarction (Fig. 3) [7]. Potential mechanisms through which HIV-1 may damage coronary arteries include activation of cytokines and cell-adhesion molecules and alteration of major histocompatibility complex class I

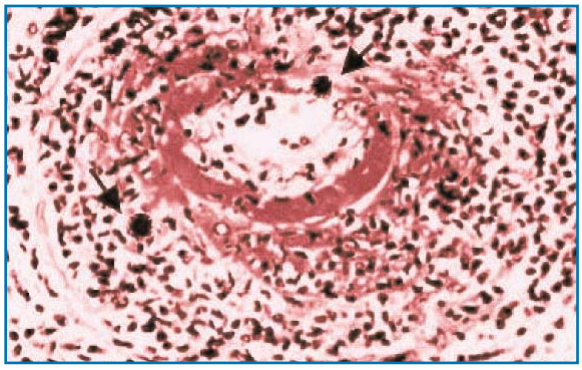


Fig. 3. In situ hybridization of an HIV-1 RNA probe in a transverse section of a branch of the anterior descending coronary artery. Intense staining indicating the presence of HIV-1 sequences within the intima and the media (*arrows*). There is a dense lymphocyte infiltrate within the media and necrosis of the intima, which is covered with swollen endothelial cells. (From [7], Copyright ©2001 Massachusetts Medical Society. All right reserved). H&E, x280

molecules on the surface of smooth muscle cells [7]. It is possible also that HIV-1-associated protein gp 120 may induce smooth muscle cell apoptosis through a mitochondrion-controlled pathway by activation of inflammatory cytokines (e.g., TNF-α) [8].The incidence of ischemic heart disease is apparently increasing among HIV-infected patients receiving protease inhibitor-based highly active antiretroviral therapy (HAART), especially in those who develop HAART-associated metabolic syndrome during therapy [9]. However, studies on the risk of coronary heart disease in this subset of patients remain controversial [10–14].

Pathologic examination of coronary arteries generally reveals eccentric fibroatheromatous plaques, with variable degrees of chronic inflammatory infiltrates. Lesions with morphologic features similar to accelerated arteriosclerosis have been described at autopsy of young HIV-infected patients [2, 3]. The pathology of coronary and peripheral vessels in HIV infection is described in detail by A. Tabib and R. Loire in a separate chapter in this volume.

Conduction System Involvement

Conduction tissue damage can be due to lymphocytic myocarditis, opportunistic infections, and drug cardiotoxicity or to the localization of HIV within the conduction system myocytes. Histological examination may reveal a lymphomonocytic infiltration, myocyte degenerative changes, and fibrosis. These changes can be associated with electrocardiographic abnormalities, most frequently first-degree atrioventricular block, left anterior hemiblock, and left bundle block [1].

Malignancies

The prevalence of cardiac Kaposi's sarcoma (KS) in AIDS patients ranged from 12% to 28% in retrospective autopsy studies in the pre-HAART period [3]. Cardiac involvement with KS usually occurs when widespread visceral organ involvement is present. The lesions are typically less than 1 cm in size and may be pericardial or, less frequently, myocardial, and are only rarely associated with obstruction, dysfunction, morbidity, or mortality [8]. Microscopically, there are atypical spindle cells lining slit-like vascular spaces (Fig. 4).

Non-Hodgkin's lymphoma (NHL) involving the heart is infrequent in AIDS [15]. Most cases are high-grade B-cell (small non-cleaved) Burkitt-like lymphomas, with the rest classified as diffuse large

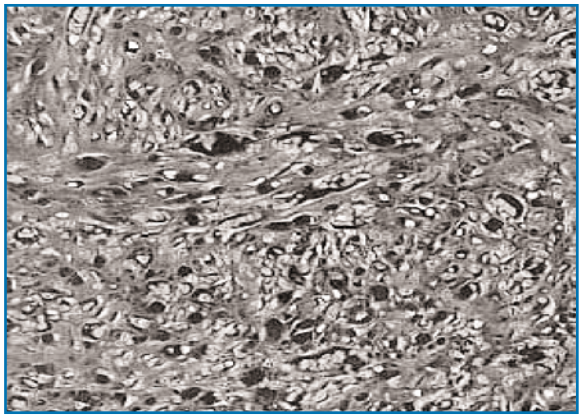


Fig. 4. Myocardial involvement by Kaposi's sarcoma. Histology shows spindle cells surrounding slit-like capillary vessels. H&E, x40

B-cell lymphomas (in the REAL classification) (Fig. 5). Lymphomatous lesions may appear grossly as either localized or more diffuse nodular to polypoid masses [16, 17]. Most involve the pericardium, with variable myocardial infiltration [16, 17]. There is little or no accompanying inflammation and necrosis. The prognosis of patients with HIV-associated cardiac lymphoma is generally poor because of widespread organ involvement, although some patients treated with combination chemotherapy have experienced clinical remission [18].

The introduction of HAART has reduced the incidence of cardiac involvement by KS and NHL, perhaps attributable to patients' improved immunologic state and to suppression of opportunistic infections with Human Herpes Virus-8 and Epstein-Barr virus that are known to play an etiologic role in these neoplasms [18].

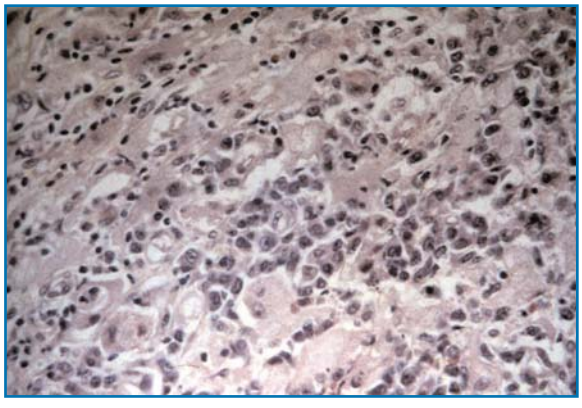


Fig. 5. Myocardial infiltration by large cell non-Hodgkin's lymphoma, associated with myocardial damage. H&E, x40

Isolated Right Ventricular Hypertrophy and Dilation

Right ventricular hypertrophy and/or dilation, often associated with pericardial effusion, can be observed in the clinical course of HIV infection. This finding is related to the presence of pulmonary hypertension, which can be due to pulmonary infections, to diffuse alveolar damage, or to recurrent pulmonary emboli from intravenous debris acquired through drug abuse [1]. In addition, the occurrence of right-sided infective endocarditis related to the high frequency of intravenous drug use among HIV-infected patients may explain right ventricular overload or recurrent pulmonary embolic events [2].

Pathology of the Endocardium

Nonbacterial Thrombotic Endocarditis

Nonbacterial thrombotic endocarditis has been reported with increasing frequency in HIV-infected patients in the terminal stage of the disease. This process, commonly associated with chronic severe wasting diseases, particularly malignancies, and severe inanition, was observed before the introduction of HAART in 3%–5% of AIDS patients at autopsy [1–3].

Pathologic Findings

Nonbacterial thrombotic endocarditis can involve all four cardiac valves [2]. Macroscopic examination reveals thrombi adherent to the endocardial surface of the valve cusps, consisting microscopically of platelets within a fibrin mesh with few inflammatory cells. Thrombotic vegetations may be either single or multiple polypoid masses, along the cusp apposition lines. The valve often shows changes due to previous inflammatory or dystrophic lesions [3].

Thrombotic vegetations of nonbacterial thrombotic endocarditis are similar to those found in infective endocarditis; the differential diagnosis is based on the absence of the other typical features of infective endocarditis, such as destruction and erosion of the cusp edges with tears and perforations through the body of the cusp itself, and valvular leaflet aneurysmal sacs [3]. Moreover, no infective pathogens are detected on histological examination. Systemic or pulmonary embolization of vegetations is usually detected at autopsy (more than 40% of patients with nonbacterial thrombotic endocarditis) and is underestimated clinically. Often, clinical symptoms of systemic thromboembolization (cerebral, pulmonary, renal, and splenic infarcts) make the valvular lesions clinically obvious. However, systemic thromboembolic disease due to nonbacterial thrombotic endocarditis is a rare cause of death (7%) in AIDS patients [1]. The vegetations in nonbacterial thrombotic endocarditis may be infected by pyogenic or fungal pathogens during a transient bacteremia, bringing about a typical infective endocarditis.

Infective Endocarditis

Infective endocarditis may be due to either pyogenic or opportunistic pathogens. In the latter case, they are often part of a systemic opportunistic infection with multiple organ localizations. Fungal endocarditis has been reported with increasing frequency as the AIDS epidemic has gained momentum, helped by the compromise of cell-mediated immunity in patients with HIV infection [2, 3].

Infective endocarditis occurs more frequently in intravenous drug users with AIDS, who comprise the second largest risk group for HIV infection after male homosexuals. These patients have frequent bacteremias, owing to the introduction of skin pathogens and talcum powder by unsterile intravenous injection, causing a higher risk of endocardial infection of right-sided cardiac valves. Infective endocarditis is higher in intravenous drug addicts who abuse multiple drugs (cocaine used intravenously in combination with heroin) in addition to alcohol.

The spectrum of pathogens responsible for endocardial infection in intravenous drug users with AIDS is not significantly different from that in HIV-uninfected drug users. However, owing to the deficit in cellular immunity, the pathogens are more virulent, leading to more significant cardiac structural damage and functional deterioration. Pyogenic bacteria more commonly causing infective endocarditis in AIDS are *Staphylococcus aureus, S. epidermidis, Streptococcus pneumoniae,* and *Haemophilus influenzae* [2]. Infective endocarditis by Gram-negative bacteria, especially *Pseudomonas* species, has become more common in patients with AIDS, perhaps owing to their repeated hospitalizations that promote the acquisition of resistant organisms. Avirulent bacteria, such as the HACEK group (*Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens* and *Kingella kingae*), which are often part of the endogenous flora of the mouth, can cause endocarditis in HIV-infected patients [2]. These bacteria are also difficult to culture from endocardial vegetations. Failure to obtain positive blood cultures in those patients with AIDS with strong clinical evidence for infective endocarditis should suggest prior antibiotic therapy or endocarditis by unusual bacteria (as well as HACEK organisms) or fungi.

Fungal endocarditis, especially from *Cryptococcus neoformans*, *Candida albicans, or Aspergillus fumigatus*, is common in AIDS, particularly in intravenous drug abusers [2, 3]. It is generally related to systemic spread of fungal infection from extracardiac foci. Candidiasis of the oropharynx and esophagus is most often the primary focus, often progressing to systemic infection. Systemic cryptococcosis is one of the most common infections in AIDS patients. Although meningitis and encephalitis are the most frequent manifestations of cryptococcosis, cardiac involvement, particularly with pericardial effusion, is common [2]. Fungal myocarditis or myocardial abscesses may also occur in association with valve destruction [2].

Pathologic Features

Infective endocarditis is an ulcerative-polypous lesion due to a destructive valve process with

thrombotic stratifications (Fig. 6). Thrombotic vegetations are usually gray, but their color is highly variable depending on the pathogen involved [2]. They are generally located on the endocardial surface of valve cusps but can be found also on mural endocardium. Their consistence is variable: they are friable at first and later become compact and adherent to the endocardium, owing to their organization. The friability is increased by lithic effects of bacteria and polymorphonuclear leukocytes [2, 3]. Valvular tissue destruction may involve the tensive apparatus with chordae tendinous rupture. Endocardial ulcerations at the cusp apposition lines are frequent, resulting in leaflets with a mouth-eaten look. On histology, thrombotic vegetations consist of fibrin and agglutinated platelets with inflammatory infiltration [3]. In the acute stage of endocardial infection there is an infiltration with polymorphonuclear leukocytes with valve tissue necrosis; later there is a chronic inflammatory infiltration, made up of macro-phages, lymphocytes and plasma cells, neoformed capillary vessels, and a fibroblastic proliferation that replaces the necrotic tissue and spreads at the base of thrombotic vegetation. In fungal endocarditis, however, the vegetations are made up essentially of fungal colonies without much fibrin and they may be so bulky that they obstruct the valve ostium [2, 3].

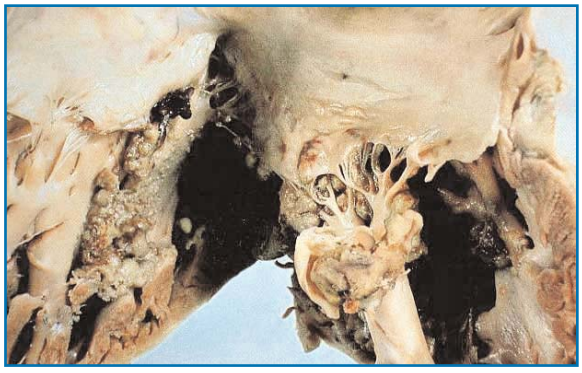


Fig. 6. *Staphilococcus aureus* endocarditis in an HIV-infected drug addicts who died of cardiogenic shock. The mitral valve shows numerous, large, grayish and friable vegetations. Involvement of the atrial endocardium is also shown. (Courtesy of Prof. D. Scevola, Department of Infectious and Parasitic Disease, University of Pavia, Italy)

When the left-side cardiac valves are involved, endocarditis can have a galloping course, with rapid onset of heart failure due to acute valvular insufficiency secondary to perforation of valve leaflets or a rupture of the tendinous chordae or papillary muscles [2]. Other complications are due to myocardial involvement with possible perforation of the ventricular septum or myocardial abscesses. The infection can extend to the pericardium with purulent pericarditis. The higher frequency of right-sided infectious endocarditis in HIV-infected intravenous drug users can explain the pulmonary embolic events with possible pulmonary cavitations and abscesses [2, 3]. The outcome is thrombous organization and fibrous repair. Residual bulky thrombotic polypi are often seen as calcific masses leaning out of both endocardial surfaces of the valvular leaflets [2].

Pathology of the Pericardium

Pericardial Effusions

Before the introduction of HAART, the prevalence of pericardial effusion in asymptomatic AIDS patients was estimated at 11% per year [19]. Although prospective data are lacking, retrospective data suggest that HAART has reduced the overall incidence of pericardial effusion in HIV disease by about 30% [20]. Most pericardial effusions are idiopathic. Infections, neoplasias, myocarditis, endocarditis, or myocardial infarct have been described as possible etiologies. Little is known about the pathogenesis of pericardial effusions in AIDS patients. However, in the absence of cardiac infection or malignancy, the pathogenesis is likely to be multifactorial. The causes can be metabolic or hemodynamic alterations, dysproteinemias, or pulmonary hypertension due to chronic lung disease (i.e., cytomegalovirus pneumonia). The presence of HIV-1 in macrophages inside the pericardium suggests that the virus may play a role in the pathogenesis of pericardial effusions in AIDS patients.

Pericarditis

Pericarditis is found at autopsy in 30% of AIDS patients [1]. It can be serous, fibrinous, serofibrinous, purulent, or hemorrhagic [2, 3].

Pericardial phlogosis may be caused by a wide array of pathogens, always in conjunction with disseminated infection. *Mycobacterium tuberculosis hominis* and *M. avium-intracellulare*, herpes simplex (by culture only), *Actinomycetales* (*Nocardia asteroides*), and bacteria such as *Staphylococcus aureus* and *Salmonella typhimurium* may be identified in pericardial fluid, even though in a few cases no pathogens can be isolated [1]. Fungal infections by *Candida albicans*, *Cryptococcus neoformans,* and *Aspergillus fumigatus* do not often involve the pericardium [2]. The pericardium may also be involved by nonmycobacterial infections such as *Actinomycetales* (*Nocardia asteroides* or *Streptomyces species*). Whereas pericardial disease in the immunocompetent host may be associated with a variety of viruses, most commonly coxsackievirus, pericardial involvement in AIDS is more frequently related to infection with other common viral pathogens, especially herpes simplex virus type 1 and 2 and cytomegalovirus [2].

Pathologic Features

The most common type of pericarditis is fibrinous or serofibrinous (Fig. 7). There is a variable amount of fibrin on the epicardium, while pericardial effusion may be absent or present in variable degrees [2]. Many cases of fibrinous pericarditis resolve without residual effects. In other instances, the fibrin deposits organize and form fibrous pericardial adhesions [2, 3]. Bacterial pericarditis is characterized by a fibrinopurulent exudate. On histology, an infiltrate of polymorphonuclear leukocytes is seen in the epicardial connective tissue. Fibrous adhesions may result, leading to pericardial constriction. Hemorrhagic pericarditis shows a serofibrinous or suppurative exudate associated with the presence of serohematic fluid in the pericardium. It is typical of tuberculosis, severe bacterial infections, or pericardial malignancy [2].

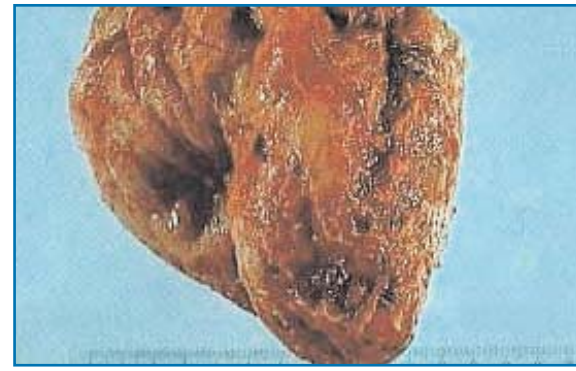


Fig. 7. Fibrinous pericarditis by *Mycobacterium avium intracellulare* in an HIV-infected subject who died of congestive heart failure. (Courtesy of Prof. D. Scevola, Department of Infectious and Parasitic Disease, University of Pavia, Italy)

Malignancies

Kaposi's Sarcoma

When Kaposi's sarcoma involves the heart, the epicardial surface is a common site of involvement. At autopsy, the pericardium and the epicardial fat show the typical nodular coalescent dark-red lesions or violaceous plaques [2, 3]. Occasionally, the myocardium may also be involved. Typically, the neoplastic infiltration then extends along the great vessels and the coronary vessels with spread of tumor through the lymph channels along the vasa vasorum [2].

Lymphomas

In contrast to non-Hodgkin's lymphomas in seronegative patients, which are epicardial or pericardial in location, in AIDS patients the tumor is most often located within the myocardium or in the subendocardial layer [2]. There may be pericardial effusion, with a mass lesion of the heart sometimes prolapsing across the tricuspid valve or involving the inferior portions of both ventricles.

References

1. Barbaro G, Di Lorenzo G, Grisorio B, Barbarini G and the Gruppo Italiano per lo Studio Cardiologico dei pazienti affetti da AIDS Investigators (1998) Cardiac involvement in the acquired immunodeficiency syndrome: a multicenter clinical-pathological study. AIDS Res Hum Retroviruses 14:1071-7107
2. D'Amati G, Di Gioia CRT, Gallo P (2001) Pathological findings of HIV-associated cardiovascular disease. Ann NY Acad Sci 946:23-45
3. Klatt EC (2003) Cardiovascular pathology in AIDS. Adv Cardiol 40:23-48
4. Aretz HT (1987) Myocarditis: the Dallas criteria. Hum Pathol 18:619-624
5. Barbaro G, Di Lorenzo G, Soldini M et al (1999) Intensity of myocardial expression of inducible nitric oxide synthase influences the clinical course of human immunodeficiency virus-associated cardiomyopathy. Circulation 100:933-939
6. Herskowitz A, Tzyy-Choou W, Willoughby SB et al (1994) Myocarditis and cardiotropic viral infection associated with severe left ventricular dysfunction in late-stage infection with human immunodeficiency virus. J Am Coll Cardiol 24:1025-1032
7. Barbaro G, Barbarini G, Pellicelli AM (2001) HIV-associated coronary arteritis in a patient with fatal myocardial infarction. N Engl J Med 344:1799-1800
8. Twu C, Liu QN, Popik W et al (2002) Cardiomyocytes undergo apoptosis in human immunodeficiency virus cardiomyopathy through mitochondrion and death receptor-controlled pathways. Proc Natl Acad Sci USA 99:14386-14391
9. Barbaro G, Klatt EC (2003) Highly active antiretroviral therapy and cardiovascular complications in HIV-infected patients. Curr Pharm Des 9:1475-1481
10. Holmberg SD, Moorman AC, Williamson JM et al (2002) Protease inhibitors and cardiovascular outcomes in patients with HIV-1. Lancet 360:1747-1748
11. Barbaro G, Di Lorenzo G, Cirelli A et al (2003) An open-label, prospective, observational study of the incidence of coronary artery disease in patients with HIV receiving highly active antiretroviral therapy. Clin Ther 25:2405-2418
12. Friis-Moller N, Weber R, Reiss P et al (2003) Cardiovascular risk factors in HIV patients – association with antiretroviral therapy. Results from DAD study. AIDS 17:1179-1193
13. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA (2003) Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. N Engl J Med 348:702-710
14. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D and the Clinical Epidemiology Group from the French Hospital Database (2003) Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. AIDS 17:2479-2486
15. Barbaro G, Di Lorenzo G, Grisorio B, Barbarini G and the Gruppo Italiano per lo Studio Cardiologico dei pazienti affetti da AIDS investigators (1998) Cardiac involvement in the acquired immunodeficiency syndrome. A multicenter clinical-pathological study. AIDS Res Hum Retroviruses 14:1071-1077
16. Duong M, Dubois C, Buisson M et al (1997) Non-Hodgkin's lymphoma of the heart in patients infected with human immunodeficiency virus. Clin Cardiol 20:497-502
17. Sanna P, Bertoni F, Zucca E et al (1998) Cardiac involvement in HIV-related non-Hodgkin's lymphoma: a case report and short review of the literature. Ann Hematol 77:75-78
18. Dal Maso L, Serraino D, Franceschi S (2001) Epidemiology of HIV-associated malignancies. Cancer Treat Res 104:1-18
19. Heidenreich PA, Eisenberg MJ, Kee LL et al (1995) Pericardial effusion in AIDS. Incidence and survival. Circulation 92:3229-3234
20. Pugliese A, Isnardi D, Saini A, Scarabelli T, Raddino R, Torre D (2000) Impact of highly active antiretroviral therapy in HIV-positive patients with cardiac involvement. J Infect 40:282-284

Pathology of Peripheral and Coronary Vessels in AIDS Patients

A. Tabib, R. Loire

HIV infection can provoke vascular complications, although they are not presently viewed as one of its most serious manifestations [1]. HIV vascular complications are general infective vascular diseases [2]. Most of the cases presented in this chapter occurred before the advent of highly active antiretroviral therapy (HAART) and mostly in AIDS patients because the majority of pathology examinations were done during necropsy.

Vasculitis

Microcirculation lesions are well documented by biopsies of the nervous system and muscles in AIDS peripheral neuromuscular localizations. In a cohort study published before HAART, vasculitis was present in 24% of biopsy samples from 225 patients: 12 cytomegalovirus vasculitis, 19 "microvasculitis," and one giant cells arteritis case [3]. Kieburtz et al. [4] described *Candida albicans* vasculitis with thrombosis and a cerebral infarction due to cytomegalovirus vasculitis in AIDS patients.

Peripheral Arterial Localizations

Clinical reports and systematic necropsies of AIDS patients pointed out arterial lesions. Kieburtz et al. [4] reported brain infarction in 20% of autopsies, Engstrom et al. [5] described 25 clinical cases.

Joshi et al. [6] described arterial lesions in kidneys, spleen, thymus, and muscles in five children aged 1–7 years, including luminal narrowing with intima fibrosis, internal elastic lamina fragmentation, and calcifications.

Husson et al. [7] in a cohort of 250 HIV-infected children noted the appearance of two fusiform cerebral aneurysms. Rautonen et al. [8] pointed out clinical and anatomic similarities with Kawasaki's disease, which may be due to a retrovirus organism.

Capron et al. [9] described toe embolism in four HIV male patients (40–56 years old) from aortic and femoral ulcerated atherosclerotic plaques.

Kabus and Greco [10] described gross intimal aortic lesions at autopsy, resembling gelatiniform syphilitic ones in children with AIDS.

Clinical information about vasculitis and peripheral arterial disease in HIV infection is given by P. Mercié et al. in a separate chapter in this volume.

Venous Thrombosis

Some authors described deep venous thrombosis in AIDS, an unsurprising complication in severely bedridden patients. Confusion is possible between pulmonary embolisms and opportunistic pulmonary infections, according to Pulik et al. [11]. Deep venous thrombosis and related coagulation disorder in HIV infection are described in detail by L. Drouet in a separate chapter in this volume.

Coronary Artery Lesions

It was a surprise for us to discover, during postmortem examination, many severe latent coronary artery lesions occurring in very young (23–31 years old) AIDS patients [1]. Both hospital and forensic necropsies were performed. The death causes were not linked with coronary lesions except in one of five sudden death cases without other pathology. Clinical coronary disease symptoms were absent in all patients. The patients were

homosexuals or drug addicts or both. Pathological analysis used transverse sections taken every 0.5 cm along the epicardial routes of the three main coronary trunks. Sections obtained every 1 cm were fixed in Bouin's solution, then embedded in paraffin for histopathological study, together with representative fragments of the left and right ventricular walls and interventricular septum making up the distal coronary network. Histological sections were stained with hemalum-phloxine-saffron and with Weigert's resorcin-fuchsin method.

Every coronary examination of AIDS patients pointed out gross and microscopic lesions (100%), although a comparative examination of patients of the same age without AIDS showed only 14% of identical lesions.

Pathological Coronary Lesions

1. Common atherosclerotic plaques were present on the three main coronary trunks in 60% of cases, with two different patterns: either young plaques consisting in macrophages, foamy cells, and a small amount of extracellular lipid deposit (Fig. 1), or adult eccentric plaque with a lipid core surrounded by a fibrous wall consisting in macrophages, fibroblasts, smooth muscle cells, a few lymphocytes, elastic fibers, and collagenous fibers. Stenosis occluded 75% or more of the lumen (Figs. 2–4). In one case, the right coronary artery was completely occluded by a massive thrombosis (Fig. 5).

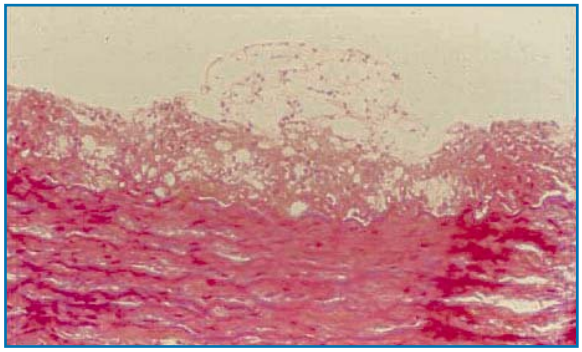


Fig. 1. Common atherosclerotic young plaque. Col HPS x100

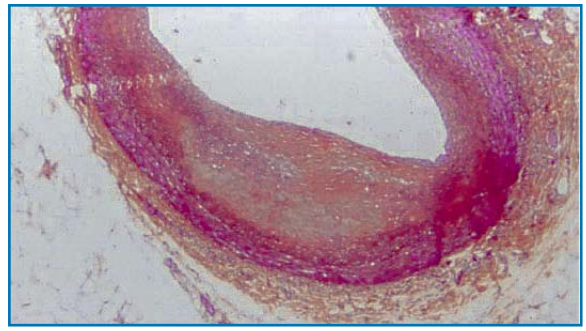


Fig. 2. Adult eccentric plaque. Col HPS, x25

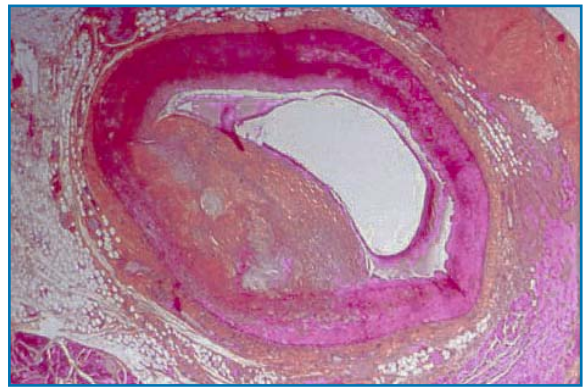


Fig. 3. Adult eccentric plaque. Col HPS, x25

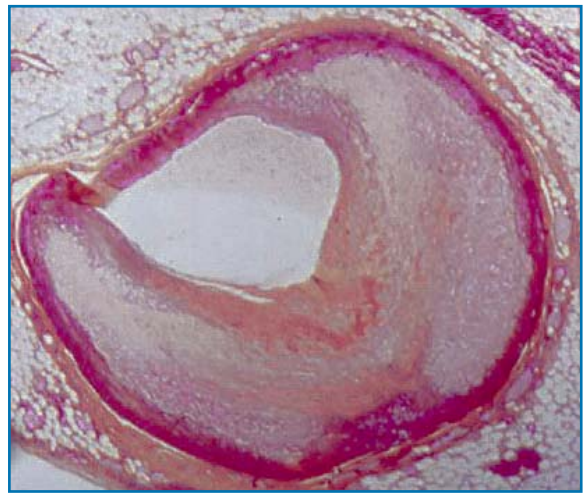


Fig. 4. Adult eccentric plaque. Col HPS, x25

2. Uncommon intimal thickening which was diffuse, circular, and concentric throughout the whole length of every coronary trunk affected all patients, occluding over 40% of the vascular

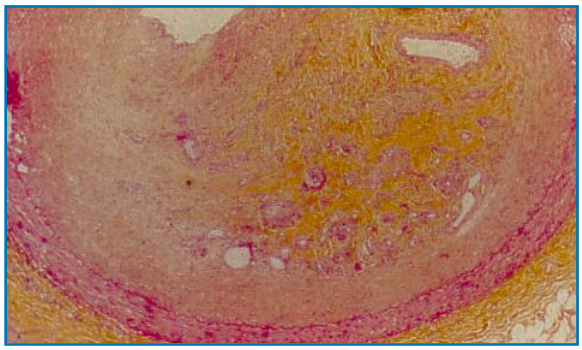


Fig. 5. Complete occlusion by fibrous organized plaque. Col HPS, x25

lumen. Collagenous and microelastic fibers were admixed with smooth muscle cells, macrophages, rare foam cells, and fibroblasts, without lymphocytes (Figs. 6–9).

3. Unusual and original lesions consisting in proliferation of smooth muscle cells mixed with numerous packed elastic fibers, which formed mamillated endoluminal protrusions resembling vegetations, were present in 40% of cases (Figs. 10–12).

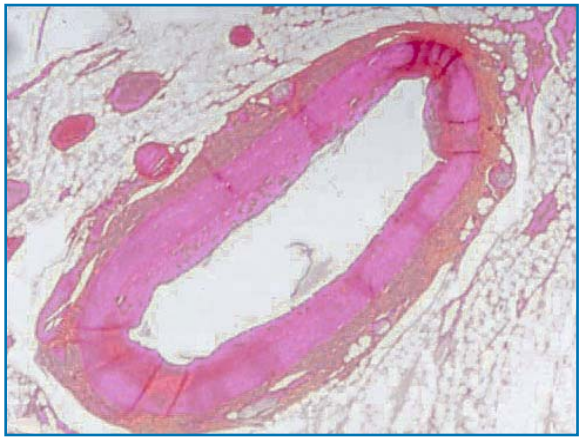


Fig. 6. Intimal diffuse and circular thickness

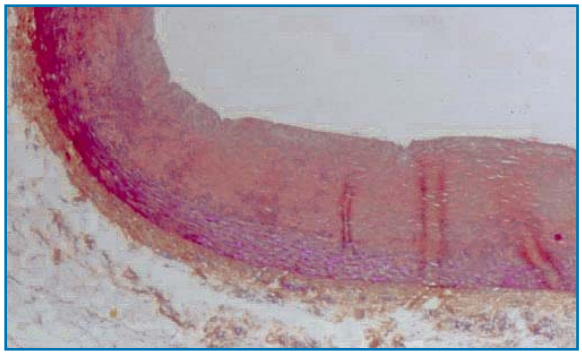


Fig. 7. Intimal diffuse and circular thickness. Col HPS, x25

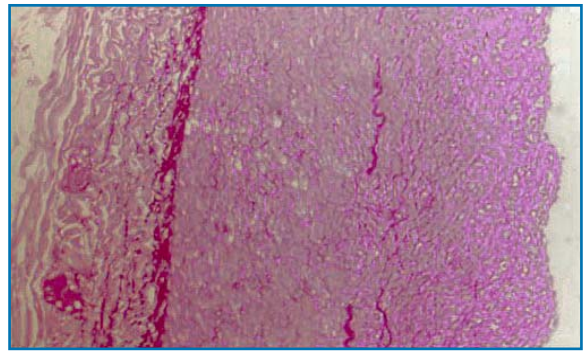


Fig. 8. Intimal diffuse and circular thickness. Col HPS, x100

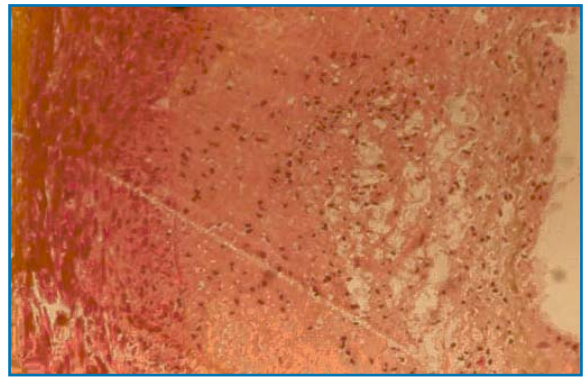


Fig. 9. Intimal diffuse and circular thickness with foamy cells. Col HPS, x100

The distal coronary network of intramural arterioles was also the site of a diffuse concentric

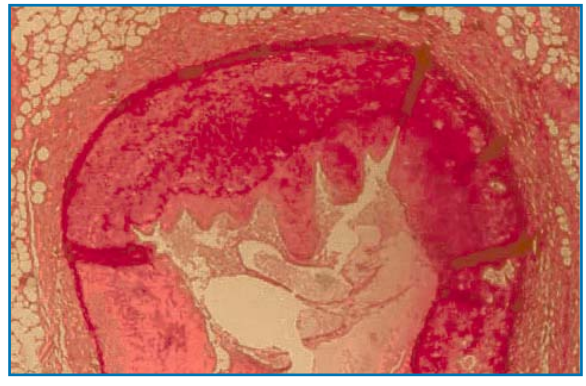


Fig. 10. Mamillated endoluminal protrusion. Col HPS, x25

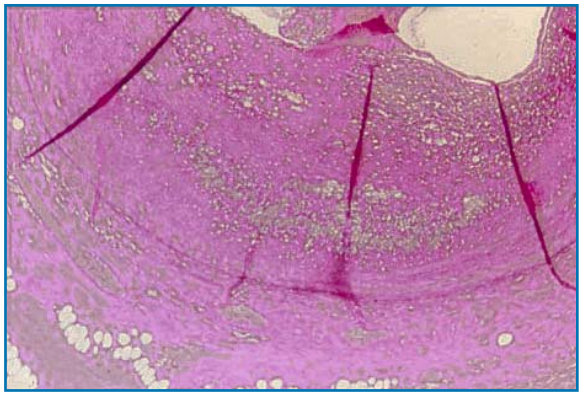


Fig. 11. Mamillated endoluminal protrusion. Col HPS, x100

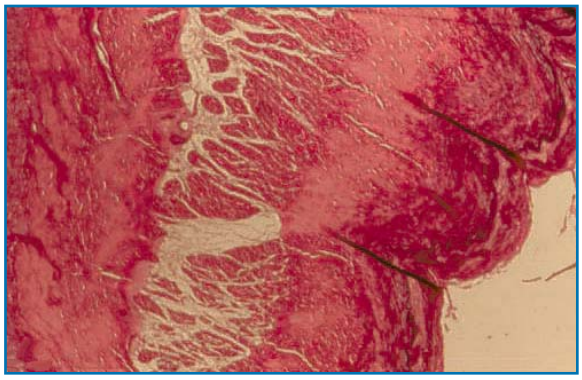


Fig. 12. Mamillated endoluminal protrusion. Col Weigert, x25

intimal wall thickening occluding more than 80% of the lumen in 25% of cases (Figs. 13–15).

Immunohistochemical data allowed true identification of smooth muscle cells (alpha-actin and

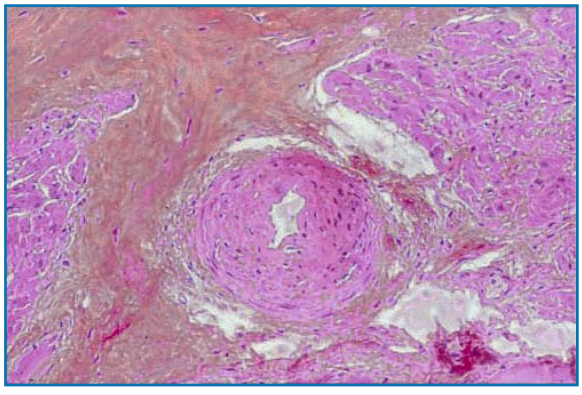


Fig. 13. Distal coronary network. Col HPS, x25

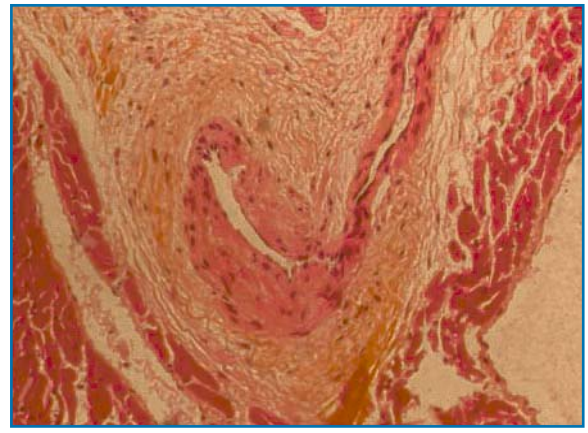


Fig. 14. Distal coronary network. Col HPS, x100

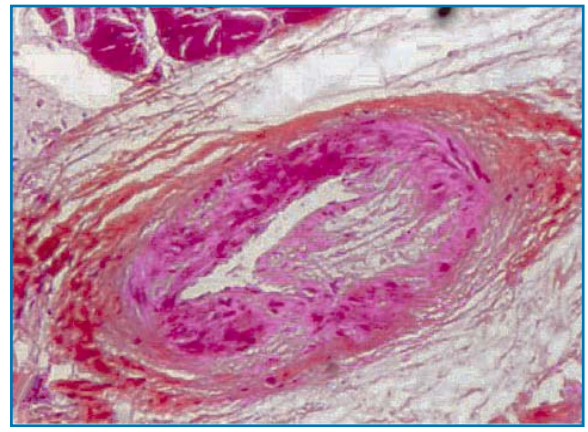


Fig. 15. Distal coronary network. Col HPS, x100

vimentin expression) as the main elements of diffuse intimal layer thickening. The expression of tumor necrosis factor-alpha (TNF-α) and interleukin-1alpha (IL-1α) in these cells was significantly greater than in smooth muscle cells of the underlying media. Fibrocytes and fibroblasts were scarcely disseminated on the periphery of atherosclerotic plaques, mixed with smooth muscle cells and some lymphocytes. CD68 expression identified macrophages, proving also TNF-α and IL-1 expression. Factor VIII expression appeared on endothelial cells.

Coronary lesions in AIDS patients have some of the characteristics of common atherosclerosis, such as eccentric fibro-lipidic plaques. But they also present similarities with coronary lesions fol-

lowing heart transplantation (so-called chronic rejection), such as diffuse concentric intimal thickening occurring in coronary trucks and in the distal network [12].

Pathogenetic Hypotheses

Three possibilities can explain HIV-associated vascular alterations: (1) direct cellular infection by HIV (macrophages, smooth muscle cells, endothelial cells), (2) blood coagulation alterations, and (3) cellular infection by opportunistic elements [13]. Every change must naturally be mediated by numerous cytokines and adhesion molecules: today it is often possible only to demonstrate the presence or absence of these mediators, which is an indirect method that cannot indicate if cells are a source or target (or both) of the mediators.

1. Direct cellular infection by HIV. This phenomenon is demonstrated for macrophages, which is the first cellular target of the virus along with CD4 lymphocytes. It has not been demonstrated in vitro for endothelial cells, but some modifications are perhaps due to this alteration: von Willebrand's factor VIII, soluble thrombomodulin, E-selectin, and CD4 molecule increase [14]. These modifications involve endothelium properties: antigen presentation – IL-1, TNF-a secretion – and IL-2 production by T cells, which secondarily involve basal membrane degradation via Tat protein [15, 16]. Morphogenetic modifications of intimal intercellular matrix facilitate the penetration of lymphocytes and macrophages that are the target cells for HIV infection and replication. Infected macrophages would initiate medial smooth muscle activation and proliferation [17]. Endothelial cells seem to be heterogeneous, with discontinuous cells of sinusoid capillary cells displaying a different behavior [18].

2. Hypercoagulability has been demonstrated in AIDS: von Willebrand's factor and tissular plasminogen activator increase, while there is a decrease in beta-2 microglobulin, S protein-free plasmatic fraction (protein C cofactor), and second heparin-cofactor (thrombin inhibitor). Other possible thrombogenic factors can be demonstrated: antiphospholipid antibodies (70% of AIDS cases) and lipoprotein LP(a) increase (common epitope for HIV and blood platelets), whereas hypertriglyceridemia and apolipoprotein AII decrease [19, 20].
3. Opportunistic infections demonstrate vascular tropism [21]. Viral cytolysis and endothelial necrosis favor the parietal adhesion of macrophages, an early known atherosclerotic stage. Cytomegalovirus alters endothelial cells as well as smooth muscle medial cells leading to multiplication, phenotype transformation with collagen and microelastic element synthesis and foam cells formation.

Experimental pathology studies in *Macacus* monkeys demonstrate a diffuse arteriopathy present in 25% of the population after *simian immunodeficiency virus (SIV) infection*, without a proven responsibility for either SIV or opportunistic infection [22].

Conclusion

Numerous hypotheses exist to explain AIDS vascular disorders. It is likely that the frequency of coronary lesions is high and underestimated because little attention is given during autopsy to coronary examination. Benditt's monoclonal origin of vascular lesions [23], depending on a viral cause, could provide a physiopathological answer.

References

1. Tabib A, Greenland T, Mercier I, Loire R, Mornex JF (1992) Coronary lesions in young HIV-positive subjects at necropsy. Lancet 340:730
2. Capron L, Loire R (1994) Passé, présent et avenir de l'infection artérielle. Rev Prat 44:906-910
3. Lacroix C, Chemoulli P, Said G (1994) Différents aspects de la pathologie neuro-musculaire chez 225 patients VIH positifs. Journées de pathologie 94:85-90
4. Kieburtz KD, Eskin TA, Ketonen I, Tuite MJ (1933) Opportunistic cerebral vasculopathy and stroke with AIDS. Arch Neurol 50:430-432
5. Engstrom JW, Lowenstein DH, Bredesen DE (1989)

Cerebral infarction and transient neurologic deficits associated with AIDS. Am J Med 86:528-532

6. Joshi VV, Pawel B, Connor E et al (1987) Arteriopathy in children with AIDS. Pediatric Pathol 7:261-275
7. Husson RN, Saini R, Lewis L et al (1992) Cerebral artery aneurysm in children infected with HIV. J Pediatr 121:927-930
8. Rautonen N, White C, Martin NL et al (1994) Antibodies to HIV Tat in Kawasaki disease. Lancet 343:920-921
9. Capron L, Kim YU, Laurian C, Bruneval P, Fiessinger JN (1992) Atheroembolism in HIV-positive individuals. Lancet 340:1039-1040
10. Kabus D, Greco MA (1991) Arteriopathy in children with AIDS: microscopic changes in the vasa vasorum with gross irregularities of the aortic intima. Pediat Patol 11:793-795
11. Pulik M, Lionnet T, Couderc U (1993) Thromboembolic disease in HIV infection. Blood 82:2931-2937
12. Loire R, Tabib A, Dureau G, Boissonnat P (1991) Les lésions coronaires du transplanté cardiaque (rejet cardiaque chronique). Etude de 15 retransplantations. Ann Pathol 11:334-341
13. Loire R, Capron L (1995) Complications vasculaires de l'infection par le VIH. Sang-Thrombose-Vaisseaux 7:487-491
14. Lafeuillade A, Alessi MC, Poizot-Martin I et al (1992) Endothelial cell dysfunction in HIV infection. J Acq Im Def Syndromes 5:127-131
15. Teitel JM, Shore A, Read SE, Schiaron E (1989) Immune function of vascular endothelial cells is impaired by HIV. J Infect Dis 160:551-552
16. Hober D, Haque A, Watter P, Beaucaire G, Mouton Y, Capron A (1989) Production of tumor necrosis factor-alpha (TNF-alpha) and interleukin-1(IL-1) in patients with AIDS. Enhanced level of TNF-alpha is related to a higher cytotoxic activity. Clin Experiment Immunol 78:329-333
17. Shattock RJ, Griffin G (1994) Cellular adherence enhances HIV replication in monocytic cells. Res Virol 145:139-145
18. Goerdt S, Sorg C (1992) Endothelial heterogenicity and the acquired immunodeficiency syndrome: a paradigm for the pathogenesis of vascular disorders. Clin Invest 70:89-98
19. Toulon P, Lamine M, LedjevI et al (1993) Heparin cofactor II deficiency in patients infected with the human immunodeficiency virus. Thromb Haemostasis 70:730-735
20. Constans J, Pellegrin JL, Peuchant E et al (1993) High plasma lipoprotein (a) in HIV-positive patients. Lancet 341:1099-1100
21. Loire R, Bastien O, Tabib A, Vigneron M (1993) Artériolite à cytomégalovirus: gangrène des pieds et maladie coronaire précoce après transplantation cardiaque. Arch Mal Cœur 86:255-258
22. Chalifoux LV, Simon MA, Pauley DR, Mackey JJ, Wyand MC, Ringler DJ (1992) Arteriopathy in macaques infected with simian immunodeficiency virus. Lab Invest 67 338-349
23. Benditt EP, Benditt JM (1973) Evidence of a monoclonal origin of human atherosclerotic plaques. Proc Nat Acad Sci USA 70:1753-1756

Coronary Heart Disease in HIV-Infected Patients: Epidemiology

M. Mary-Krause, D. Costagliola

Introduction

Cardiovascular disease continues to be the leading cause of death among the general population of industrialized countries. It is also the main reason for hospitalization. But what about HIV-infected subjects?

With the advent of highly active antiretroviral treatments (HAART) for HIV infection, including protease inhibitors (PIs), in April 1996 in France, the morbidity of AIDS-defining illnesses has been reduced and HIV-infected patients are living longer [1, 2]. Thus, the spectrum of diseases related to HIV is shifting from opportunistic diseases towards long-term complications such as cancers, co-infection with other viruses such as hepatitis C virus, and the metabolic effects of HAART. Cardiovascular diseases currently account for 7% of deaths among HIV-infected subjects in France, for 14% of non-HIV-related deaths [3], and about 16% of deaths among subjects with a good immunovirologic response to HAART [4].

HAART, defined as any combination of three antiretroviral drugs [usually two nucleoside analog reverse transcriptase inhibitors (NRTI) and either a PI or a non-nucleoside reverse transcriptase inhibitor (NNRTI)], is the current reference standard of antiretroviral treatment [5, 6]. The adverse effects of HAART have received much attention in recent years. Although lipid disorders were described in HIV-infected patients before the advent of HAART [7, 8], several class-specific metabolic effects of HAART may have a deleterious impact on the heart, including increased insulin resistance, hypercholesterolemia and/or hypertriglyceridemia, and lipodystrophy syndromes [9–12]. Likewise, although coronary lesions were described well before the advent of PIs [13, 14], HAART has been implicated in the aggravation of coronary heart diseases (CHD) and in other vascular complications [15–20]. However, the impact of the PIs on the risk of CHD and myocardial infarction (MI) remains controversial.

Estimation of the Coronary Risk

The two traditional components of epidemiological research (descriptive/analytical) contribute to improve our knowledge of diseases. Analysis of incidence and mortality data, which provide a description of a given disease at the population level, and knowledge of general characteristics (age, sex, transmission group, etc.) that are associated with a higher risk also contribute towards identifying areas for improvement in access to care and generate etiologic assumptions. Analytical studies are designed to test these hypotheses and to characterize risk factors (i.e., any attribute, characteristic, or exposure of an individual which increases the likelihood of a disease or injury). However, epidemiological studies (descriptive or analytical) are solely observational: they describe what is happening in the "real world" and may suggest causality; the level of causal presumption depends on the strength of the association, its consistency (observed repeatedly by different persons, in different circumstances and times), specificity (limited to specific sets of characteristics), relationship in time, biological gradient (dose response), biological plausibility (the weakest link, depending on the current state of knowledge), and coherence.

However, epidemiological studies have important implications for prevention, early detection, diagnosis, and access to care.

The importance of a phenomenon can be characterized by the use of crude numbers (frequency) or rates and ratios. The numerator is included in

the denominator of the incidence or prevalence rate. But rates, as opposed to frequencies, imply an element of time. With incidence rates, for example, only new cases of the disease occurring during a defined time period (e.g., 1 year) are taken into account, being divided by the average size of the population exposed during the same period. If the observation period is not a 1-year period, the denominator is usually expressed as the number of "person–time" of observation. Person–time is calculated as the sum total of the time all individuals remain in the study without developing the outcome of interest (the total amount of time that the study members are at risk of developing the outcome of interest). Person–time can be measured in days, months, or years (1,000 subjects followed for 2 years=2,000 person–years). The incidence or death rate definitions correspond to a "dynamic" dimension of the rate, that is, the rapidity of occurrence of disease or death in the population. These rates can be used to assess the risk of disease or death, but such health indicators (expressed per unit time) are not, strictly speaking, probabilities.

To quantify the association between a disease and a risk factor, one generally uses relative risk (RR) – R1/R0 – where R1 is the risk of disease or death among the population exposed to the risk factor and R0 is the risk among unexposed subjects. Usually, RR above 1 denotes a deleterious effect of the risk factor, while an RR below 1 suggests a beneficial effect. An RR of 1 suggests that there is no correlation. Another index is the odds ratio (OR), defined as (R1/(1-R1))/(R0/(1-R0)).

When comparing morbidity rates in a cohort with those of the general population, for example, direct comparison of crude rates can lead to erroneous conclusions. Indeed, it is known, for example, that the risk of almost all diseases, and particularly cardiovascular diseases, increases with age. If the age distribution is different between the two populations, the comparison of the risk will be affected by this confounding bias. Standardization appears the best way to avoid this kind of bias, and is based on the crude disease rate that would be observed in the cohort if its age distribution were the same as that of the comparator population. Thus, the standardized morbidity or mortality ratio compares the observed number of cases of disease or death in the cohort with an expected number of cases. The expected number is calculated by (a) classifying the study group in terms of demographic variables such as age and sex; (b) computing the expected number of cases or deaths for each class (by multiplying the number of individuals in the study group in that class by the class-specific death rate in a standard reference population); and (c) adding together the expected cases or deaths in all classes.

Impact of Antiretroviral Treatments on Coronary Heart Disease

Although it is now clearly established that HAART is linked to metabolic disorders, the long-term impact of these disorders is still discussed. The first questions concerning an increase in the risk of CHD and the possible responsibility of PIs were raised in May 1998.

Henry et al. [15] described two cases of coronary artery disease in HIV-infected patients treated with PIs. One of the subjects had lipodystrophy and hypercholesterolemia with no other known risk factors, while the second patient had traditional risk factors such as smoking and cocaine use. Similar series of cases were reported in the medical literature in subsequent months [16, 19, 21–23]. Gallet et al. [17] reported the cases of three patients with ischemic cardiopathy, including two with MI. All were being treated with PIs, and two had high lipid levels that were not present before antiretroviral treatment. Similarly, Vittecoq et al. [24] described four young patients with ischemic coronary events (MI in three cases). Three subjects were being treated with PIs, and three had major lipid disorders, associated with smoking and familial factors in two cases. Passalaris et al. [25] described six subjects with coronary artery disease who were receiving PI-containing combinations of antiretroviral drugs; four of these patients had acute MI. Coronary angiography revealed thrombotic lesions in two subjects, atheromatous lesions in two subjects, and both types of lesions in one subject. Friedl et al. [20] later described 14 coronary events in 11 subjects treated with PIs or NNRTIs. However, none of these studies proved a link

between CHD and antiretroviral treatment.

Some studies [26–31], but not others [32–35], have shown a link between the risk of CHD and exposure to PIs (Table 1). Some suffered from methodological problems, such as small sample size, median PI treatment periods of less than 12 months (two studies), and likely underreporting relative to the general population. In addition, the incidence of MI in people under 50 years of age is very low, meaning that lengthy follow-up of large populations (person–years) is necessary to observe a small difference between the HIV-infected population and the general population, or between two HIV-infected populations treated/not treated with HAART.

Far from increasing the incidence of cardiovascular events, a recent study from a database on administrative data [35] showed that HAART tended to reduce the short-term risk in a population of more than 36,000 HIV-infected U.S. army veterans. Between 1995 and 2001, the rate of hospital admission for cardiovascular or cerebrovascular disease fell from 1.7 to 0.9 per 100 person–years (PY), while the overall mortality rate fell from 21.3 to 5.0 per 100 PY during the same period.

A study based on the French Hospital Database on HIV (FHDH) using DMI2 software (property of the French Ministry of Health) included 34,976 men with a total follow-up of 88,029 PY between 1996 and 1999 [31]. There were 49 cases of MI during 39,023 PI-exposed PY. The incidence rate of MI among subjects exposed to PIs between 1996 and 1999 was estimated according to the duration of PI therapy, based on three periods: <18 months (group 1), 18–29 months (group 2), and ≥30 months (group 3). The authors compared the 1996–1999 MI incidence rates estimated from the FHDH dataset with the 1997–1998 incidence rates estimated from the French general male population of the same age, obtained from three French regional registries (Lille, Strasbourg, and Toulouse) [36]. This analysis accounted only for age and sex. Then, in order to take into account potential differences in other CHD risk factors (family history, smoking, hypertension, and diabetes mellitus) between the general population and the HIV-infected population [37–40], the authors compared the MI incidence rates in groups 2 and 3 with those in group 1. There were 21 cases of MI among patients exposed to PIs for less than 18 months (25,734 PY), 15 cases among subjects exposed for 18–29 months (9,440 PY), and 13 among patients exposed for 30 months or more (3,849 PY). The expected incidence of MI in the general male population with the same age distribution was 10.8 cases per 10,000 PY. The estimated incidence of MI was 8.2 per 10,000 PY (95% CI=4.7–11.7) in group 1, 15.9 (95% CI=7.9–23.9) in group 2 and 33.8 (95% CI=15.4–52.1) in group 3 (Fig. 1). No significant difference was observed between the general male population of the same age and the patients treated with PIs for less than 18 months. Although not significantly so, the risk of MI increased among patients treated with PIs for 18–29 months. In contrast, the risk of MI among patients exposed to PIs for 30 months or more was three times that of the general population (standardized morbidity ratio, SMR=2.9, 95% CI=1.5–5.0). Compared to patients exposed to PIs for less than 18 months, those treated for 18 months or more were at an increased risk of MI (SMR=1.9, 95% CI=1.0–3.1 for group 2 and SMR=3.6, 95% CI=1.8–6.2 for group 3). These results show that the risk of MI in HIV-infected men increases with the duration of PI treatment, while other antiretroviral classes are not associated with an increased risk of MI.

How can this this discordance between the results of Bozzette et al. [35] and Mary-Krause et al. [31] be explained? A direct comparison of the results of the two studies is impossible because they did not examine the same types of event. Mary-Krause et al. [31] examined admissions for and deaths from MI, whereas Bozzette et al. [35] only looked at admissions for cardiovascular disease, without taking deaths into account (especially deaths occurring outside hospital), probably leading to an underestimation of the number of cases. Also, this latter study grouped together deaths and admissions for cardiovascular and cerebrovascular disease. Holmberg et al. [28], who found an effect of PIs on the risk of MI, did not observe an increased risk of cerebrovascular disease. Results from the recently published DAD study (Data Collection on Adverse Events of Anti-HIV Drugs) indicated that there is an increasing

Table 1. Risk of coronary heart disease among HIV-infected subjects treated with HAART

Studies	Study design	Studied event	Study period	Number of subjects	Number of coronary events	Number of subjects exposed to HAART	Duration of follow-up with HAART	Results
Jütte, 1999 [26]	Database on medical records No validation of case	Myocardial infarction	Between January 1990 and August 1998	1,324 subjects 1,911 PY	8	373 subjects 469 PY	10 months (med)	Incidence of 0.21 pe 100 PY in non-PI group and of 1.06 per 100 PY in PI group
Rickerts, 2000 [27]	Database on medical records Validation of cases	Myocardial infarction	From 1 January 1983 to 31 December 1998	4,993 subjects 16,478 PY	29	1,572		OR=2.61 (1.19–5.66) HAART vs non-HAART
David, 2002 [32]	Database on medical records Case-control analysis No validation of cases	Ischemic cardiovascular diseases	From 1 April 1999 through 25 April 2000	48 subjects	16	34 subjects	27 months for cases (med) 14 months for controls (med)	PI not directly associated with greater risk of ischemic CVD
Holmberg, 2002 [28]	Database on medical records Validation of cases	Myocardial infarction	Between January 1993 and January 2002	5,672 subjects 17,712 PY	21	3,247 subjects	49 months (mean)	Higher risk HR=6.5 (0.9–47.8) PI vs non-PI
Bozzette, 2003 [35]	Database on administrative data No validation of cases	Cardio- and cerebrovascular diseases	Between 1 January 1993 and 30 June 2001	36,766 subjects 121,935 PY	1207	15,296 subjects 26,957 PY	16 months (med)	HR=1.23 (0.78–1.93) 24 months of PI exposure vs 0 months

cont. →

Table 1 *cont.* →

Studies	Study design	Studied event	Study period	Number of subjects	Number of coronary events	Number of subjects exposed to HAART	Duration of follow-up with HAART	Results
Klein, 2003 [33, 34]	Database on administrative data No validation of cases	Myocardial infarction	Between 1 January 1996 and 31 December 2002	4,408 subjects 18,792 PY	65	2,860 subjects 10,686 PY	47 months (med)	4.0 cases/1,000 PY if no PI vs. 3.9/1,000 PY if PI
Friis-Moller, 2003 [29]	Specifically designed cohort Validation of cases	Myocardial infarction	Between December 1999 and February 2002	23 468 subjects 36 199 PY	126			RR=1.26 per year of combination antiretroviral treatment exposure
Moore, 2003 [30]	Database on medical records Case-control analysis No validation of cases	Myocardial infarction + unstable angina	After 1 January 1996	2,671 subjects 7,330 PY	43			Observed incidence of 5.9 events/1,000 PY vs expected incidence of 2/1,000 PY PI as independent factor
Mary-Krause, 2003 [31]	Database on medical records Validation of cases	Myocardial infarction	Between 1 January 1996 and 31 December 1999	34,976 men 88,029 PY	60 49 treated with PI	21,906 subjects 39,023 PY	34 months (med)	Higher risk SMR=3.6 (1.8–6.2) =30 months of PI exposure vs <18 months
D'Arminio Monforte, 2004 [41]	Specifically designed cohort Validation of cases	Cardio- and cerebrovascular events	Between December 1999 and July 2002	36,145 PY	207			RR=1.26 per year of combination antiretroviral treatment exposure

PY, person–years; *med*, median

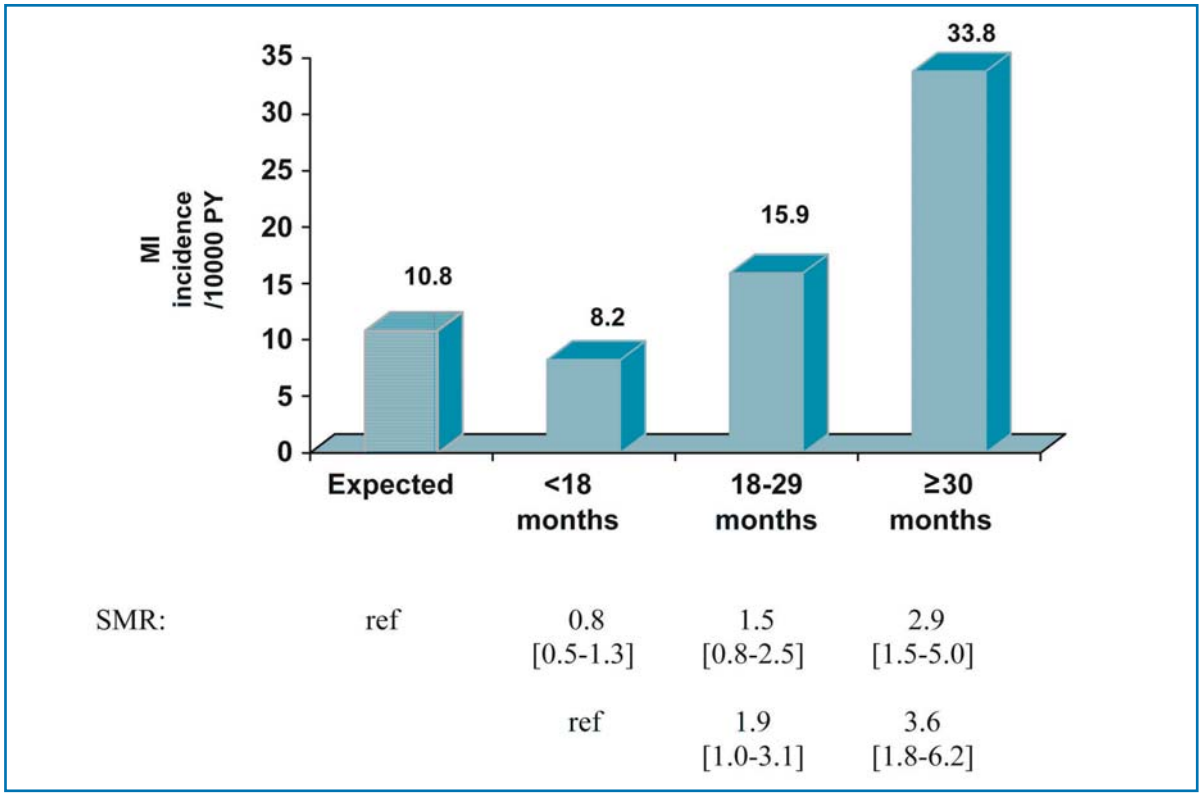


Fig. 1. Incidence of myocardial infarction (*MI*) per 10,000 person–years (*PY*) among HIV-infected men according to the duration of PI exposure (in months) compared to the incidence of MI among the general male population of the same age. The standardized morbidity ratios (*SMR*) with their 95% confidence intervals in *brackets* were used to test the differences between incidence rates. (From [31] with permission)

risk of first cardio- and cerebrovascular events with longer exposure to combination antiretroviral treatment [41]. The ninth version of the international classification of diseases [42], used by Bozzette et al. [35], includes codes 410 (acute MI), 411 (other acute and subacute forms of ischemic heart disease), 413 (angina pectoris), and 414 (other forms of chronic ischemic heart disease), whereas Mary-Krause et al. [31] used only code 410. It would be interesting to study the impact of PIs on each pathology separat. It should be noted that, although not significant, Bozzette et al. observed a higher risk of admission for cardiovascular diseases [35] among subjects exposed to PIs for 24 months as compared with 0 months (RR=1.23). It is surprising that the incidence of admissions for cardiovascular disease – more than 10 cases per 1,000 PY – observed in the study by Bozette et al. [35] was much higher than the incidence rates of CHD observed among seropositive American subjects exposed to PIs in other studies (5.9–6.6 events per 1,000 PY) [30, 34]. It is also surprising that Bozzette et al. found that the rate of CHD fell with time despite the increasing age of HIV-infected subjects.

The DAD study [29], a prospective observational study of 23,468 patients enrolled in 11 cohorts on 3 continents from December 1999 to July 2002, showed a similar relationship between exposure to combination antiretroviral therapy (including PIs or NNRTIs) and the risk of MI to that found by Mary-Krause et al. [31], the risk increasing with the duration of HAART. In the same way, Moore et al. [30] reported a study of 2,671 subjects followed up after 1 January 1996, in which the risk of cardiovascular events was higher among subjects exposed to PIs. Of 3,083,209 individuals analyzed among them, 28,513 were HIV-infected. Currier et al. [39] found a higher incidence of CHD among young men and women with

HIV infection than that among non-HIV-infected individuals. Their results also suggest that any exposure to potent combination antiretroviral therapy may contribute to the incidence of CHD among younger individuals when controlling for certain comorbidities.

Outcome of Coronary Heart Disease in HIV-Infected Subjects

Few data have been published on the outcome of acute coronary events among HIV-infected patients compared to HIV-seronegative subjects. Compared with HIV-seronegative patients with idiopathic dilated cardiomyopathy, HIV-infected counterparts had markedly reduced survival and a hazards ratio for death of 4.0 [43]. A study of 24 HIV-seropositive subjects with acute MI [44] showed that characteristics at hospital admission, the treatment strategy, and the relatively benign in-hospital outcome were similar to those of HIV-seronegative subjects admitted for acute MI. In contrast, after 15 months of follow-up, a higher incidence of recurrent infarction was observed among HIV-infected patients (20% vs. 4%, p=0.07), together with a higher incidence of hospitalization for other recurrent coronary events (45% vs. 11%, p=0.007). Although the TIMI risk scores of HIV-infected patients with acute coronary syndromes (ACS) are lower and these patients have less extensive coronary disease than HIV-seronegative patients with ACS, percutaneous coronary intervention in HIV-infected patients is associated with high restenosis rates [45].

Further studies are necessary to confirm this worse long-term prognosis of HIV-seropositive subjects with CHD.

Conclusion

Available data suggest that exposure to PIs increases the risk of MI, to a degree that depends on the duration of exposure. However, the risk–benefit ratio of PIs remains positive, as the increase in life expectancy conferred by HAART far outweighs the associated risk of MI. Indeed, one study showed that the 3-year risk of MI increased from 0.30% (95% CI=0.20–0.38%) in antiretroviral-naive patients to 1.07% (95% CI=0.43–1.77%) in patients receiving antiretrovirals of all three classes. The estimated 3-year risk of AIDS or death is between 6.2% and 11.1% among patients receiving antiretroviral therapy when they continue treatment, and from 22.5% to 29.4% when they stop treatment [46].

In keeping with current guidelines [5, 47, 48], the risk of CHD must be taken into account in PI treatment decisions, especially for patients with known vascular risk factors. Other factors significantly associated with MI are older age, current or former smoking, previous cardiovascular disease, and male sex, but not a family history of CHD [29]. A higher total serum cholesterol level, a higher triglyceride level, and diabetes mellitus were also associated with an increased incidence of MI [29]. Thus, cholesterol, triglyceride, and blood glucose levels must be determined before and regularly during HAART in order to diagnose any abnormalities as they occur.

If lipid-lowering drug therapy is indicated, it should be limited to those agents with a low risk of interaction with antiretroviral drugs [49]. It is also necessary to keep in mind that the fight against CHD includes action on modifiable risk factors such as smoking, diabetes mellitus, arterial hypertension, and lipid disorders. Prevention should be promoted among patients with CHD risk factors.

Longer follow-up of PI therapy is needed to tell whether the risk of MI continues to increase with the duration of PI exposure, and further studies are necessary to confirm the possible impact of NNRTIs on CHD observed in the DAD study [29].

References

1. Palella FJ Jr, Delaney KM, Moorman AC et al (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 338:853-860
2. The CASCADE Collaboration (2000) Survival after introduction of HAART in people with known duration of HIV-1 infection. Lancet 355:1158-1159
3. Lewden C, Salmon D, Morlat P et al (2004) Causes of

death among HIV-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS. Int J Epidemiol (in press)
4. May T, Lewden C, Bonnet F et al (2004) Causes et caractéristiques des décès des patients infectés par le VIH-1, en succes immuno-virologique sous traitement antirétroviral. Presse Med (in press)
5. – (2004) Prise en charge thérapeutique des personnes infectées par le HIV. Mise à jour 2004. Recommandations du groupe d'experts sous la direction du Pr JF Delfraissy. Flammarion Médecine-Sciences, Paris
6. Yeni PG, Hammer SM, Hirsch MS et al (2004) Treatment for adult HIV infection: 2004 recommendations of the International AIDS Society-USA Panel. JAMA 292:251-265
7. Grunfeld C, Pang M, Doerrler W, Shigenaga JK, Jensen P, Feingold KR (1992) Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. J Clin Endocrinol Metab 74:1045-1052
8. Feingold KR, Krauss RM, Pang M, Doerrler W, Jensen P, Grunfeld C (1993) The hypertriglyceridemia of acquired immunodeficiency syndrome is associated with an increased prevalence of low density lipoprotein subclass pattern B. J Clin Endocrinol Metab 76:559-565
9. Carr A, Samaras K, Burton S et al (1998) A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitor. AIDS 12:F51-F58
10. Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA (1999) Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. Lancet 353:2093-2099
11. Safrin S, Grunfeld C (1999) Fat distribution and metabolic changes in patients with HIV infection. AIDS 13:2493-2505
12. Hadigan C, Meigs JB, Corcoran C et al (2001) Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. Clin Infect Dis 32:130-139
13. Tabib A, Greenland T, Mercier I, Loire R, Mornex JF (1992) Coronary lesions in young HIV-positive subjects at necropsy. Lancet 340:730
14. Paton P, Tabib A, Loire R, Tete R (1993) Coronary artery lesions and human immunodeficiency virus infection. Res Virol 144:225-231
15. Henry K, Melroe H, Huebsch J, Hermundson J, Levine C, Swensen L (1998) Severe premature coronary artery disease with protease inhibitors. Lancet 351:1328
16. Behrens G, Schmidt H, Meyer D, Stoll M, Schmidt RE (1998) Vascular complications associated with use of HIV protease inhibitors. Lancet 351:1958
17. Gallet B, Pulik M, Genet P, Chedin P, Hiltgen M (1998) Vascular complications associated with use of HIV protease inhibitors. Lancet 351:1958-1959
18. Laurence J (1998) Vascular complications associated with use of HIV protease inhibitors. Lancet 351:1960
19. Flynn TE, Bricker LA (1999) Myocardial infarction in HIV-infected men receiving protease inhibitors [Letter]. Ann Intern Med 131:548
20. Friedl AC, Attenhofer Jost CH, Schalcher C et al (2000) Acceleration of confirmed coronary artery disease among HIV-infected patients on potent antiretroviral therapy. AIDS 14:2790-2792
21. Karmochkine M, Raguin G (1998) Severe coronary artery disease in a young HIV-infected man with no cardiovascular risk factors who was treated with indinavir. AIDS 12:2499
22. Eriksson U, Opravil M, Amann FW, Schaffner A (1998) Is treatment with ritonavir a risk factor for myocardial infarction in HIV-infected patients? AIDS 12:2079-2080
23. Koppel K, Bratt G, Rajs J (1999) Sudden cardiac death in a patient on 2 years of highly active antiretroviral treatment: a case report. AIDS 13:1993-1994
24. Vittecoq D, Escaut J, Monsuez JJ (1998) Vascular complications associated with use of HIV protease inhibitors. Lancet 351:1959
25. Passalaris JD, Sepkowitz KA, Glesby MJ (2000) Coronary artery disease and human immunodeficiency virus infection. Clin Infect Dis 31:787-797
26. Jütte A, Schwenk A, Franzen D et al (1999) Increasing morbidity from myocardial infarction during HIV protease inhibitor treatment? [Letter] AIDS 13:1796-1797
27. Rickerts V, Brodt HR, Staszewski S, Stille W (2000) Incidence of myocardial infarctions in HIV-infected patients between 1983 and 1998: The Frankfurt HIV-cohort study. Eur J Med Res 5:329-333
28. Holmberg SD, Moorman AC, Williamson JM et al (2002) Protease inhibitors and cardiovascular outcomes in patients with HIV-1. Lancet 360:1747-1748
29. Friis-Møller N, Sabin CA, Weber R et al (2003) Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med 349:1993-2003
30. Moore RD, Keruly JC, Lucas G (2003) Increasing incidence of cardiovascular disease in HIV-infected per-

sons in care. 10th conference on retroviruses and opportunistic infections, Boston, USA, February 10–14, 2003. Abstract no. 132
31. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D (2003) Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. AIDS 17:2479-2486
32. David MH, Hornung R, Fichtenbaum CJ (2002) Ischemic cardiovascular disease in persons with human immunodeficiency virus infection. Clin Infect Dis 34:98-102
33. Klein D, Hurley LB, Quesenberry CP, Sidney S (2002) Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? J Acquir Immune Defic Syndr 30:471-477
34. Klein D, Hurley M (2003) Hospitalizations for coronary heart disease and myocardial infarction among men with HIV-1 infection: Additional follow-up. 10th conference on retroviruses and opportunistic infections, Boston, USA, February 10–14, 2003. Abstract no. 747
35. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA (2003) Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. N Engl J Med 348:702-710
36. Anonymous (2000) Les registres français de cardiopathies ischémiques 1997–1998. Fédération Française de cardiologie, 5 rue du Rocher, 75008 Paris
37. Depairon M, Chessex S, Sudre P et al (2001) Premature atherosclerosis in HIV-infected individuals – focus on protease inhibitor therapy. AIDS 15:329-334
38. Savès M, Chêne G, Ducimetière P et al (2003) Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. Clin Infect Dis 37:292-298
39. Currier JS, Taylor A, Boyd F et al (2003) Coronary heart disease in HIV-infected individuals. J Acquir Immune Deficit Syndr 35:506-512
40. Smith C, Levy I, Sabin C, Kaya E, Johnson M, Lipman M (2004) Cardiovascular disease risk factors and antiretroviral therapy in HIV-positive UK population. HIV Med 5:88-92
41. d'Arminio Monforte A, Sabin CA, Phillips AN et al (2004) Cardio- and cerebrovascular events in HIV-infected persons. AIDS 18:1811-1817
42. Anonymous (1977) Manuel de la classification statistique internationale des maladies, traumatismes et causes de décès, Révision 1975. Organisation Mondiale de la Santé, Geneva
43. Barbaro G, Di Lorenzo G, Soldini M, Giancaspro G, Grisorio B, Pellicelli A (1999) Intensity of myocardial expression of inducible nitric oxide synthase influences the clinical course of human immunodeficiency virus-associated cardiomyopathy. Gruppo Italiano per lo Studio Cardiologico dei pazienti affetti da AIDS (GISCA). Circulation 100:933-939
44. Matetzky S, Domingo M, Kar S et al (2003) Acute myocardial infarction in human immunodeficiency virus-infected patients. Arch Intern Med 163:457-460
45. Hsue PY, Giri K, Erickson S et al (2004) Cinical features of acute coronary syndromes in patients with human immunodeficiency virus infection. Circulation 109:316-319
46. Law M, Friis-Møller N, Weber R et al (2003) Modelling the 3-year risk of myocardial infarction among participants in the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study. HIV Med 4:1-10
47. Dube MP, Stein JH, Aberg JA et al (2003) Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. Clin Infect Dis 37: 613-627
48. Department of Health and Human Services (2004) Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. http://www.AIDSinfo.nih.gov/guidelines. Cited 23 March 2004
49. Falusi OM, Aberg JA (2001) HIV and cardiovascular risk factors. AIDS Reader 11:263-268

Coronary Artery Disease in HIV-Infected Patients: Clinical Presentation, Pathophysiology, Prognosis, Prevention, and Treatment

F. Boccara, A. Cohen

Introduction

The advent of new antiretroviral agents has dramatically reduced mortality and HIV-associated morbidity. In the highly active antiretroviral therapy (HAART) era, long-term side effects have been reported, such as severe metabolic disorders and related acute cardiovascular complications including myocardial infarction, peripheral vascular disease, and stroke. Prevention and therapeutics for cardiovascular complications in HIV-infected patients are a new and emerging challenge for physicians involved in HIV infection care because of the prolongation of survival and long-term complications of HAART. In the present overview, we discuss the clinical presentation, pathophysiology, prognosis, prevention, and treatment of coronary heart disease (CHD) in HIV-infected patients.

The incidence of acute myocardial infarction in HIV-infected patients (HIV+) tends to be higher than in the general population [1, 2] particularly in those undergoing HAART [3] including protease inhibitors [2, 4]. The relationship between coronary artery disease (CAD) and the use of protease inhibitors in HIV-infected patients is still under debate [5]. The epidemiology of CHD in HIV-infected patients is discussed in the chapter by M. Mary-Krause and D. Costagliola in this volume.

Clinical Presentation and Vascular Risk Factors

The spectrum of CAD in HIV-infected patients is similar to non-HIV-infected patients with various clinical presentations including silent ischemia, stable angina, and acute coronary syndrome (unstable angina, non-ST elevation myocardial infarction, ST elevation myocardial infarction) (Figs. 1–6). The first case of CAD in the HAART era was published in 1998 followed by several case reports and series [6–13].

Whether protease inhibitors are directly responsible for CAD remains a matter of debate [5, 14].

In our cardiology department [13], 1 female and 19 male patients (mean age, 44±8 years; range, 34–65 years), infected with HIV since 9±4 years

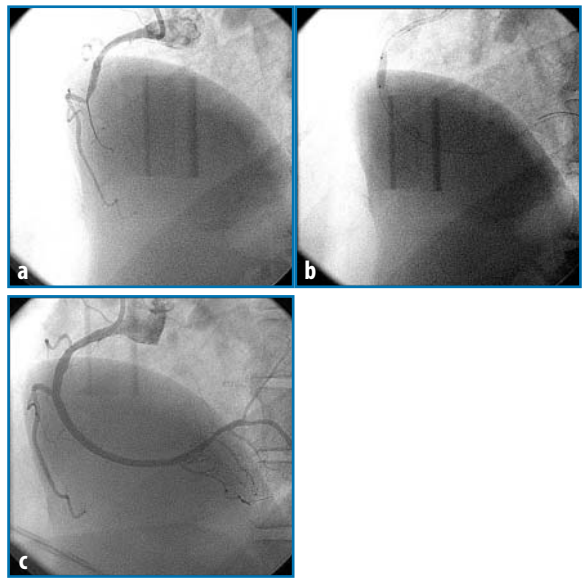


Fig. 1a–c. Patient 1. **a** Coronary angiogram revealed an acute occlusion of the right coronary artery in a 38-year-old HIV-infected man (since 1995) during inferior acute myocardial infarction. A guide-wire is introduced into the lumen artery to pass the thrombotic occlusion. His vascular risk factors were smoking and mild dyslipidemia (high LDL cholesterol, low HDL cholesterol, and high triglyceride levels). **b** Balloon angioplasty performed at the site of the occlusion with 10-atmosphere expansion pressure. **c** Result after inflation of the balloon and implantation of a long bare stent (3.5 mm diameter×32 mm length)

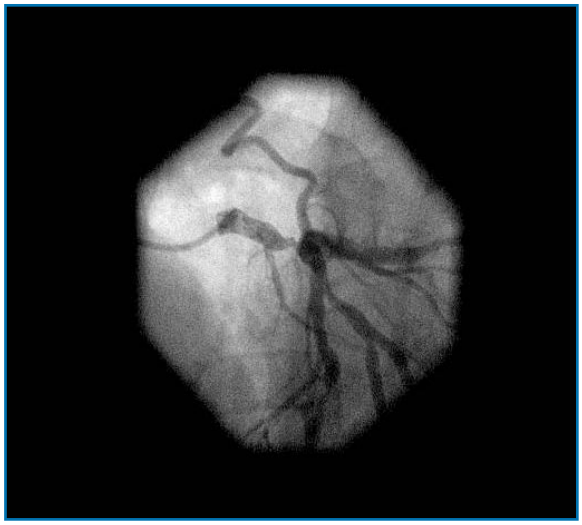


Fig. 2. Patient 2. Coronary angiogram finding a left main coronary stenosis (70%) in a 62-year-old HIV-infected woman (since 1987) who was admitted for an episode of unstable angina. Vascular risk factors were smoking and mixed dyslipidemia. She underwent a coronary artery bypass including the left internal mammary artery

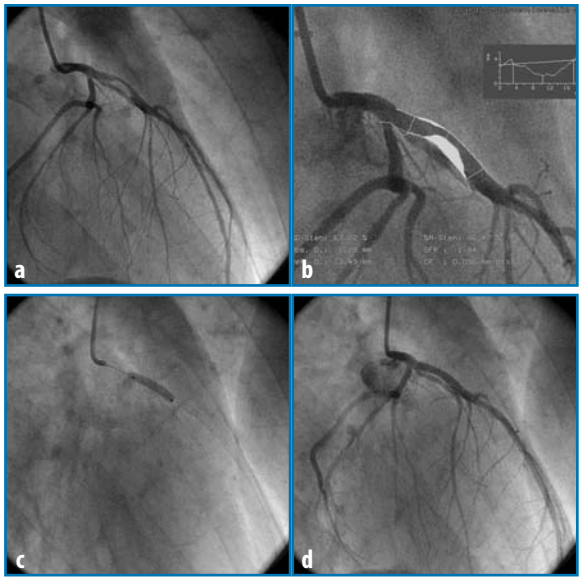


Fig. 3a–d. Patient 3. **a** Coronary angiogram revealed a 65% diameter stenosis (eccentric) on the left anterior descending (LAD) artery in a 40-year-old HIV-infected man (since 1989) who was admitted for a non-ST elevation myocardial infarction (NSTEMI). Smoking and intravenous drug abuse were the only known vascular risk factors. **b** Quantitative coronary angiography revealed a 63% diameter stenosis, a 3.5-mm reference diameter and 18 mm in length. **c, d** Direct stenting of the lesion with a 3.5-mm diameter and 20-mm length stent. Excellent result without residual stenosis

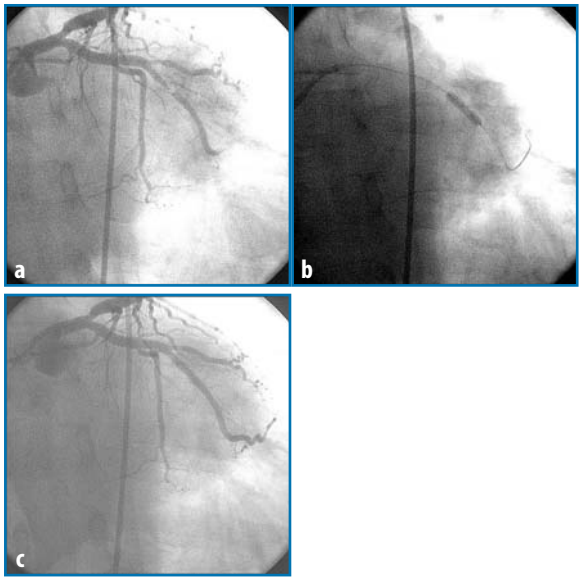


Fig. 4a–c. Patient 4. **a** Coronary angiogram revealed a thrombotic stenosis of the first lateral artery (circumflex) in a 50-year-old HIV-infected man (since 1988) who was admitted for a NSTEMI. His only vascular risk factor was a high LDL cholesterol, a low HDL cholesterol, and mild elevated triglyceride levels. **b** Direct stenting (drug-eluted stent: 3 mm diameter×13 mm length) of the lesion was performed. **c** Excellent result after stent implantation with TIMI 3 flow, no dissection and no residual stenosis

ago, were admitted from 1996 to 2002 for acute coronary syndrome (18 had myocardial infarction and 2 had unstable angina). Tobacco consumption (80%) and dyslipidemia (65%) were the most frequent cardiovascular risk factors. The median CD4 cell count was 387±184/mm^3 and the median viral load was 8,000±23,000 copies/ml. Fourteen patients were treated with protease inhibitors for a mean duration of 19±13 months. Five patients were treated with acute thrombolysis, three had primary angioplasty.

Duong et al. [12] showed that silent myocardial ischemia (detected by treadmill test) was increased in HIV-infected patients without CHD (11%) and that age, central fat accumulation, and hypercholesterolemia were independent predictive factors.

HIV-infected patients seem to be at higher risk of CAD than the general population as demonstrated recently by Bergersen et al. [15], who reported that compared to control subjects, twice as many HIV-infected patients on HAART had an estimated 10-year CHD Framingham risk above 20%.

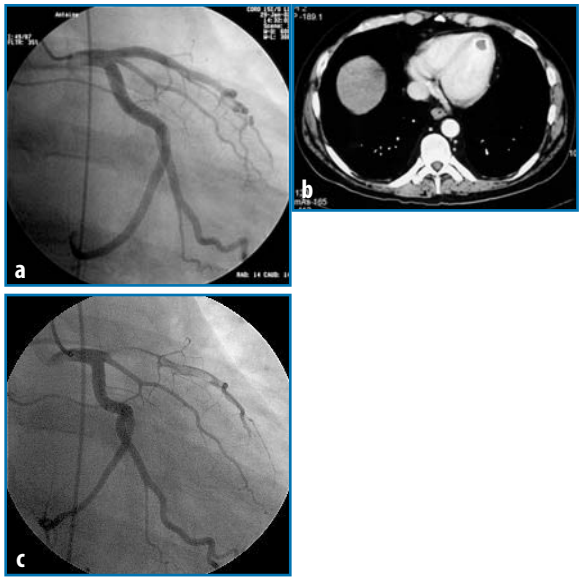


Fig. 5a–c. Patient 5. **a** Coronary angiogram of a 35-year-old HIV-infected man (since 1992) with normal left and right coronary arteries. No atherosclerotic lesions were visualized. This examination was performed because he was admitted with congestive heart failure (NYHA class IV) and echocardiography revealed a cardiomyopathy with severe left ventricular global hypokinesia, poor ejection fraction (20%), and a suspected apical thrombus. **b** A CT scan confirmed the presence of a left ventricle apical thrombus. The patient underwent anticoagulation therapy with coumadine. **c** Three months later, he was admitted for an acute anterior myocardial infarction and the coronary angiogram revealed a long thrombus in the left anterior descending artery (TIMI flow 1). He had stopped taking coumadine 2 months earlier. After 1 month of efficient anticoagulation plus aspirin therapy, the coronary angiogram revealed no remaining thrombus and no atherosclerosis stenosis or plaque rupture. Coronary embolism from the apical left ventricle thrombus was evoked

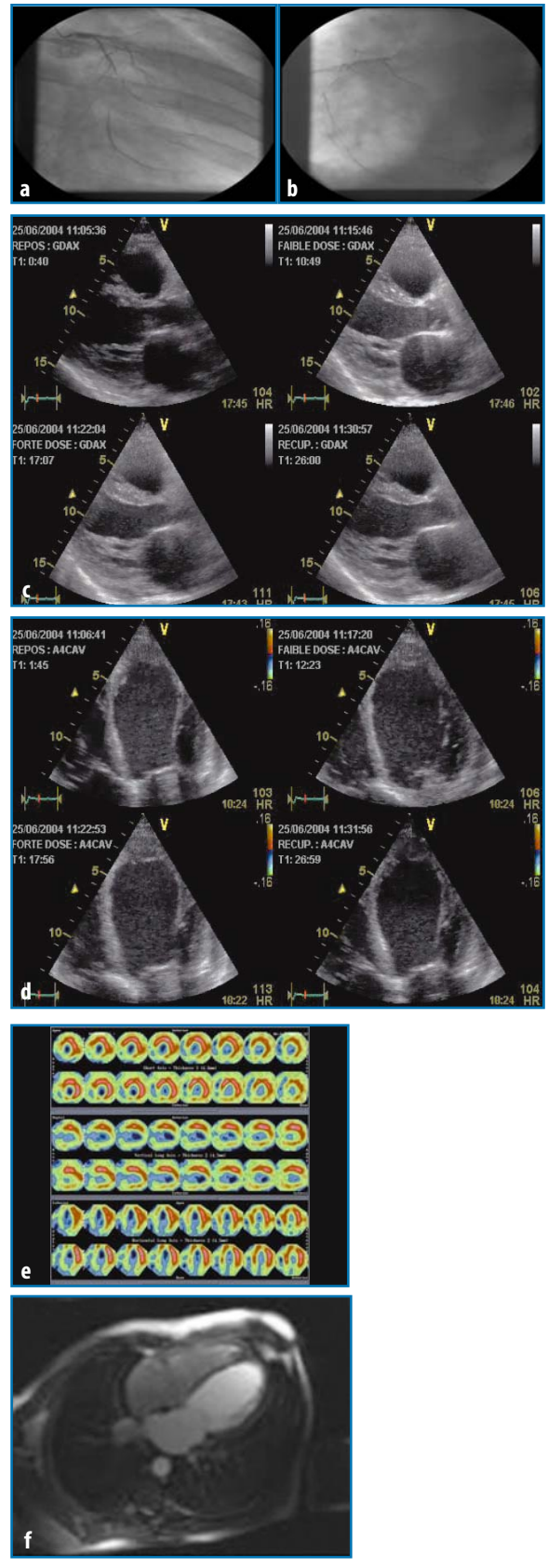


Fig. 6a–f. Patient 6. **a** Coronary angiogram showing three-vessel coronary artery disease in a 43-year-old HIV-infected man admitted for a NSTEMI. Occlusion of proximal LAD and proximal circumflex artery. One lateral artery is visualized, but no LAD without controlateral filling. **b** Proximal right coronary occlusion. **c, d** Dobutamine stress echocardiography (**c** parasternal long axis, **d** apical four chambers) demonstrated apical viability. **e** Rest thallium-201 single-photon emission tomography (SPECT) finding of anterior and lateral myocardial viability. **f** Heart cine magnetic resonance imaging (long-axis) finding severe left ventricular dysfunction (LVEF 15%)

Neumann et al. [16], in a cohort of 309 HIV-infected patients, demonstrated that the risk of cardiovascular events is related to the age of HIV-infected patients. The overall 10-year probability for cardiovascular events was higher in the oldest group (>50 years; median, 20.5%) than in the youngest group (18–30 years; 1.9%; $p<0.01$). Therefore, an increased duration of life due to a more effective antiretroviral therapy will have a significant impact on the rate of cardiovascular events in this patient population.

Hadigan et al. [17] estimated the 10-year CHD risk among 91 HIV-infected men and women with fat redistribution and compared it with the risk estimated for 273 age-, sex-, and body mass index (BMI)-matched subjects enrolled in the Framingham Offspring Study. The 10-year CHD risk estimate was significantly elevated among HIV-infected patients with fat redistribution, particularly among men; however, when they were matched with control subjects by waist-to-hip ratio, the 10-year CHD risk estimate did not significantly differ between groups. HIV-infected patients without fat redistribution did not have a greater CHD risk estimate than did control subjects. The CHD risk estimate was greatest in HIV-infected patients who had primary lipoatrophy, compared with those who had either lipohypertrophy or mixed fat redistribution.

The APROCO study group (France) [18] compared the distribution of risk factors for cardiovascular disease in 227 HIV-infected patients (35–44 years) who were treated with protease inhibitors with 527 HIV-1-uninfected men from the MONICA project. HIV-infected patients had a lower prevalence of hypertension, a lower mean high-density lipoprotein (HDL) cholesterol level, a higher prevalence of smoking, a higher mean waist-to-hip ratio, and a higher mean triglyceride level. No difference was found for total plasma or low-density cholesterol levels, nor for the prevalence of diabetes. The predicted risk of CHD was greater among HIV-1-infected men (RR, 1.20) and women (RR, 1.59; $p<10^{-6}$ for both) compared with the HIV-1-uninfected cohort.

Our cohort [13] of HIV-infected patients with acute coronary syndrome in a single cardiologic French center seems to be at higher risk of cardiovascular events compared with non-HIV-infected patients less than 45 years old reported in previous series [19–21]. A traditional risk factor of 2 or higher was found in 75% of our cohort compared to 20%–30% reported in the literature, with the same prevalence of tobacco consumption (80%) and more frequent dyslipidemia (50% and 15%–50%, respectively) [18–21]. On the other hand, a family history of premature CAD was less frequent (10% and 15%–60%, respectively). Angiographic findings appeared to be more severe in our patients, with a higher frequency of three-vessel disease (25% and 8%–12%, respectively) and fewer normal coronary angiograms (5% and 14%–20%, respectively) [21]. Our study points to the important time delay (17 h) of hospitalization after the onset of symptoms, underlining the need for physicians to take into account any acute cardiovascular symptom in HIV-infected patients in order to offer the best treatment strategy, i.e., early reopening of the infarct-related coronary artery. Thrombolytic therapy and primary angioplasty should be used in the HIV population without any limitation since reported adverse effects are not increased [22].

In conclusion, HIV-infected patients undergoing HAART seem to be at a higher risk of CAD because of the higher incidence of traditional vascular risk factors compared with same-age non-HIV-infected patients. Whether protease inhibitors have a direct impact on atherosclerosis remains hypothetical [23].

Pathophysiology

Several hypotheses have been raised regarding the pathophysiology of atherosclerotic CAD in HIV-infected patients undergoing HAART. Many factors could increase the rate of cardiovascular events and accelerate atherosclerosis:

1. Insulin resistance (reported in 25%–62% of HIV-infected patients), diabetes mellitus (5%–10%), and lipodystrophy syndrome (20%–83%) [24–27]
2. Resistant dyslipidemia [lower level of HDL cholesterol, higher level of triglycerides (50%–90%), small and dense LDL particles] with lower effica-

cy of lipid-lowering therapy [27–32]
3. Chronic inflammation and infection with increased cytokine levels (tumor necrosis factor-alpha, interleukin-1, interleukin-6, interleukin-10) [33–37]
4. Enhanced endothelial injury due to dyslipidemia [38], oxidant stress [39], adhesion molecules [40], HIV Tat protein, and related angiogenic effects [33, 41, 42]
5. A prothrombotic state linked to HIV status and/or antiretroviral therapy [43, 44]

The role of metabolic disorders (low level of HDL cholesterol and hypertriglyceridemia) is highlighted in different studies [45, 46] that included HIV+ patients with acute coronary syndrome compared with HIV+ subjects without cardiovascular manifestations. These disorders can be partly explained by HIV treatments that result in higher hypertriglyceridemia and lower levels of HDL cholesterol compared with non-infected-HIV patients. The low level of HDL cholesterol may play a major role in the pathophysiologic mechanism of atherothrombosis [31]. Another aspect is the degree of the immunologic status reflected by the CD4 cell count level, which has been demonstrated to be lower in HIV+ patients with ACS compared with HIV+ patients without ACS [45, 46].

Direct vascular toxicity of the virus has been suggested in a report from Barbaro et al. [47]. They found HIV-1 sequences within the arterial wall in a 32-year-old man without vascular risk factors who died from an anterior myocardial infarction. In addition, Schecter et al. [34] demonstrated that HIV-envelope glycoprotein gp120 activates human arterial smooth muscle cells to express tissue factor and promote the coagulation cascade and plaque rupture, supporting the observation of a correlation between plasma HIV load, a prothrombotic state, and cellular apoptosis.

Tabib et al. [48] found that coronary artery lesions of young HIV-infected patients at autopsy, whose death was caused from other cardiovascular disease, were of an intermediate type, between those observed in coronary atherosclerosis and chronic rejection in cardiac transplant patients. Subclinical atherosclerosis in HIV-infected patients has been reported [49–53] with increased intima-media thickness and atherosclerotic plaques of the carotid and femoral arteries correlated to age, dyslipidemia, and tobacco use, but not with protease inhibitor therapy. Coronary artery calcifications, another surrogate marker and prognostic factor of atherosclerosis visualized with electron beam computed tomography, are under evaluation in HIV-infected patients, with controversial results [54–56]. Coronary magnetic resonance angiography could be a further diagnostic tool for detecting infraclinic coronary atherosclerosis in the near future (Fig. 7).

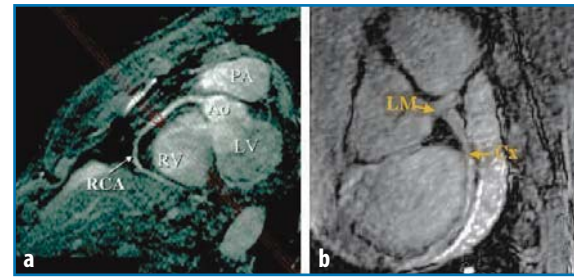


Fig. 7a, b. Magnetic resonance angiography finding of normal coronary arteries. *PA*, pulmonary artery; *Ao*, aorta; *LV*, left ventricle; *RV*, right ventricle; *RCA*, right coronary artery; *LM*, left main coronary artery; *Cx*, circumflex

Prognosis

The prognosis of CAD in HIV-infected patients has been evaluated in few series [57–61]. Matetzky et al. [57] compared the characteristics and long-term course of 24 HIV-infected patients with acute myocardial infarction with matched non-HIV patients. The in-hospital course was similar without death or re-infarction. After a 15-month follow-up, HIV-infected patients had a higher incidence of re-infarction, recurrent cardiovascular event, and target vessel revascularization independently of the type of antiretroviral therapy.

Hsue et al. [58], in a recent case-control study, reported a higher rate of coronary restenosis after percutaneous coronary intervention (PCI) in HIV-infected patients compared with non-HIV-infected patients with acute coronary syndrome [52% (15/22 patients) vs. 14% (3/21 patients), p=0.032]. There was no significative difference in the subgroup of patients who had stenting (50% vs. 18%, p=0.078).

Ambrose et al. [59] reported the outcome of 51 HIV-infected patients with acute coronary syndrome. Forty-five had coronary angiography and 25 had PCI with an excellent initial result and no hospital death in the PCI subgroup. In our cohort [13], no patient died during initial hospitalization. At the end of follow-up (37±15 months), nine patients were free of symptoms. We reported one cardiovascular death (cardiogenic shock) and one death from suicide. Four patients had recurrent myocardial ischemia (2 myocardial infarctions, 4 unstable angina). Two patients had coronary angioplasty with stenting and two had coronary artery bypass surgery and percutaneous intervention. Three patients developed congestive heart failure secondary to left ventricular systolic dysfunction (1 patient with initial acute left main coronary occlusion had sustained ventricular tachycardia and a cardioverter-defibrillator was implanted). In non-HIV-infected patients, young age is an independent predictor of good prognosis. In our cohort [13], when excluding the patient who killed himself, only nine patients (45%) were free of symptoms at 3 years' follow-up, whereas in non-HIV patients less than 45 years old the incidence is over 80%.

The prognosis of coronary revascularization in HIV-infected patients needs to be compared with a large cohort of HIV-negative subjects.

Prevention and Treatment

As in the general population, cardiovascular risk stratification in HIV-infected patients needs to be evaluated before and during HAART. The "traditional" cardiovascular risk factors are present in the HIV-infected population: smoking, dyslipidemia, diabetes mellitus, hypertension, premature familial cardiovascular disease, and poor physical fitness. Reducing risk factors should become a routine aspect in the care of HIV-infected patients, who now live longer because of the steep decline in morbidity and mortality as a result of HAART. Large prospective and matched control studies in HIV-infected patients in primary cardiovascular prevention are needed so as to identify specific risk factors and stratify the cardiovascular risk. Intervention studies on reducing the cardiovascular risk in HIV-infected patients, as in the general population, are needed (smoking cessation, physical activity, lipid-lowering drugs, aspirin).

The first step is to evaluate the relative risk or the absolute risk of a cardiovascular event in each patient by using the Framingham risk score (www.CHD-taskforce.com) [62] and/or the recommendations of the International Society of Atherosclerosis (www.athero.org). The objective is to identify, in primary prevention, patients who require risk reduction by prescribing aspirin, lipid-lowering, or antihypertensive medication to decrease mortality and morbidity as proven in the general population.

Primary Prevention

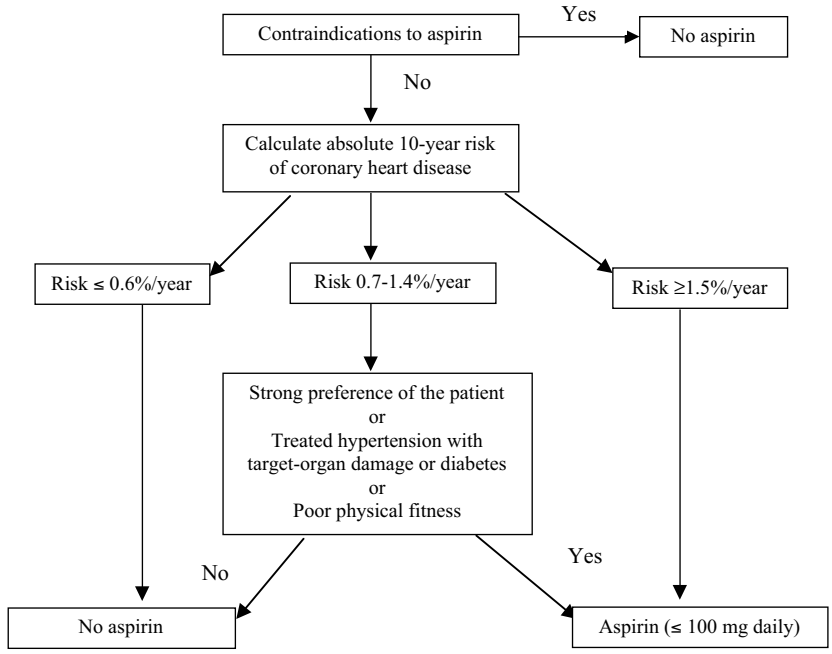
Aspirin

According to the North American and European task force, aspirin should be prescribed in primary prevention using Lauer's algorithm (Scheme 1) [63] driven by the Framingham risk score, which is similar[64, 65]. Special caution should be recommended in patients with untreated or unstable hypertension because of the increased risk of hemorrhagic stroke and in the overall population because of the risk of major gastrointestinal bleeding. For the low-risk population (<0.6% per year), the reduction of absolute risk of myocardial infarction is equivalent to the risk of gastrointestinal bleeding.

Lipid-Lowering Therapy

Serum lipid levels should be evaluated in a fasting patient (12 h), particularly for triglycerides, before HAART is started and then every 3–6 months. National Cholesterol Education Program III (66) guidelines should be applied to HIV-infected patients (Table 1), as suggested in the guidelines for the management of dyslipidemia in HIV-infected patients by Dube et al. [29]. If dyslipidemia is present, secondary causes should be screened: diabetes mellitus, hypothyroidism, excessive alcohol use, obstructive liver disease, chronic renal failure, hypogonadism, and drug-

Scheme 1. Algorithm for making decisions about the use of aspirin for primary prevention of coronary heart disease according to Lauer [63]



Suggested algorithm for making decisions about the use of aspirin for primary prevention of coronary heart disease. Contraindications to aspirin therapy include known allergy, bleeding diathesis, platelet disorders, and active peptic ulcer disease. Relative contraindications include renal failure, concurrent use of nonsteroidal anti-inflammatory agents or anticoagulants, and uncontrolled hypertension. The risk of coronary heart disease is estimated by using the Framingham risk score. Poor physical fitness is defined as impaired exercise capacity for age and sex

Table 1. National Cholesterol Education Program treatment decisions made on the basis of LDL cholesterol levels: NCEP III guidelines [66]

Risk category	LDL goal	Initiate lifestyle changes	Initiate drug therapy
Primary prevention			
0–1 Risk factor	<160 mg/dl	≥160 mg/dl	≥190 mg/dl
≥ 2 Risk factors 10-year risk 10-20%	<130 mg/dl	≥130 mg/dl	≥130 mg/dl
≥ 2 Risk factors 10-year risk <10%	<130 mg/dl	≥130 mg/dl	≥160 mg/dl
Secondary prevention			
CHD or 10-year risk >20 %	<100 mg/dl	≥100 mg/dl	≥130 mg/dl

Risk factors include age (men aged ≥45 years, women aged ≥55 years or who experienced premature menopause that was not being treated with estrogen replacement therapy), family history of CHD (first-degree male relative with CHD before 55 years of age or first-degree female relative with CHD before 65 years of age), current cigarette smoking, hypertension, low HDL cholesterol (<35 mg/dl), diabetes mellitus. In the presence of high HDL cholesterol (≥60 mg/dl), subtract 1 risk factor.

induced elevated LDL cholesterol (progestins, anabolic steroids, and corticosteroids).

Lipid-lowering therapy should be prescribed cautiously in HIV-infected patients because of the potentially severe interaction between statins, fibrates on the one hand and protease inhibitors on the other hand [67].

Several statins, listed in Table 2, are metabolized via the cytochrome P-450 3A4 pathway. Protease inhibitors inhibit cytochrome P-450 and could increase statin toxicity, thereby reducing the efficacy of protease inhibitors. Non-nucleoside reverse transcriptase inhibitors are inducers of cytochrome P-450 and could reduce statin efficacy.

As demonstrated by Fichtenbaum et al. [67] in patients receiving ritonavir and saquinavir, the area under the curve increased about fivefold for atorvastatin, 32-fold for simvastatin, and decreased 0.5-fold for pravastatin.

Recently, two studies used pravastatin [30, 68] and fluvastatin [69]. Stein et al. [30] demonstrated in a double-blind, placebo-controlled study that pravastatin (40 mg/day) resulted in a 20.8% reduction in LDL particles (p=0.030), a 26.7% reduction in small LDL (p=0.100), and a 44.9% reduction in small VLDL (p=0.023). Total and non-HDL cholesterol levels decreased by 18.3% (p<0.001) and 21.7% (p<0.001), respectively. Beneisc et al. [69] compared fluvastatin (40 mg daily) with pravastatin (20 mg daily) in 25 HIV-infected patients. The reduction of LDL levels was 30.2% in the fluvastatin group and 14.4% in the pravastatin group with no effect observed on triglyceride or HDL levels.

Table 2. Different cytochrome P450 (CYP) pathways of lipid-lowering agents

	CYP	Interactions with PI	Recommendations
Statins			
Atorvastatin	3A4	Fivefold increased AUC with RITO-SAQ	Recommended at 10 mg daily
Lovastatin	3A4	High toxicity with PI	Not recommended
Simvastatin	3A4	High toxicity with PI 32-fold increased AUC with RITO-SAQ	Not recommended
Fluvastatin	2C9	Not tested	Recommended at 40 mg daily
Pravastatin	No P450 interactions	0.5-fold decreased AUC with RITO-SAQ	Recommended at 20–40 mg daily
Fibrates			
Bezafibrate	No P450 interactions	Not tested	Recommended at 400 mg daily
Fenofibrate	No P450 interactions	Not tested	Recommended at 200 mg daily
Gemfibrozil	No P450 interactions; interaction with simvastatin, cerivastatin, rosuvastatin but not atorvastatin	Not tested	Recommended at 900–1,200 mg daily

AUC, area under the curve; *RITO*, ritonavir; *SAQ*, saquinavir; *PI*, protease inhibitor

Table 3. Recommendations for the choice of drug therapy in dyslipidemia for HIV-infected patients undergoing HAART according to Dube et al. [29]

Lipid abnormalities	First choice	Second choice
Isolated high LDL cholesterol	Statin	Fibrate
Combined hyperlipidemia	Fibrate or statin	If starting fibrate, add statin
Isolated hypertriglyceridemia	Fibrate	Statin

Palacios et al. [70] demonstrated a significant reduction of 27% in total cholesterol, 37% in LDL cholesterol, with atorvastatin 10 mg/day. Lovastatin and simvastatin should be avoided in patients receiving drugs that might interact with CYP-450.

Bezafibrate, gemfibrozil, and fenofibrate have been tested in HIV-infected patients with isolated or combined hypertriglyceridemia and proved safe and well tolerated, whereas the efficacy seemed to be reduced in this population [71–73]. Fibrates have no proven interaction with the cytochrome P-450 pathway and protease inhibitors.

Henry et al. [72] tested the combination of atorvastatin (10 mg daily) with gemfibrozil (600 mg twice daily) in 24 HIV-infected subjects with pronounced hyperlipidemia. This association (after 6 months) led to a 30% and 60% drop, respectively, of cholesterol and triglyceride plasma levels in 80% of the subjects.

The use of a standard dose of pravastatin (20–40 mg daily) or fluvastatin (40 mg daily) seems to be the safest choice because of the lack of interaction with cytochrome P-450 in predominant hypercholesterolemia. A reduced dose of atorvastatin (10 mg daily) can be used also with monitoring of CK values because of a potential interaction with cytochrome P-450. Fibrates should be prescribed in the presence of an elevated triglyceride level (>5 g/l) with a normal or near-normal LDL cholesterol level after diet and exercise recommendations have failed.

The association of statin and fibrate should not be recommended as a first-line treatment because of their potentially high toxicity (rhabdomyolysis, hepatitis) and interaction with protease inhibitors. If necessary, in high-risk patient for CAD and uncontrolled combined dyslipidemia, this association should be used with caution: start at a low dose and titrate upward with regular control of signs of myopathy and CK plasma levels.

Table 3 indicates how lipid-lowering therapy should be prescribed, according to Dube et al. [29].

The risk–benefit ratio in treating HIV-infected patients with dyslipidemia is unknown. Male patients aged over 45 years and female patients over 55 years with hypertension and/or diabetes and/or familial premature CAD are candidates for lipid-lowering therapy. Switching from one protease inhibitor, ritonavir or indinavir to nelfinavir or nevirapine [74, 75], could have beneficial effects on the reversal of dyslipidemia. The effect of a switch to efavirenz on hypercholesterolemia is unclear [76, 77]. The advent of a new protease inhibitor (atazanavir) with a low risk of inducing dyslipidemia should be evaluated in patients with a high-risk cardiovascular profile or dyslipidemia. Whether protease inhibitor therapy should be discontinued after an acute coronary syndrome and treatment switched to a non-nucleoside reverse transcriptase inhibitor (efavirenz, nevirapine) or to other nucleoside or nucleotide analogs (abacavir, tenofovir) with a better "atherogenic profile" needs further investigation. Domingo et al. [78] demonstrated a decrease in triglyceride and total cholesterol levels after switching from stavudine to tenofovir (after 12 weeks).

Smoking Cessation

The prevalence of cigarette smoking among HIV-infected patients is higher compared to the general population [79, 80]. Louie et al. [81] reported that smoking-associated pulmonary diseases such as obstructive lung disease, chronic bronchitis, and bronchiectasis were increased in the HIV-infected population. Lung cancer was the most common cause of death from non-AIDS-defining

malignancies (11%) followed by Hodgkin's disease (5%), hepatocellular cancer (4%), and anal cancer (3%). Smoking cessation should be a priority for HIV-infected patients and physicians, integrated into a global risk reduction approach (dyslipidemia, diabetes mellitus, overweight, inactivity) to prevent future coronary events.

Exercise Training and Healthy Diet

Exercise has been shown to improve strength, cardiovascular function, psychological status, and reduce cardiovascular disease in the general population [82]. Exercise training also reduces total and abdominal fat. These changes in body composition mediate improvements in insulin sensitivity and blood pressure and may improve endothelial vasodilator function [83]. Encouraging lifestyle changes should be done as soon as possible, as HIV infection becomes a chronic disease. Various clinical interventions, including diet and exercise [84–86], switching antiretroviral agents, use of lipid-lowering and insulin-sensitizing agents, recombinant human growth hormone therapy, and plastic surgery, are under investigation in the treatment of morphologic changes (lipodystrophy syndrome).

Nutrition deficiencies (selenium, vitamin B_{12}, carnitine, growth and thyroid hormones) should be sought because they are easily treatable and because of their great impact on ventricular function [87, 88]. Hyperhomocysteinemia is associated with an increased risk of heart and vascular diseases [89]. Vilaseca et al. [90] demonstrated that HIV-infected children undergoing protease inhibitor treatment have higher homocysteine concentrations and lower folate values compared with patients on other antiretroviral therapies, as in adults [91, 92]. In case of hyperhomocysteinemia, folic acid supplements should be prescribed.

Diabetes Mellitus

New-onset diabetes mellitus affects an increasing number of HIV-infected patients (5%–10%) [93–95]. Impaired glucose tolerance and early insulin resistance are more frequent (10%–25%) in HIV-infected patients mostly treated with HAART including protease inhibitors [95]. Insulin resistance is often accompanied by hyperinsulinemia and may predispose patients to atherosclerosis. Henry et al. [96] demonstrated that impaired fasting glucose (fasting plasma glucose 6.1–6.9 mmol/l) in seronegative patients was associated with the level of systolic blood pressure and could help predict cardiovascular mortality. Metformin increases the sensitivity of peripheral tissues to insulin and should be recommended for the treatment of type 2 diabetes mellitus in HIV-infected patients with documented insulin-resistance syndrome [93]. No cases of lactic acidosis have been reported in serial trials [97, 98], but warranted a regular follow-up.

New oral antidiabetic drugs such as thiazolidinediones (pioglitazone, rosiglitazone) could be promising therapy for lipodystrophy, metabolic syndrome, and insulin resistance in HIV-infected patients [99, 100]. Thiazolidinediones reduce insulin resistance not only in type 2 diabetes but also in non-diabetic conditions associated with insulin resistance such as obesity. Recently, Hadigan et al. [101] demonstrated positive effects of rosiglitazone on lipoatrophy, insulin sensitivity, and metabolic indices, including adiponectin levels, in HIV-infected patients with lipoatrophy and insulin resistance (see the chapter by J. Capeau in this volume).

Systemic Hypertension

Few data are available regarding the frequency and mechanisms of hypertension in HIV-infected patients. Sattler et al. [102] showed that hypertension was more frequent in HIV-infected patients with lipodystrophy compared with HIV-infected patients without (74% vs. 48%, $p=0.01$). In a recent cohort of 214 HIV-1-infected patients (Frankfurt) [103], the prevalence of systemic hypertension was 29%. As in the general population, hypertensive subjects were older (49.1±11.1 vs. 39.0±8.1 years; $p<0.0001$) and the waist-to-hip ratio was higher than in normotensive individuals (0.99±0.07 vs. 0.93±0.08; $p<0.0001$). Hypertension was associated

with a much higher frequency of persistent proteinuria (41.1% vs. 2.8%; $p<0.001$), CHD (16.1% vs. 1.3%; $p<0.0001$), and myocardial infarction (8.1% vs. 0.7%; $p<0.005$), whereas most cardiovascular risk factors were similar in both groups.

Physicians should follow the current guidelines recommended for the general population by the Joint National Committee (JNC VII) [104] when treating hypertension in HIV-infected patients.

Secondary Prevention

Acute coronary syndromes in HIV-infected patients with or without ST-segment elevation should be managed as recommended by international guidelines for the general population [105–108]. There are no specific recommendations for acute coronary syndrome occurring in HIV-infected patients concerning thrombolytic, antithrombotic therapy, and coronary revascularization modalities. Medical treatment should include β-blockers, aspirin, ACE inhibitors, lipid-lowering therapy, and management of other cardiovascular risk factors (tobacco, diabetes mellitus, hypertension, obesity). Coronary revascularization modalities (PCI, stenting, and coronary artery bypass graft) have not been specifically studied in HIV-infected patients. Few series of coronary artery bypass graft, valve replacement [109], and PCI [22, 59–61] have been reported in HIV-infected patients. Large controlled trials of coronary revascularization after acute coronary syndromes in HIV-infected patients in comparison with non-HIV-infected patients are needed to develop specific recommendations. Concerning heart transplantation in HIV-infected patients with severe left ventricular dysfunction, few data are available [110–112]. Cardiopulmonary bypass has no immunosuppressive effects and does not worsen the prognosis of HIV disease.

Conclusion

Multifactorial causes of atherosclerosis and thrombosis are involved in HIV-infected patients, which might be accelerated with HAART including protease inhibitors. Further experimental and clinical studies are required to understand whether this accumulation of cardiovascular risk factors promotes acute coronary syndrome so as to develop appropriate new strategies for HIV patients. It is necessary to focus on primary preventive campaigns, mainly against tobacco addiction and hyperlipidemia, in order to reduce the frequency of acute coronary syndromes in this population. Although HAART increases the risk of metabolic complications, this does not outweigh the benefits in terms of survival.

References

1. Klein D, Hurley LB, Quesenberry CP J, Sidney S (2002) Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? J Acquir Immune Defic Synd 30:471-477
2. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D and the Clinical Epidemiology Group from the French Hospital Database (2003) Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. AIDS 17:2479-2486
3. Friis-Moller N, Sabin CA, Weber R, et al (2003) Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med 349:1993-2003
4. Holmberg SD, Hamburger ME, Moorman AC et al (2002) HIV Outpatient Study (HOPS) investigators. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. Lancet 360:1747-1748
5. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA (2003) Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. N Engl J Med 348:702-710
6. Henry K, Melroe H, Huebsch J et al (1998) Severe premature coronary artery disease with protease inhibitors. Lancet 351:1328
7. Berhens G, Schmidt H, Meyer D, Stoll M, Schmidt RE (1998) Vascular complications associated with use of HIV protease inhibitors. Lancet 351:1958
8. Gallet B, Pulik M, Genet P, Chedin P, Hiltgen M (1998) Vascular complications associated with use of HIV protease inhibitors. Lancet 351:1958-1959
9. Vittecoq D, Escaut L, Monsuez JJ (1998) Vascular complications associated with use of HIV protease inhibitors. Lancet 351:1959

10. Jutte A, Schwenk A, Franzen C et al (1999) Increasing morbidity from myocardial infarction during HIV protease inhibitor treatment? AIDS 13:1796-1797
11. Rickerts V, Brodt H-R, Staszewski S, Stille W (2000) Incidence of myocardial infarction in HIV-infected patients between 1983 and 1998: the Frankfurt HIV-cohort study. Eur J Med Res 5:329-333
12. Duong M, Cottin Y, Piroth L et al (2002) Exercise stress testing for detection of silent myocardial ischemia in human immunodeficiency virus-infected patients receiving antiretroviral therapy. Clin Infect Dis 34:523-528
13. Boccara F, Adda N, Rozenbaum W, Cohen A (2002) Acute coronary syndrome in HIV-infected patients. European Society of Cardiology, Berlin, September 2002. Europ Heart J vol 4, Abstr. Suppl. August 2002, abstract no. 3000, p 585
14. Barbaro G, Di Lorenzo G, Cirelli A et al (2003) An open-label, prospective, observational study of the incidence of coronary artery disease in patients with HIV infection receiving highly active antiretroviral therapy. Clin Ther 25:2405-2418
15. Bergersen BM, Sandvik L, Bruun JN, Tonstad S (2004) Elevated Framingham risk score in HIV-positive patients on highly active antiretroviral therapy: results from a Norwegian study of 721 subjects. Eur J Clin Microbiol Infect Dis 23:625-630
16. Neumann T, Woiwod T, Neumann A et al (2004) Cardiovascular risk factors and probability for cardiovascular events in HIV-infected patients – part III: age differences. Eur J Med Res 9:267-272
17. Hadigan C, Meigs JB, Wilson PW et al (2003) Prediction of coronary heart disease risk in HIV-infected patients with fat redistribution. Clin Infect Dis 36:909-916
18. Saves M, Chene G, Ducimetiere P et al (2003) French WHO MONICA Project and the APROCO (ANRS EP11) Study Group. Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. Clin Infect Dis 37:292-298
19. Doughty M, Mehta R, Bruckman D et al (2002) Acute myocardial infarction in the young – The University of Michigan experience. Am Heart J 143:56-62
20. Akosah KO, Cerniglia RM, Havlik P et al (2001) Myocardial infarction in young adults with low-density lipoprotein cholesterol levels < or = 100 mg/dL: clinical profile and 1-year outcomes. Chest 120:1953-1958
21. Fournier JA, Sanchez-Gonzalez A, Quero J et al (1997) Normal angiogram after myocardial infarction in young patients: a prospective clinical angiographic and long-term follow-up study. Int J Cardiol 60:281-287
22. Boccara F, Teiger E, Cohen A (2002) Stent implantation for acute left main coronary artery occlusion in an HIV-infected patient on protease inhibitors. J Invasive Cardiol 14:343-346
23. d'Arminio A, Sabin CA, Phillis AN et al (2004) Writing Committee of the DAD Study Group. Cardio- and cerebrovascular events in HIV-infected persons. AIDS 18:1811-1817
24. Carr A, Samaras K, Burton S et al (1998) A syndrome of peripheral lipodystrohy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 12:F51-8
25. Carr A, Samaras K, Chisholm DJ, Cooper DA (1998) Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. Lancet 352:1881-1883
26. Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA (1999) Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. Lancet 353:2093-2099
27. Piériard D, Telenti A, Sudre P et al (1999) Atherogenic dyslipidemia in HIV-infected individuals treated with protease inhibitors. The Swiss HIV Cohort Study. Circulation 100:700-705
28. Fichtenbaum CJ, Gerber JG, Rosenkranz SL et al (2002) NIAID AIDS Clinical Trials Group. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. AIDS 16:569-577
29. Dube MP, Stein JH, Aberg JA et al (2003) Adult AIDS Clinical Trials Group Cardiovascular Subcommittee. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. Clin Infect Dis 37:613-627
30. Stein JH, Merwood MA, Bellehumeur JL et al (2004) Effects of pravastatin on lipoproteins and endothelial function in patients receiving human immunodeficiency virus protease inhibitors. Am Heart J 147:713
31. Toth PP (2004) High-density lipoprotein and cardiovascular risk. Circulation 109:1809-1812
32. Shah PK, Amin J (1992) Low high-density lipoprotein level is associated with increased restenosis rate after coronary angioplasty. Circulation 85:1279-1285
33. Khan NA, Di Cello F, Nath A, Kim KS (2003) Human

immunodeficiency virus type 1 Tat-mediated cytotoxicity of human brain microvascular endothelial cells. J Neurovirol 9:584-593
34. Schecter AD, Berman AB, Yi L, Mosoian A et al (2001) HIV envelope gp120 activates human arterial smooth muscle cells. Proc Natl Acad Sci 98:10142-10147
35. Barbaro G (2002) Cardiovascular manifestations of HIV infection. Circulation 106:1420-1425
36. de Larranaga GF, Petroni A, Deluchi G, Alonso BS, Benetucci JA (2003) Viral load and disease progression as responsible for endothelial activation and/or injury in human immunodeficiency virus-1-infected patients. Blood Coagul Fibrinolysis 14:15-18
37. Stins MF, Pearce D, Di Cello F, Erdreich-Epstein A, Pardo CA, Sik Kim K (2003) Induction of intercellular adhesion molecule-1 on human brain endothelial cells by HIV-1 gp120: role of CD4 and chemokine coreceptors. Lab Invest 83:1787-1798
38. Stein JH, Klein MA, Bellehumeur JL et al (2001) Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction. Circulation 104:257-262
39. Hulgan T, Morrow J, D'Aquila RT et al (2003) Oxidant stress is increased during treatment of human immunodeficiency virus infection. Clin Infect Dis 37:1711-1717
40. de Gaetano Donati K, Rabagliati R, Iacoviello L, Cauda R (2004) HIV infection, HAART, and endothelial adhesion molecules: current perspectives. Lancet Infect Dis 4:213-222
41. Wu RF, Gu Y, Xu YC, Mitola S, Bussolino F, Terada LS (2004) Human immunodeficiency virus type 1 Tat regulates endothelial cell actin cytoskeletal dynamics through PAK1 activation and oxidant production. J Virol 78:779-789
42. Paladugu R, Fu W, Conklin BS et al (2003) HIV Tat protein causes endothelial dysfunction in porcine coronary arteries. J Vasc Surg 38:549-555
43. Zandman-Goddard G, Shoenfeld Y (2002) HIV and autoimmunity. Autoimmun Rev 1:329-337
44. Karmochkine M, Ankri A, Calvez V, Bonmarchant M, Coutellier A, Herson S (1998) Plasma hypercoagulability is correlated to plasma HIV load. Thromb Haemost 80:208-209
45. Escaut L, Monsuez JJ, Chironi G et al (2003) Coronary artery disease in HIV infected patients. Intensive Care Med 29:969-973
46. David MH, Hornung R, Fichtenbaum CJ (2002) Ischemic cardiovascular disease in persons with human immunodeficiency virus infection. Clin Infect Dis 34:98-102
47. Barbaro G, Barbarini G, Pellicelli AM (2001) HIV-associated coronary arteritis in a patient with fatal myocardial infarction. N Engl J Med 344:1799-1800
48. Tabib A, Leroux C, Mornex JF, Loire R (2000) Accelerated coronary atherosclerosis and arteriosclerosis in young human-immunodeficiency-virus-positive patients. Coron Artery Dis 11:41-46
49. Hsue PY, Lo JC, Franklin A et al (2004) Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. Circulation 109:1603-1608
50. Mercie P, Thiebaut R, Lavignolle V et al (2002) Evaluation of cardiovascular risk factors in HIV-1 infected patients using carotid intima-media thickness measurement. Ann Med 34:55-63
51. Depairon M, Chessex S, Sudre P et al (2001) Premature atherosclerosis in HIV-infected individuals – focus on protease inhibitor therapy. AIDS 15:329-334
52. Maggi P, Serio G, Epifani G et al (2000) Premature lesions of the carotid vessels in HIV-1-infected patients treated with protease inhibitors. AIDS 14:F123-128
53 . Seminari E, Pan A, Voltini G et al (2002) Assessment of atherosclerosis using carotid ultrasonography in a cohort of HIV-positive patients treated with protease inhibitors. Atherosclerosis 162:433-438
54. Acevedo M, Sprecher DL, Calabrese L et al (2002) Pilot study of coronary atherosclerotic risk and plaque burden in HIV patients: a call for cardiovascular prevention. Atherosclerosis 163:349-354
55. Talwani R, Falusi OM, Mendes de Leon CF et al (2002) Electron beam computed tomography for assessment of coronary artery disease in HIV-infected men receiving antiretroviral therapy. J Acquir Immune Defic Syndr 30:191-195
56. Meng Q, Lima JA, Lai H et al (2002) Coronary artery calcification, atherogenic lipid changes, and increased erythrocyte volume in black injection drug users infected with human immunodeficiency virus-1 treated with protease inhibitors. Am Heart J 144:642-648
57. Matetzky S, Domingo M, Kar S et al (2003) Acute myocardial infarction in human immunodeficiency virus-infected patients. Arch Intern Med 163:457-460
58. Hsue PY, Giri K, Erickson S et al (2004) Clinical features of acute coronary syndromes in patients with human immunodeficiency virus infection. Circulation 109:316-319
59. Ambrose JA, Gould RB, Kurian DC et al (2003) Frequency of and outcome of acute coronary syndromes in patients with human immunodeficiency virus infection. Am J Cardiol 92:301-303

60. Varriale P, Saravi G, Hernandez E, Carbon F (2004) Acute myocardial infarction in patients infected with human immunodeficiency virus. Am Heart J 147:55-59
61. Boccara F, Odi G, Teiger E, Di Angelantonio E, Cohen A, Barbarini G, Barbaro G, on behalf the French Italian Study on Coronary artery disease in AIDS patients (2004) Coronary revascularization in HIV-infected patients with coronary artery disease: a multicenter case-control study. 11th CROI (Conference on Retrovirus and Opportunistic Infections), Feb 2004, San Francisco, USA, poster no. 740
62. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P (2001) Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 286:180-187
63. Lauer MS (2002) Aspirin for primary prevention of coronay events. N Engl J Med 346:1468-1474
64. Preventive services task force (2002) Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. Ann Intern Med 136:157-160
65. Wood D, De Backer G, Faergeman O, Graham I, Mancia G, Pyorala K (1998) Prevention of coronary heart disease in clinical practice: recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention. Atherosclerosis 140:199-270
66. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (2001) Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (adults treatment panel III). JAMA 285:2486-2497
67. Fichtenbaum CJ, Gerber JG, Rosenkranz SL et al (2002) Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. AIDS 16:569-577
68. de Luis DA, Bachiller P, Aller R, Eiros Bouza J, Izaola O (2003) Pravastatin in hyperlipidemia secondary to HIV protease inhibitors without response to fenofibrate: a brief preliminary report. Nutrition 19:903-904
69. Benesic A, Zilly M, Kluge F et al (2004) Lipid lowering therapy with fluvastatin and pravastatin in patients with HIV infection and antiretroviral therapy: comparison of efficacy and interaction with indinavir. Infection 32:229-333
70. Palacios R, Santos J, Gonzalez M et al (2002) Efficacy and safety of atorvastatin in the treatment of hypercholesterolemia associated with antiretroviral therapy. J Acquir Immune Defic Syndr 30:536-537
71. Calza L, Manfredi R, Chiodo F (2002) Use of fibrates in the management of hyperlipidemia in HIV-infected patients receiving HAART. Infection 30:26-31
72. Henry K, Melroe H, Huebesch J, Hermundson J, Simpson J (1998) Atorvastatin and gemfibrozil for protease-inhibitor-related lipid abnormalities. Lancet 352:1031-1032
73. Thomas JC, Lopes-Virella MF, Del Bene VE et al (2000) Use of fenofibrate in the management of protease inhibitor-associated lipid abnormalities. Pharmacotherapy 20:727-734
74. Van der Valk M, Kastelein JJ, Murphy RL et al (2001) Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an anti-atherogenic lipid profile. AIDS 15:2407-2414
75. Negredo E, Ribalta J, Paredes R et al (2002) Reversal of atherogenic lipoprotein profile in HIV-1 infected patients with lipodystrophy after replacing protease inhibitors by nevirapine. AIDS 16:1383-1389
76. Bonnet F, Bonarek M, De Witte S, Beylot J, Morlat P (2002) Efavirenz-associated severe hyperlipidemia. Clin Infect Dis 3:776-777
77. Murphy RL, Smith WJ (2002) Switch studies: a review. HIV Med 3:146-155
78. Domingo P, Labarga P, Palacios R et al (2004) RECOVER Study Group. Improvement of dyslipidemia in patients switching from stavudine to tenofovir: preliminary results. AIDS 18:1475-1478
79. Niaura R, Shadel WG, Morrow K, Tashima K, Flanigan T, Abrams DB (2000) Human immunodeficiency virus infection, AIDS, and smoking cessation: the time is now. Clin Infect Dis 31:808-812
80. Stall RD, Greenwood GL, Acree M, Paul J, Coates TJ (1999) Cigarette smoking among gay and bisexual men. Am J Public Health 89:1875-1878
81. Louie JK, Hsu LC, Osmond DH, Katz MH, Schwarcz SK (2002) Trends in causes of death among persons with acquired immunodeficiency syndrome in the era of highly active antiretroviral therapy, San Francisco, 1994–1998. J Infect Dis 186:1023-1027
82. The Writing Group for the Activity Counseling Trial Research Group (2001) Effects of physical activity counseling in primary care : the Activity Counseling Trial: a randomized controlled trial. JAMA 286:677-687
83. Stewart KJ (2002) Exercise training and the cardiovascular consequences of type 2 diabetes and hypertension: plausible mechanisms for improving cardiovascular health. JAMA 288:1622-1631
84. Roubenoff R, Schmitz H, Bairos L et al (2002) Reduction of abdominal obesity in lipodystrophy associat-

ed with human immunodeficiency virus infection by means of diet and exercise: case report and proof of principle. Clin Infect Dis 34:390-393
85. Moyle G, Baldwin C, Phillpot M (2001) Managing metabolic disturbances and lipodystrophy: diet, exercise, and smoking advice. AIDS Read 11:589-592
86. Thoni GJ, Fedou C, Brun JF et al (2002) Reduction of fat accumulation and lipid disorders by individualized light aerobic training in human immunodeficiency virus infected patients with lipodystrophy and/or dyslipidemia. Diabetes Metab 28:397-404
87. Barbaro G, Fisher SD, Lipshultz SE (2001) Pathogenesis of HIV-associated cardiovascular complications. Lancet Infect Dis 1:115-124
88. Lewis W (2001) AIDS cardiomyopathy: physiological, molecular, and biochemical studies in the transgenic mouse. Ann N Y Acad Sci 946:46-56
89. Nakai K, Itoh C, Nakai K, Habano W, Gurwitz D (2001) Correlation between C677T MTHFR gene polymorphism, plasma homocysteine levels and the incidence of CAD. Am J Cardiovasc Drugs 1:353-361
90. Vilaseca MA, Sierra C, Colome C et al (2001) Hyperhomocysteinaemia and folate deficiency in human immunodeficiency virus-infected children. Eur J Clin Invest 31:992-998
91. Cohn JE (2001) Homocysteine, HIV, and heart disease. AIDS Treat News 370:5-6
92. Bernasconi E, Uhr M, Magenta L, Ranno A, Telenti A (2001) Swiss HIV Cohort Study. Homocysteinaemia in HIV-infected patients treated with highly active antiretroviral therapy. AIDS 15:1081-1082
93. Dube MP (2003) Disorders of glucose metabolism in patients infected with human immunodeficiency virus. Clin Infect Dis 31:1467-1475
94. Walli R, Herfort O, Michl GM et al (1998) Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1-infected patients. AIDS 12:F167-173
95. Gougeon ML, Penicaud L, Fromenty B, Leclercq P, Viard JP, Capeau J (2004) Adipocytes targets and actors in the pathogenesis of HIV-associated lipodystrophy and metabolic alterations. Antivir Ther 9:161-177
96. Henry P, Thomas F, Benetos A, Guize L (2002) Impaired fasting glucose, blood pressure and cardiovascular disease mortality. Hypertension 40:458-463
97. Hadigan C, Rabe J, Grinspoon S (2002) Sustained benefits of metformin therapy on markers of cardiovascular risk in human immunodeficiency virus-infected patients with fat redistribution and insulin resistance. J Clin Endocrinol Metab 87:4611-4615
98. Hadigan C, Corcoran C, Basgoz N, Davis B, Sax P, Grinspoon S (2000) Metformin in the treatment of HIV lipodystrophy syndrome: A randomized controlled trial. JAMA 284:472-477
99. Garg A (2004) Acquired and inherited lipodystrophies. N Engl J Med 350:1220-1234
100. Yki-Jarvinen H, Sutinen J, Silveira A et al (2003) Regulation of plasma PAI-1 concentrations in HAART-associated lipodystrophy during rosiglitazone therapy. Arterioscler Thromb Vasc Biol 23:688-694
101. Hadigan C, Yawetz S, Thomas A, Havers F, Sax PE, Grinspoon S (2004) Metabolic effects of rosiglitazone in HIV lipodystrophy: a randomized, controlled trial. Ann Intern Med 140:786-794
102. Sattler FR, Qian D, Louie S et al (2001) Elevated blood pressure in subjects with lipodystrophy. AIDS 15:2001-2010
103. Jung O, Bickel M, Ditting T et al (2004) Hypertension in HIV-1-infected patients and its impact on renal and cardiovascular integrity. Nephrol Dial Transplant 19:2250-2258
104. Chobanian AV, Bakris GL, Black HR et al (2003) National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 289:2560-2572
105. Braunwald E, Antman EM, Beasley JW et al (2002) ACC/AHA Guideline Update for the Management of Patients With Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction-2002: summary article: A Report of the American College of Cardiology/American Heart Association Task Force On Practice Guidelines (Committee on the Management of Patients With Unstable Angina). Circulation 106:1893-1900
106. Hamm CW, Bertrand M, Braunwald E (2001) Acute coronary syndrome without ST elevation: implementation of new guidelines. Lancet 358:1533-1538
107. Antman EM, Anbe DT, Armstrong PW et al (2004) American College of Cardiology; American Heart Association Task Force on Practice Guidelines; Canadian Cardiovascular Society. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 110:e82-292

108. Volberding PA, Murphy RL, Barbaro G et al (2003) The Pavia consensus statement. AIDS 17 [Suppl 1]:S170-179
109. Trachiotis GD, Alexander EP, Benator D, Gharagozloo F (2003) Cardiac surgery in patients infected with the human immunodeficiency virus. Ann Thorac Surg 76:1114-1118
110. Halpern SD, Ubel PA, Caplan AL (2002) Solid-organ transplantation in HIV-infected patients. N Engl J Med 347:284-287
111. Morgan JA, Bisleri G, Mancini DM (2003) Cardiac transplantation in an HIV-1-infected patient. N Engl J Med 349:1388-1389
112. Bisleri G, Morgan JA, Deng MC, Mancini DM, Oz MC (2003) Should HIV-positive recipients undergo heart transplantation? J Thorac Cardiovasc Surg 126:1639-1640

Cerebrovascular Disease in HIV-Infected Patients

A. Moulignier

Neurological complications of HIV-1 infection, due either to the immunosuppression (opportunistic infections and neoplasms) or the neurotropism of the virus, are common and add considerably to the morbidity and mortality of the infection. Their frequency varies according to the stage of the disease. They have been reported to represent 10%–15% of symptomatic primo-infection, and are the first manifestation of AIDS in 10%–20% of symptomatic HIV-1 infection cases. Their prevalence in clinical studies has been estimated to range from 40% to 70%, and a prospective study revealed that neurological findings were present in 90% of AIDS patients examined by a neurologist [1]. Some autopsy series showed brain lesions in up to 100% of patients [2, 3].

The incidence rate of HIV-1-associated neurological diseases has significantly decreased since the introduction of combined multitherapies, generally including a protease inhibitor (PI) and HAART (highly active antiretroviral therapy), and the widespread use of prophylactic medications for opportunistic infections [4]. From a neurological point of view, however, the success of HAART is tempered by the occurrence of numerous drug-related neurotoxic effects (neuropathies, seizures, mitochondrial myopathy, psychiatric disorders, etc.), the immune reconstitution's pathology, the sanctuary provided by the nervous system for lentiviruses, and the development of resistance mutations with subsequent decline in CD4 cell counts. The incidence of HIV-1-associated neurological complications may begin to rise again because HIV-1 infection is now becoming a chronic disease [4]. Uncommon types of brain infection and new forms of encephalopathy are arising [5] and questions are emerging about the development of some neurodegenerative diseases. For all these reasons, the nervous system is still the second most frequently affected organ in HIV infection [6].

Among neurological complications in HIV-1 infection, cerebrovascular events were described long before the HAART era [7]. Yet, little is known about their real frequency and their specific etiologies [2, 8]. Several methodological limitations in the published literature have been noted, including the definition of stroke, the unclear identification of etiologies and the potential confounders, and the small sample size of the studies. Moreover, with longer-term survival, especially in Western countries, HIV-1-infected patients are now of middle age or older and therefore at higher risk for cerebrovascular diseases whatever the cause.

Epidemiology

The occurrence of cerebrovascular events, either ischemic or hemorrhagic, was recognized as early as 1983 in HIV-1 infection, before any antiretroviral therapy was available [7]. Ischemic strokes are usually more frequent than intracerebral hemorrhages, roughly in a proportion of 2/3–1/3 in several series [9], but a 50% ratio has also been reported [10]. Both types of stroke are frequently asymptomatic and associated with opportunistic infections or tumors [9].

Although studies have often reached conflicting conclusions, there is evidence for an increased general risk of cerebrovascular events during HIV-1 infection. As early as 1988, a large study of AIDS patients found that 1.6% of the subjects had cerebrovascular complications [11]. A population-based study conducted in the USA before the HAART era showed that AIDS was strongly associated with both ischemic stroke and intracerebral

hemorrhage, with a similar incidence rate of 0.2% per year [10]. After exclusion of cases with AIDS-related medical conditions or other concomitant etiologies for stroke, the adjusted relative risk was still high: 10.4 for both types of stroke (95% confidence interval, 4.9–22.0) and 9.1 for cerebral infarction (95% confidence interval, 3.4–24.6) [10]. A European study including patients treated with HAART found the same annual incidence rate for transient ischemic accident (TIA) or ischemic stroke (0.216%), five times higher than in the non-HIV-infected population of the same age and country [12]. By contrast, there was no significant overall increase in the stroke rate in HIV-1-infected patients as compared to noninfected subjects in an African-population-based case-control retrospective study performed in South Africa [13]. There was, however, a higher rate of large-vessel cryptogenic strokes in the HIV population (91%) than in age- and sex-matched HIV-seronegative control subjects (36%), suggesting a possible intrinsic predisposition to stroke among HIV-infected patients [10, 13]. Recent results from the DAD (Data collection on Adverse events of anti-HIV Drugs) study, involving over 36,145 person–years of follow-up, confirm that combination antiretroviral treatment increases the risk of cardio- and cerebrovascular disease [14]. The incidence of first cardio- and cerebrovascular events was 5.7 per 1,000 person–years and increased with longer exposure to antiretroviral treatment (relative risk per year of exposure=1.26) above that which can be explained by increasing age. This study, however, had insufficient statistical power to determine whether PIs and non-nucleoside reverse transcriptase inhibitors were associated with the same vascular risk.

The majority of available clinical and autopsy series were performed before the HAART era. Nonetheless, combined therapies with PIs do not seem to modify the incidence of stroke. No significant association was found between the use of any class of antiretroviral agent and the incidence of cerebrovascular events in a recent retrospective study [15]. The incidence of cerebrovascular accidents was not different between patients receiving PIs and those not receiving PIs [16]. No difference in the incidence rate of stroke before and after the introduction of HAART was observed in the series of Evers et al. [12], but the sample was too small to draw firm conclusions. The atherogenic metabolic side effects of HAART are discussed further.

The prevalence of cerebral infarction varies in clinical series from 0.3% to 6% [7, 17–21], and in autopsy series from 2% to 34% [9, 22–29]. In radiological series it has been reported to be 18% [30]. Engstrom et al. [21] retrospectively identified 12 cases of ischemic stroke among 1,600 AIDS patients studied over a period of 5 years. The annual risk of ischemic stroke of these patients (0.75%) was higher than that expected (0.010%–0.034%) in the general population younger than 45 years of age [31–33]. In a retrospective case-control study [34], HIV-1 infection was particularly associated with the occurrence of ischemic stroke (odds ratio, 3.4; 95% confidence interval, 1.1–8.9; p=0.03) after adjustment for several cerebrovascular risk factors. But this association was no longer statistically significant if cases with meningitis and protein S deficiency were excluded, suggesting that the excess risk of stroke in HIV-1 patients could be mediated by these two mechanisms. In a cohort study performed over a 9-year period (1993–2001), 15 patients were diagnosed with TIA (n=6) or ischemic stroke (n=9) out of 772 HIV-1-infected patients, representing a total prevalence rate of 1.9% (1.2% for ischemic stroke only) whatever the age [12]. The prevalence for juvenile ischemic strokes occurring under the age of 46 years was 1.6%, higher than in the HIV-negative population [12]. The stroke patients were older, had a lower CD4 cell count, and were in more advanced stages of the disease than infected patients without stroke. The prevalence of ischemic cerebrovascular events according to the CDC classification increased with the stage of the disease: 0.6% for stage A, 1.1% for stage B, and 3.2% for stage C [12]. However, Bajwa et al. [35] did not find differences between asymptomatic, AIDS-related-complex, or AIDS patients.

The prevalence of TIA is about 0.8%–0.9% [11, 21, 36], and the annual incidence in a prospective study reached 0.8% in HIV-1-infected patients versus 0.4% in noninfected individuals [37]. Whether these attacks are truly ischemic is unknown and transient neurological deficits (TNDs) is a better

definition. A local vasospasm comparable to migrainous aura is also evoked [38]. The differential diagnosis of focal TND includes a variety of nonvascular causes such as toxoplasmic abscess, primary cerebral lymphoma, and cryptococcal and cytomegalovirus infection [37, 39]. Recurrent TNDs are usually described in late stages of HIV-1 infection and have been associated with AIDS dementia complex [37]. They can, however, occur in primary infection and can be associated with a high viral load [40]. Brain infarction rarely follows TND. Only 2 of 27 patients progressed to cerebral infraction in the series of Brew and Miller [37] and none in the series of Baily and Mandal [36].

It is disputed whether hemorrhagic strokes are more frequent in the HIV-1-infected population [9, 34], but some authors have suggested that could be the case [10, 41]. A recently published study [10] has indeed demonstrated an adjusted relative risk of 25.5 for intracerebral hemorrhage (95% confidence interval, 11.2–58.0). Moreover, the increased hepatic involvement and longer survival in HIV-1-infected patients could be responsible for prolonged hemostatic perturbations and consequently cerebral hemorrhages.

Ischemic Cerebrovascular Events

Clinicopathological Aspects

There is no peculiar clinical presentation of HIV-1-related strokes [8, 21], although they are usually asymptomatic [25]. Hemiparesis, hemiplegia, and hemianesthesia are the most common presenting signs. Encephalopathy seems more common in cerebral infarction [21], whereas headache, language disturbance, and abnormal vision are more common in TND [21, 37]. A transient chorea has exceptionally been reported as a TND [42]. TNDs can be isolated [37, 40, 43] but are more frequently recurrent [36, 38]. Their association with PIs is controversial [44]. Although rarely reported as the presenting manifestation of HIV infection [45, 46], stroke was the first manifestation of HIV-1 in up to 50% of African patients described by Mochan et al. [46]. Infarcts are usually lacunar rather than infarcts in large-vessel territories [8, 9, 25]. Yet, in a prospective clinical study of black heterosexual nonintravenous drug users, 61% of ischemic strokes were large-vessel infarcts with cortical involvement and only 39% were small-vessel infarcts with subcortical involvement [46]. These findings have also been observed in another black population cohort [13]. Autopsy series confirm, however, that infarcts are usually small, located in the basal ganglia or the thalamus and the deep white matter, more rarely in the brain stem or the cerebellum, and frequently multiple [25]. Occlusion of large vessels seems to be the exception [13, 41, 46].

Mechanisms of Ischemic Stroke

The exact distribution of the different causes of strokes in HIV-1 infection cannot be determined because a thorough exploration has not always been performed in the published series. However, two causes emerge: cardioembolism and vasculitis [8] (see Table 1).

Cardioembolism

Cardiac disease may be found in as many as 50% of AIDS patients [47], and is regarded as the main cause of embolic stroke (Fig. 1) in HIV-1-infected individuals [27]. It includes viral myocarditis, bacterial and nonbacterial (marantic) endocarditis (both with and without history of intravenous drug abuse), dilated cardiomyopathy, mural thrombi, myxoid degeneration of the valves, and HIV myocarditis [7, 8, 11, 21, 27, 47]. Aortic root dilatation associated with left ventricular dilatation, increased viral load, and lower CD4 cell count, documented in HIV-1-infected children [48], has not been described in adults.

Opportunistic/Tumoral Vasculitis/Vasculopathy

Vasculitic changes in intracerebral vessels associated with ischemic strokes can be due to opportunistic infections as diverse as tuberculosis, cytomegalovirus, varicella-zoster virus (Fig. 2),

Table 1. Causes of ischemic stroke in HIV-infected patients

Cardioembolism
Infectious and noninfectious endocarditis
Cardiomyopathy
HIV myocarditis
Myxoid valvular degeneration
Arrhythmias
Mural thrombi
Intra-atrial septal defect
Patent foramen ovale
Hematological
Protein S deficiency
Antiphospholipid antibodies
Disseminated intravascular coagulation
Neoplasm
Hyperviscosity syndrome
Vasculitis
Opportunistic infections
Aspergillosis
Candidiasis
Cytomegalovirus
Cryptococcosis
Herpes simplex virus
Mucormycosis
Syphilis
Toxoplasmosis
Trypanosomiasis
Tuberculosis
Varicella-zoster virus
Neoplasm
Non-Hodgkin's lymphoma
HIV-related vasculitis
HIV itself
Immune reconstitution
Premature atherosclerosis with protease inhibitors
Dyslipidemia
Insulin resistance
Endothelial dysfunction
Hyperhomocysteinemia
Drugs (especially cocaine and heroin)
Cryptogenic

herpes simplex virus, syphilis, cryptococcosis, candidiasis, aspergillosis, mucormycosis, coccidioidomycosis, and trypanosomiasis (reviewed in [8, 28]). Several cases of lymphomatoid granulomatosis and malignant lymphoma have also been associated with infarcts [8, 28, 49]. The frequency of nervous system opportunistic infections and neoplasms has dramatically decreased with the current use of combined multitherapies in Western countries, and the actual incidence of stroke due to these etiologies is most likely lower today.

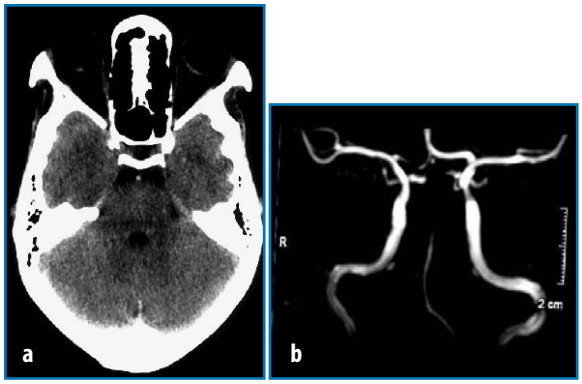


Fig. 1a, b. Cardioembolic acute basilar artery occlusion. **a** Noncontrast CT scan shows a spontaneous hyperdensity of the basilar artery. **b** MR angiogram shows the acute basilar artery occlusion

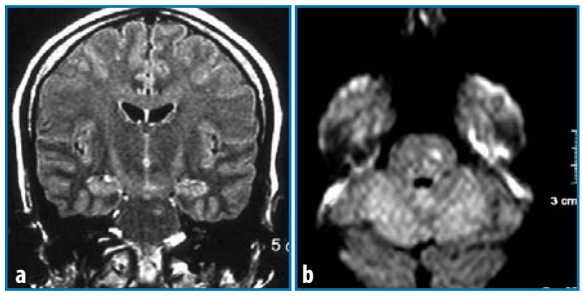


Fig. 2a, b. Varicella-zoster virus-related lacunar infarct in the pons. **a** Fluid-attenuated inversion recovery MR image obtained in the coronal plane shows a left infarct in the pons. **b** Diffusion-weighted MR image shows a recent ischemic stroke in the pons

HIV-Related Vasculitis/Vasculopathy

The frequent formation of cotton-wool spots in HIV-1-infected patients' eyes is ascribed to vasculitis-induced ischemic injury [50]. Indeed, in some cases, HIV-1 itself appears to be the cause of vasculitis [12, 30, 51–53]. As part of the immunodepression caused by the virus, a granulomatous inflammation involving small arteries and veins of the brain surface and leptomeninges, termed primary angiitis of the central nervous system (CNS), is a rare vasculitis (less than 25 cases reported,

principally reviewed in [53]) usually associated with high mortality [53], although a benign course has been described [43]. Moreover, two patients in the series of Evers et al. [12] had fluctuating intracranial stenosis which resolved within months, suggesting an inflammatory origin. It has been reported once that HIV-1 vasculitis could principally concern the cerebral posterior circulation [54]. The pathogenesis of primary angiitis of the CNS is speculative and mechanisms such as infection of endothelial cells by HIV-1, increased deposition of circulating immune complexes, and impaired regulation of cytokines and adhesion molecules have been proposed [55]. For others, cerebral vasculitis in the absence of infections or tumors is controversial [29]. Immune reconstitution promoted by HAART may exceptionally induce cerebral vasculitis (Fig. 3) in HIV-infected patients [56, 57].

Evidence supports the occurrence of a vasculopathy involving the CNS small vessels in HIV-1-infected patients free of risk factors for these vascular changes [25]. The autopsy series of the Edinburgh HIV Cohort revealed the presence of an asymptomatic vasculopathy characterized by small-vessel wall thickening, perivascular space dilatation, rarefaction and pigment deposition with vessel wall mineralization, and occasional perivascular inflammatory cell infiltrates without evidence of vasculitis [8, 29]. These patients were young (range 22–47 years) and free of vascular risk factors, although 48% of them were intravenous drug users. Features

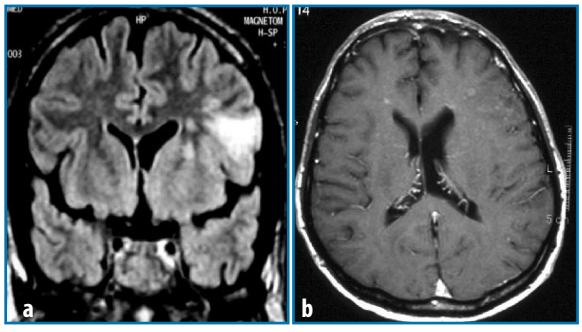


Fig. 3a, b. Immune reconstitution vasculitis confirmed by brain biopsy. **a** Fluid-attenuated inversion recovery MR image obtained in the coronal plane shows an infarct in the left middle cerebral artery territory. **b** Gadolinium-enhanced T1-weighted MR image obtained in the axial plane shows punctiform bilateral enhancement

of this microvasculopathy are similar to those observed in the brains of non-HIV aging patients with high blood pressure or diabetes mellitus [29]. Cranial nerve mononeuritis (left trochlear nerve palsy) and HIV-1 microangiopathy have been described [57]. Calcification of the vessel wall and calcium deposits occurred less often in adults than in children [25].

The alteration of the cerebral microvascularization in HIV-1-infected patients induces disturbed vasoreactivity, as demonstrated by reduced baseline cerebral flow and decreased cerebrovascular reserve capacity in response to acetazolamide challenge [59]. Abnormalities of cerebral perfusion have also been documented in the early stages of the infection and in asymptomatic HIV-1-infected patients [60]. Transcranial Doppler imaging has been used to monitor the progression of a reversible form of symptomatic cerebral vasospasm observed in two HIV-1-infected patients with presumed underlying HIV-related vasculopathy [43]. Vasoreactivity was confined to small cerebral arterioles, the same vessels showing pathologic changes in the autopsy series of Connor et al. [29]. These disturbances may represent a predisposing factor for the development of cerebral microinfarcts.

Increasingly, severe treatment-associated metabolic side effects have been observed with combined antiretroviral therapy, among them dyslipidemia, insulin resistance, and overt diabetes mellitus, which are well-known risk factors for cardiovascular disease. The results of the DAD study support the hypothesis that early atherosclerosis is a side effect of combined antiretroviral therapies [14]. In a recent review [61], 88% of studies measuring carotid intima thickness or atherosclerotic lesions reported worsening of these conditions in association with PIs. An increased prevalence of premature carotid atherosclerosis is observed using ultrasonography in HIV-1-infected patients treated [62] or not treated [63] with PI-containing regimens. In the latter study, the presence of atherosclerotic plaques was not associated with the use of PIs, but rather with classic vascular risk factors, especially smoking. Carotid intima-media thickness appears a stronger predictor of incident stroke than carotid plaque [64], and arterial intima-media thickness per se is an important deter-

minant of vascular disease in young HIV-negative individuals. This risk must be evaluated in HIV-1-positive patients, because the effectiveness of medical therapy such as antiplatelet agents or anticoagulants in the setting of HIV-associated vasculopathy is unknown.

Hematological Disorders

Elevated levels of antiphospholipid IgG antibodies occur frequently in patients with HIV-1 infection and AIDS, but the clinical relevance of this remains uncertain. Indeed, the role of these antibodies in the pathogenesis of stroke in HIV-1/AIDS patients is not understood [9], and their importance as a cardiovascular risk factor is even controversial in noninfected patients [65].

A frequent prothrombotic state in HIV-1-infected patients is protein S deficiency [34, 37, 46], also involved in ischemic stroke in noninfected individuals. However, its role in predisposing HIV-1-infected patients to cerebral infarction is not well established [34, 66]. A single retrospective case-control study showed a significant association of protein S deficiency in HIV-1-positive stroke patients compared with HIV-negative stroke patients [34]. A high prevalence of IgG anticardiolipin antibodies and protein S deficiency was also reported in TND [37].

Disseminated intravascular coagulation [22, 23, 27] and hyperviscosity related to polyclonal hypergammaglobulinemia [67] have also been documented in rare cases.

Drugs

Associations have been reported between over-the-counter prescription and illicit drugs with sympathomimetic properties and cerebral infarction [68, 69]. Except for a few instances of vasculitis and pharmacologically induced focal vasospasm, the etiology of drug-related cerebrovascular accidents is often unclear. Other mechanisms are arrhythmias and foreign embolism from impurities. However, these mechanisms are not specific to HIV infection.

Unknown Mechanism

As in noninfected young individuals, the proportion of ischemic stroke whose causes remain unidentified despite complete investigations is high and varies from 24% to 40% in HIV-1-infected patients [8, 21, 35, 70]. However, a thorough exploration has not always been performed in published series.

Intracerebral, Subarachnoid Hemorrhages and Subdural Hematoma

Intracerebral hemorrhages are less frequent than ischemic strokes in the majority of published series (32% vs. 68% in [9]), but an equivalent ratio has also been reported [10]. Mainly localized in the sustentorial regions, their localizations are various, sometimes multiple. They could be asymptomatic if of small size [25], but mortality tends to be high. The most frequent causes (Table 2) are opportunistic diseases (notably toxoplasmosis, tuberculosis, cytomegalovirus, HSV-1), mycotic aneurysms (Fig. 4), lymphoma, thrombocythemia, and metastatic Kaposi's sarcoma [8, 9, 17, 27, 41, 71]. Risk factors like alcoholism, drug abuse (especially cocaine and crack, amphetamine, phenylpropanolamine, phencyclidine), high blood pressure, or hemophilia are sometimes found [8, 26, 35, 41, 72]. Cocaine-associated intracranial hemorrhages seem to be a consequence of the pharmacodynamic effect of cocaine and not of a cocaine-induced vasculopathy [73, 74]. Other occasion-

Table 2. Causes of intracerebral hemorrhage

Thrombocythemia
Autoimmune
Drug-induced
Disseminated intravascular coagulation
Hemophilia
Aneurysmal dilatation
Mycotic aneurysm
Vasculitis
Opportunistic infections
Drug-induced
Neoplasms
Aspergillosis
Metastatic Kaposi's sarcoma
Alcoholism

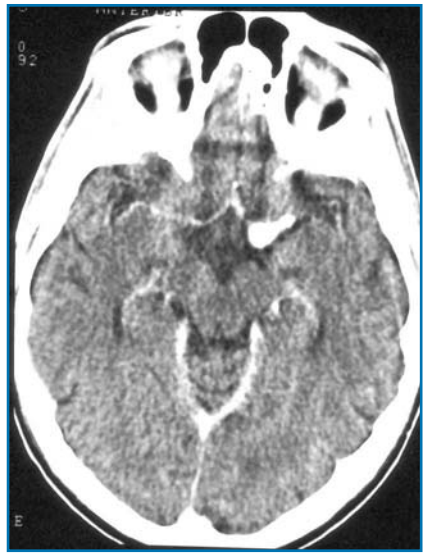


Fig. 4. Contrast-enhanced CT scan shows a mycotic aneurysm of the left middle cerebral artery

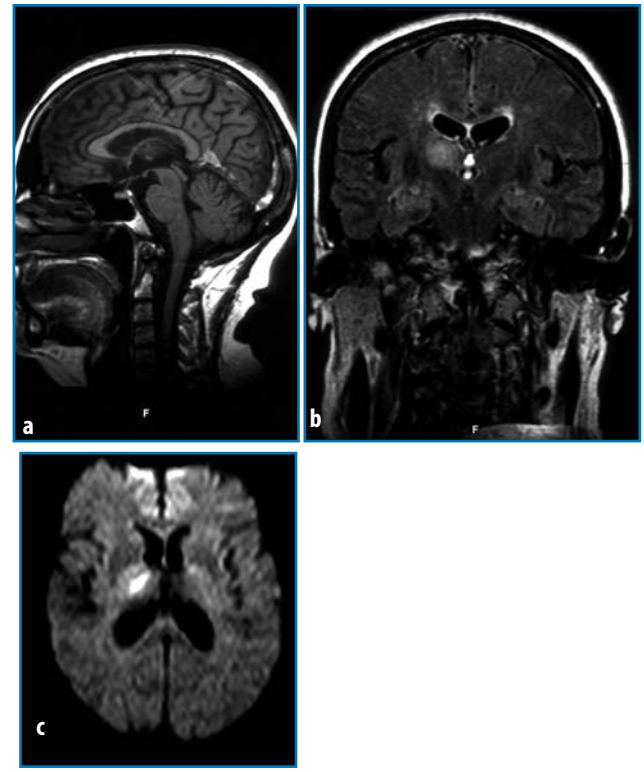


Fig. 5a–c. Cerebral venous thrombosis. **a** T1-weighted MR image obtained in the sagittal plane shows superior longitudinal and rectus sinus thrombosis. **b** Fluid-attenuated inversion recovery MR image obtained in the coronal plane shows a right thalamus venous infarct. **c** Diffusion-weighted MR image confirms a recent right thalamus venous infarct

al causes include disseminated intravascular coagulation, ruptured mycotic aneu-rysms, or disruption of congenital aneurysm [7, 8, 22, 23]. Subarachnoid hemorrhage and subdural hematoma in clinical [41] and autopsy series [9, 25] are more anecdotal. A subdural hematoma was reported in an HIV-1-infected patient with an HIV-associated encephalopathy and cerebral atrophy [75].

Cerebral Venous Thrombosis

Except for the involvement of small veins in the vasculitis process, cerebral venous thrombosis is very rare in HIV-1 infection (Fig. 5). One case of superior longitudinal sinus out of 118 patients is reported in the series of Jordan et al. [76]. The frequency is also probably underestimated because clinical and radiological diagnosis is difficult and cerebral sinuses were not always examined at autopsy. Causes include primary HIV-1 infection with concomitant cytomegalovirus infection [77], primary cerebral lymphoma, toxoplasmosis [78], cryptococcosis, protein S deficiency [79], dehydration, or cachexy [80]. Extensive intracranial sinus thrombosis was also the consequence of hypercoagulable state complicating AIDS-associated nephrotic syndrome [81].

Miscellaneous

Apart from illicit drugs, common medications have been involved in some cases of stroke in young persons. Listing them is beyond the purpose of this review. However, we want to emphasize the risk of drug interaction with antiretroviral therapies, even with a normal dosage. For instance, cerebral ergotism due to vasospasm has been described with a usual dose of ergotamine in association with ritonavir [82]. Such an association is then contraindicated. Allergic reaction with shock and low cerebral blood flow responsible for brain infarction has also been reported with rifampicine in an HIV-1-infected patient [83].

Common causes of stroke in non-HIV-infected individuals should be investigated also in HIV-1-infected patients, such as arterial dysplasia and carotid or vertebral artery dissection (Fig. 6).

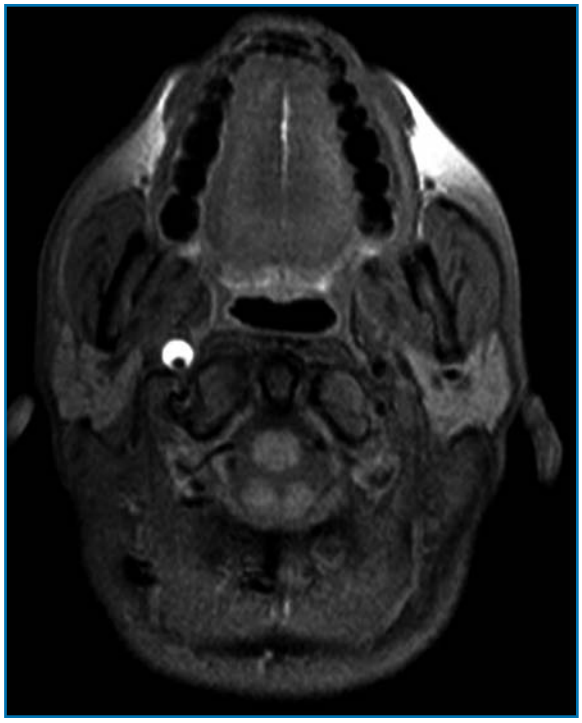


Fig. 6. MR image shows the parietal hematoma characteristic of a right carotid dissection

Ischemic Myelopathy

Ischemic myelopathy has been occasionally reported in HIV-1 infection. Brown-Sequard syndrome secondary to intravascular coagulation and ischemic lesions of the spinal cord [84] or varicella zoster virus-related necrotizing vasculitis of the CNS, predominating in the spinal cord [85, 86], have been observed.

Stroke in HIV-1-Infected Children

The clinical incidence of stroke in HIV-1-infected children has been estimated to be 1.3% in a longitudinal study [87] and 2.6% in a retrospective radiological study [88], higher than that in noninfected children [88]. At autopsy, cerebrovascular disease was documented in 25% of children, confirming that as in adults, most strokes in children are asymptomatic [87]. Both ischemic stroke and intracerebral hemorrhages have been described, and the reported mechanisms are similar to those reported in adults [8, 87, 88]. Strokes are principally associated with severe immunodepression and with vertically acquired HIV-1 infection or exposure to the virus in the neonatal period [87]. Cerebrovascular accident may be the initial presentation of HIV-1 infection [89]. Aneurysmal dilatation is more frequently observed in children than in adults, and infection of the parenchymal and leptomeningeal vessels by HIV-1 itself is one of the proposed mechanisms [90]. The presence of the gp41 transmembrane protein in the walls of aneurysms of the circle of Willis found by some investigators [87, 91], although not found by others [92], supports this hypothesis. Independently of exposure to antiretroviral therapy, the carotid arterial wall was also stiffer in HIV-infected children than in control subjects of the same age, but without concomitant increase of the intima-media thickness [93]. These results are of importance because antiretroviral therapy could counterbalance this possible HIV-induced vascular pathology [94]. Hyperhomocysteinemia has been observed in HIV-1-infected children on antiretroviral therapy, particularly when PIs are used [95]. Whether these children have an increased risk of premature stroke still remains unknown.

Conclusion

Some evidence shows that HIV-1 itself changes the predilection for stroke, whose causes are also related to the immunosuppression, to the risk behaviors for HIV-1 infection, and to the metabolic effects of combined therapies, especially those with PIs. In Western countries, the survival of patients infected with a neuro- and possibly vasculotropic virus has increased considerably. Moreover, with the aging of this population, the frequency of cerebrovascular diseases in the context of immunodepression and chronic viral infection may only increase in the near future. HIV-1-infected patients presenting with a suspicion of stroke must undergo an exhaustive work-up, because therapeutic decisions in that particular situation should be rapidly individualized. If HIV-1 can indeed participate in the pathogenetic role of cerebrovascular diseases, the good blood–brain barri-

er penetration of new antiretroviral therapies could be a suitable therapeutic approach for this process.

References

1. Malouf R, Jacquette G, Dobkin J, Brust JCM (1990) Neurologic disease in human immunodeficiency virus-infected drug abusers. Arch Neurol 47:1002-1007
2. Mréjen S, Moulignier A (2000) Atteintes neurologiques et infection par le VIH. Flammarion Médecine-Sciences, Paris
3. Moulignier A, Moulonguet A (2003) Complications neurologiques in VIH 2004. In: VIH 2004. Katalama C, Girard P-M, Pialoux G (eds) Doin, Reuil Malmaison, pp 95-123
4. Sacktor N (2002) The epidemiology of human immunodeficiency virus-associated neurological disease in the era of highly active antiretroviral therapy. J Neurovirol 8[Suppl 2]:115-121
5. Gray F, Chrétien F, Vallat-Decouvelaere AV, F Scaravilli (2003) The changing pattern in HIV neuropathology in the HAART era. J Neuropathol Exp Neurol 62:429-440
6. Jellinger KA, Setinek U, Drlicek M, Böhm G, Steurer A, Lintner F (2000) Neuropathology and general autopsy findings in AIDS during the last 15 years. Acta Neuropathol 100:213-220
7. Snider WD, Simpson DM, Nielsen S, Gold JWM, Metroka CE, Posner JB (1983) Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. Ann Neurol 14:403-418
8. Rabinstein AA (2003) Stroke in HIV-infected patients: a clinical perspective. Cerebrovasc Dis 15:37-44
9. Pinto AN (1996) AIDS and cerebrovascular disease. Stroke 27:538-543
10. Cole JW, Pinto AN, Hebel JR et al (2004) Acquired immunodeficiency syndrome and the risk of stroke. Stroke 35:51-56
11. Levy RM, Bredesen DE (1988) Central nervous system dysfunction in acquired immunodeficiency syndrome. J Acquir Immune Defic Syndr 1:41-64
12. Evers S, Nabavi D, Rahmann A, Heese C, Reichelt D, Husstedt IW (2003) Ischaemic cerebrovascular events in HIV Infection. A cohort study. Cerebrovasc Dis 15:199-205
13. Hoffmann M, Berger JR, Nath A, Rayens (2000) Cerebrovascular disease in young, HIV-infected black Africans in the KwaZulu natal province of South Africa. J Neurovirol 6:229-236
14. d'Arminio A, Sabin CA, Phillips AN et al (2004) Writing Committee of the DAD Study Group. Cardio- and cerebrovascular events in HIV-infected persons. AIDS 18:1811-1817
15. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA (2003) Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. N Engl J Med 348:702-710
16. Holmberg SD, Moorman AC, Williamson JM et al (2002) Protease inhibitors and cardiovascular outcomes in patients with HIV-1. Lancet 306:1747-1748
17. Levy RM, Bredesen DE, Rosenblum ML (1985) Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): experience at UCSF and review of the literature. J Neurosurg 62:475-495
18. Koppel BS, Wormser GP, Tuchman AJ, Maayan S, Hewlett D Jr, Daras M (1985) Central nervous system involvement in patients with acquired immunodeficiency syndrome (AIDS). Acta Neurol Scand 71:337-353
19. Berger JR, Moskowitz L, Fischl M, Kelley RE (1987) Neurological disease as the presenting manifestation of acquired immunodeficiency syndrome. South Med J 80:683-686
20. McArthur JC (1987) Neurological manifestations of AIDS. Medicine 66:407-437
21. Engstrom JW, Lowenstein DH, Bredesen DE (1989) Cerebral infarctions and transient neurologic deficits associated with acquired immunodeficiency syndrome. Am J Med 86:528-532
22. Moskowitz LB, Hensley GT, Chan JC, Gregorios J, Conley FK (1984) The neuropathology of acquired immunodeficiency syndrome. Arch Pathol Lab Med 108:867-872
23. Anders KH, Guerra WF, Tomiyasu U, Vinters HV (1986) The neuropathology of AIDS: UCLA experience and review. Am J Pathol 124:537-558
24. Rosemberg S, Lopes MBS, Tsanadis AM (1986) Neuropathology of acquired immunodeficiency syndrome: analysis of 22 Brazilian cases. J Neurol Sci 76:187-198
25. Mizusawa H, Hirano A, Llena SF, Shintaku M (1988) Cerebrovascular lesions of AIDS. Acta Neuropathol 76:451-457
26. Esiri MM, Scaravilli F, Millard PR, Harcourt-Webster JN (1989) Neuropathology of HIV infection in hemophiliacs: comparative necropsy study. Br Med J 299:1312-1315
27. Berger JR, Harris JO, Gragorios J, Norenberg M (1990) Cerebrovascular disease in AIDS: a case control study. AIDS 4:239-244

28. Kieburtz KD, Eskin TA, Ketonen L, Tuite MJ (1993) Opportunistic cerebral vasculopathy and stroke in patients with AIDS. Arch Neurol 50:430-432
29. Connor MD, Lammie GA, Bell JE, Warlow CP, Simmonds P, Brettle RD (2000) Cerebral infarction in adult AIDS patients: observations from the Edinburgh HIV Autopsy Cohort. Stroke 31:2117-2126
30. Gillams AR, Allen E, Hrieb K, Venna N, Craven D, Carter AP (1997) Cerebral infarction in patients with AIDS. Am J Neuroradiol 18:1581-1585
31. Grindal AB, Cohen RJ, Saul RF et al (1978) Cerebral infarction in young adults. Stroke 9:39-42
32. Kristensen B, Malm J, Carlberg B et al (1997) Epidemiology and etiology of ischemic stroke in young adults aged 18 to 44 years in northern Sweden. Stroke 28:1702-1709
33. Berger K, Schulte H, Stögbauer F, Assmann G (1998) Incidence and risk factors for stroke in an occupational cohort: the PROCAM study. Stroke 29:1562-1566
34. Qureshi AI, Janssen RS, Karon JM et al (1997) Human immunodeficiency virus infection and stroke in young patients. Arch Neurol 54:1150-1153
35. Bajwa ZH, Libman R, Lipton RB et al (1991) Cerebrovascular disease in patients with HIV. Neurology 41[Suppl 1]:S295
36. Baily GG, Mandal BK (1995) Recurrent transient neurological deficits in advanced HIV infection. AIDS 9:709-712
37. Brew BJ, Miller J (1996) Human immunodeficiency virus type 1-related transient neurological deficits. Am J Med 10:257-261
38. Rinaldi R, Manfredi R, Azzimondi G et al (1997) Recurrent 'migrainelike' episodes in patients with HIV disease. Headache 37:443-448
39. Klein JL, Price DA, Fisher M, Coker RJ (1996) Cytomegalovirus infection: a possible cause of recurrent transient neurological dysfunction in advanced HIV infection. AIDS 10:345-346
40. Card T, Wathen CG, Luzzi GA (1998) Primary HIV-1 infection presenting with transient neurological deficit. J Neurol Neurosurg Psychiatry 6:281-282
41. Atalaia A, Ferro J, Antunes F (1992) Stroke in an HIV-infected patient J Neurol 239:356-357
42. Bradley TP, Vas G (1997) HIV type-1-related transient neurologic deficits. Am J Med 103:250
43. Zunker P, Nabavi DG, Allardt A, Husstedt IW, Schuierer G (1996) HIV-associated stroke: report of two unusual cases. Stroke 27:1694-1696
44. Vittecoq D, Escaut L, Monsuez JJ (1998) Vascular complications associated with use of HIV protease inhibitors. Lancet 351:1959
45. Casado-Naranjo I, Toledo-Santos JA, Antolin-Rodriguez MA (1992) Ischemic stroke as the sole manifestation of HIV infection. Stroke 23:117-118
46. Mochan A, Modi M, Modi G (2003) Stroke in black South African HIV-positive patients. A prospective analysis. Stroke 34:10-15
47. Roldan EO, Moskowitz L, Hensley GT (1987) Pathology of the heart in acquired immunodeficiency syndrome. Arch Pathol Lab Med 111:943-946
48. Lai WW, Colan SD, Easley KA et al (2001) Dilation of the aortic root in children infected with human immunodeficiency virus type 1: The Prospective P2C2 HIV Multicenter Study. Am Heart J 141:661-670
49. Anders KH, Latta H, Chang BS, Tomiyasu U, Quddusi AS, Vinters HV (1989) Lymphomatoid granulomatosis and malignant lymphoma of the central nervous system in the acquired immunodeficiency syndrome. Hum Pathol 20:326-334
50. Geier SA, Perro C, Klauss V et al (1993) HIV-related ocular microangiopathic syndrome and cognitive functioning. J Acquir Immune Defic Syndr 6:252-258
51. Scaravilli F, Daniel SE, Harcourt-Webster N, Guiloff RJ (1989) Chronic basal meningitis and vasculitis in acquired immunodeficiency syndrome. A possible role for human immunodeficiency virus. Arch Pathol Lab Med 113:192-195
52. Yankner BA, Skolnik PR, Shoukimas GM, Gabuzda DH, Sobel RA, Ho DD (1986) Cerebral granulomatous angiitis associated with isolation of human T-lymphotropic virus type III from the central nervous system. Ann Neurol 20:362-364
53. Nogueras C, Sala M, Sasal M et al (2002) Recurrent stroke as a manifestation of primary angiitis of the central nervous system in a patient infected with human immunodeficiency virus. Arch Neurol 59:468-473
54. Evidente V, Yagnik P (1995) Stroke and stroke-like syndromes in the acquired immunodeficiency syndrome. Neurology 45 [Suppl 4]:A444
55. Brannagan TH (1997) Retroviral-associated vasculitis of the nervous system. Neurol Clin 15:927-944
56. van der Ven AJ, van Oostenbrugge RJ, Kubat B, Tervaert JW (2002) Cerebral vasculitis after initiation of antiretroviral therapy. AIDS 16:2362-2364
57. Dehais C, Moulignier A, Deschamps R, Mikol J, Thiébaut J-B, Gout O (2004) Immune reconstitution vasculitis in an HIV-infected patient (abstract). Program of the Journées de Neurologie de Langue Française, Strasbourg 2004
58. Moulignier A, Laloum L, Chauveau E, Gout O, Rozenbaum W (2003) HIV-1-related ischaemic trochlear nerve palsy. J Neurol 250:108-109

59. Brilla R, Nabavi DG, Schulte-Atedorneburg G et al (1999) Cerebral vasculopathy in HIV infection revealed by transcranial Doppler: a pilot study. Stroke 30:811-813
60. Tran Dinh YR, Mamo H, Cervoni J, Caulin C, Saimot AC (1990) Disturbances in the cerebral perfusion of human immune deficiency virus-1 seropositive asymptomatic subjects: a quantitative tomography study of 18 cases. J Nucl Med 31:1601-1607
61. Rhew DC, Bernal M, Aguilar D, Lloeje U, Goetz MB (2003) Association between protease inhibitor use and increased cardiovascular risk in patients infected with human immunodeficiency virus: a systematic review. Clin Infect Dis 31:959-972
62. Maggi P, Serio G, Epifani G et al (2000) Premature lesions of the carotid vessels in HIV-1-infected patients treated with protease inhibitors. AIDS 14:123-128
63. Depayron M, Chessex S, Sudre P et al (2001) Premature atherosclerosis in HIV-infected individuals. Focus on protease inhibitor therapy. AIDS 15:329-334
64. Hollander M, Hak AE, Koudstaal PJ et al (2003) Comparison between measures of atherosclerosis and risk of stroke: the Rotterdam Study. Stroke 34:2367-2372
65. Brey RL, Chapman J, Levine SR et al (2003) Stroke and the antiphospholipid syndrome: consensus meeting, Taormina 2002. Lupus 12:508-513
66. Hassell KL, Kressin DC, Neumann A, Ellison R, Marlar RA (1994) Correlation of antiphospholipid antibodies and protein S deficiency with thrombosis in HIV-infected men. Blood Coagul Fibrinolysis 5:455-462
67. Martin CM, Matlow AG, Chew E, Sutton D, Pruzanski W (1989) Hyperviscosity syndrome in a patient with acquired immunodeficiency syndrome. Arch Intern Med 149:1435-1436
68. Bruno A (2003) Cerebrovascular complications of alcohol and sympathomimetic drug abuse. Curr Neurol Neurosci Rep 3:40-45
69. Hanyu S, Ikeguchi K, Imai H, Imai N, Yoshida M (1995) Cerebral infarction associated with 3,4-methylenedioxymethamphetamine ('ecstasy') abuse. Eur Neurol 35:173
70. Strobel M, Lamaury I, Brouzes F et al (1995) Accidents vasculaires cérébraux et sida. Rev Med Interne 16:743-746
71. Moulignier A, Baudrimont M, Martin-Negrier ML, Mikol J, Lapresle C, Dupont B (1996) Fatal brain stem encephalitis due to herpes simplex virus type 1 in AIDS. J Neurol 243:491-493
72. Brust JC (2002) Neurologic complications of substance abuse. J Acquir Immune Defic Syndr 31 [Suppl 2]:S29-S34
73. Nolte KB, Brass LM, Fletterick CF (1996) Intracranial hemorrhage associated with cocaine abuse: a prospective autopsy study. Neurology 46:1291-1296
74. Buttner A, Mall G, Penning R, Sachs H, Weis S (2003) The neuropathology of cocaine abuse. Leg Med 5 [Suppl 1]:S240-242
75. Cohen JE, Eger K, Montero A, Israel Z (1998) Rapid spontaneous resolution of acute subdural hematoma and HIV related cerebral atrophy: case report. Surg Neurol 50:241-244
76. Jordan BD, Navia BA, Petito C, Cho ES, Price RW (1985) Neurological syndromes complicating AIDS. Front Radiat Ther Oncol 19:82-87
77. Meyohas MC, Roullet E, Rouzioux C et al (1989) Cerebral venous thrombosis and dual primary infection with human immunodeficiency virus and cytomegalovirus. J Neurol Neurosurg Psychiatry 52:1010-1011
78. Doberson MJ, Kleinschmidt-DeMasters BK (1994) Superior sagittal sinus thrombosis in a patient with acquired immunodeficiency syndrome. Arch Pathol Lab Med 118:844-846
79. Iranzo A, Domingo P, Cadafalch J, Sambeat MA (1998) Intracranial venous and dural sinus thrombosis due to protein S deficiency in a patient with AIDS. J Neurol Neurosurg Psychiatry 64:688
80. Berger JR, Harris JO, Gregorios J, Norenberg M (1990) Cerebrovascular disease in AIDS: a case control study. AIDS 4:239-244
81. Afsari K, Frank J, Vaksman Y, Nguyen TV (2003) Intracranial venous sinus thrombosis complicating AIDS-associated nephropathy. AIDS Read 13:143-148
82. Spiegel M, Schmidauer C, Kampfl A, Sarcletti M, Poewe W (2001) Cerebral ergotism under treatment with ergotamine and ritonavir. Neurology 57:743-744
83. Martinez E, Collazos J, Mayo J (1998) Shock and cerebral infarct after rifampicin re-exposure in a patient infected with human immunodeficiency virus. Clin Infect Dis 27:1329-1330
84. Fénelon G, Gray F, Scaravilli F et al (1991) Ischemic myelopathy secondary to disseminated intravascular coagulation in AIDS. J Neurol 238:51-54
85. Gray F, Belec L, Lescs MC (1994) Varicella-zoster virus infection of the central nervous system in the acquired immune deficiency syndrome. Brain 117:987-999
86. Kenyon LC, Dulaney E, Montone KT, Goldberg HI, Liu GT, Lavi R (1996) Varicella-zoster ventriculoencephalitis and spinal cord infarction in a patient

with AIDS. Acta Neuropathol 92:202-205
87. Park YD, Belman AL, Kim TS et al (1990) Stroke in pediatric acquired immunodeficiency syndrome. Ann Neurol 28:303-311
88. Patsalides AD, Wood LV, Atac GK, Sandifer E, Butman JA, Patronas NJ (2002) Cerebrovascular disease in HIV-infected pediatric patients: neuroimaging findings. Am J Roentgenol 179:999-1003
89. Visudtibhan A, Visudhiphan P, Chiemchanya S (1999) Stroke and seizures as the presenting signs of pediatric HIV infection. Pediatr Neurol 20:53-56
90. Husson RN, Saini R, Lewis LL, Butler KM, Patronas N, Pizzo PA (1992) Cerebral artery aneurysms in children infected with human immunodeficiency virus. J Pediatr 121:927-930
91. Kure K, Llena JF, Lyman WD et al (1991) Human immunodeficiency virus-1 infection of the nervous system: an autopsy study of 268 adult, pediatric, and fetal brains. Hum Pathol 22:700-710
92. Lang C, Jacobi G, Kreuz W et al (1992) Rapid development of giant aneurysm at the base of the brain in an 8-year-old boy with perinatal HIV infection. Acta Histochem Suppl 42:83-90
93. Bonnet D, Aggoun Y, Szezepanski I, Bellal N, Blanche S (2004) Arterial stiffness and endothelial dysfunction in HIV-infected children. AIDS 18:1037-1041
94. Mazzoni P, Chiriboga CA, Millar WS, Rogers A (2000) Intracerebral aneurysms in human immunodeficiency virus infection: case report and literature review. Pediatr Neurol 23:252-255
95. Vilaseca MA, Sierra C, Colome C et al (2001) Hyperhomocysteinaemia and folate deficiency in human immunodeficiency virus-infected children. Eur J Clin Invest 31:992-998

Peripheral Arterial Disease in HIV-Infected Patients: Atherosclerosis and Vasculitic Syndromes

P. Mercié, B. Le Bail, C. Cipriano

The various cardiovascular diseases observed in HIV-infected patients and widely described in the literature have been predominantly coronary and peripheral arterial diseases (PAD) and remain poorly known. Classically, PAD is expressed as two forms: atherosclerosis, defined as an *atheromatous inflammatory disease,* and vasculitic syndromes, known as *non-atheromatous inflammatory diseases*.

The prevalence and severity of peripheral arterial atherosclerosis in HIV-infected patients remain, at the moment, poorly known mostly because study protocols failed to require that it and coronary arterial disease be dissociated. Several cases of vasculitic syndromes have been reported, such as pseudonecrotizing polyangiitis, Kawasaki's syndrome, Behçet's disease, Henoch-Schönlein purpura, and essential mixed cryoglobulinemia in patients co-infected with HIV and hepatitis C virus, but they remain extremely rare.

Peripheral Arterial Disease

In the retrospective and/or prospective longitudinal studies that have been published to date, symptoms suggestive of PAD, their frequency and severity, and other pertinent characteristics were not collected and reported in detail [1–5]. In the Aquitaine France Cohort, among 2,744 HIV-infected patients followed up and on file in 2002, we retrospectively identified 43 (non-coronary) peripheral arterial and/or venous PAD symptoms that had occurred in 35 patients (0.01%) (P. Mercié, unpublished data from the Cohort Aquitaine Database). Although vasculitic syndromes are uncommon even in the large cohorts, several case reports and some small series have been published.

Infraclinical Atherosclerosis (Intima-Media Thickness)

Progressive atherosclerosis has been assessed using carotid or femoral intima-media thickness (IMT) measurements, and the prevalence of arterial plaques and their percentage of lumen narrowing due to stenosis have been used to estimate peripheral atherosclerosis dissemination and severity in HIV-infected patients, as shown in Fig. 1.

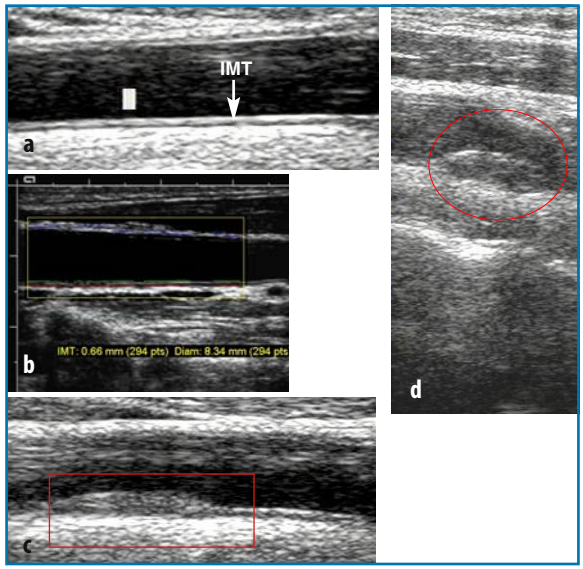


Fig. 1a–d. Progressive stages of atherosclerotic plaque build-up in the carotid artery in HIV-infected patients. **a** An increase of the arterial intima-media thickness (*IMT*) is the first step of this evolution. It occurs before plaque build-up in the arterial wall. **b** IMT can be measured ultrasonographically using specific analytical software with a limit of detection below 1 mm. **c** Atherosclerotic plaque progressively accumulates and projects into the arterial lumen. **d** A more advanced stage of plaque build-up. The speed of plaque accumulation is not predicable. Plaque constitution can be homogeneous or heterogeneous, with a smooth or irregular surface, and be hypoechogenic or calcified. Its evolution depends on a variety of phenomena (e.g. rupture, hemorrhage, and growth)

The multicenter SUPRA study was conducted among 423 of the 2,744 HIV-infected patients in the Aquitaine Cohort [6]. Their median carotid IMT was 0.54 mm (range, 0.50–0.60). Lipodystrophy syndrome was diagnosed in 161 (38.1%) of these patients. According to univariate linear regression analysis, increased IMT was significantly associated ($p<0.05$) with older age, male gender, higher body mass index, higher waist-to-hip ratio, higher systolic blood pressure, total cholesterol, glucose disorders, elevated homocysteine level, smoking and alcohol consumption, lipodystrophy, and highly active antiretroviral therapy (HAART). After adjustment for other cardiovascular risk factors, lipodystrophy and HAART disappeared from the multivariate analysis model.

Depairon et al. [7] reported a higher percentage of HIV-infected patients with at least one plaque compared with HIV-negative individuals (55 vs. 38%, respectively; $p=0.02$). Among HIV-seropositive subjects, protease inhibitor (PI) therapy was not associated with the presence of plaques.

Maggi et al. [8] ultrasonographically detected acquired vessel wall lesions in 29 of 55 PI-treated patients (52.7%) as opposed to 7 out of 47 (14.9%) PI-naive patients. Among the 104 healthy individuals, 7 (6.7%) had a wider carotid IMT. In that study, median IMT in HIV-infected patients was 1.2 mm and the median percentage of stenotic narrowing of the vascular lumen was estimated to be 41.9%.

Recently, Maggi et al. reported a color Doppler ultrasonographic study of carotid vessels in 293 HIV-infected patients. More than 52% of the patients treated with PIs presented acquired lesions of the vascular wall at ultrasonography, whereas similar lesions were found in 15.2% of PI-naive patients and 14.3% of patients treated with non-nucleoside reverse transcriptase inhibitors or naive to antiretroviral therapy. This study confirms the hypothesis of a higher prevalence of premature carotid lesions in the PI-treated patients [9], even if the definition of plaque used in this study is debatable.

In a longitudinal study of 148 HIV-infected adults and 63 age- and sex-matched HIV-uninfected control subjects, conducted over a 12-month period, Hsue et al. reported at baseline a carotid IMT measurement of 0.91±0.33 mm and 0.74±0.13 mm ($p=10^{-4}$), respectively. The rate of progression among 121 HIV patients with a repeated IMT measurement at 1 year was significantly increased to 0.074±0.13 mm, compared with -0.006±0.05 mm in 25 control subjects ($p=0.002$). Age, Latino race, and a very low $CD4^+$ count (≤200; $p=0.082$) were multivariable predictors of IMT progression in this cohort of HIV-infected American patients [10].

In contrast to these results, we found a lower prevalence of carotid atherosclerotic plaques and less stenotic narrowing, based on 152 HIV-infected Aquitaine Cohort patients followed up in a single center. In this Cohort, median right and left carotid IMT were 0.53 mm [interquartile range (IR), 0.39–0.85] and 0.54 mm (IR, 0.39–0.86), respectively; plaque prevalence was 17.1% [95% confidence interval (CI), 11.1–23.1] and the median percentage of stenotic narrowing was 24.2% [11]. Further studies are needed before any definitive conclusions can be drawn concerning these parameters.

Vasculitic Syndromes

Publications on vasculitic syndromes are even scarcer. The incidence of vasculitides (excluding adverse drug reactions) in HIV-infected patients has been estimated to be 1% or lower. Barbaro [12] distinguished three basic categories of vasculitides observed in HIV-infected patients.

Category 1

Vasculitides, rarely reported in HIV-infected patients, include temporal arteritis, Takayasu's arteritis [13], Behçet's syndrome [14–16], Churg-Strauss syndrome [17], Wegener's granulomatosis, essential mixed cryoglobulinemia (hepatitis C virus-related) vasculitides, and Henoch-Schönlein purpura [18, 19]. To date, the role of HIV in the development of these diseases has not yet been proven.

Category 2

This category comprises vasculitides including adverse drug reactions and diseases caused by/associated with infectious agents. Hypersensitivity reactions to drugs are common in HIV patients because of the number and types of medications they take. Directly or indirectly, microbial pathogens [cytomegalovirus, *Toxoplasma gondii* (central nervous system vasculitis), *Pneumocystis jiroveci (*ex *carinii*) pneumonia (pulmonary vasculitis) and hepatitis B virus] have been considered the causal agents of vasculitides, whose development may be directly influenced by preexisting HIV disease. Hepatitis B virus is a well-known cause of polyarteritis nodosa (PAN) in the HIV-negative population. Approximately 5% of PAN in HIV individuals can be attributed to hepatitis B [20].

Category 3

Vasculitides with no known etiologies that appear to have a relationship with HIV disease comprise category 3. In most cases, the association is inferential, based on unusual presentations that do not fit previously defined clinical diseases or disproportionate numbers of rare illnesses among HIV-infected patients. In the absence of epidemiological studies specifically designed to collect data in this setting, it is impossible to definitively know whether these diseases are directly linked to HIV. Microscopic polyangiitis-like and PAN-like illnesses in the absence of hepatitis B virus infection have been reported in HIV patients; however, the real numbers remain unknown [22–24]. HIV patients can develop gangrene in the fingers and/or toes [22–24]. Kawasaki-like syndrome appears to be associated with HIV infection, based on 11 adult cases reported in the literature [25–32].

Case Reports

Case 1

A 49-year-old homosexual man known to be HIV-infected since 1986 (CDC-C) suddenly developed intermittent claudication within a walking distance of 100 m. His medical history associated nephrocalcinosis under indinavir and ophthalmic shingles. His weight was 58 kg and height 1.60 m. Blood pressure was 130/80 mmHg. He was an active smoker (45 pack–years). Results of laboratory analyses were: hypertriglyceridemia (4.23 mmol/l), normal total cholesterol (TC; 5.40 mmol/l) and low HDL cholesterol (0.78 mmol/l) giving an increased TC/HDL ratio (6.92). Antiretroviral treatment associated stavudine, lamivudine, and indinavir. HIV viral load was undetectable (<50 copies/ml) and the $CD4^+$ lymphocyte count was 1,086/mm^3.

Arteriography showed advanced atherosclerosis with severe aortoiliac occlusive disease (Leriche's syndrome; Fig. 2a), and the subsequent development of a collateral network arising from the inferior mesenteric artery responsible for poor irrigation of the lower limb arteries (Fig. 2b, c). He received an aortobifemoral graft.

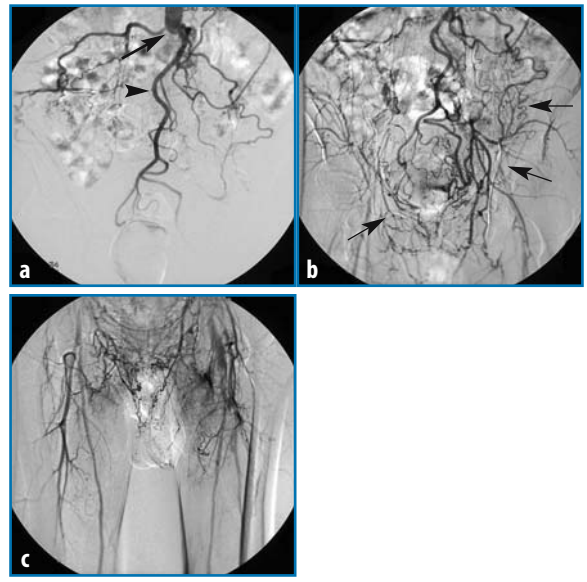


Fig. 2a-c. Arteriography of the abdominal aorta and thighs of patient 1. **a** The aortoiliac artery is totally occluded (Leriche's syndrome; *arrow*) blocking the supply of the iliac arteries, but the inferior mesenteric artery (*arrowhead*) remains well perfused. **b** Aortoiliac arteriography performed at a later date. The iliac arteries are still not visualized. Note the development of a secondary vascular network arising from the inferior mesenteric artery (*arrows*). **c** Final arteriography of the aortoiliac junction and the thighs. The collateral network arising from the inferior mesenteric artery now assures the reperfusion of the arterial network of the thighs, bypassing the atherosclerotic lesions

Case 2

A 50-year-old HIV-infected homosexual man (CDC-C) had non-Hodgkin's lymphoma, treated with chemotherapy, and *Mycobacterium avium intracellulare* septicemia. His CD4 lymphocyte count was 143/mm^3 (8.1%) and HIV viral load was 123,658 copies/ml. Erectile dysfunction became manifest several months earlier. He also had intermittent claudication within a walking distance of 250 m. Arteriography of the lower limbs showed a bilateral severe atheromatosis of the lower limb arteries associated with right external iliac stenotic narrowing evaluated at 50%, and detected thrombosis of the left external iliac at its origin with the collateral arteries arising from the internal iliac artery assuring reperfusion (Fig. 3a, b).

Case 3

In 2000, a 37-year-old HIV-infected woman, seropositive since 1988 (CDC-C), was undergoing HAART. She was treated with zidovudine, lamivudine, and invirase for the last year. Her CD4 lymphocyte count was 497/mm^3 and HIV viral load was undetectable (<50 copies/ml). She was a smoker (35 pack–years) and had an episode of tricuspid endocarditis in 1989. The month before being hospitalized, she developed numerous clinical symptoms, e.g., pyrexia, asthenia, arthralgia, myalgia, and ulceration of the left-foot toes that resolved under corticosteroids. She was admitted with acute ischemia of the left upper limb, with blue fingers, and coldness extending into the forearm that had first manifested as intense pain in the hand followed by a drop in its temperature. Chest radiography showed cardiomegaly (Fig. 4a). Arteriography showed a thrombus in the humeral artery (Fig. 4b). Antiplatelet aggregating agents were administered and in a single night she underwent five successive thombectomies, one each time after a new arterial thrombotic event occurred. Heparin-induced thrombocytopenia was suspected; sodium danaparoid was started then switched to antivitamin K anticoagulants. Fifteen days later, she developed a new thrombosis in her left upper arm. Doppler ultrasonography of the limb detected an occlusion of the left radial artery and a regular stenosis (Fig. 4c) in the left cubital artery,

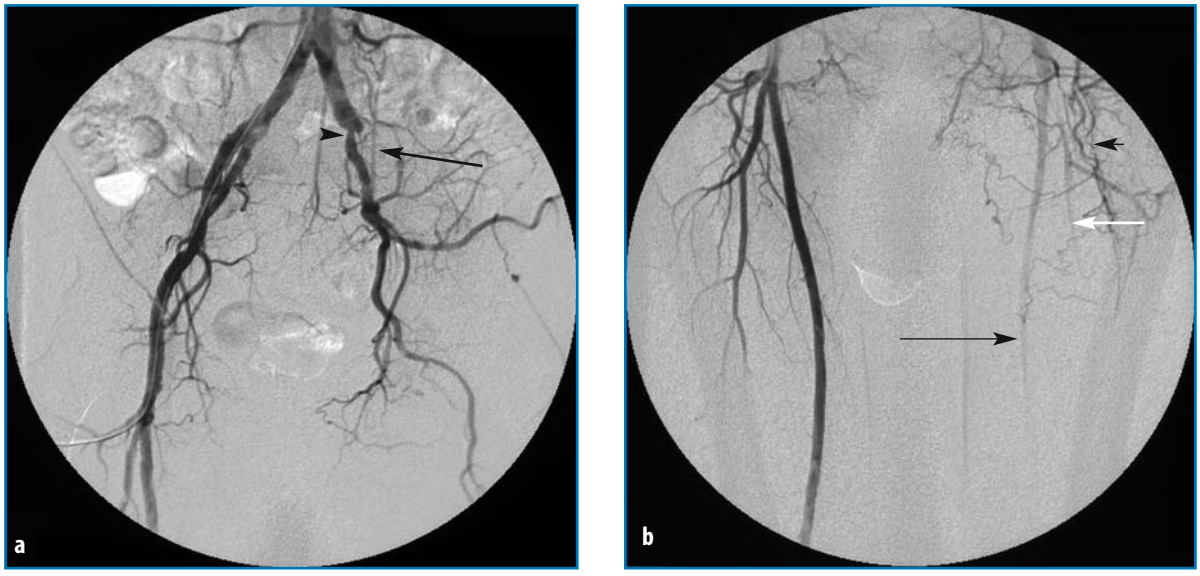


Fig. 3. a Aortoiliac arteriography of case 2. Severe atherosclerosis of the arterial axes. Note the left external iliac artery thrombosis (*arrow*) and the severe stenotic narrowing of the left internal iliac artery (*arrowhead*) evaluated at 50%. **b** Arteriography of the thighs. The occluded left deep (*white arrow*) and superficial femoral (*black arrow*) arteries are moderately reperfused by the left internal iliac artery (*arrowhead*). Contralateral arterial network is normal, showing no signs of atherosclerosis

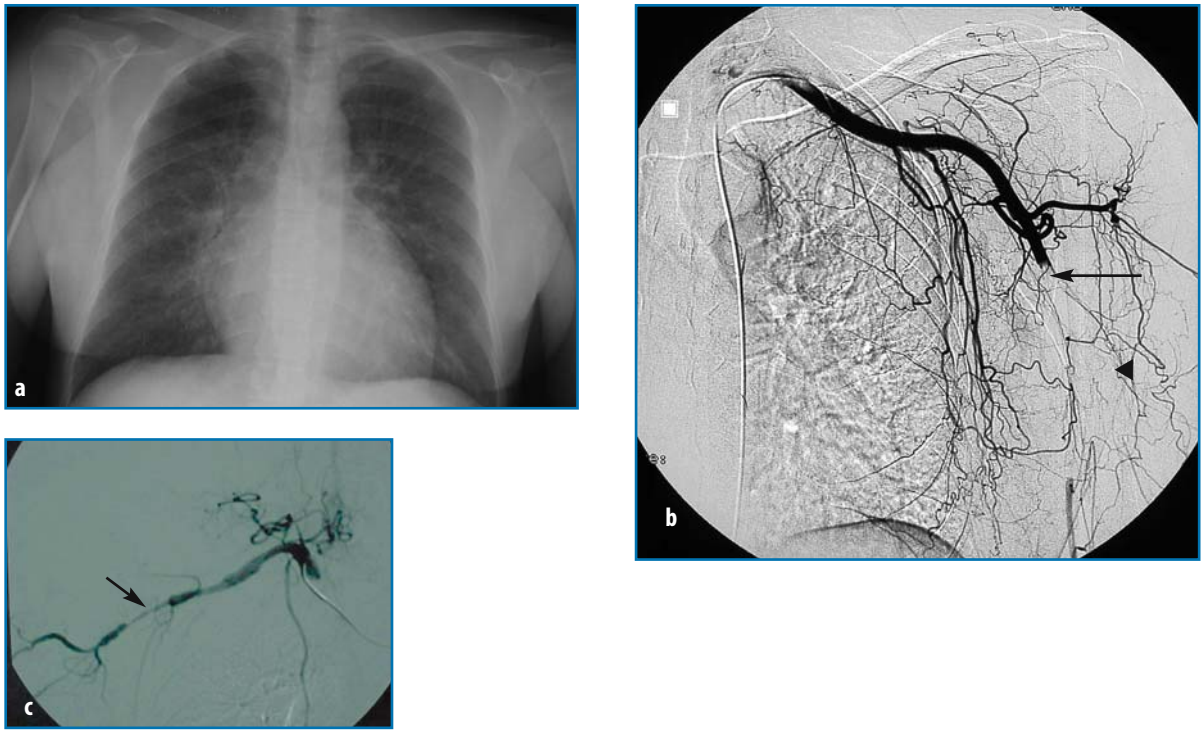


Fig. 4. a Chest X-ray of patient 3. Cardiomegaly in a young HIV-infected woman with peripheral vasculitis of the arms. **b** Arteriography of the left arm. Note the thrombosis in the left humeral artery (*arrow*) and the development of a collateral network of arteries to supply the arm (*arrowhead*). **c** A typical long inflammatory stenosis in the right subclavian artery (*arrow*). This image was obtained in a non-HIV-infected patient with giant-cell arteritis and is similar to that of the stenosis that developed in our case 3

suggestive of inflammatory stenosis. The patient was given a daily intravenous infusion of corticosteroids (500 mg/day for 3 days). In January 2001, her left forearm was amputated below the elbow and corticosteroids were continued. Histopathologic examination of the amputated limb revealed many signs of atypical vasculitis evocative of necrotizing arteritis of unknown etiology associated with a leukocytoclastic vasculitis and multiple arterial thromboses (Fig. 5a–e). Two weeks later, Doppler ultrasonography showed severe stenosis of the left axillary artery consistent with a thrombotic arterial inflammatory disease. One month later the patient died, probably consecutively to an advanced dilated cardiomyopathy.

Conclusion

PAD in HIV-infected patients is not well understood. So far, peripheral atherosclerosis has not been well dissociated from coronary artery disease in these patients. Vasculitides remain very rare in HIV individuals and their prevalence may be underestimated. More detailed studies are needed to improve our understanding of this particular pathology in HIV-1 infected patients.

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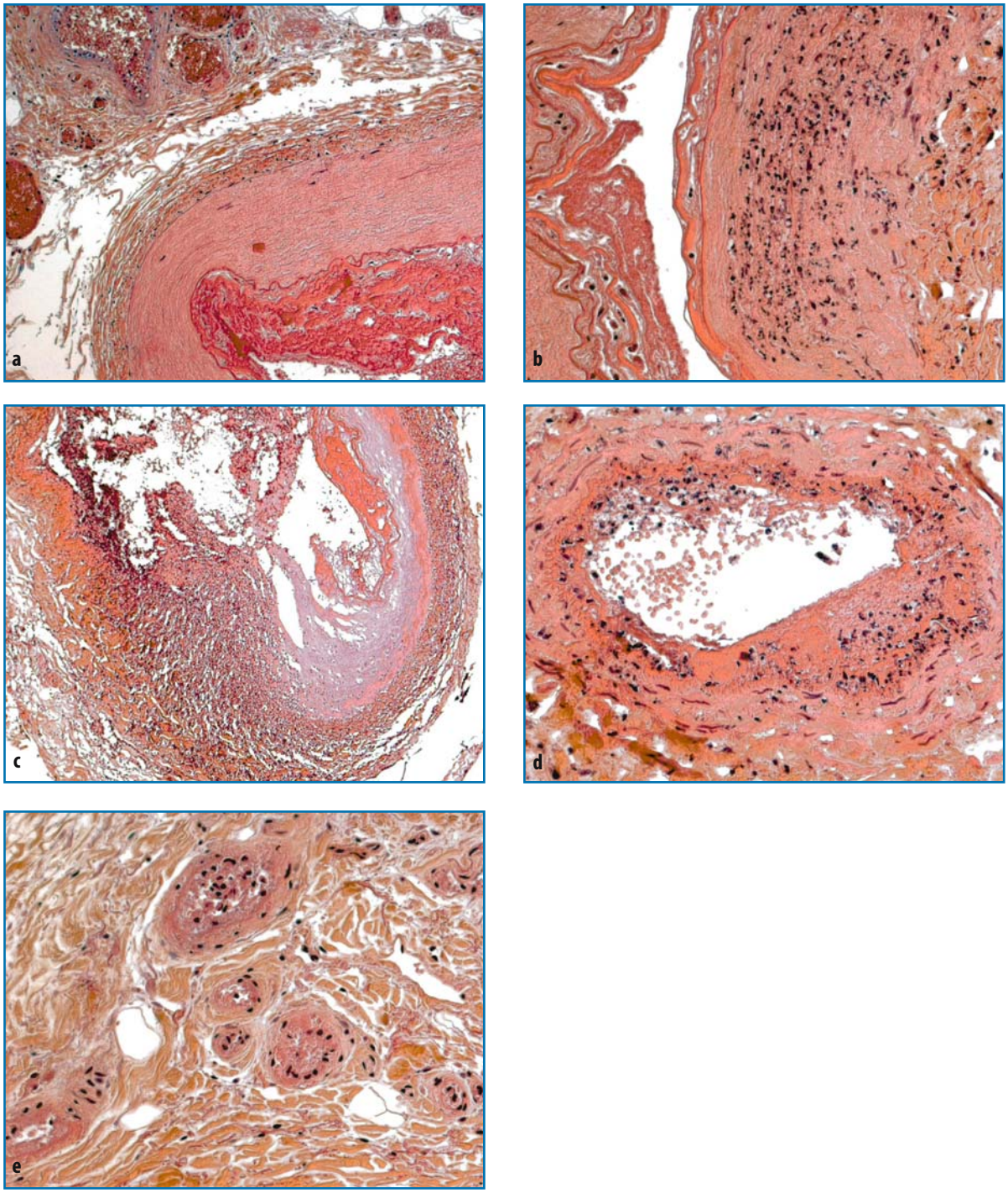

Fig. 5a–e. Serial sections of radial, cubital, and palmar arteries showing alternating alternance of normal and necrotic–inflammatory aspects of the wall [hematein-eosin-saffron (HES) stain]. In some segments, the entire thickness of the arterial wall contained diffuse acidophilic necrosis, and fibrinous thrombi were visible in the lumen (**a**; original magnification ×100); in others, numerous neutrophils had infiltrated the media (**b**; ×200) or populated the entire wall thickness (**c**; ×50). In adjacent veins (**d**; ×200) and capillaries (**e**; ×200), leukocytoclasia and fibrinoid necrosis were sometimes observed. Specific stains were negative for bacteria and fungi. No viral inclusions were detected and in situ hybridization for varicella zoster virus and cytomegalovirus were negative. Muscles were necrotic. The vascular lesions were difficult to classify, because of the diversity of types and calibers of affected vessels, the types and locations of the cellular infiltrates, and it was unknown whether the vascular necrotic–inflammatory changes were primary or secondary

References

1. Bozette SA, Ake CF, Tam HK, Chang SW, Louis TA (2003) Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. N Engl J Med 348:702-710
2. Friis-Møller N, Weber R, Reiss P et al (2003) Cardiovascular disease risk factors in HIV patients – association with antiretroviral therapy. Results from the DAD study. AIDS 17:1179-1193
3. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group (2003) Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med 349:1993-2003
4. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D, and the Clinical Epidemiology Group from the French Hospital Database (2003) Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. AIDS 17:2479-86
5. Savès M, Chêne G, Ducimetière P et al (2003) Risk factors of coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. Clin Infect Dis 37:292-298
6. Mercié P, Lavignolle V, Thiébaut R et al (2002) Evaluation of cardiovascular risk factors in HIV-1 infected patients using carotid intima-media thickness measurement. Ann Med 34:55-63
7. Depairon M, Chessex S, Sudre P et al (2001) Premature atherosclerosis in HIV-infected individuals focus on protease inhibitor therapy. AIDS 15:329-334
8. Maggi P, Serio G, Epifani G et al (2000) Premature lesions of the carotid vessels in HIV-1-infected patients treated with protease-inhibitors. AIDS 14:F123-F128
9. Maggi P, Lillo A, Perilli F, Maserati R, Chirianni A, on behalf of the PREVALEAT Group (2004) Color Doppler ultrasonography of carotid vessels in patients treated with antiretroviral therapy: a comparative study. AIDS 18:1023-1028
10. Hsue PY, Lo JC, Franklin A (2004) Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. Circulation 109:1603-1608
11. Cipriano C, Mercié P, Balestre E et al (2004) Cardiovascular risk related with prevalence and percentage of stenosis of the carotid atherosclerosis plaques in HIV-infected patients: the CAPE study. 11th Conference on Retrovirus and Opportunistic Infection, 8–11 February 2004, San Francisco, abstract N81:734
12. Barbaro G (2003) HIV infection in the cardiovascular system. Vasculitic syndromes in HIV-infected patients. Adv Cardiol 40:185-196
13. Shingadia D, Das L, Klein-Gitelman M, Chadwick E (1999) Takayasu's arteritis in a human immunodeficiency virus-infected adolescent. Clin Infect Dis 29:458-459
14. Stein CM, Thomas JE (1991) Behçet's disease associated with HIV infection. J Rheumatol 18:1427-1428
15. Mercié P, Viallard JF, Cipriano C, Tchamgoué S, Leng B, Pellegrin JL (2002) Aphthous stomatitis in a patient with Behçet's disease and HIV was associated with an increased HIV load. Clin Exp Rheumatol 20 [Suppl. 26]:S54
16. Buskila D, Gladman DD, Gilmore J, Saliut IE (1991) Behçet's disease in a patient with immunodeficiency virus infection. Ann Rheum Dis 50:115-116
17. Cooper LM, Patterson JA (1989) Allergic granulomatosis and angiitis of Churg-Strauss: case report in a patient with antibodies to human immunodeficiency virus and hepatitis B virus. Int J Dermatol 28:597-599
18. Hall TN, Brennan B, Leahy MF, Woodroffe AJ (1998) Henoch-Schönlein purpura associated with human immunodeficiency virus infection. Nephrol Dial Transplant 13:988-990
19. Gherardi R, Belec L, Mhiri C et al (1993) The spectrum of vasculitis in human immunodeficiency virus-infected patients: a clinicopathologic evaluation. Arthritis Rheum 36:1164-1174
20. Font C, Miro O, Pedrol E et al (1996) Polyarteritis nodosa in human immunodeficiency virus infection: report of four cases and review of the literature. Br J Rheumatol 35:796-799
21. Calabrese LH (1991) Vasculitis and infection with the human immunodeficiency virus. Rheum Dis Clin North Am 17:131-147
22. Libman BS, Quismorio FP, Jr, Stimmler MM (1995) Polyarteritis nodosa-like vasculitis in human immunodeficiency virus infection. J Rheumatol 22:351-355
23. Gisselbrecht M, Cohen P, Lortholary O et al (1997) HIV-related vasculitis: clinical presentation and therapeutic approach on six patients. AIDS11:121-123
24. O'Grady NP, Sears CL (1996) Therapeutic dilemmas in the care of a human immunodeficiency virus-infected patient with vasculitis: case report. Clin Infect Dis 23:559-561
25. Porwancher RSS (1992) Adult Kawasaki disease in HIV-infected patients. 8th International Conference on AIDS, Amsterdam, 1992
26. Martinez-Escibano JA, Redondo C, Galera S, Sanchez-Pedreno P, Abel JL, Frias JF (1998) Recur-

rent Kawasaki syndrome in an adult with HIV-1 infection. Dermatology 197:96-97
27. Wolf CV 2nd, Wolf JR, Parker JS (1995) Kawasaki's syndrome in a man with the human immunodeficiency virus. Am J Ophthalmol 120:117-118
28. Porneuf M, Sotto A, Barbuat C, Ribou G, Jourdan J (1996) Kawasaki syndrome in an adult AIDS patient. Int J Dermatol 35:292-294
29. Viraben R, Dupre A (1987) Kawasaki disease associated with HIV infection. Lancet 1:1430-1431
30. Bayrou O, Philippoteau C, Artigou C, Haddad T, Leynadier F (1993) Adult Kawasaki syndrome associated with HIV infection and anticardiolipin antibodies. J Am Acad Dermatol 29:663-664
31. Yoganathan K, Goodman F, Pozniak A (1995) Kawasaki-like syndrome in an HIV-positive adult. J Infect 30:165-166
32. Johnson RM, Little JR, Storch GA (2001) Kawasaki-like syndromes associated with human immunodeficiency virus infection. Clin Infect Dis 32:1628-1634

HIV-Associated Pulmonary Hypertension

G. Barbaro

About 14 years ago, Kim and Factor reported the first case of HIV-associated pulmonary hypertension [1]. Since then more than 131 cases have been described in the literature [2]. For this reason, HIV-associated pulmonary hypertension has been included as a definite cause of precapillary pulmonary hypertension according to the executive summary of the World Health Organization (WHO) [3]. The incidence of HIV-associated pulmonary hypertension is 1 in 200, much higher than 1 in 200,000 found in the general population [3]. No differences have been found in the clinical, histologic, and hemodynamic features between patients with HIV-associated pulmonary hypertension and HIV-uninfected patients affected by primary pulmonary hypertension.

Pathogenesis of HIV-Associated Pulmonary Hypertension

The histopathology of HIV-associated pulmonary hypertension is similar to that of primary pulmonary hypertension. The most common alteration in HIV-associated pulmonary hypertension is plexogenic pulmonary arteriopathy (Fig. 1), while thrombotic pulmonary arteriopathy and pulmonary veno-occlusive disease are more rare histologic findings. This observation may suggest that similar etiopathogenetic mechanisms are at the basis of both HIV-associated pulmonary hypertension and primary pulmonary hypertension.

The finding of an increased incidence of pulmonary hypertension in HIV-infected patients was at first related to viral infection. Although a direct role of HIV-1 in HIV-associated pulmonary hypertension has not been demonstrated [4, 5], several indirect mechanisms may link HIV infection to the pulmonary vascular changes.

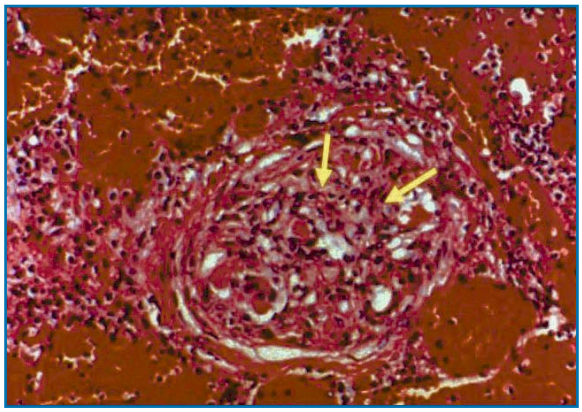

Fig. 1. Plexogenic pulmonary arteriopathy (*arrows*) in a patient with HIV-associated pulmonary hypertension (autopsy specimen). H&E, x20

The principal pathogenetic hypotheses formulated for development of HIV-associated pulmonary hypertension with related clinical evidence are reported in Table 1.

Clinical Manifestations and Diagnosis of HIV-Associated Pulmonary Hypertension

In the largest clinical series of HIV-associated pulmonary hypertension, 47%–54% of all the patients were male, and the age at the time of diagnosis ranged from 2 to 56 years (mean 33 years). Intravenous drug use was the most common risk factor and ranged from 50% to 58%, while homosexual behavior was present in 20% of the patients, hemophilia in 9%, heterosexual contacts in 9%, and other risk factors in 6% of the patients [2, 12, 13], reflecting the epidemiology of HIV infection in the general population. The mean $CD4^+$ count was 300 mm^3 (range 0–937/mm^3). Currently, no correlation has been found between the $CD4^+$ count and the presence of opportunistic infections and the development of pulmonary hypertension.

Table 1. Pathogenetic hypotheses of HIV-associated pulmonary hypertension

Pathogenetic hypothesis	Clinical evidence
Cytokines hypothesis (Fig. 2)	Several studies have found an increased production of cytokines [e.g., endothelin-1 (ET-1), interleukin-6 (IL-6), interleukin-1-beta (IL-1β), platelet-derived growth factor (PDGF), and tumor necrosis-factor-alpha (TNF-α)] in patients affected by primary pulmonary hypertension, evoking a potential role of these substances in the pathogenesis of the disease [7–10].
α_1-Adrenergic hypothesis (Fig. 3)	In HIV-infected patients different factors can induce a chronic stimulation of α_1-adrenoreceptors of the pulmonary vasculature, including: chronic hypoxia, high circulating levels of norepinephrine, appetite suppressant agents, or cocaine use. The chronic stimulation of pulmonary vascular α_1- adrenoreceptors can induce the local production of a large amount of cytokines and in particular of ET-1, IL-1β, IL-6, and PDGF, which in turn stimulate the growth of new pulmonary capillaries, induce vasoconstriction of resistance-sized pulmonary arteries, and have an anti-apoptosis effect [11].
Toxic substances	Patients with a history of chronic intravenous drug use may develop pulmonary hypertension. Pulmonary artery thrombosis is the main pathological finding in such conditions, and is believed to be due to foreign particle pulmonary emboli, following injections of solutions derived from heroin or from crushed oral medications in which talc was a frequent component [12, 13]. The use of appetite suppressant agents and/or cocaine has been associated with pulmonary hypertension, even in HIV-infected patients, possibly as a consequence of an increased α_1-adrenoreceptor stimulation [13, 14].
Liver disease and HIV-associated pulmonary hypertension	Porto-pulmonary hypertension is now a well-described disease characterized by a clinical and hemodynamic picture substantially identical to primary pulmonary hypertension. In liver cirrhosis, an increased production and a decreased metabolism of some cytokines (e.g., ET-1) have been reported. Kuddus et al. demonstrated that an enhanced synthesis and a reduced metabolism of ET-1 in hepatocytes can be an important mechanism of elevated endogenous and circulating ET-1 in patients affected by liver cirrhosis [15, 16]. Pellicelli et al. reported higher values of systolic pulmonary arterial pressure in HIV-infected patients with HCV/HBV-associated liver cirrhosis compared to other HIV-infected patients without cirrhosis [13].
Genetic factors (HLA antigens)	In a study conducted by Morse and co-workers, it was found that in ten racially mixed HIV-infected patients with HIV-associated pulmonary hypertension, there was a significant increase in the frequency of human leukocyte antigen (HLA) class II DR52 and DR6, and of the linked alleles HLA-DRB1-1301/2, -DRB3-0301, -DQB1 0603/4, compared to the frequencies of the same alleles in normal Caucasian control subjects [17]. HLA-DR6 and its DRB1-1301/2 subtypes were also significantly increased in HIV-associated pulmonary hypertension patients compared to the respective frequencies of racially diverse HIV-positive control subjects. Furthermore, HLA-DR6 and the DRB1-1301 subtype have also been reported to increase in HIV-positive patients who develop diffuse infiltrative lymphocytosis syndrome [18, 19]. It is possible that both entities represent different spectra of a common HLA-DR-determined host response to HIV-1.

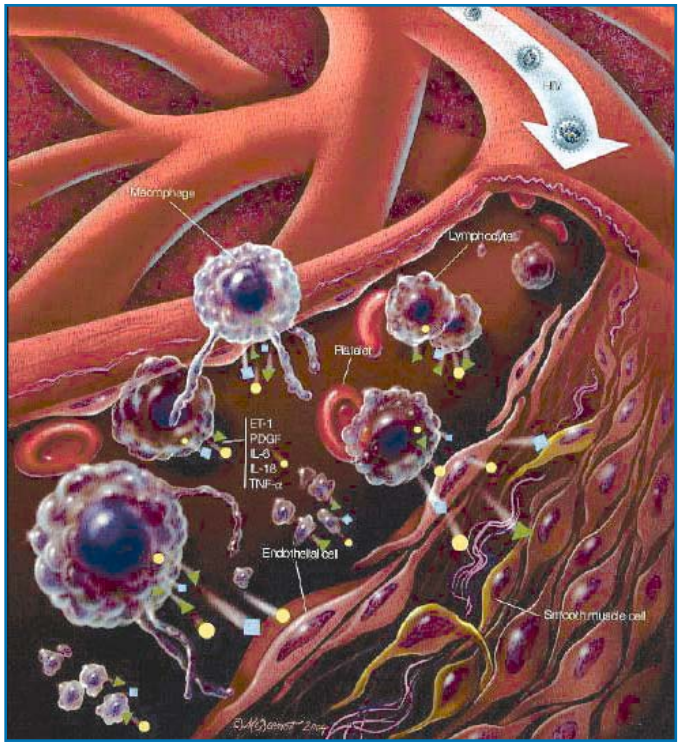

Fig. 2. The possible pathogenetic mechanisms involved in the development of HIV-associated pulmonary hypertension. HIV-infected macrophages, platelets, and lymphocytes may release multifunctional cytokines [endothelin-1 (*ET-1*), platelet-derived growth factor (*PGDF*), interleukin-6 (*IL-6*), interleukin-1 beta (*IL-1β*), tumor necrosis factor alfa (*TNF-α*)], which may affect the endothelial cells of the pulmonary vessels, inducing their proliferation and vasoconstriction by a reduction of nitric oxide (*NO*) production. Moreover, ET-1 produced by endothelial cells may affect the smooth muscle cells of the pulmonary vessels inducing their migration and proliferation. (From [25])

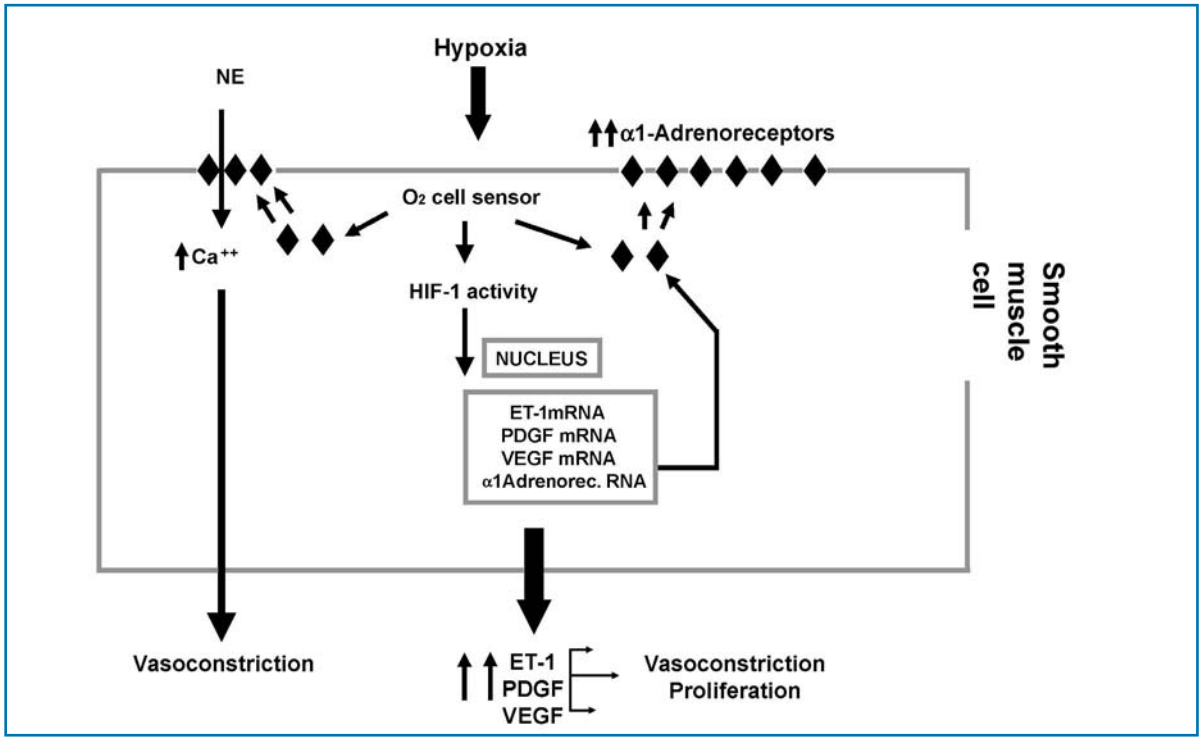

Fig. 3. Chronic stimulation of α_1-adrenoreceptors of the pulmonary vasculature can induce the local production of a large amount of cytokines and particularly of ET-1, IL-1β, IL-6, and PDGF, which in turn stimulate the growth of new pulmonary capillaries, induce vasoconstriction of resistance-sized pulmonary arteries, and have an anti-apoptosis effect. (From [26])

The most common presenting symptom was dyspnea (from 49% to 85%), while pedal edema ranged from 11% to 30% of the patients, nonproductive cough from 7% to 19%, syncope from 8% to 12%, and chest pain was present in 7% of the patients. Raynaud's syndrome, which is more frequently found in patients affected by pulmonary hypertension associated to connective tissue disease, was present in only one patient (1%) [2, 13].

Signs of pulmonary hypertension on physical examination are subtle and often overlooked. An accentuated pulmonary component of the second heart sound, audible at the apex, may be noted in more than 90% of patients, reflecting an increased force of pulmonary valve closure due to elevated pulmonary artery pressure [6]. Other signs of increased pulmonary artery pressure may include the following [6]:

a) An early systolic ejection click due to sudden interruption of pulmonary valve opening
b) A midsystolic ejection murmur caused by turbulent transvalvular pulmonary flow
c) A palpable left parasternal lift produced by the impulse of the hypertrophied high-pressure right ventricle
d) A right ventricular S4 gallop
e) A prominent jugular "*a*" wave suggesting high right ventricular filling pressure

Physical signs of more advanced disease include the diastolic murmur of pulmonary regurgitation and the holosystolic murmur of tricuspid valve regurgitation, which is audible at the lower left sternal border and augmented with inspiration. A right ventricular S3 gallop, marked distension of the jugular veins, pulsatile hepatomegaly, peripheral edema, and ascites are indicative of right ventricular failure [6].

The principal diagnostic tests used for diagnosis of HIV-associated pulmonary hypertension with related clinical verification are reported in Table 2.

Table 2. Principal diagnostic tests for diagnosis of HIV-associated pulmonary hypertension

Diagnostic test	Clinical verification
Laboratory tests	A comprehensive laboratory evaluation which includes complete blood count, prothrombin time, partial thromboplastin time, hepatic profile, autoimmune panel, HIV viral load, HCV antibodies, and HBsAg may be helpful in excluding pulmonary hypertension secondary to systemic diseases. Serum D-dimer, produced during fibrinolysis, if higher than 500 ng/ml may be suggestive of pulmonary thromboembolism.
Electrocardiogram (ECG) (Fig. 4)	The ECG most often (15%–50%) shows right-axis deviation (S1Q3T3 aspect or McGinn-White sign) along with R>7 mm in V1-V2. Other findings on the ECG include tall, prominent P waves in leads II, III, aVF (secondary to right atrial enlargement), complete or incomplete right bundle branch block, or sinus tachycardia.
Chest radiogram (Fig. 5)	The chest radiograph frequently has a prominent main pulmonary artery (71%–90%) along with enlarged hilar vessels (80%), "pruning," or a decrease in peripheral vessels (51%) and cardiomegaly (72%).
Transthoracic echocardiography (TTE) (Figs. 6–9)	The most frequent findings on TTE are: systolic flattening of the interventricular septum, right atrial and right ventricular enlargement, and tricuspid regurgitation. Additionally, TTE can estimate pulmonary arterial systolic pressure by measuring the Doppler flow through the tricuspid valve according to the modified Bernulli formula: $P=4V^2$ (where P is pressure gradient and V is peak retrograde velocity). The right atrial pressure is nominally estimated at 10 mmHg. The grade of pulmonary hypertension is categorized as grade I (36–45 mmHg), grade II (46–55 mmHg), and grade III ($\geq$ 56 mmHg). Finally, the TTE can evaluate secondary causes of pulmonary hypertension, such as congenital heart disease or valvular disease.

cont. →

Table 2 *cont.*

Diagnostic test	Clinical verification
Pulmonary function tests (PFTs) and arterial blood gases (ABG)	The most frequent abnormality seen on PFTs in patients with pulmonary hypertension is a decrease in the diffusing capacity for carbon monoxide (DL_{co}) (mean, 69% of predicted). A mild restrictive pattern (mild decrease in total lung capacity) may also be seen. ABG are frequently obtained along with the PFTs and most commonly demonstrate hypoxemia and a respiratory alkalosis (hypocapnea).
Ventilation-perfusion (V/Q) scan	An abnormal V/Q scan should not necessarily be interpreted as evidence of thromboembolic disease; patients with non-thromboembolic pulmonary hypertension often have abnormal V/Q scans, most commonly displaying a diffuse patchy pattern. In HIV-associated pulmonary hypertension the most common findings observed in V/Q scans is a patchy distribution of the tracer or normal lung scan.
Spiral computerized tomography (CT)	It is a fast, safe, minimally invasive procedure which shows the thrombus in segmental and subsegmental arteries and gives further information suggesting or confirming alternative clinical diagnoses frequently observed in HIV-infected patients (pneumonia, pulmonary fibrosis, cardiovascular diseases, pulmonary neoplasms, pleural diseases).
Pulmonary angiography and right heart cardiac catheterization (Fig. 10)	Pulmonary angiography is restricted to cases with unclear or negative spiral CT scans but with a strong clinical suspicion of pulmonary hypertension. Right heart cardiac catheterization is the standard for diagnosis and measurement of hemodynamic values.

Treatment of HIV Pulmonary Hypertension

The treatment of HIV-associated pulmonary hypertension is complex and controversial. To date, no controlled clinical trial has evaluated the agent of choice for the treatment of this disease. The principal drugs currently used in the treatment of HIV-associated pulmonary hypertension with related clinical evidence are reported in Table 3.

Conclusions

Pulmonary hypertension associated with HIV infection is a cardiovascular complication that has been recognized with increasing frequency in the last few years. The etiology of HIV-associated pulmonary hypertension is unknown. At present, a multifactorial pathogenesis of HIV-associated pulmonary hypertension has been hypothesized. In this clinical condition, the endothelial dysfunction, the deregulation of circulating cytokines, and genetic factors seem to be implicated in the pathogenesis of this disease. In particular, as in primary pulmonary hypertension, an increase in the plasma concentrations of endothelin-1 (ET-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF)-alpha has been found in patients with HIV-associated pulmonary hypertension. The role of antiretroviral therapy is still being debated. Vasodilator agents such as prostaglandin I2 analog (beraprost) or calcium channel blockers seem to be interesting therapeutic alternatives in the treatment of HIV-associated pulmonary hypertension compared to continuous intravenous infusion of epoprostenol. The use of cGMP-specific phosphodiesterase inhibitors and oral bosentan is promising, but long-term controlled clinical trials are needed in this specific subset of patients.

Table 3. Treatment of HIV-associated pulmonary hypertension

Therapy	Clinical evidence
Highly active antiretroviral therapy (HAART)	Opravil et al. [20] reported that there was a reduction of right systolic ventricular pressure–right atrial pressure gradient in six patients who received antiretroviral treatment compared to seven patients not receiving antiretroviral therapy. All six patients were treated with a single antiretroviral therapy [20]. According to Pellicelli et al., pulmonary hypertension developed in three patients despite HAART and a low HIV viral load [10]. Zuber et al. retrospectively analyzed 47 patients with HIV-associated pulmonary hypertension in the Swiss HIV Cohort Study [21]. According to the data reported by these authors, HAART significantly decreased mortality caused by HIV-associated pulmonary hypertension as well as other causes, suggesting a beneficial effect of HAART in this condition [21].
Epoprostenol	In a study by Petiprez et al., a short-term treatment with i.v. administered epoprostenol was evaluated in 19 HIV-infected patients with pulmonary hypertension compared to 86 control patients.The proportion of responders to epoprostenol was equal in both groups, and the level of acute pulmonary vasodilatation (percent fall in total pulmonary resistance) achieved with epoprostenol in HIV-infected and non-HIV-infected patients was similar [22]. Aguilar et al. treated six patients with HIV-associated pulmonary hypertension with continuous i.v. infusion of epoprostenol. At 1 year, the mean pulmonary artery pressure and the pulmonary vascular resistance decreased by 21% and 54% with respect to baseline values. They concluded that epoprostenol infusion is effective in improving hemodynamic and functional status acutely as well as in the long term in patients with HIV-associated hypertension [23]. Currently, it is not clear whether early administration of epoprostenol could substantially improve the prognosis of HIV-infected patients with pulmonary hypertension. Epoprostenol therapy is generally limited to seriously ill patients because of its cost and the need for continuous i.v. infusion with associated risk of infection.
Beraprost	Beraprost can improve the adherence to a long-lasting antiretroviral therapy. Beraprost can be absorbed easily and can be administered in a t.i.d. or q.i.d. fashion. In different studies in non-HIV-associated pulmonary hypertension, the oral administration of beraprost seemed to have beneficial effects on the survival and on the hemodynamic parameters of the patients [13]. Indeed, controlled clinical studies are needed to establish the efficacy of this treatment in HIV-associated pulmonary hypertension.
Bosentan	Bosentan is an endothelin-1 antagonist and may be an effective approach to therapy for pulmonary arterial hypertension [24]. Bosentan increased exercise capacity and improved hemodynamics in patients with primary pulmonary hypertension [24]. However, the therapeutic efficacy of bosentan in patients with HIV-associated pulmonary hypertension needs to be tested in controlled prospective studies.
Calcium channel blockers	Treatment with calcium channel blockers seems to be another alternative in the therapy of HIV-associated pulmonary hypertension. However, reports regarding a small sample of patients with HIV-associated pulmonary hypertension treated with this kind of therapy have shown contrasting response rates [13]. Moreover, calcium channel blockers should be used with caution in patients receiving HAART, since they interact with protease inhibitors.
Sildenafil	Oral sildenafil seems to be beneficial as a selective pulmonary vasodilator in patients with primary pulmonary hypertension. Sildenafil may preferentially inhibit cGMP-specific phosphodiesterase, which is abundant in lung tissue [13, 22]. Therefore, the possibility of treatment needs to be evaluated prospectively in patients with HIV-associated pulmonary hypertension.

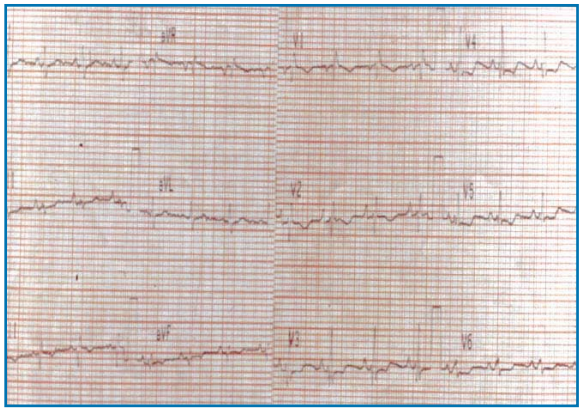

Fig. 4. ECG recording in a patient with HIV-associated pulmonary hypertension. A right-axis deviation ($S_1Q_3T_3$ aspect or McGinn-White sign) along with tall, prominent P waves in leads II, III, aVF (secondary to right atrial enlargement) and complete right bundle branch block is evident

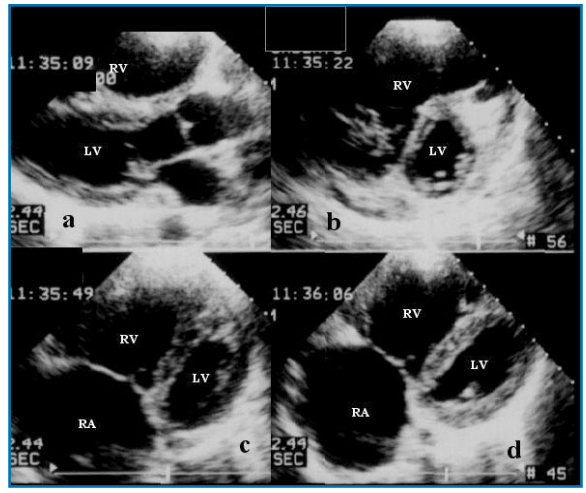

Fig. 6a-d. Transthoracic ecochardiographic findings in HIV-associated pulmonary hypertension. It is possible to observe a systolic flattening of the interventricular septum and right atrial and right ventricular enlargement. (From [27])

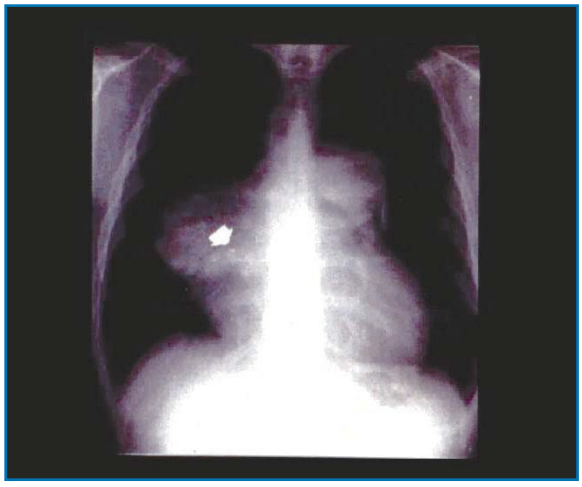

Fig. 5. Chest radiogram in a patient with HIV-associated pulmonary hypertension. A prominent main pulmonary artery along with enlarged hilar vessels (*arrow*) accompanied by a decrease in peripheral vessels and cardiomegaly is evident. (From [27])

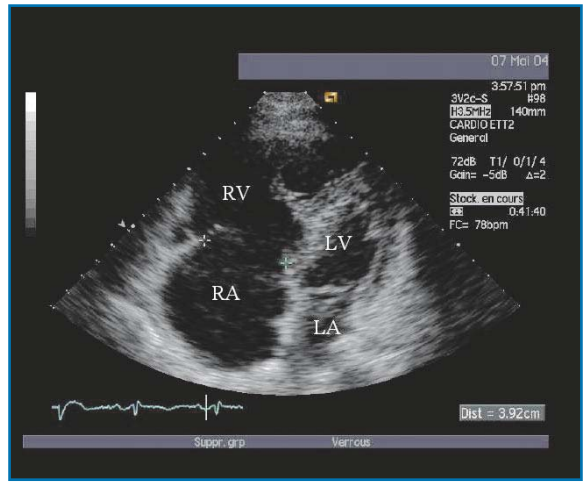

Fig. 7. Transthoracic ecochardiographic findings in HIV-associated pulmonary hypertension. A systolic flattening of the interventricular septum and right atrial and right ventricular enlargement can be observed

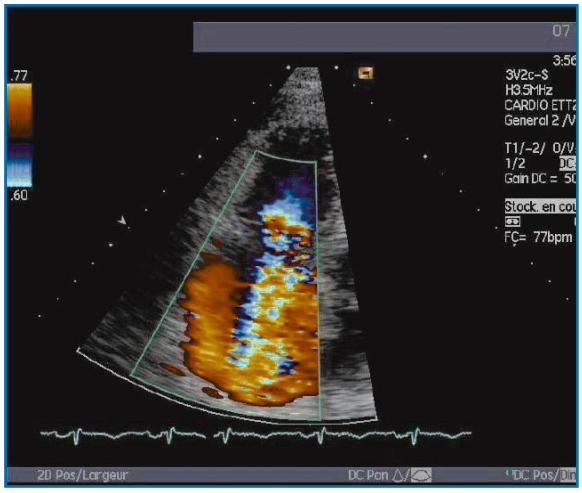

Fig. 8. Transthoracic ecochardiographic findings in HIV-associated pulmonary hypertension. A significant tricuspid regurgitation is observed

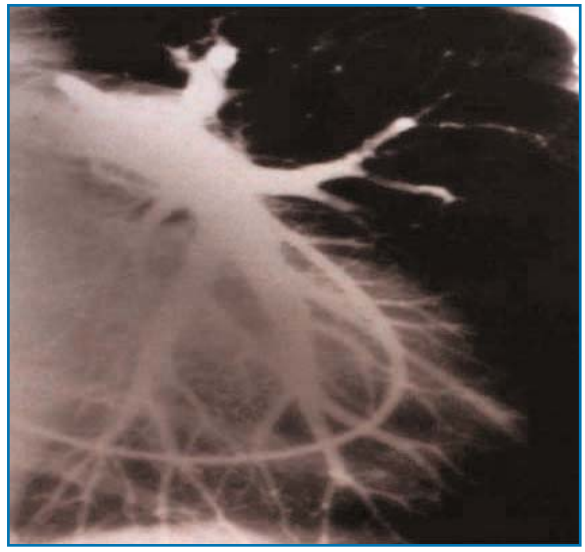

Fig. 10. Pulmonary angiography in a patient with HIV-associated pulmonary hypertension. It is possible to observe a "pruning" aspect with enlargement of the left pulmonary artery and decrease in peripheral vessels

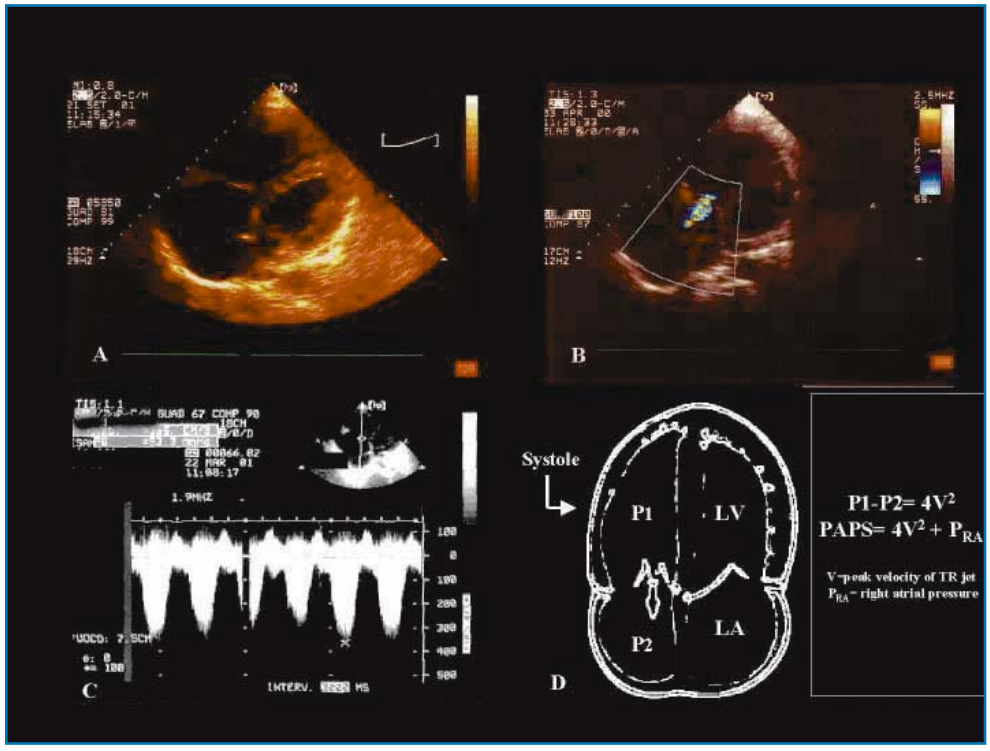

Fig. 9a-d. Transthoracic ecochardiographic findings in HIV-associated pulmonary hypertension. The pulmonary arterial systolic pressure can be estimated by measuring the Doppler flow through the tricuspid valve according to Bernulli's modified formula: $P=4V^2$ (where P is pressure gradient and V is peak retrograde velocity). The right atrial pressure (P_{RA}) is nominally estimated at 10 mmHg

References

1. Kim KK, Factor SM (1987) Membrano-proliferative glomerulonephritis and plexogenic pulmonary arteriopathy in a homosexual man with acquired immunodeficiency syndrome. Hum Pathol 18:1293-1296
2. Mehta NJ, Khan IA, Mehta RN et al (2000) HIV-related pulmonary hypertension. Analytic review of 131 cases. Chest 118:1133-1141
3. Rich S (2000) Executive summary from the world symposium on primary pulmonary hypertension. Evian, France, 6-10 September 1998, cosponsored by World Health Organization. Cited 14 April 2000 http://www.who.int/ncd/cvd/pph.html
4. Mette SA, Palevsky HI, Pietra GG et al (1992) Primary pulmonary hypertension in association with human immunodeficiency virus infection: a possible viral etiology for some forms of hypertensive pulmonary arteriopathy. Am Rev Respir Dis 145:1196 –1200
5. Humbert M, Monti G, Fartouk M et al (1998) Platelet-derived growth factor expression in primary pulmonary hypertension: comparison of HIV seropositive and HIV seronegative patients. Eur Respir J 11:554-559
6. McGoon M, Gutterman D, Steen V et al (2004) Screening, early detection and diagnosis of pulmonary arterial hypertension. ACCP Evidence-Based Clinical Practice Guidelines. Chest 126:14S-34S
7. Giaid A, Yanagisawa M, Langleben D (1993) Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med 328:1732-1739
8. Giaid A (1998) Nitric oxide and endothelin-1 in pulmonary hypertension. Chest 114:208S-212S
9. Cacoub P, Dorent R, Nataf P et al (1997) Endothelin-1 in the lungs of patients with pulmonary hypertension. Cardiovasc Res 33:196-200
10. Pellicelli AM, Palmieri F, D'Ambrosio C et al (1998) Role of human immunodeficiency virus in primary pulmonary hypertension – case reports. Angiology 49:1005-1011
11. Salvi SS (1999) Alfa1-adrenergic hypothesis for pulmonary hypertension. Chest 115:1708-1719
12. Tomashefski JF, Hirsch CS (1980) The pulmonary vascular lesions of intravenous drug abuse. Hum Pathol 11:133-145
13. Pellicelli AM, Barbaro G, Palmieri F et al (2001) Primary pulmonary hypertension in HIV patients: a systematic review. Angiology 52:31-41
14. Branch CA, Knuepfer MM (1992) Adrenergic mechanisms underlying cardiac and vascular responses to cocaine in conscious rats. J Pharmacol Exp Ther 263:742-751
15. Hadengue A, Benhayoun MK, Lebrec D et al (1991) Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics.Gastroenterology 100: 520-528
16. Kuddus RH, Nalesnik MA, Subbotin VM et al (2000) Enhanced synthesis and reduced metabolism of endothelin-1 (ET-1) by hepatocytes – an important mechanism of increased endogenous levels of ET-1 in liver cirrhosis. J Hepatol 33:725-732
17. Morse JH, Barst RJ, Itescu S et al (1996) Primary pulmonary hypertension in HIV infection. An outcome determined by particular HLA class II alleles. Am J Respir Crit Care Med 153:1299-1301
18. Itescu S, Dalton J, Zhang HZ, Winchester R (1993) Tissue infiltration in a CD8 lymphocytosis syndrome associated with human immunodeficiency virus-1 infection has the phenotypic appearance of an antigenically driven response. J Clin Invest 91:2216-2225
19. Itescu S, Brancato LJ, Winchester W (1989) A sicca syndrome in HIV infection: association with HLA-DR5 and CD8 lymphocytosis. Lancet 2:466-468
20. Opravil M, Pechère M, Speich R et al (1997) HIV-associated primary pulmonary hypertension. Am J Respir Crit Care Med 155:990-995
21. Zuber JP, Calmy A, Evison JM et al (2004) Pulmonary arterial hypertension related to HIV infection: improved hemodynamics and survival associated with antiretroviral therapy. Clin Infect Dis 38:1178-1185
22. Petiprez P, Brenot F, Azarian R et al (1994) Pulmonary hypertension in patients with human immunodeficiency virus infection. Comparison with primary pulmonary hypertension. Circulation 89:2722-2727
23. Aguilar RV, Farber HW (2000) Epoprostenol (prostacyclin) therapy in HIV-associated pulmonary hypertension. Am J Respir Crit Care 162:1846-1850
24. Sitbon O, Gressin V, Speich R et al (2004) Bosentan for the treatment of human immunodeficiency virus-associated pulmonary arterial hypertension. Am J Respir Crit Care Med 170:1212-1217
25. Barbaro G (2004) Reviewing the clinical aspects of HIV-associated pulmonary hypertension. J Respir Dis 25:289-293
26. Pellicelli A, Palmieri F, Cicalini S et al (2001) Pathogenesis of HIV-related pulmonary hypertension. Ann NY Acad Sci 946:82-94
27. Petrosillo N, Pellicelli AM, Boumis F et al (2001) Clinical manifestations of HIV-related pulmonary hypertension. Ann NY Acad Sci 946:223-235

Coagulative Disorders in HIV-Infected Patients

L. Drouet

Coagulative disorders in human immunodeficiency virus (HIV)-infected patients can lead to two opposite conditions:

1. Thrombotic conditions
2. Hemorrhagic conditions

Coagulative Disorders in HIV-Infected Patients Leading to Thrombotic Conditions

Coagulative Disorders in HIV Patients Undergoing HAART and Arterial Risk of Thrombosis

Emphasis has been placed on the deleterious associations/consequences of coagulative disorders and the two main high cardiovascular risk conditions of HIV patients undergoing highly active antiretroviral therapy (HAART): the metabolic and lipodystrophic syndromes. These conditions are associated with an overwhelming risk of cardiovascular events among the numerous metabolic and hemostatic pathways that are modified in these conditions: the coagulative systems and mostly the fibrinolytic systems are affected. The best documented coagulative abnormalities associated with these conditions are an increase of plasminogen activator inhibitor-1 (PAI-1) and a decrease of fibrinolytic potential.

Coagulative Disorders in HIV Patients Undergoing HAART Linked to the Increased Risk of Cardiovascular Disorders

Hypofibrinolysis is associated with insulin resistance in HIV-infected patients receiving HAART, especially in those with metabolic syndrome.

The levels of PAI-1 and fibrinogen are significantly increased in patients receiving protease inhibitors (PIs) compared with control subjects, independently of HAART-associated metabolic syndrome. PAI-1 [and tissue plasminogen activator (tPA)] levels have been shown to be independently correlated to the use of PIs, to triglyceride and insulin levels, to body mass index, and to gender in several studies (Fig. 1) [1]. Metformin treatment induces an improvement in PAI-1 levels. Changes in insulin AUC correlate significantly with changes in tPA antigen concentration. By reducing PAI-1 and tPA antigen concentrations, metformin may ultimately reduce the cardiovascular risk in patients with fat redistribution and insulin resistance [2].

Plasma PAI-1 concentrations are increased in direct proportion to liver fat content in HIV patients with lipodystrophy receiving HAART.

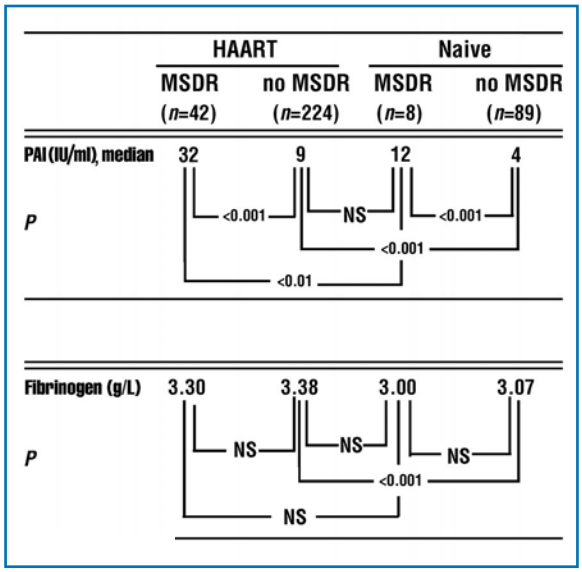

Fig. 1. Levels of plasminogen activator inhibitor type 1 (*PAI-1*) and fibrinogen in HIV-1-infected patients receiving protease inhibitor-containing higly active antiretroviral therapy (*HAART*) and treatment-naive HIV-1-infected patients with and without metabolic syndrome (*MSDR*) at the time of the cross-sectional study. *NS*, not significant. (From [1] with permission)

Rosiglitazone decreases liver fat content, serum insulin, and plasma PAI-1 without changing the size of other fat depots or PAI-1 mRNA in subcutaneous fat. These observations suggest that liver fat contributes to plasma PAI-1 concentrations in these patients (Fig. 2) [3].

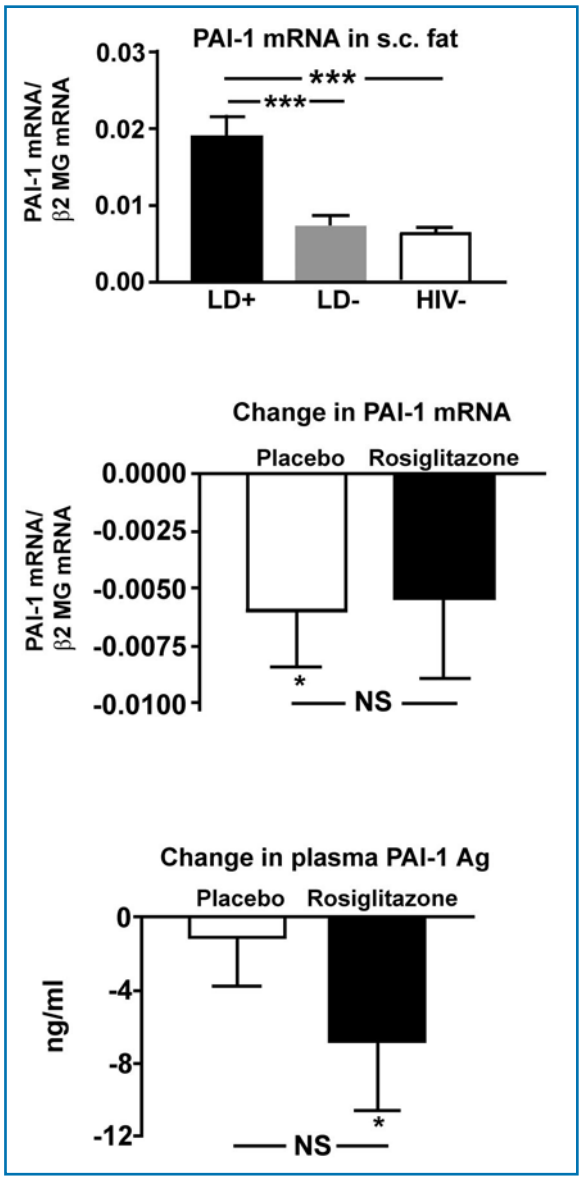

Fig. 2. PAI-1 mRNA expression in subcutaneous (*s.c.*) adipose tissue (*top*) and the change by rosiglitazone versus placebo treatment in PAI-1 mRNA (*middle*) and plasma PAI-1 antigen concentration (*bottom*). *LD*$^+$ indicates HIV$^+$ patients with HAART-associated lipodystrophy; *LD*–, HIV$^+$ patients using HAART but without LD; *HIV*–, HIV-normal subjects; *β2 MG*, β_2-microglobulin. *p<0.05, ***p<0.005. (From [3] with permission)

HAART Reduces Markers of Endothelial and Coagulation Activation in HIV-1-Infected Patients

Endothelial-derived proteins [soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1), and von Willebrand's factor (VWF)] are markers of endothelial lesion and/or activation. These markers are increased in HIV-infected patients and they are usually considered as markers and/or agents of the accelerated atherosclerosis which characterizes HIV-infected patients independently of HAART and HAART-associated metabolic syndrome. The increased plasma level of VWF [4] could be related to the inflammatory status, to antiretroviral treatment, but also to the direct lesion of endothelium by HIV-1, and levels of sVCAM-1 and VWF factor are significantly correlated with HIV-1 viral load.

Great attention has been focused on VWF. In longitudinal testing, a persistent rise in VWF was associated with progression of HIV disease. The persistent elevation of functionally normal VWF during HIV infection, possibly reflecting a persistent endothelial cell activation, may have an important role in the pathogenesis of HIV infection. This elevated VWF is functionally normal as evaluated by plasma factor VIII (FVIII), ristocetin cofactor assay, and VWF multimer analyses. While HIV-infected patients showed enhanced platelet activation, platelets did not contribute substantially to the increased plasma VWF levels [5].

VWF plasma levels are correlated with HIV-1 viral load. Plasma levels of sVCAM-1, sICAM-1, and VWF decrease significantly after 5–13 months of HAART (Fig. 3). The pronounced decline in HIV RNA levels is associated with a corresponding decrease in VWF levels. D-dimer concentrations also decrease significantly after initiation of treatment. PI- and non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimens have similar effects. However, contrary to markers of endothelial lesion/activation, HAART does not reduce the levels of the soluble markers of platelet activation (sP-selectin and CD40 ligand) (Table 1) [6]. The inhibition of markers of endothelial activation may be of benefit by counterbalancing the consequences of

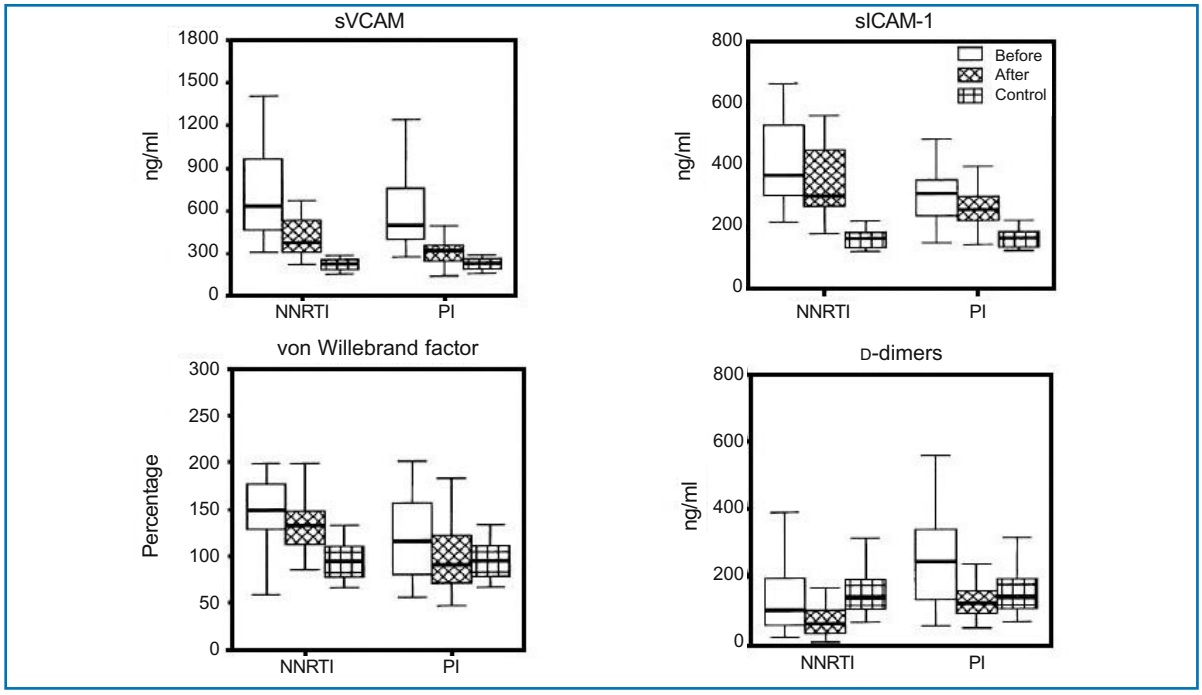

Fig. 3. Plasma levels of soluble vascular cell adhesion molecule (*sVCAM*)-1, soluble intercellular adhesion molecule (*sICAM*)-1, von Willebrand's factor, and D-dimers in HIV-infected patients who received treatment with protease inhibitors (*PIs*; *n*=21) or a non-nucleoside reverse transcriptase inhibitor (*NNRTI*; *n*=20), before and after initiation of treatment, compared to levels in healthy, HIV-negative control subjects (*n*=21). (From [6] with permission)

Table 1. Levels of endothelial, coagulation, and platelet activation markers in HIV-infected patients receiving protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs) compared with levels in HIV-negative control subjects (from [6] with permission)

	Patients receiving PIs (*n*=21)		Patients receiving NNRTIs (*n*=20)		
Activation marker	**Before initiation of treatment**	**After initiation of treatment**	**Before initiation of treatment**	**After initiation of treatment**	**Control subjects (*n*=21)**
Endothelial, mean (±SD)					
sVCAM-1, ng/ml	595 (266)[a]	381 (98)[a,b]	790 (442)[a]	515 (324)[a,b]	223 (42)
sICAM-1, ng/ml	313 (125)[a]	267 (86)[a,b]	444 (218)[a]	401 (249)[a,b]	168 (30)
von Willebrand factor, %	120 (45)	99 (39)[b]	149 (35)[a]	129 (33)[a,b]	98 (28)
Thrombomodulin, ng/ml	78 (16)[a]	77 (14)	46 (16)[a]	47 (17)[a]	67 (11)
Coagulation, mean (±SD)					
D-dimers, ng/ml	311 (248)	224 (320)b	141 (118)	74 (57)[b]	153 (68)
Thrombinantithrombin III complex, g/l	4.9 (7.7)	3.5 (2.6)	5.5 (5.7)	13 (18.3)[a]	3.2 (0.6)
Platelet, mean (±SD)					
sP-selectin, ng/ml	79 (84)[a]	67 (16)	49 (32)	58 (44)	34 (9)
Soluble CD40 ligand, ng/ml	2.3 (2.3)[a]	1.9 (0.7)[a]	2.3 (3.0)	3.1 (3.4)[a]	0.7 (0.3)

sICAM, soluble intercellular adhesion molecule; *sP*, soluble platelet; sVCAM, soluble vascular cell adhesion molecule.
[a] Statistically significantly higher than that of the control group (calculated using 1-way analysis of variance, Scheffé test, and Bonferroni correction; $p<0.05$).
[b] Statistically significantly lower than values before initiation of treatment (calculated using paired Wilcoxon rank sum test; $p< 0.01$)

HAART-associated metabolic syndrome and potentially preventing the development of atherosclerosis in HIV-infected patients.

HAART May Induce Thrombocytosis

Thrombocytosis has been reported in 9% of patients receiving HAART, with vascular complications being reported in up to 25% of the cases [7]. This side effect could contribute to the increased risk of arterial thrombosis among these patients.

Coagulative Disorders in HIV-Infected Patients Undergoing HAART Leading to the Risk of Venous Thrombosis

In recent years, several case reports [8] and a first epidemiological study [9] have focused attention on HIV-infected patients developing venous thromboembolic events under HAART [10, 11].

Thromboembolic Events and HIV Infection

Deep venous thrombosis of the lower arms [12, 13], pulmonary embolism [12], as well as thrombosis involving jugular and subclavian veins [14, 15], upper arm veins (apparently independent of intravenous drug abuse) [16], and cerebral [17], portal [18, 19], and retinal veins [20–23] have been described in HIV-infected patients, especially in those receiving HAART.

The risk factors of venous thromboembolic events identified in the general population (venous stasis, vascular lesions, hypercoagulability, and deficiency in the fibrinolytic system) are often found in HIV-infected patients, but additional factors may be present such as:

1. Acquired deficiency in coagulation inhibitors (protein S [23, 24], heparin cofactor II [25]).
2. Endothelial lesions.
3. Infection by HIV-1 itself [26;27] or opportunistic infections (e.g., cytomegalovirus [28], chlamydia [29]).
4. Treatments (endothelial toxicity due to PIs and more specifically to indinavir [18] and ritonavir [30]).
5. Inflammatory and/or dysmetabolic states associated with HIV infection and HAART inducing hypofibrinolysis [increase in fibrinolysis inhibitors (mainly PAI-1) and a hypercoagulability state with increased coagulation factors (fibrinogen, VWF]. This results in an increase in global markers (D-dimers), due to inflammatory cytokines which induce a prothrombotic endothelial phenotype (decreased expression by endothelial cells of membrane thrombomoduline, of protein C receptor, hyperexpression by endothelial cells of tissue factor, increased synthesis of PAI-1 and of VWF) and the acquisition by leukocytes of a prothrombotic phenotype (mainly shedding of membrane microvesicles expressing tissue factor, complexes between leukocytes and platelets), and indirectly platelet activation.
6. Autoimmune state with a high frequency of auto-antibodies which act on coagulation such as those with specificity against phospholipids, cardiolipids, and prothrombinase (also called lupus anticoagulant) [31–34].
7. Potentially prothrombotic therapeutic molecules (as reported for indinavir [18], ritonavir [30], or megestrol acetate [18, 35, 36]), or invasive procedures (such as permanent indwelling catheters and implantable chambers).
8. HIV-associated malignancies (e.g., Kaposi's sarcoma [37]).
9. Vascular lesions related to intravenous drug administration [16].

Few studies have tried to quantify the incidence of venous thromboembolic events (VTEE) in large cohorts of HIV patients. The Adult/Adolescent Spectrum of HIV Disease Project [9] reported the incidence of clinical VTEE and the associated risk factors in a population of HIV patients. This large epidemiological study had the advantage of being based on high numbers of patients (42,935 patients) with a long follow-up (2.4 years) and of being representative of a large spectrum of patients aged 13 years and over from more than 100 specialized medical centers in the United States. The calculated incidence of VTEE was 2.6/1,000 patient–years compared to 1/1,000 in the general population [38]. However, in this study,

the incidence of VTEE was not the main endpoint, thus the real incidence may be underestimated.

The risk factors associated to VTEE were [9]:

- Age: above 45 years, the adjusted odds ratio (AOR) was 1.9 (CI 95%: 1.4–2.7).
- Cytomegalovirus infection or retinitis: AOR 1.9 (CI 95%: 1.2–2.9).
- Other opportunistic infection: AOR 1.5 (CI 95%: 1.1–2.2).
- Hospitalization: AOR 3.3 (CI 95%: 2.5–4.4).
- Use of megestrol acetate: AOR 2.0 (CI 95%: 1.3–3.9).
- Use of indinavir: AOR 2.4 (CI 95%: 1.4–4.3).

The occlusion of the retinal veins is mostly related to ocular infection such as that by herpes virus [39], but can be of other origin [22], especially when they are bilateral [40] (it could be related to the endothelial affinity of HIV). Cerebral venous thrombosis can be associated to a deficiency of inhibitors such as protein S [41] or to local infections (meningitis or cerebral localization of cytomegalovirus [42], coccidioidomycosis [43]) or malignancy (e.g., non-Hodgkin's immunoblastic lymphoma) [44].

The increased plasma level of VWF and fibrinogen is more frequently associated with arterial thrombosis than venous thrombosis.

In HIV-infected patients, a high incidence of antiphospholipid antibodies has been reported. In a French study involving 342 HIV-infected patients, 64% had positive anticardiolipin antibodies, 50% had positive antiphosphatidyl choline antibodies, and 39% had antibodies with double specificity [45]. However, the specificity of the antiphospholipid antibodies usually associated with lupus and lupus-like syndromes was exceptional (anti-β2GP-1, lupus anticoagulant with antiprothrombinase specificity). Alteration of the immune system associated with HIV infection is different from that of lupus, probably explaining the differences in the specificity of antiphospholipid antibodies in the two diseases, but without explaining the pathogeny of their occurrence. One of theses differences is that although antiphospholipid antibodies are commonly detected in patients with HIV disease, the clinical manifestations of antiphospholipid syndrome are uncommon and are still reported as case reports [46]. In HIV-infected patients, the main features of the antiphospholipid antibodies are not thrombotic but avascular (bone and cutaneous necrosis) [47].

Protein S has been studied in HIV-infected children (characterized by a minimal association of confounding risk factors), showing that the deficiency was mostly due to a deficit in free protein S antigen with a global functional deficiency in protein S [48]. This deficiency was correlated with the clinical evolution of the disease. The incidence was 33% in asymptomatic HIV-infected children and 75% in symptomatic HIV-infected children. The occurrence of protein S deficiency appears linked to the duration of the disease but not to the degree of immunodeficiency, since it is not correlated to the $CD4^+$ lymphocytes count. Cell membrane phospholipids are usually not accessible, but if they are exposed in large amounts they could form a complex with and absorb protein S (in a process similar to that observed during the hemolytic crisis of sickle cell anemia). Similar exposure of cell membrane phospholipids (e.g., from endothelial origin during HIV contamination) could induce occurrence of antiphospholipid antibodies.

Most of these factors are correlated with each other [34] and with the markers of activation of the coagulation/fibrinolysis reaction (such as the D-dimers), with the status of immunodeficiency, with opportunistic infections, with cancer complications, and with the inflammatory status.

Three different types of mechanisms of VTEE linked to treatments can be differentiated:

- Those due to the central catheters required in patients with severe undernourishment [49]. It seems that among HIV-infected patients requiring total intravenous nutrition, a low-dose oral anticoagulant regimen does not have the efficacy encountered in other types of patients treated with a central catheter [50].
- Those related to the administration of megestrol acetate [35].
- Those related to PIs [18, 51]. This observation is in apparent opposition with two other types of observations on PI-related effects in HIV-infected patients:

- Effective antiretroviral treatment in HIV-infected patients decreases markers of endothelial activation/lesion [5] and markers of coagulation activation [6].
- Antiretroviral treatment exerts a prohemorrhagic effect in hemophilic patients infected by HIV-1 [52].

Treatment-Related VTEE in HIV-infected Patients

PIs are large lipophilic molecules metabolized by P450 cytochromes. The same P450 cytochrome system also metabolizes oral anticoagulants (warfarin) [53]. HIV-infected patients often have complex clinical signs such as thrombocytopenia or other clinical manifestations or treatment which often represent a contraindication to warfarin treatment so that other types of therapy may be required, such as the use of low-molecular-weight heparin for long periods.

Coagulative Disorders in HIV-Infected Patients Leading to Microvascular Risk of Thrombosis

Microthrombotic Disease in HIV Patients

Thrombotic thrombocytopenic purpura (TTP) is a microthrombotic disease of rare occurrence. The most clinically sensitive microcirculations to TTP are those of the brain, kidney, and liver, explaining the most frequent clinical manifestations of the disease. One of the main pathogenic mechanism of TTP is a deficiency (hereditary or acquired) of an endogenous metalloprotease (ADAMS 13) which physiogically degrades the highest-molecular-weight forms of VWF into lower-molecular-weight fragments. The increased concentration of higher-molecular-weight forms of VWF triggers in vivo platelet aggregation and formation of platelet microthrombi, which plug the microcirculations of the most sensitive organs. The treatment is based on plasma exchange and infusion of fresh frozen plasma to remove the highest-molecular-weight forms of VWF, to remove the inhibitors of ADAMS 13, and to resplenish ADAMS 13. From an epidemiologic point of view, TTP in HIV infection is associated with opportunistic infections (cryptosporidiosis, cytomegalovirus infection) [54], with HIV-associated malignancies, or with HIV-associated wasting syndrome. The incidence of TTP is significantly reduced after the introduction of HAART (Fig. 4) [55, 56].

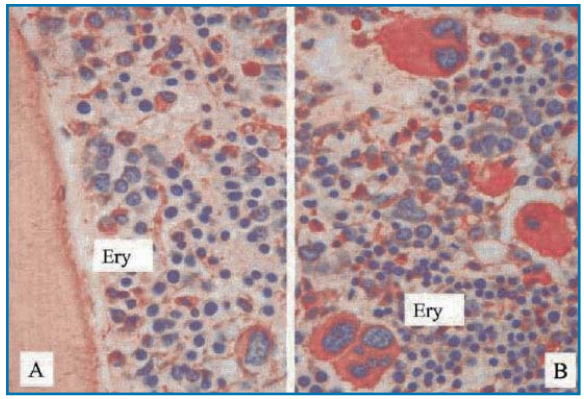

Fig. 4a, b. Photomicrographs of bone marrow core biopsy. **A**. Paratrabecular aggregates of erythroid precursor cells as seen in myelodysplasia. H&E, ×400. **B** Hypercellularity with erythroid and megakaryocytes hyperplasia. PAS, ×400. (From [56] with permission)

Coagulative Disorders in HIV-Infected Patients Leading to Hemorrhagic Condition

Thrombocytopenia

The most frequent hemorrhagic condition associated with HIV infection is thrombocytopenia [57]. Although often asymptomatic, thrombocytopenia may be linked to a variety of bleeding abnormalities. The underlying pathophysiology includes accelerated peripheral platelet destruction and decreased ("ineffective") production of platelets from the infected megakaryocytes. In drug users, the disease appears to be of more rapid progression and more frequently complicated. HIV-associated thrombocytopenia responds to antiretroviral therapy, but this is less effective in drug users [58]. Some studies have evaluated the use of zidovudine (AZT) and have shown increased platelet production. HAART induces a sustained platelet response in HIV-associated thrombocytopenia, even in antiretroviral-experienced sub-

jects and in those with AZT-resistant thrombocytopenia (Table 2) [59]. If antiretroviral agents fail to improve the platelet count or if antiretroviral agents cannot be used, other treatments, similar to those used in "classic" immune thrombocytopenia (ITP), can be employed, including steroids and intravenous immunoglobulins (intravenous anti-D). Splenectomy has been used to treat HIV-infected patients with refractory thrombocytopenia. Although it is an effective treatment, there are concerns about infections and selection of appropriate candidates. Other treatment modalities, such as interferon, vincristine, danazol, low-dose splenic irradiation, and staphylococcal protein A immunoadsorption have shown limited success in HIV-associated thrombocytopenia. Alternatively, thrombocytopenia in HIV-infected patients may be treated with pharmacological hyperstimulation of megakaryocytopoiesis (administration of PEG-rHuMGDF or TPO). The latest evidence indicates that the chemokine receptor CXCR4 (co-receptor for the cellular entry of lymphotropic HIV strains) is expressed on megakaryocytes; as a result, the development of chemokine receptor antagonists may modify the course of the disease.

Increased Hemorrhagic Tendency and Hemophiliac HIV Patients

One concerning side effect of HAART is the increased hemorrhagic tendency of hemophiliac patients contaminated and treated for HIV. Shortly after the introduction of PIs for the treatment of HIV infection, an association between these drugs and an increased bleeding tendency in patients with hereditary bleeding disorders was observed. The patients experience not only an increased bleeding frequency in usual sites, but bleeding can also occur in unusual sites such as the finger joints. Mucus membrane bleeding and hematuria are also common. Ritonavir appears to be associated with the highest risk of bleeding followed by indinavir. PI-associated bleeds tend to be more resistant to factor VIII concentrate treatment, and periods of prophylaxis may be required in individuals with frequent persistent bleeding. Patients continuing PI therapy tend to develop a tolerance to this adverse effect over time. The mechanism of the bleeding tendency has not been elucidated. There is no consistent evidence of a disturbance of coagulation, fibrinolysis, or platelet function, which raises the possibility that PIs may exert a

Table 2. Platelet and $CD4^+$ response to antiretroviral therapy in 34 HIV-infected patients with severe thrombocytopenia (from [59] with permission from the British Infection Society)

Variable	No. of patients	Baseline*	Treatment*		Overall†		0–3rd month¥	3rd–6th month¥
			3rd month	6th month	χ^2	*p*	*p*	*p*
HAART treatment	15							
PLT count (PLT x 10^9/1)		32 (6–49)	87 (34–259)	108 (20–195)	10.53	0.01	0.01	NS
CD4+ (cells/µl)		58 (1–392)	127 (10–503)	142 (4–387)	8.1	0.02	0.05	NS
AZT treatment	19							
PLT count (PLT x 10^9/1)		29 (6–47)	49 (12–429)	79 (9–253)	20.63	0.001	0.01	NS
CD4+ (cells/µl)		96 (9–177)	144 (16–528)	99 (15–378)	6.63	0.03	0.01	NS

* Values of each variable are median (range); † Friedmann test; ¥ Wilcoxon-Wilcox test

direct local effect on blood vessels. It is very important that this class-specific side effect is recognized and understood by both the physicians and the patients [52].

References

1. Koppel K, Bratt G, Schulman S, Bylund H, Sandstrom E (2002) Hypofibrinolytic state in HIV-1-infected patients treated with protease inhibitor-containing highly active antiretroviral therapy. J Acquir Immune Defic Syndr 29:441-449
2. Hadigan C, Meigs JB, Rabe J et al (2001) Increased PAI-1 and tPA antigen levels are reduced with metformin therapy in HIV-infected patients with fat redistribution and insulin resistance. J Clin Endocrinol Metab 86:939-943
3. Yki-Jarvinen H, Sutinen J, Silveira A et al (2003) Regulation of plasma PAI-1 concentrations in HAART-associated lipodystrophy during rosiglitazone therapy. Arterioscler Thromb Vasc Biol 23:688-694
4. Drouet L, Scrobohaci ML, Janier M, Baudin B (1990) Endothelial cells: target for the HIV1 virus? Nouv Rev Fr Hematol 32:103-106
5. Aukrust P, Bjornsen S, Lunden B et al (2000) Persistently elevated levels of von Willebrand factor antigen in HIV infection. Downregulation during highly active antiretroviral therapy. Thromb Haemost 84:183-187
6. Wolf K, Tsakiris DA, Weber R, Erb P, Battegay M (2002) Antiretroviral therapy reduces markers of endothelial and coagulation activation in patients infected with human immunodeficiency virus type 1. J Infect Dis 185:456-462
7. Miguez-Burbano MJ, Burbano X, Rodriguez A, Lecusay R, Rodriguez N, Shor-Posner G (2002) Development of thrombocytosis in HIV$^+$ drug users: impact of antiretroviral therapy. Platelets 13:183-185
8. Saif MW, Greenberg B (2001) HIV and thrombosis: a review. AIDS Patient Care STDS 15:15-24
9. Sullivan PS, Dworkin MS, Jones JL, Hooper WC (2000) Epidemiology of thrombosis in HIV-infected individuals. The Adult/Adolescent Spectrum of HIV Disease Project. AIDS 14:321-324
10. Majluf-Cruz A, Silva-Estrada M, Sanchez-Barboza R et al (2004) Venous thrombosis among patients with AIDS. Clin Appl Thromb Hemost 10:19-25
11. Callens S, Florence E, Philippe M, Van Der PM, Colebunders R (2003) Mixed arterial and venous thromboembolism in a person with HIV infection. Scand J Infect Dis 35:907-908
12. Becker DM, Saunders TJ, Wispelwey B, Schain DC (1992) Case report: venous thromboembolism in AIDS. Am J Med Sci 303:395-397
13. Tanimowo M (1996) Deep vein thrombosis as a manifestation of the acquired immunodeficiency syndrome? A case report. Cent Afr J Med 42:327-328
14. Vielhauer V, Schewe CK, Schlondorff D (1998) Bilateral thrombosis of the internal jugular veins with spasmodic torticollis in a patient with acquired immunodeficiency syndrome and disseminated cytomegalovirus infection. J Infect 37:90-91
15. Bayer DD, Sorbello AF, Condoluci DV (1995) Bilateral subclavian vein thrombosis in a patient with acquired immunodeficiency syndrome. J Am Osteopath Assoc 95:276-277
16. Laing RB, Brettle RP, Leen CL (1996) Venous thrombosis in HIV infection. Int J STD AIDS 7:82-85
17. Meyohas MC, Roullet E, Rouzioux C et al (1989) Cerebral venous thrombosis and dual primary infection with human immunodeficiency virus and cytomegalovirus. J Neurol Neurosurg Psychiatry 52:1010-1011
18. Carr A, Brown D, Cooper DA (1997) Portal vein thrombosis in patients receiving indinavir, an HIV protease inhibitor. AIDS 11:1657-1658
19. Narayanan TS, Narawane NM, Phadke AY, Abraham P (1998) Multiple abdominal venous thrombosis in HIV-seropositive patients. Indian J Gastroenterol 17:105-106
20. Roberts SP, Haefs TM (1992) Central retinal vein occlusion in a middle-aged adult with HIV infection. Optom Vis Sci 69:567-569
21. Mansour AM, Li H, Segal EI (1996) Picture resembling hemicentral retinal vein occlusion in the acquired immunodeficiency syndrome: is it related to cytomegalovirus? Ophthalmologica 210:108-111
22. Park KL, Marx JL, Lopez PF, Rao NA (1997) Noninfectious branch retinal vein occlusion in HIV-positive patients. Retina 17:162-164
23. Stahl CP, Wideman CS, Spira TJ, Haff EC, Hixon GJ, Evatt BL (1993) Protein S deficiency in men with long-term human immunodeficiency virus infection. Blood 81:1801-1807
24. Bissuel F, Berruyer M, Causse X, Dechavanne M, Trepo C (1992) Acquired protein S deficiency: correlation with advanced disease in HIV-1-infected patients. J Acquir Immune Defic Syndr 5:484-489
25. Toulon P, Lamine M, Ledjev I et al (1993) Heparin cofactor II deficiency in patients infected with the human immunodeficiency virus. Thromb Haemost 70:730-735

26. Muller MM, Griesmacher A (2000) Markers of endothelial dysfunction. Clin Chem Lab Med 38:77-85
27. Gujuluva C, Burns AR, Pushkarsky T et al (2001) HIV-1 penetrates coronary artery endothelial cells by transcytosis. Mol Med 7:169-176
28. Madalosso C, de SN Jr, Ilstrup DM, Wiesner RH, Krom RA (1998) Cytomegalovirus and its association with hepatic artery thrombosis after liver transplantation. Transplantation 66:294-297
29. Kaukoranta-Tolvanen SS, Ronni T, Leinonen M, Saikku P, Laitinen K (1996) Expression of adhesion molecules on endothelial cells stimulated by *Chlamydia pneumoniae*. Microb Pathog 21:407-411
30. Zhong DS, Lu XH, Conklin BS et al (2002) HIV protease inhibitor ritonavir induces cytotoxicity of human endothelial cells. Arterioscler Thromb Vasc Biol 22:1560-1566
31. Stimmler MM, Quismorio FP Jr, McGehee WG, Boylen T, Sharma OP (1989) Anticardiolipin antibodies in acquired immunodeficiency syndrome. Arch Intern Med 149:1833-1835
32. Karmochkine M, Raguin G (1998) Severe coronary artery disease in a young HIV-infected man with no cardiovascular risk factor who was treated with indinavir. AIDS 12:2499
33. Ankri A, Bonmarchand M, Coutellier A, Herson S, Karmochkine M (1999) Antiphospholipid antibodies are an epiphenomenon in HIV-infected patients. AIDS 13:1282-1283
34. Feffer SE, Fox RL, Orsen MM, Harjai KJ, Glatt AE (1995) Thrombotic tendencies and correlation with clinical status in patients infected with HIV. South Med J 88:1126-1130
35. Force L, Barrufet P, Herreras Z, Bolibar I (1999) Deep venous thrombosis and megestrol in patients with HIV infection. AIDS 13:1425-1426
36. Hirsh J, Hull RD, Raskob GE (1986) Epidemiology and pathogenesis of venous thrombosis. J Am Coll Cardiol 8 [6 Suppl B]:104B-113B
37. Kaufmann T, Nisce LZ, Metroka C (1991) Thromboembolism in AIDS-related Kaposi's sarcoma. JAMA 266:2834
38. Heit JA (2002) Venous thromboembolism epidemiology: implications for prevention and management. Semin Thromb Hemost 28 [Suppl 2]:3-13
39. Biswas J, Roy CB, Krishna KS, Lily TK, Madhavan HN (2001) Detection of *Mycobacterium tuberculosis* by polymerase chain reaction in a case of orbital tuberculosis. Orbit 20:69-74
40. Friedman SM, Margo CE (1995) Bilateral central retinal vein occlusions in a patient with acquired immunodeficiency syndrome. Clinicopathologic correlation. Arch Ophthalmol 113:1184-1188
41. Iranzo A, Domingo P, Cadafalch J, Sambeat MA (1998) Intracranial venous and dural sinus thrombosis due to protein S deficiency in a patient with AIDS. J Neurol Neurosurg Psychiatry 64:688
42. Biswas J, Kumar AA, George AE et al (2000) Ocular and systemic lesions in children with HIV. Indian J Pediatr 67:721-724
43. Kleinschmidt-DeMasters BK, Mazowiecki M, Bonds LA, Cohn DL, Wilson ML (2000) Coccidioidomycosis meningitis with massive dural and cerebral venous thrombosis and tissue arthroconidia. Arch Pathol Lab Med 124:310-314
44. Doberson MJ, Kleinschmidt-DeMasters BK (1994) Superior sagittal sinus thrombosis in a patient with acquired immunodeficiency syndrome. Arch Pathol Lab Med 118:844-846.
45. Abuaf N, Laperche S, Rajoely B et al (1997) Autoantibodies to phospholipids and to the coagulation proteins in AIDS. Thromb Haemost 77:856-861
46. Shahnaz S, Parikh G, Opran A (2004) Antiphospholipid antibody syndrome manifesting as a deep venous thrombosis and pulmonary embolism in a patient with HIV. Am J Med Sci 327:231-232
47. Ramos-Casals M, Cervera R, Lagrutta M et al (2004) Clinical features related to antiphospholipid syndrome in patients with chronic viral infections (hepatitis C virus/HIV infection): description of 82 cases. Clin Infect Dis 38:1009-1016
48. Sugerman RW, Church JA, Goldsmith JC, Ens GE (1996) Acquired protein S deficiency in children infected with human immunodeficiency virus. Pediatr Infect Dis J 15:106-111
49. Melchior JC, Messing B (1999) Home parenteral nutrition in acquired immunodeficiency syndrome patients. Nutrition 15:68-69
50. Duerksen DR, Ahmad A, Doweiko J, Bistrian BR, Mascioli EA (1996) Risk of symptomatic central venous thrombotic complications in AIDS patients receiving home parenteral nutrition. JPEN J Parenter Enteral Nutr 20:302-305
51. George SL, Swindells S, Knudson R, Stapleton JT (1999) Unexplained thrombosis in HIV-infected patients receiving protease inhibitors: report of seven cases. Am J Med 107:624-630
52. Wilde JT, Lee CA, Collins P, Giangrande PL, Winter M, Shiach CR (1999) Increased bleeding associated with protease inhibitor therapy in HIV-positive patients with bleeding disorders. Br J Haematol 107:556-559
53. Llibre JM, Romeu J, Lopez E, Sirera G (2002) Severe interaction between ritonavir and acenocoumarol.

Ann Pharmacother 36:621-623
54. Rerolle JP, Canaud G, Fakhouri F et al (2004) Thrombotic microangiopathy and hypothermia in an HIV-positive patient: importance of cytomegalovirus infection. Scand J Infect Dis 36:234-237
55. Gervasoni C, Ridolfo AL, Vaccarezza M et al (2002) Thrombotic microangiopathy in patients with acquired immunodeficiency syndrome before and during the era of introduction of highly active antiretroviral therapy. Clin Infect Dis 35:1534-1540
56. Gruszecki AC, Wehrli G, Ragland BD et al (2002) Management of a patient with HIV infection-induced anemia and thrombocytopenia who presented with thrombotic thrombocytopenic purpura. Am J Hematol 69:228-231
57. Scaradavou A (2002) HIV-related thrombocytopenia. Blood Rev 16:73-76
58. Burbano X, Miguez MJ, Lecusay R et al (2001) Thrombocytopenia in HIV-infected drug users in the HAART era. Platelets 12:456-461
59. Carbonara S, Fiorentino G, Serio G et al (2001) Response of severe HIV-associated thrombocytopenia to highly active antiretroviral therapy including protease inhibitors. J Infect 42:251-256

Cardiovascular Complications in HIV-Infected Children

D. Bonnet

Longitudinal cardiovascular follow-up of HIV-infected children has shown that all components of the cardiovascular system might be affected during the course of the disease. The most frequent feature observed in the pediatric population is left ventricular dysfunction [1–12]. In developed countries, antiviral therapy has dramatically improved morbidity and mortality in HIV-infected children. Consequently, the spectrum of HIV-related concerns has shifted from reduction of mortality towards longer-term complications of HIV infection and adverse effects associated with the use of antiretroviral therapy. With regards to the cardiovascular system, efforts have been made to describe the long-term outcome in children. In this chapter, we review the different cardiac diseases that occur in HIV-infected children. HIV-related cardiac complications are very similar to the spectrum of disease described in adults, with a few exceptions. There have been descriptions of fetal and neonatal complications due to the common vertical transmission of the virus in most cases and the possible adverse intrauterine effects of maternal HIV infection with or without fetal HIV infection [12, 13]. The pathogenesis of some cardiac manifestations remains uncertain. Although in some cases the myocardial [14], endocardial [15], or pericardial disease [16, 17] may be attributed to an opportunistic infection, it is likely that HIV-related cardiac disease has a multifactorial origin due to HIV, secondary infections, other concurrent disease states, side effects of therapy, nutritional deficiencies, or yet-unknown mechanisms. However, it is recommended that children with active HIV infection should be monitored for cardiac disease because symptoms of cardiac failure are delayed and interventions might be required to reduce cardiac morbidity and mortality. Finally, the long-term "vascular" outcome might be impaired either by the HIV infection or by the metabolic effects of the antiretroviral therapy or their synergistic effect on endothelium. Early atherosclerosis may be a new emerging disease in HIV-infected children, and this raises concern on the prevention of vascular damage.

Myocardial Involvement

Dilated cardiomyopathy is the most common cardiac complication of HIV infection in children and is an adverse prognostic indicator in patients with HIV infection. The Prospective Pediatric Pulmonary and Cardiac Complications Study of HIV (P2C2) showed a 5-year cumulative incidence of dilated cardiomyopathy as high as 28% in vertically HIV-infected children [12]. Further, the mortality rate in children who exhibited congestive heart failure was 52.5% (95% CI, 30.5–74.5) in this study. In addition, the authors suggest that the incidence of left ventricular dysfunction in HIV-infected children is underestimated in this population because of the low sensitivity of the commonly used noninvasive echocardiographic techniques to examine left ventricular performance [18].

The reported incidence of cardiac involvement in HIV-infected children varies from 0.9% of congestive heart failure in a study using hospital diagnosis codes [19] to 14% in later studies using the shortening fraction of the left ventricle as an indicator of systolic function [20]. Lipshultz et al. reported that cardiac abnormalities were seen in up to 93% of patients who had undergone more extensive cardiac testing at a referral center [16]. Two patterns of left ventricular function abnormalities were described when using load-independent indexes of contractility: (a) hyperdynamic left ventricular performance with enhanced

contractility and reduced afterload, and (b) diminished contractility associated with symptomatic cardiomyopathy. Serial evaluations revealed that 89% of the patients had progressive left ventricular dysfunction.

The most important study designed to assess the incidence of cardiac dysfunction in HIV-infected children is the P2C2 HIV study [10, 12, 21–23]. This study began in 1990 and data collection continued through January 1997. Left ventricular function was evaluated every 4–6 months for up to 5 years in a birth cohort of 805 infants born to women infected with HIV-1. In total, 205 vertically HIV-infected children (group I) and 600 subjects enrolled during fetal life (group II, neonatal inception cohort; n=432) or before 28 days of age (n=168) were included in the study. Their final HIV status was unknown at the time of enrollment in the study. Of these, 93 were finally HIV-infected and 463 HIV-uninfected. In addition, a cross-sectionally measured comparison group of 195 healthy children born to mothers who were not infected with HIV was also recruited as external controls. Main outcome measures were the cumulative incidence of an initial episode of left ventricular dysfunction, cardiac enlargement, and congestive heart failure. Because cardiac abnormalities tended to cluster in the same patients, the number of children who had cardiac impairment defined as having left ventricular fractional shortening (LV FS) $\leqslant$25% after 6 months of age, congestive heart failure, or treatment with cardiac medications was also determined. In group I, the cumulative incidence of left ventricular dysfunction after 5 years in the study was 28%. In group II, the 5-year cumulative incidence of left ventricular dysfunction was 9.3% in the HIV-infected neonatal group compared with 2.9% in the uninfected children (p=0.02). During the follow-up period, 21 children in group I had congestive heart failure (cumulative incidence rate 14%). The use of cardiac medication after a diagnosis of cardiomyopathy was 25%. In the group II-infected children, four cases of congestive heart failure occurred and the 5-year cumulative incidence rate was 5.1%, with four additional patients receiving medications for a cardiomyopathy. This study and the previous reports show that cardiac dysfunction occurs frequently in HIV-infected children with a wide range of abnormalities. The relative risk of death in infected children is 8.5–14.6 times higher than in children without these complications. This risk is even higher in rapid progressors defined as infants having an AIDS-defining condition, severe immunodepression (CDC immunologic category 3), or both [12]. This worrisome study has led to controversies regarding the fact that cardiomyopathy is a major cause of or contributor to mortality in HIV-infected children, since several groups in Europe did not have this experience. However, it suggests strongly that a routine echocardiographic follow-up should be proposed in this population.

When analyzing more precisely the echocardiographic parameters of left ventricular function and mass, additional prognostic factors appear [24]. Indeed, an abnormal thickness-to-dimension ratio from progressive left ventricular dilatation and inadequate hypertrophy and an increased ventricular mass are related with patient morbidity and mortality. Diastolic function estimated by isovolumic relaxation time was also found to be impaired in HIV-infected children and to decline further with time. These markers may be a harbinger of congestive heart failure.

The pathogenesis of left ventricular dysfunction in HIV-infected children remains unclear and its specific origin might be difficult to address as the prevalence of this complication is thought to be rare today. HIV cardiomyopathy is probably not due to any one single mechanism. In the majority of cases of AIDS-related cardiomyopathy in both pediatric and adult age groups, no precise etiology is found. A few autopsy studies described the pathologic findings of cardiomyopathy in pediatric patients with HIV. In one of the earlier series of five fatal pediatric cases, the heart showed biventricular dilatation with an increased diameter of myocardial fibers, nuclear enlargement, myocyte vacuolation, interstitial edema with or without foci of myxoid change, small foci of myocardial fibrosis, and endocardial thickening [25]. Mononuclear inflammatory infiltrates with small foci of myocyte necrosis were not found in any patient in this study or in later ones. The pathologic findings of lymphocytic myocarditis, which is common in adults with AIDS, are similar to those

found in pediatric age groups [26]. Electron microscopy, done in very few cases, showed mitochondrial and sarcoplasmic reticulum changes. The specificity of these anomalies and the fact that these structures may be related to the development of cardiomyopathy in AIDS patients have not been demonstrated [27].

In a minority of cases of lymphocytic myocarditis in adults, an associated pathogen is found. In one pediatric case, cytomegalovirus inclusions were noted in the endocardium and endothelial cells without myocardial involvement [25]. The other microorganisms reported to involve the heart in cases of AIDS (cryptococcus, *Candida*, *Toxoplasma gondii*, *Sarcocystis*, bacterial infection during tuberculosis, coxsackie virus, and *Aspergillus*) are only rarely reported or have not been described yet.

HIV has been detected within myocardial cells by different methods, suggesting that the virus itself may be a cause of cardiomyopathy and lymphocytic myocarditis in some patients. The role of dendritic cells in the pathogenesis has been suggested because PCR detected HIV more frequently in these cells [28]. The mechanism leading to cardiac dysfunction remains unclear. It may involve cytokines, a susceptibility to myocarditis in HIV-infected patients, and/or auto-immunity [29].

The toxicity of antiretroviral therapy may also contribute to the pathogenesis of cardiomyopathy. The introduction of highly active antiretroviral therapy regimens has significantly modified the course of HIV disease particularly in children, with longer survival rates and improvement of life quality in HIV-infected subjects. However, adverse cardiovascular effects of different drugs have been proposed. In a retrospective study of 137 HIV-infected children, Domanski et al. found that a cardiomyopathy was 8.4 times more likely to occur in children who had been previously given zidovudine than in those who had never taken this drug [30]. Although the cause of this difference is uncertain, it may be due to an inhibition of cardiac mitochondrial DNA replication by zidovudine. In our experience, we had only one case with proven mitochondrial respiratory chain deficiency on endomyocardial biopsy in a child receiving zidovudine. In a more recent study [31], 382 infants without HIV infection born to HIV-infected women (36 with zidovudine exposure) and 58 HIV-infected infants (12 with zidovudine exposure) underwent serial echocardiography from birth to 5 years of age. Zidovudine exposure was not associated with significant abnormalities in mean left ventricular fractional shortening, end-diastolic dimension, contractility, or mass in both the non-HIV-infected and the HIV-infected infants. The authors concluded that zidovudine was not associated with acute or chronic abnormalities in left ventricular structure or function in infants exposed to the drug in the perinatal period. While controversial, these results suggest that careful follow-up is necessary in an HIV-infected child with cardiomyopathy receiving zidovudine. Finally, nutritional deficiencies such as selenium deficiency and prolonged immunosuppression have also been proposed to be causal or deleterious additional factors [32].

The treatment of congestive heart failure in children with HIV should begin with routine anti-congestive measures. Although not formally studied in HIV-infected children, angiotensin converting inhibitors can be used judiciously. Recent non-randomized studies using chronic beta-blockers in children yielded encouraging preliminary results [33]. Lipshultz et al. reported normalization of the left ventricular dilatation and diminished wall thickness of HIV-infected children with monthly intravenous immunoglobulin infusion, possibly because of an improvement in immunologically mediated left ventricular dysfunction [34]. The question of whether asymptomatic HIV-infected children with left ventricular dilatation should be treated with angiotensin-converting inhibitors is unresolved.

Pericardial Involvement

Pericardial effusion has been reported in pediatric patients infected with HIV and even in fetuses. The prevalence of this cardiac complication may increase as the incidence of HIV infection rises in the pediatric age group. In children, pericardial effusion has been reported in up to 26% of cases [16]. These pericardial effusions are usually small

and asymptomatic. Kovacs et al. reported three cases of sudden death of infants with HIV who had symptomatic pericardial effusions, two with tamponade and one with large pericardial effusion and cardiac compromise [35]. In most cases of pericardial effusion, no established cause is found. In the published studies, there was no evidence of cardiac infection by pathogens other than HIV. Noninfectious causes such as lymphoma, Kaposi's sarcoma, or myocardial infarction have not been reported in children.

Endocardial Involvement

Infective endocarditis, either acute or subacute, has been rarely reported in pediatric AIDS patients [1]. Nonbacterial thrombotic endocarditis, usually an incidental finding in adults, has not yet been described in children.

Vascular Involvement

Although rare, coronary artery abnormalities have been described in the earliest case reports of cardiac complications in children [35–38]. Joshi et al. found macroscopic lesions in small and medium-sized arteries in six children with AIDS. The pathologic findings in the coronary artery wall were characterized by intimal fibrosis, fragmentation of the elastic lamellae, and calcification of the media. In one out of six cases, this arterial remodeling involved the coronary arteries and had led to a fatal myocardial infarction by aneurysms and thrombosis of the right coronary artery. The pathophysiology of these arterial anomalies is unknown. It may be related to the viral infection, given the absence of other cardiovascular risk factors. Whether HIV itself is the causal agent or other viruses such as herpes or cytomegalovirus has to be elucidated. The adverse effects of antiretroviral drugs, including dyslipidemia, lipodystrophy, and insulin resistance, are problems in the long-term management of HIV infection. This is of particular importance in children because HIV infection has become a chronic disease in this population. HIV-infected children may live two decades longer than HIV-infected adults. As in the adult population, metabolic toxicity of antiretroviral therapy has been observed in children [39–41], but the long-term cardiovascular consequences in children are unknown. Atherogenic lipoprotein changes in adults treated with protease inhibitors (PIs) have been found and are associated with endothelial dysfunction and increased intima-media thickness [42–44]. However, the relative contributions of antiretroviral therapy, chronic inflammation due to the viral infection, classic cardiovascular risk factors, and their interactions are very difficult to identify. Bozzette et al. showed that the benefit in terms of mortality associated with the extensive use of therapies for HIV was not diminished by any increase in the rate of cardiovascular or cerebrovascular events or related mortality [45]. The pediatric population offers a unique opportunity to study vascular function during HIV infection in the absence of classic cardiovascular risk factors. Symptomatic atherosclerosis is evidently absent at this age, but endothelial function and arterial stiffness can be investigated by noninvasive echotracking techniques. We have recently shown that HIV-infected children have a vascular dysfunction that may be an early step in the development of atherosclerosis. We did not find any difference between children receiving antiretroviral therapy and patients who had never been treated [46]. Differences with the control subjects indicate that the HIV infection itself may have a deleterious effect on vascular function. This is consistent with autopsy studies during the pre-antiretroviral era, reporting eccentric atherosclerosis lesions in the absence of traditional risk factors [36]. The HIV envelope protein, gp120, activates human arterial smooth muscle cells to express tissue factor, the initiator of the coagulation cascade [47]. In addition, inflammatory cytokines and viral proteins synergistically promote endothelial activation, apoptosis, or cell proliferation [48]. Consequently, the arterial remodeling observed in patients who had never been treated could be a result of direct viral infection, or of the activation of bystander cells (smooth muscle cells and endothelial cells), by HIV viral proteins. Hsue et al. recently proposed that in adults, immunodeficiency and traditional coro-

nary risk factors might contribute to atherosclerosis rather than the deleterious effects of PI treatment [49]. In children, it is possible that antiretroviral therapy counterbalances, at least transiently, HIV-induced injury to the developing vascular bed by reversing or stabilizing the HIV-induced vascular dysfunction.

Mild and nonprogressive aortic root dilation was also seen in children with vertically transmitted HIV infection from 2 to 9 years of age. Aortic root size was not significantly associated with markers for stress-modulated growth; however, aortic root dilation was associated with left ventricular dilation, increased viral load, and lower CD4 cell count in HIV-infected children. The aortic root dilation could also be a consequence of increased arterial stiffness affecting the aorta. As prolonged survival of HIV-infected patients becomes more prevalent, some patients may require long-term follow-up of aortic root size [50].

Conduction System Involvement

Various atrial and ventricular arrhythmias as well as atrioventricular blocks have been described in patients with HIV. Bharati et al. studied histologically the conduction system in six children who died of AIDS [51]. Vasculitis, myocarditis, and fragmentation with lobulation and fibrosis of the conduction system were found. In a prospective series of 31 pediatric patients with AIDS, Lipshultz et al. found frequent conduction defects and dysarrhythmias [16]. Brady et al. reported the case of an infant with AIDS who died suddenly of probable cardiac arrhythmia due to involvement of the conduction system by myocarditis [14].

Fetal Heart Involvement

A recent study by Hornberger sought to determine whether vertically transmitted HIV infection and maternal infection with HIV are associated with altered cardiovascular structure and function in utero. Fetal echocardiography was performed in 173 fetuses of 169 HIV-infected mothers (mean gestational age, 33.0 weeks; SD=3.7 weeks) at five centers. Fetuses determined after birth to be HIV-infected had similar echocardiographic findings as fetuses determined to be HIV-uninfected later, except for slightly smaller left ventricular diastolic dimensions (p=0.01). Differences in cardiovascular dimensions and Doppler velocities were identified between fetuses of HIV-infected women and previously published normal fetal data. The reason for the differences may be a result of maternal HIV infection, maternal risk factors, or selection bias in the external control data [52]. The P2C2 study describing the cardiovascular status of infants and children of HIV-infected women shows that children infected with HIV-1 had significantly more cardiac abnormalities than external control subjects [13]. Study analysis showed that HIV-1-infected children had a statistically significant higher heart rate at all ages. In addition, all children born to HIV-1-infected women had a low left ventricular fractional shortening at birth, which improved in the uninfected children by 8 months of age but not quite up to the normal level as seen in children in the external control group. The left ventricular fractional shortening remained persistently lower in the HIV-infected children for up to 20 months. Similarly, left ventricular mass was the same at birth for both HIV-infected and uninfected children but became significantly higher in HIV-infected children aged between 4 and 30 months. The study results extend previous reports from the P2C2 study showing that fetal echocardiograms indicated fetal cardiovascular abnormalities in pregnant HIV-1-infected women, irrespective of whether the children turned out to be HIV-1 infected after birth. Based on the results of the current cohort study, the authors conclude that irrespective of their HIV-1 status, infants born to HIV-1-infected women have significantly worse cardiac function than other infants, suggesting that the uterine environment has an important role in postnatal cardiovascular abnormalities. The authors also suggest that appropriate treatment strategies should be considered for all children born to HIV-1-infected women, as even mild left ventricular dysfunction has shown to effect mortality over time. The P2C2 study led to many commentaries dealing particularly with the reliability of the methods used to assess ventricular function.

Indeed, in another P2C2 report, there was unacceptable variability of many M-mode cardiac measurements, including fractional shortening, between the local and central institutions [18]. A less variable method of measuring cardiac function should be identified and used in future studies that attempt to evaluate early treatment of HIV-associated cardiac depression with novel therapeutic approaches. Other groups have not confirmed the results of this study [10], which do no reflect the experience of European countries.

The effects of maternal HIV infection and mother–infant HIV transmission on the prevalence and distribution of congenital cardiovascular malformations in the children of HIV-infected mothers have been investigated in few studies. The Italian Multicenter Study demonstrated a trend toward a higher prevalence of congenital cardiovascular malformations in HIV-infected children as compared to general population-based data, but the number of cases was small (5/165, 2.4%) [53]. There was no difference between HIV-infected and HIV-uninfected children. Vogel et al. reported a series of five patients with congenital heart disease from a population of 175 children exposed prenatally to maternal HIV infection (2.8%) [54]. The P2C2 HIV study indicates a congenital cardiovascular malformation prevalence of 12.3% in children of HIV-infected mothers [55]. Again, this proportion is very surprising and has not been confirmed. It is of note that in the first study [52], the methodology pertaining to the identification of cardiac defects was not provided and that in the P2C2 study, most of the lesions were clinically unapparent and were detected by routine echocardiography as part of the study protocol. Our personal experience shows that the prevalence of symptomatic heart defects in children born to HIV-infected mothers is comparable to the general population. The pathophysiologic factors leading to a higher prevalence of cardiac malformations in fetuses of HIV-infected mothers may include alterations of fetal flow patterns related to increased placental vascular resistances. Additional maternal risk factors that may significantly affect fetal organogenesis such as increased alcohol use, cocaine addiction, and poor nutritional status also have to be considered. There are no reports on cardiac teratogenicity related to zidovudine.

Cardiac complications of AIDS or vertically transmitted HIV in children appear to be frequent. However, the actual prevalence of severe cardiac compromise remains difficult to assess and very few groups have reported their own experience. The P2C2 HIV study is the most important study sharing its data with the medical community in charge of these infants and children. This study presents very disquieting results regarding cardiac involvement in infants from HIV-infected mothers, but the numbers of commentaries published after these results were evidence of a rising controversy. The evolving antiviral therapy may change the profile of cardiac manifestations of HIV in the pediatric age group, as fewer children are infected in developed countries. The emerging concern is the vascular dysfunction that may lead to early atherosclerosis. Longitudinal studies are needed to address this worrisome issue in the pediatric population.

References

1. Stewart JM, Kaul A, Gromisch DS, Reyes E, Woolf PK, Gowitz MH (1989) Symptomatic cardiac dysfunction in children with human immunodeficiency virus infection. Am Heart J 117:140-144
2. Bierman FZ (1991) Guidelines for diagnosis and management of cardiac disease in children with HIV infection. J Pediatr 119(Pt 2):S53-56
3. Lewis W, Dorn GW 2nd (1993) Cardiac structure and function in HIV-infected children. N Engl J Med 328:513-514
4. Croft NM, Jacob AJ, Godman MJ, Boon NA, Mok JY (1993) Cardiac dysfunction in paediatric HIV infection. J Infect 26:191-194
5. Luginbuhl LM, Orav EJ, McIntosh K, Lipshultz SE (1993) Cardiac morbidity and related mortality in children with HIV infection. JAMA 269:2869-2875
6. Levin BW, Krantz DH, Driscoll JM Jr, Fleischman AR (1995) The treatment of non-HIV-related conditions in newborns at risk for HIV: a survey of neonatologists. Am J Public Health 85:1507-1513
7. Johann-Liang R, Cervia JS, Noel GJ (1997) Characteristics of human immunodeficiency virus-infected children at the time of death: an experience in the 1990s. Pediatr Infect Dis J 16:1145-1150

8. Plein D, Van Camp G, Cosyns B, Alimenti A, Levy J, Vandenbossche JL (1999) Cardiac and autonomic evaluation in a pediatric population with human immunodeficiency virus. Clin Cardiol 22:33-36
9. Bowles NE, Kearney DL, Ni J et al (1999) The detection of viral genomes by polymerase chain reaction in the myocardium of pediatric patients with advanced HIV disease. J Am Coll Cardiol 34:857-865
10. Lipshultz SE, Easley KA, Orav EJ et al (2000) Cardiac dysfunction and mortality in HIV-infected children: The Prospective P2C2 HIV Multicenter Study. Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection (P2C2 HIV) Study Group. Circulation 102:1542-1548
11. Keesler MJ, Fisher SD, Lipshultz SE (2001) Cardiac manifestations of HIV infection in infants and children. Ann N Y Acad Sci 946:169-178
12. Starc TJ, Lipshultz SE, Easley KA et al (2002) Incidence of cardiac abnormalities in children with human immunodeficiency virus infection: The Prospective P2C2 HIV Study. J Pediatr 141:327-334
13. Lipshultz SE, Easley KA, Orav EJ et al (2002) Cardiovascular status of infants and children of women infected with HIV-1 (P2C2 HIV): a cohort study. Lancet 360:368-373
14. Brady MT, Reiner CB, Singley C, Roberts WH 3rd, Sneddon JM (1988) Unexpected death in an infant with AIDS: disseminated cytomegalovirus infection with pancarditis. Pediatr Pathol 8:205-214
15. Anderson DW, Virmani R (1990) Emerging patterns of heart disease in human immunodeficiency virus infection. Hum Pathol 21:253-259
16. Lipshultz SE, Chanock S, Sanders SP, Colan SD, Perez-Atayde A, McIntosh K (1989) Cardiovascular manifestations of human immunodeficiency virus infection in infants and children. Am J Cardiol 63:1489-1497
17. Rudin C, Meier D, Pavic N et al (1993) Intrauterine onset of symptomatic human immunodeficiency virus disease. The Swiss Collaborative Study Group "HIV and Pregnancy". Pediatr Infect Dis J 12:411-414
18. Lipshultz SE, Orav EJ, Sanders SP, McIntosh K, Colan SD (1994) Limitations of fractional shortening as an index of contractility in pediatric patients infected with human immunodeficiency virus. J Pediatr 125:563-570
19. Turner BJ, Denison M, Eppes SC, Houchens R, Fanning T, Markson LE (1993) Survival experience of 789 children with the acquired immunodeficiency syndrome. Pediatr Infect Dis J 12:310-320
20. Scott GB, Hutto C, Makuch RW et al (1989) Survival in children with perinatally acquired human immunodeficiency virus type 1 infection. N Engl J Med 321:1791-1796
21. Starc TJ, Langston C, Goldfarb J et al (1999) Unexpected non-HIV causes of death in children born to HIV-infected mothers. Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection Study Group. Pediatrics 104:e6
22. Pitt J, Schluchter M, Jenson H et al (1998) Maternal and perinatal factors related to maternal–infant transmission of HIV-1 in the P2C2 HIV study: the role of EBV shedding. Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV-1 Infection (P2C2 HIV) Study Group. J Acquir Immune Defic Syndr Hum Retrovirol 19:462-470
23. Lipshultz SE, Easley KA, Orav EJ et al (1998) Left ventricular structure and function in children infected with human immunodeficiency virus: the prospective P2C2 HIV Multicenter Study. Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection (P2C2 HIV) Study Group. Circulation 97:1246-56
24. Lipshultz SE, Grenier MA (1997) Left ventricular dysfunction in infants and children infected with the human imunodeficiency virus. Prog Pediatr Cardiol 7:33-43
25. Joshi VV, Gadol C, Connor E, Oleske JM, Mendelson J, Marin-Garcia J (1988) Dilated cardiomyopathy in children with acquired immunodeficiency syndrome: a pathologic study of five cases. Hum Pathol 19:69-73
26. Anderson DW, Virmani R, Reilly JM (1988) Prevalent myocarditis at necropsy in the acquired immunodeficiency syndrome. J Am Coll Cardiol 11:792-799
27. Flomenbaum M, Soeiro R, Udem SA, Kress Y, Factor SM (1989) Proliferative membranopathy and human immunodeficiency virus in AIDS hearts. J Acquir Immune Defic Syndr 2:129-135
28. Rodriguez ER, Nasim S, Hsia J et al (1991) Cardiac myocytes and dendritic cells harbor human immunodeficiency virus in infected patients with and without cardiac dysfunction: detection by multiplex, nested, polymerase chain reaction in individually microdissected cells from right ventricular endomyocardial biopsy tissue. Am J Cardiol 68:1511-1520
29. Beschorner WE, Baughman K, Turnicky RP et al (1990) HIV-associated myocarditis. Pathology and immunopathology. Am J Pathol 137:1365-1371
30. Domanski MJ, Sloas MM, Follmann DA et al (1995) Effect of zidovudine and didanosine treatment on

heart function in children infected with human immunodeficiency virus. J Pediatr 127:137-146
31. Lipshultz SE, Easley KA, Orav EJ et al (2000) Absence of cardiac toxicity of zidovudine in infants. Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection Study Group. N Engl J Med 343:759-766
32. Dworkin BM, Antonecchia PP, Smith F et al (1989) Reduced cardiac selenium content in the acquired immunodeficiency syndrome. JPEN J Parenter Enteral Nutr 13:644-647
33. Shaddy RE, Curtin EL, Sower B et al (2002) The Pediatric Randomized Carvedilol Trial in Children with Heart Failure: rationale and design. Am Heart J 144:383-389
34. Lipshultz SE, Orav EJ, Sanders SP, Colan SD (1995) Immunoglobulins and left ventricular structure and function in pediatric HIV infection. Circulation 92:2220-2225
35. Kovacs A, Hinton DR, Wright D et al (1996) Human immunodeficiency virus type 1 infection of the heart in three infants with acquired immunodeficiency syndrome and sudden death. Pediatr Infect Dis J 15:819-824
36. Joshi VV, Pawel B, Connor E et al (1987) Arteriopathy in children with acquired immune deficiency syndrome. Pediatr Pathol 7:261-275
37. Bharati S, Lev M (1989) Pathology of the heart in AIDS. Prog Cardiol 2:261-272
38. Lipshultz SE (1994) Cardiovascular problems. In: Pizzo PA, Wilfert CM (eds) Pediatric AIDS, the challenge of HIV infection in infants, children and adolescents, 2nd edn. Williams and Wilkins, Baltimore, pp 122–148
39. Melvin AJ, Lennon S, Mohan KM, Purnell JQ (2001) Metabolic abnormalities in HIV type 1-infected children treated and not treated with protease inhibitors. AIDS Res Hum Retroviruses 17:1117-1123
40. Lainka E, Oezbek S, Falck M, Ndagijimana J, Niehues T (2002) Marked dyslipidemia in human immunodeficiency virus-infected children on protease inhibitor-containing antiretroviral therapy. Pediatrics 110:e56
41. Jaquet D, Levine M, Ortega-Rodriguez E et al (2000) Clinical and metabolic presentation of the lipodystrophic syndrome in HIV-infected children. AIDS 14:2123-2128
42. Seminari E, Pan A, Voltini G et al (2002) Assessment of atherosclerosis using carotid ultrasonography in a cohort of HIV-positive patients treated with protease inhibitors. Atherosclerosis 162:433-438
43. Mercie P, Thiebaut R, Lavignolle V et al (2002) Evaluation of cardiovascular risk factors in HIV-1 infected patients using carotid intima-media thickness measurement. Ann Med 34:55-63
44. Chironi G, Escaut L, Gariepy J et al (2003) Brief report: carotid intima-media thickness in heavily pretreated HIV-infected patients. J Acquir Immune Defic Syndr 32:490-493
45. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA (2003) Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. N Engl J Med 348:702-710
46. Bonnet D, Aggoun Y, Szezepanski I, Bellal N, Blanche S (2004) Arterial stiffness and endothelial dysfunction in HIV-infected children. AIDS 18:1037-1041
47. Schecter AD, Berman AB, Yi L et al (2001) HIV envelope gp120 activates human arterial smooth muscle cells. Proc Natl Acad Sci U S A 98:10142-10147
48. Chi D, Henry J, Kelley J, Thorpe R, Smith JK, Krishnaswamy G (2000) The effects of HIV infection on endothelial function. Endothelium 7:223-242
49. Hsue PY, Lo JC, Franklin A et al (2004) Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. Circulation 109:1603-1608
50. Lai WW, Colan SD, Easley KA et al (2001) Dilation of the aortic root in children infected with human immunodeficiency virus type 1: The Prospective P2C2 HIV Multicenter Study. Am Heart J 141:661-670
51. Bharati S, Joshi VV, Connor EM, Oleske JM, Lev M (1989) Conduction system in children with acquired immunodeficiency syndrome. Chest 96:406-413
52. Hornberger LK, Lipshultz SE, Easley KA et al (2000) Cardiac structure and function in fetuses of mothers infected with HIV: the prospective PCHIV multicenter study. Am Heart J 140:575-584
53. Italian Register for HIV Infection in Children (1994) Features of children perinatally infected with HIV-1 surviving longer than 5 years. Lancet 22;343:191-195
54. Vogel RL, Alboliras ET, McSherry GD, Levine OR, Antillon JR (1988) Congenital heart defects in children of human immunodeficiency virus positive mothers. Circulation 78:II-17
55. Lai WW, Lipshultz SE, Easley KA et al (1998) Prevalence of congenital cardiovascular malformations in children of human immunodeficiency virus-infected women: the Prospective P2C2 HIV Multicenter Study. P2C2 HIV Study Group, National Heart, Lung, and Blood Institute, Bethesda, Maryland. J Am Coll Cardiol 32:1749-1755

Cardiac Surgery and the Human Immunodeficiency Virus

N. Bonnet, P. Leprince, S. Varnous, I. Gandjbakhch

Twenty years after the first antibody test for the human immunodeficiency virus (HIV), highly active antiretroviral therapy (HAART) became available in Western countries. Although cardiac surgery in HIV-infected patients remains rare [0.2% of interventions with extracorporeal circulation (ECC) in La Pitié Institute] and has some particularities, the majority of cardiac surgeons believe that the surgical strategies and techniques should be the same for HIV-infected patients as for other patients.

Although some standard cardiac operations have been performed on asymptomatic and unknown-HIV-infected patients, the first deliberate open heart operation on a patient known to be infected with HIV was performed by Frater et al. in December 1984 for tricuspid endocarditis in a bisexual heroin addict [1–3]. During the 1980s, the indications for cardiac surgery in AIDS patients were limited to urgent life-threatening conditions: severe infectious endocarditis and tamponade [4]. These urgent indications are still frequent in patients with advanced AIDS, but standard elective cardiac surgery in asymptomatic HIV-infected patients is increasing proportionally.

From the beginning of the AIDS pandemic, surgical teams were faced with unusual questions in this new and very peculiar population of patients, whose main characteristic was to be young. The first questions were about the feasibility of surgery in patients with severe immunodeficiency and the benefit of surgery in patients with poor short-term prognosis. Other questions concerned the risk of HIV transmission from the patient to the surgical staff and vice versa during surgery.

The risk of blood-borne virus transmission between the patient and the surgical team is now well known and fortunately low after the adoption of universal precautions.

We can now briefly answer the first and second questions: surgery, even complex cardiac surgery with ECC, is feasible in patients with severe immunodeficiency with higher but tolerable mortality, but the benefit is low a fortiori in patients with uncontrolled HIV and opportunistic infections. Every surgeon agrees to operate a life-threatening lesion despite poor conditions in HIV-infected patients, but thanks to HAART this situation is now less frequently encountered, and a new question arises: how to operate on a patient with HIV-controlled infection and good long-term prognosis.

Today, this disease is considered to be a chronic illness. For this reason, it is reasonable to expect an increasing number of HIV-infected patients who will require heart surgery. Cardiac surgeons should be prepared to manage these patients.

HIV-Infected Patients Referred for Cardiac Surgery and Indications for Surgery

In most cardiac centers, 0.2%–0.4% of cardiac surgeries are performed on HIV-infected patients [4, 5] (La Pitié experience). It is a relatively rare but increasing situation. The routine use of antiretroviral therapies has led directly to dramatic declines in morbidity and mortality among HIV-1-infected patients with advanced immunodeficiency [6]. Mortality declined from 29.4 per 100 person–years in 1995 to 8.8 per 100 person–years in mid-1997. A number of patients infected with HIV-1 may develop cardiovascular diseases or complications and require cardiac surgery.

During the last 10 years, the profile of HIV-infected patients referred for cardiac surgery in Western countries has changed. These patients are still young – 41 years old for Trachiotis et al. [7],

36 years old for Mestres et al. [8], 44 for Abad et al. [4] – the majority are men (100% for Abad et al. [4]), frequently drug addicts or homosexual, but there is also an increasing proportion of women and older patients. At La Pitié, only one of 22 patients (4.5%) operated on during the 1990s was a woman; since the beginning of 2000, five of 27 patients (14.8%) operated on have been women.

The indications for cardiac surgery in HIV-infected patients have increased and changed for three reasons. First, the survival is greater and HIV-infected patients are exposed for longer periods to specific and classic cardiac lesions requiring surgery. Second, HAART itself is suspected to induce specific cardiac lesions, particularly coronary artery disease. Third, because the HIV infection is controlled with a long survival, we can consider complex therapeutic strategies in these patients, such as heart transplantation and soon artificial hearts. Figure 1 reports the increasing number of coronary artery bypass grafting in HIV-infected patients during the last 6 years at La Pitié Institute. Because of the epidemiological profile of the HIV-infected population in Western countries in the HAART era, the major indications for cardiac surgery are coronary artery disease and cardiomyopathy.

Pericardial Effusion and Tamponade

Before the introduction of HAART, the prevalence of pericardial effusion in asymptomatic AIDS patients was estimated at 11% [9], and was particularly high in those with end-stage disease. HAART has significantly reduced the overall incidence of pericardial effusion in HIV patients. Pericardial effusion in HIV disease may be related to opportunistic infections (tuberculosis and nontuberculosis mycobacteria [10], *Nocardia* [11], *Cryptococcus* [12], and cytomegalovirus), malignancy (Kaposi's sarcoma [13], non-Hodgkin's lymphoma [14]), and valve endocarditis or bacterial pericarditis [15] (*Streptococcus pneumoniae*), but most often a clear etiology is not found. Hypoalbuminemia, which is associated with ascites and pleural effusions, is a potential cause of pericardial effusion in end-stage HIV infection. Pericardial effusion may be part of capillary leak syndrome. A pericardial effusion is a marker of shortened survival.

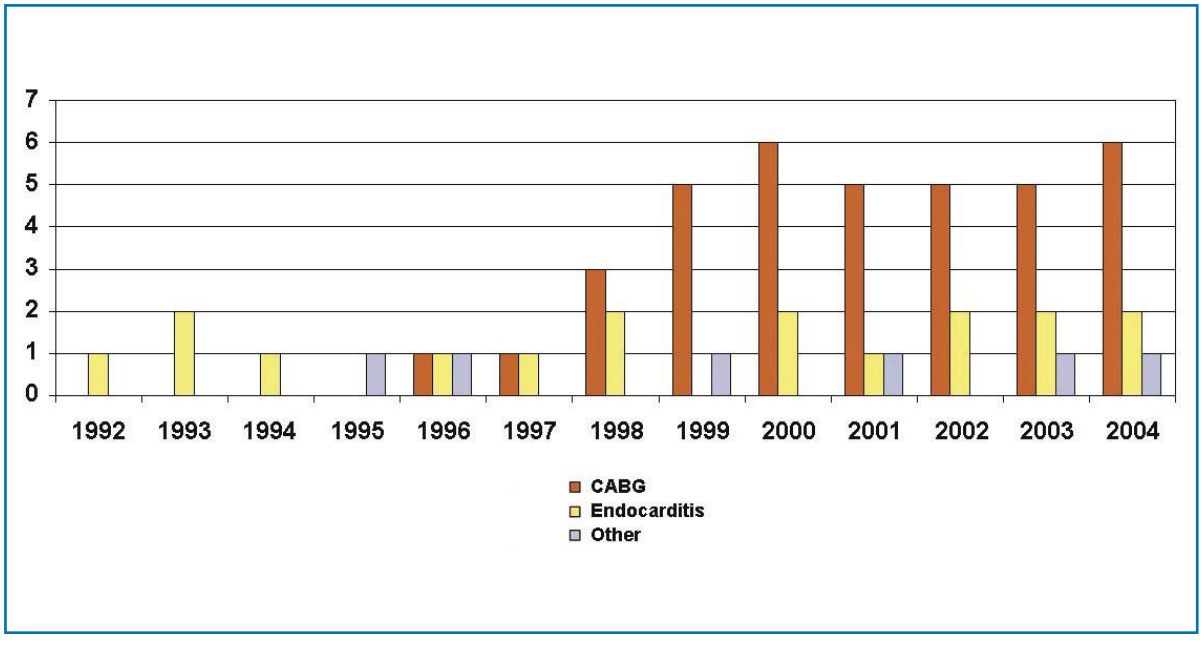

Fig. 1. Evolution of cardiac surgery in La Pitié Institute, Paris. *CABG*, coronary artery bypass grafting

The majority of pericardial effusions are small and asymptomatic but sometimes there is a cardiac tamponade, which requires urgent pericardial drainage (only 1 case among 231 patients over a 5-year period for Heidenreich) [9]. An HIV test is required for each patient with pericardial effusion. In young patients with cardiac tamponade, the coexistence of fever and pulmonary infiltrates is suggestive of underlying HIV infection [16]. The indications of pericardiocentesis or pericardial window are not different between HIV-infected and other patients in cases of cardiac tamponade. Because the effusions are frequently small and rarely progressive, an exhaustive search for a diagnosis with pericardiocentesis is not indicated. The surgical techniques are the same as those used on non-HIV patients, with a preference for percutaneous or videoscopic techniques limiting the risk of viral transmission to the surgical team.

Valvular Surgery

Valvular surgery is the most common cardiac surgery performed on HIV patients, particularly in the pre-HAART era when severe infectious endocarditis was frequent in patients with significant immunodeficiency. In these patients, two factors are frequently associated, which increases the incidence of infective endocarditis: intravenous drug abuse and immunodeficiency [17] – this association was found in 85% of 40 patients reported by Aris et al. [18] in 1993 and in all 11 patients for Frater et al. [1] in 1989. The indications for cardiac surgery (replacement or valve repair) are classic (heart failure, valve destruction, emboli, annular abscess) with a higher number of interventions for persistent infection despite proper antibiotic treatment. In cases of tricuspid endocarditis, the indication for cardiac surgery is rare except for infections with yeasts.

The prevalence of infective endocarditis in HIV-infected patients is similar to that of patients in other risk groups such as intravenous drug users. Estimates of endocarditis prevalence vary from 6.3% to 34% in HIV-infected patients who use intravenous drugs, independently of HAART regimens. Right-sided valves are predominantly affected and the most frequent agents are *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemo-philus influenzae*, *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans* [19, 20]. Infective organisms are common; nevertheless, yeasts (*Candida albicans*) and rare bacteria such as corynebacteria should be suspected particularly in right-sided endocarditis in intravenous drug abusers.

Good results have been achieved with the use of mechanical heart valves, bioprosthetic valves, and homografts (Fig. 2) in patients who have endocarditis. Most surgeons use the following standards for heart valve replacement: (a) a mechanical heart valve in adults, young patients, and pediatric patients when there is no contraindication to long-term anticoagulation; (b) a bioprosthetic valve in most patients over 65 or 70 years, patients with a proven short life expectancy, those requiring right-heart valve replacement, those in whom anticoagulation poses a high risk, and those with contraindication to long-term anticoagulation. Like Abad et al. [4], at La Pitié, because survival is longer in HIV-controlled infection, the same policies are applied to all patients who are HIV-positive, whether they are drug addicts or not. Using a homograft in an aortic position is supported when the lesions are very

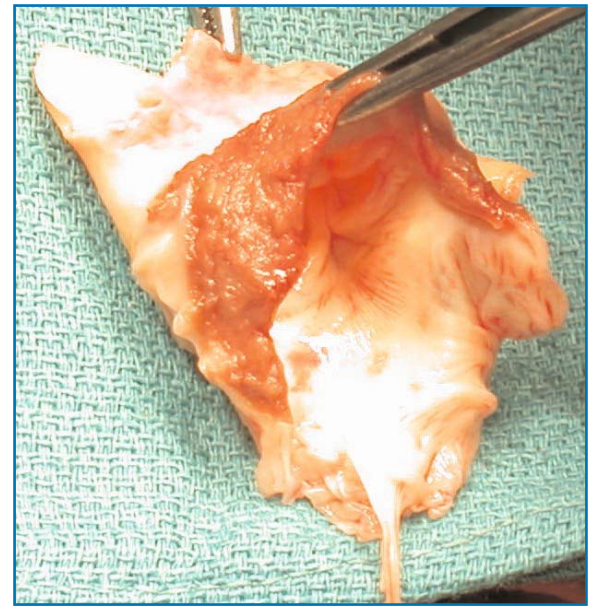

Fig. 2. Aortic homograft

destructive with a large annular abscess [4]. In summary, the policy for choosing a valve substitute is identical in HIV-positive and HIV-negative patients (Figs. 2–4).

Valvular endocarditis is still the most common finding in HIV-positive patients (Figs. 3, 4). However, it is possible that in the future, with the aging of this population due to longer survival as a result of HAART, valvular surgery will be performed for noninfective lesions like aortic stenosis.

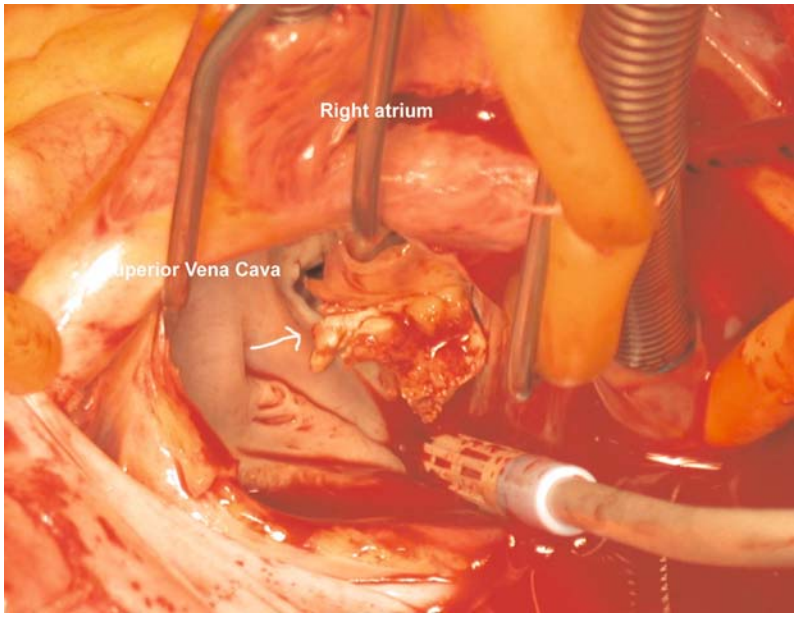

Fig. 3. Mitral vegetations

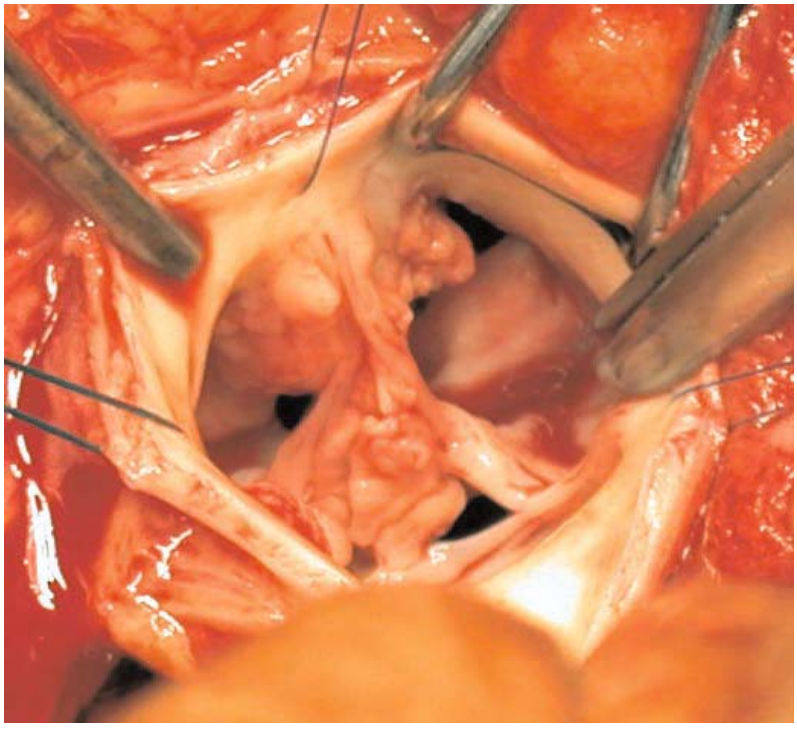

Fig. 4. Aortic vegetations

Coronary Artery Bypass Grafting

An increased rate of acute coronary syndromes has been reported in HIV-infected patients after the introduction of protease inhibitors. However, the substantial benefits of combination antiretroviral therapy clearly continue to outweigh the increased risk of myocardial infarction associated with this therapy [21]. Although valvular surgery was and is still the most common cardiac intervention in HIV-infected patients (70% of the HIV-infected patients for Mestre et al. [8], 65% at La Pitié), coronary artery bypass grafting (CABG) is more and more frequent in HIV-infected patients (30 CABG among 37 interventions for Trachiotis et al. [7]). According to the limited experience reported by different surgical centers (Table 1), the perioperative course of these patients is unremarkable [22]. Surgical revascularization is sometimes performed in an urgent or emergent condition involving the lesions of coronary arteries but never in patients with end-stage HIV disease. These patients are younger than other patients referred for CABG, with the majority being men. The surgical strategy and technique are unremarkable. Full arterial revascularization is a good option because of the age of these patients. The incidence of mediastinitis despite bilateral mammary harvesting, frequent diabetes mellitus, and immunodeficiency is not higher than in comparable patients (2.7%) [7]. Due to the lack of controlled trials and large patient reviews, no firm recommendations about the strategy and technique of surgical revascularization can be provided [22].

Aneurysm or false aneurysm of the coronary artery is a rare lesion in HIV-positive patients; it can require cardiac surgery under ECC (exclusion of the aneurysm and CABG).

After CABG, lipid-lowering therapy should be prescribed cautiously in HIV-infected patients because of the potential of a lethal interaction between statin (except pravastatin and fluvastatin) and protease inhibitors.

Table 1. Cardiac surgery excluding transplantation in HIV-infected patients

Author	Year of publication	Number of patients	Valvular surgery	CABG	Pericardium
Frater [1]	1989	11	11		
Sousa Uva [42]	1992	10	10		
Carrel [17]	1993	6	6 Endocarditis		
Aris [18]	1993	40	38		
Flum [22]	1997	4	4	0.13% of CABG	
Abad [4]	2000	5	4 Endocarditis		1 Tamponade
Trachiotis [7]	2001	37	9 - 3 with CABG	27	
Mestres [8]	2003	31	26 - 21 Endocarditis	5	
La Pitié (personal data)	2004	60	21 - (16 Endocarditis)	37	2

CABG, coronary artery bypass grafting

Heart Transplantation

HIV disease is recognized as an important cause of dilated cardiomyopathy with a reported prevalence of 3.6% among patients with cardiomyopathy, a proportion that is increasing as patients with HIV infection live longer. The pathogenesis of HIV-related cardiomyopathy is very likely to be multifactorial. HIV-associated symptomatic heart

failure may become one of the leading causes of heart failure worldwide [19]. It explains why despite a complex pharmacological and immunological status in these patients, several heart transplantations following other solid-organ transplantations [23–25] have been reported in HIV-positive recipients (Table 2) [26]. Although Calabrese et al. [27] reported a successful cardiac transplantation in 2003 in an HIV-infected patient with advanced disease, we reserve this therapeutic strategy to well-controlled HIV-positive patients (undetectable viral load, CD4 count >400/mm^3) without opportunistic infection and without a history of Kaposi's sarcoma. Two cardiac transplantations have been performed at La Pitié during the last 2 years, with a simple postoperative course and no specific complications during follow-up. A multidisciplinary team is required for this therapeutic technique because numerous complex and unpredictable pharmacological and immunological adverse events can occur (Fig. 5).

Table 2. Cardiac transplantations

Author	Year of publication	Number
Tzakis [44]	1990	1
Calabrese [27]	2003	1
Bisleri [26]	2003	1
La Pitié (personal data)	2004	2

There is no report of a cardiac assist device in HIV-infected patients, but it is only a mater of time before these devices are used in HIV patients. When the patient is on the waiting list for cardiac transplantation, he or she is eligible for a mechanical bridge. Nevertheless, this therapy will be a challenge because the major complication of ventricular assist devices is sepsis.

If the number of HIV-infected patients on waiting lists for cardiac transplantation increases in a high proportion, we should ask the controversial question concerning the harvesting of a heart in HIV-infected donors.

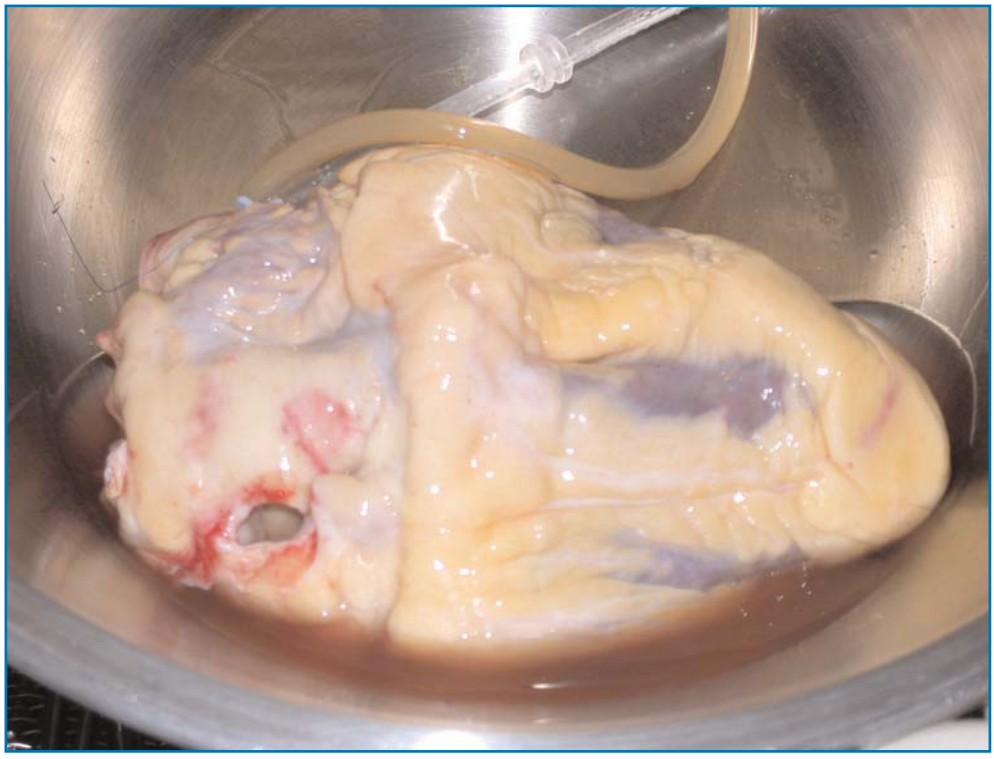

Fig. 5. Heart prepared for transplantation

Cardiac Malignancy

Malignant cardiac tumor is rare in HIV- and non-HIV-infected patients. Cardiac Kaposi's sarcoma and non-Hodgkin's lymphoma have been described in HIV-infected patients, but there is no specific surgery for these tumors except pericardial drainage and biopsy for diagnosis or tamponade.

Risk of HIV Transmission to Operating Room Personnel

From the beginning of the HIV pandemic, the risk of HIV transmission by contact with infected blood, a fortiori, in case of injuries was put forward. This fear was so high that some surgeons asked if it was possible to refuse an intervention in HIV-infected patients under the pretext that the risk for themselves was too high. In France and in the majority of European countries, the law does not permit routine testing for HIV infection in all surgical candidates. At La Pitié Institute, we performed this test after the patient's consent in more than 80% of cases; this test is always done before transplantation.

Accidents involving exposure to blood are not rare during surgery and particularly cardiac surgery. For example, Trachiotis [7] reported six injuries with a solid needle during 37 cardiac operations, and three injuries occurred (one with a hollow needle, two with sternal wire) at La Pitié during 49 interventions. These accidents needed prophylactic antiretroviral therapy. It is now standard practice to prescribe a course of anti-HIV agents in the event of a percutaneous injury based on the evidence that early use after exposure to the virus reduces the chance of infection [28]. No cases of seroconversion were observed. Moreover, there continues to be no known case of transmission of HIV to personnel as a result of a solid needle injury.

According to Beekman et al. [29] and Klatt et al. [30], the risk of accidental infection to operating room personnel through blood contact during surgical procedures is low and can be avoided by adherence to universal precautions with proper training of personnel.

The universal precautions are:

- Impermeable gowns.
- Two pairs of surgical gloves [31].
- Protective glasses.
- Reinforced masks.
- Needles and other sharp instruments should be handled cautiously (one operator, count of sharp tools, solid box for infected sharps tools).
- Knowledge of the serology of the patient. This point is questionable because the universal precautions should be precisely universal and thus followed independently of the serological status of the patient. Moreover, knowledge of the serological status can generate fear and stress and could be a risk factor for percutaneous injuries. Nevertheless, in our institution when a patient is known to be HIV-infected, this fact is clearly mentioned in the medical file. HIV testing is not systematic before cardiac surgery in our institution and this practice is very different from one center to another [32]. HIV testing in patients and personnel is systematic and urgently done in case of percutaneous injury with bleeding .
- Continuous training of the entire staff about these universal precautions.
- Continuous training of the entire staff about the procedure in case of percutaneous injury with blood from the patient.
- Antiretroviral therapy should be continued until the day of surgery and restarted as soon as possible.
- The patient should have a viral load as low as possible; the intervention can be reported in case of excessive viral load, nonurgent surgery, and high probability of reducing the viral load with antiretroviral therapy adaptation.

Because the risk of contact with the patient's blood is higher during cardiac surgery, particularly in cases of extracorporeal bypass, special precautions have to be taken and if possible generalized to all patients:

- The kit for ECC is preconnected.
- The ECC machine is handled with gloves.
- Suturing and reparation of the sternum with steel wire should be done very cautiously and with only one operator (no tandem surgery) [33].

Videoscopic surgery, even robotically assisted surgery (Fig. 6), reduces the risk of percutaneous injuries compared to open surgery (0.01% vs. 1% for Kjaegard et al. [33] in thoracic surgery).

The fear of HIV transmission should not divert surgeons' attention from the higher risk of acquiring other fatal infections such as HBV and HCV. This is why precautions against blood-borne infection have to be universal.

Risk of HIV Transmission to Patients

The risk of HIV transmission through blood transfusion is well known in France, and is higher during cardiac surgery because blood transfusion is very common during cardiac surgery with ECC. (In our institution, 41% of patients who underwent cardiac surgery with ECC were transfused with heterologous blood). This risk was reduced by screening blood donors and blood units. Serologic screening of donors for antibodies to HIV-1 and HTLV-I coupled with exclusion of donors from groups having a relatively high risk for infection has led to a low incidence of transfusion-transmitted HIV-1 and HTLV-I/II infection. A small risk remains, however, despite these measures. The residual risk for HIV-1 and HTLV-II infection from transfusion of screened blood was about 1 in 60,000 units [34], 1 in 100,000 per unit for Cohen et al. [35], and is now 1 in 32,5000 for Pillonel et al. [36].

Pooling of plasma donations increases the risk for blood-borne infections. In solvent- or detergent-treated plasma, lipid-enveloped viruses are efficiently inactivated; transfusion of solvent-/detergent-treated plasma was found to be safe with regard to lipid-enveloped viruses [37].

The risk of infection was further reduced by limitation of blood transfusion itself. After the discovery in the 1980s that HIV can be transmitted via blood transfusion, there has been increased

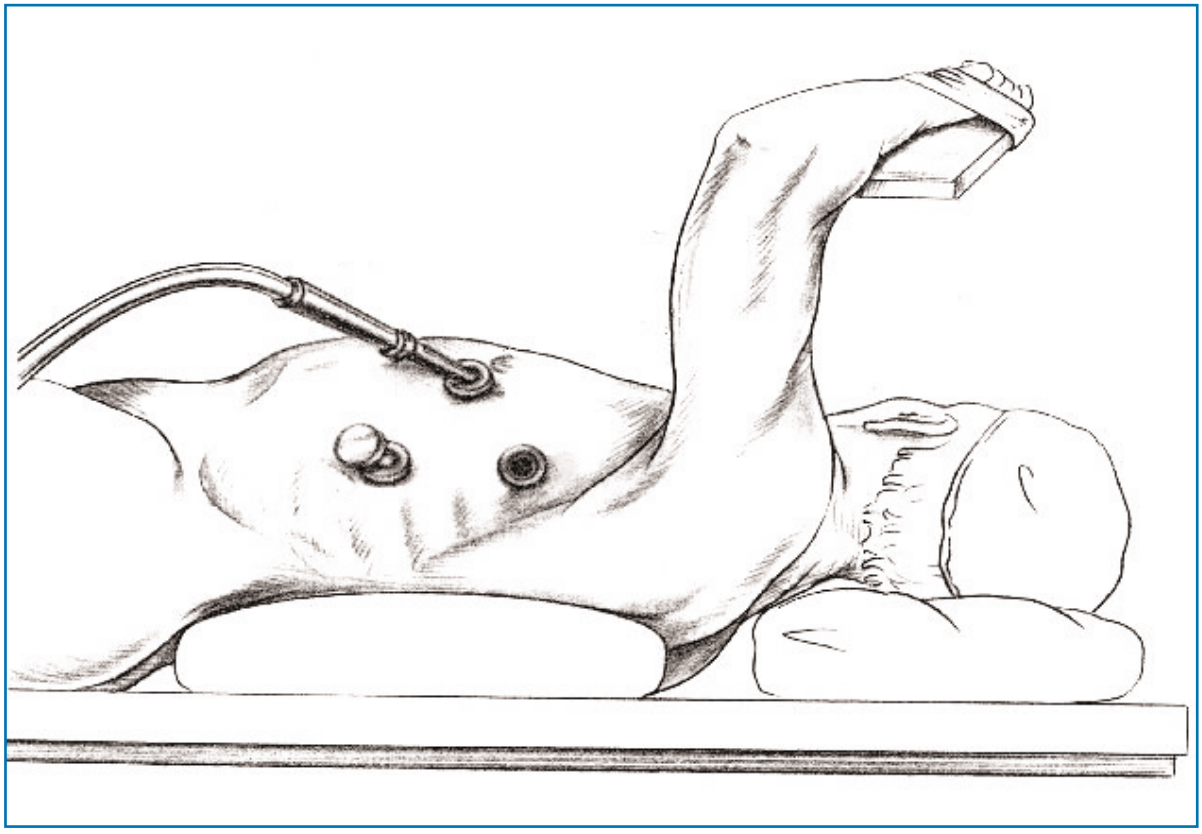

Fig. 6. Videoscopic surgery

interest in technologies that reduce the amount of allogeneic blood used during and after surgery. These technologies include various drugs (aprotinin, tranexamic acid, epsilon-aminocaproic acid, erythropoietin), devices (cell salvage; Fig. 7), and techniques (acute hemodilution, predeposited autologous donation). Enhancement of comprehension and assumption of hemostasis before, during, and after cardiac surgery was followed by a major reduction in the incidence of reoperation for bleeding and heterologous blood transfusion. Other new therapeutics such as the recombinant factor VIIa (NovoSeven) should be of interest for reduction of blood transfusions [38].

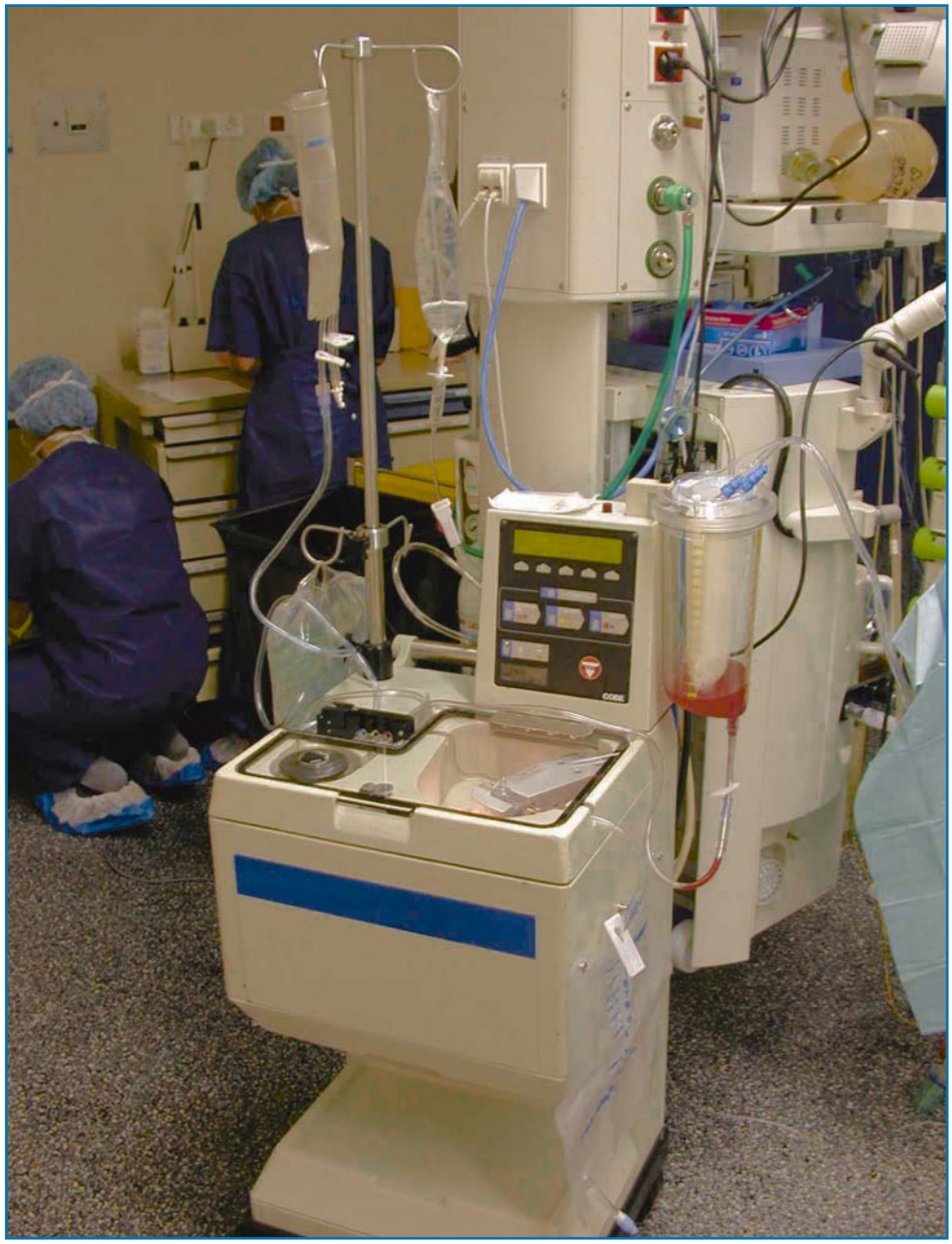

Fig. 7. Cell saver

Information of the transfused patient is legal in France. Thus, in the HIV Information Project, six previously unsuspected HIV-seropositive cases were diagnosed after studying 1,793 patients who underwent cardiac surgery between 1980–1985 [39].

Transmission of HIV from healthcare workers to patients has been documented in one report. A retrospective review was conducted of 612 patients of an HIV-positive cardiothoracic surgeon, in an attempt to identify any instance of viral transmission. A total of 189 patients received HIV testing and counseling. No positive test results were obtained [40]. Pathogens can be transferred through contact between patients undergoing surgery and the surgical team, resulting in postoperative or blood-borne infections in patients or blood-borne infections in the surgical team. Both the patient and the surgical team need to be protected from this risk. Implementing protective barriers such as wearing surgical gloves can reduce this risk. Wearing two pairs of surgical gloves instead of one pair is considered to provide an additional barrier and to further reduce the risk of contamination. Wearing two pairs of latex gloves significantly reduces the number of perforations to the innermost glove.

Results

Data available to date show no conclusive evidence of acceleration of HIV infection into AIDS associated with cardiac surgery [5]. Five of 25 investigators (20%) saw HIV infection progress to AIDS within a maximum period of 74 months [5]. In a short report of six patients, Lemma et al. [41] could not demonstrate any deleterious effect of ECC in HIV-infected patients. Preoperative and postoperative absolute lymphocyte T-helper (CD4) and T-suppressor (CD8) counts did not show a close association between the temporary lymphopenia induced by cardiopulmonary bypass and progression to AIDS [41]. The fear that cardiopulmonary bypass might cause acceleration of the disease has not been borne out [3].

Cardiac surgery in HIV-infected patients is complicated by higher mortality and morbidity rates than in other patients (20% hospital death for Aris et al. [18] with the majority occurring in valvular surgery [42]), but this fact tends to disappear (2.7% of hospital death for Trachiotis et al. [7] with the majority involving a CABG). This group of high-risk patients has the following characteristics: immunodepression, poor general condition, associated diseases, infections, intravenous drug abuse, homosexual/bisexual behavior, high rate of infectious valve endocarditis, frequent recurrence of postoperative infection, and increased risk of transmission to clinical staff. The long-term survival is difficult to describe because there is still a high mortality in patients operated on for severe endocarditis; however, the mid-term results of CABG are unremarkable.

Risk of Lactic Acidosis

Open-heart surgery may be a risk factor for nonischemic (type B) lactic acidosis in patients taking nucleoside analog reverse transcriptase inhibitors [43]. This rare complication should be weighed against the benefit of antiretroviral therapy and particularly the interest of reducing the viral load in order to lower the risk of HIV transmission to the surgical staff.

Conclusion

HIV-infected patients are eligible for classic cardiac surgery, even for cardiac transplantation. The surgical strategy and technique should be the same for HIV-infected and other patients.

References

1. Frater RW, Sisto D, Condit D (1989) Cardiac surgery in human immunodeficiency virus (HIV) carriers. Eur J Cardiothorac Surg 3:146-150
2. Frater RW (1999) As originally published in 1989: human immunodeficiency virus and the cardiac surgeon: a survey of attitudes. Update in 1999. Ann Thorac Surg 67:1203-1204
3. Frater RW (2000) Cardiac surgery and the human immunodeficiency virus. Semin Thorac Cardio-

vasc Surg 12:145-147
4. Abad C, Cardenes MA, Jimenez PC, Armas MV, Betancor P (200) Cardiac surgery in patient infected with human immunodeficiency virus. Tex Heart Inst J 27:356-360
5. Everson, Zeigler R, Sabbaga AM et al (1999) Significance of the human immunodeficiency infection in patients submitted to cardiac surgery. J Cardiovasc Surg 40:477-479
6. Palella FJ Jr, Delaney KM, Moorman AC et al (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 338:853-860
7. Trachiotis GD, Alexander EP, Benator D, Gharagozloo F (2003) Cardiac surgery in patients infected with the human immunodeficiency virus. Ann Thorac Surg 76(4):1114-1118
8. Mestres CA, Chuquire JE, Claramonte X et al (2003) Long-term results after cardiac surgery in patients infected with the human immunodeficiency virus type-1 (HIV-1). Eur J Cardiothorac Surg 23:1007-1016
9. Heidenreich PA, Eisenberg MJ, Kee LL et al (1995) Pericardial effusion in AIDS, incidence and survival. Circulation 92:3229-3234
10. Cegielski JP, Ramiya K, Lallinger GJ, Mtulia IA, Mbaga IM (1990) Pericardial disease and human immunodeficiency virus in Dar es Salaam, Tanzania. Lancet 335:209-212
11. Holtz H, Lavery D, Kapila R (1985) Actinomycetales infection in AIDS. Ann Intern Med 102:203-205
12. Schuster M, Valentine F, Holzman R (1985) Cryptococcal pericarditis in an intravenous drug abuser. J Infect Dis 152:842
13. Stotka JL, Good CB, Downer WR, Kapoor WN (1989) Pericardial effusion and tamponade due to Kaposi's sarcoma in acquired immunodeficiency syndrome. Chest 95:1359-1361
14. Holladay AO, Siegel RJ, Schwartz DA (1992) Cardiac malignant lymphoma in acquired immune deficiency syndrome. Cancer 70:2203-2207
15. Karve MM, Murali MR, Shah HM, Phelps KR (1992) Rapid evolution of cardiac tamponade due to bacterial pericarditis in two patients with HIV-1 infection. Chest 101:1461-1463
16. Kwan T, MM, Emerole O (1993) Cardiac tamponade in patients infected with HIV. A report from an inner-city hospital. Chest 104:1059-1062
17. Carrel T, Schaffner A, Vogt P et al (1993) Endocarditis in intravenous drug addicts and HIV infected patients: possibilities and limitations of surgical treatment. J Heart Valve Dis 2:140-147
18. Aris A, Pomar JL, Saura E (1993) Cardiopulmonary bypass in HIV-positive patients. Ann Thorac Surg 55:1104-1107
19. Barbarini G, Barbaro G (2003) Incidence of the involvement of the cardiovascular system in HIV infection. AIDS 17 [Suppl 1]:S46-50
20. Nahass RG, Weinstein MP, Bartels J, Gocke DJ (1990) Infective endocarditis in intravenous drug users: a comparison of human immunodeficiency virus type 1-negative and -positive patients. J Infect Dis 162:967-970
21. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group (2003) Combination Antiretroviral Therapy and the Risk of Myocardial Infarction. N Engl J Med 349:1993-2003
22. Flum DR, Tyras DH, Wallack MK (1997) Coronary artery bypass grafting in patients with human immunodeficiency virus. J Card Surg 12:98-101
23. Ragni MV, Dodson SF, Hunt SC, Botempo FA, Fung JJ (1999) Liver transplantation in a hemophilia patient with acquired immunodeficiency syndrome. Blood 93:113-114
24. Roland ME, Stock PG (2003) Review of solid-organ transplantation in HIV-infected patients. Transplantation 75:425-429
25. Halpern SD, Ubel PA, Caplan AL (2002) Solid-organ transplantation in HIV-infected patients. N Engl J Med 347:284-287
26. Bisleri G, Morgan J, Deng M, Mancini D, Oz M (2003) Should HIV-positive recipients undergo heart transplantation? J Thorac Cardiovasc Surg 126:1639-1640
27. Calabrese LH, Albrecht M, Young Y et al (2003) Successful cardiac transplantation in an HIV-1-infected patient with advanced disease. N Engl J Med 348:2323-2328
28. Henderson DK (1997) Postexposure antiretroviral chemoprophylaxis: embracing risk for safety's sake. N Engl J Med 337:1542-1543
29. Beekman SE, Vlahov D, Koziol DE et al (1994) Implementation of universal precautions was temporally associated with a sustained progressive decrease in percutaneous exposures to blood or body fluids. Clin Infect Dis 18:562-569
30. Klatt EC (1994) Surgery and human immunodeficiency virus infection: indications, pathologic findings, risks, and risk prevention. Int Surg 79:1-5
31. Tanner J, Parkinson H (2004) Double gloving to reduce surgical cross-infection (Cochrane Review). In: The Cochrane Library, issue 3. John Wiley & Sons, Chichester
32. Kendall JB, Hart CA, Pennefather SH, Russel GN

(2003) Infection control measures for adult cardiac surgery in the UK - a survey of current pratice. J Hosp Infect 54:174-178

33. Kjaegard HK, Thiis J, Wiinberg N (1992) Accidental injuries and blood exposure to cardiothoracic surgical teams. Eur J Cardiothorac Surg 6:215-217
34. Nelson KE, Donahue JG, Munoz A et al (1992) Transmission of retroviruses from seronegative donors by transfusion during cardiac surgery. A multicenter study of HIV-1 and HTLV-I/II infections. Ann Intern Med 117:612-614
35. Cohen ND, Munoz A, Reitz BA et al (1989) Transmission of retroviruses by transfusion of screened blood in patients undergoing cardiac surgery. N Engl J Med 320:1172-1176
36. Pillonel J, Laperche S, Groupe "Agents Transmissibles par Transfusion" de la Societe francaise de transfusion sanguine, Etablissement francais du sang, Centre de transfusion sanguine des armees (2004) Risque résiduel de transmission du VIH, du VHC et du VHB par transfusion sanguine entre 1992 et 2002 en France et impact du dépistage génomique viral. Transfus Clin Biol 11:81-86
37. Solheim BG, Rollag H, Svennevig JL, Arafa O, Fosse E, Bergerud U (2000) Viral safety of solvent/detergent-treated plasma. Transfusion 40:1149-1150
38. Tanaka K, Waly A, Cooper W, Levy J (2003) Treatment of excessive bleeding in Jehovah's witness patients after cardiac surgery with recombinant factor VIIa (NovoSeven). Anesthesiology 98:1513-1515
39. King SM, Murphy T, Corey M et al (1995) The HIV information project: transfusion recipients a decade after transfusion. Arch Pediatr Adolesc Med 149:680-685
40. Babinchak TJ, Renner C (1994) Patients treated by thoracic surgeon with HIV. A review. Chest 106:681-683
41. Lemma M, Vanelli P, Beretta L, Botta M, Antinori A, Santoli C (1992) Cardiac surgery in HIV-positive intravenous drug addicts: influence of cardiopulmonary bypass on the progression to AIDS. Thorac Cardiovasc Surg 40:279-282
42. Sousa Uva M, Jebara VA, Fabiani JN et al (1992) Cardiac surgery in patients with human immunodeficiency virus infection: indication and results. J Card Surg 7:204-204
43. Vasseur BG, Kawanishi H, Shah N, Anderson ML (2002) Type B lactic acidosis: a rare complication of antiretroviral therapy after cardiac surgery. Ann Thorac Surg 74:1251-1252
44. Tzakis AG, Cooper MH, Dummer JS, Ragni M, Ward JW, Starzl TE (1990) Transplantation in HIV(+) patients. Translantation 49:354-358

Cardiological Emergencies in HIV-Infected Patients

G. Barbaro

Many cardiac complications in acquired immunodeficiency syndrome (AIDS) that may be faced by emergency department (ED) physicians are due to opportunistic infections or malignancy, but they may also be associated with other aspects of human immunodeficiency virus (HIV) disease and its treatment (Table 1) [1]. The clinical expression of cardiac involvement is variable and is affected by

Table 1. Frequent cardiac abnormalities in HIV disease and related emergencies [1]

HIV-associated cardiac disease	Cardiac emergencies
Myocardial	
Dilated cardiomyopathy Lymphocytic myocarditis	Congestive heart failure (CHF), cardiogenic pulmonary edema, arrhythmias
Noninflammatory myocardial necrosis (microvascular spasm, catecholamine excess, opportunistic infections, toxic drug reaction)	CHF
Right ventricular hypertrophy due to HIV-associated pulmonary hypertension Right ventricular hypertrophy with secondary pulmonary hypertension (pulmonary infections, pulmonary emboli)	CHF, pulmonary embolism, pulmonary infarction
Coronary artery disease (atherogenic effects of protease inhibitors, coronary arteritis, aortitis)	Unstable angina, myocardial infarction
Neoplastic (Kaposi's sarcoma, non-Hodgkin's lymphoma)	Arrhythmias, pericardial tamponade
Endocardial	
Infective endocarditis A. Autoimmune response to infection B. Bacterial (*Staphylococcus aureus*, *Salmonella* species, *Streptococcus* species, *Enterococcus*, *Haemophilus parainfluenza*, *Staphylococcus epidermidis*, *Pseudallescheira boydii*) C. Fungal/yeast (*Candida albicans*, *Aspergillus fumigatus*, *Cryptococcus neoformans*)	Septic shock, acute valvular regurgitation (cardiogenic pulmonary edema, CHF), septic embolization (pulmonary and cerebral infarction)
Nonbacterial thrombotic endocarditis	Systemic embolization (lung, brain, kidney, spleen) Disseminated intravascular coagulopathy
Pericardial	
Pericardial effusion/pericarditis A. Infectious 1. Bacterial (*M. tuberculosis*, *M. avium intracellulaire*, *N. asteroides*) 2. Viral (Coxsackievirus, Epstein-Barr virus, cytomegalovirus, adenovirus, herpes virus) 3. Fungal (*Histoplasma capsulatum*, *Cryptococcus neoformans*) B. Idiopathic (HIV, autoimmune) C. Uremic D. Neoplastic (Kaposi's sarcoma, non-Hodgkin's lymphoma)	Cardiac tamponade, arrhythmias, CHF (for chronic pericardial effusions)

the stage of HIV disease, the degree of immunodeficiency, and the drugs used to treat HIV disease [i.e., zidovudine and protease inhibitors (PIs) in the era of highly active antiretroviral therapy (HAART) regimens] or to treat or prevent opportunistic infections and neoplasms (e.g., pentamidine, cotrimoxazole, interferon alpha) [2].

Myocarditis

In the ED, suspecting acute myocarditis in HIV-infected patients is important as this condition may evolve to include life-threatening congestive heart failure and arrhythmias. Fever and infection of the upper respiratory tract or flu-like symptoms may precede exertional dyspnea by as little as hours or days. Signs and symptoms may occur at rest and include palpitations, atypical chest pain, and electrocardiographic alterations (ST-segment elevation followed by T-wave inversion in different leads). Laboratory alterations may include elevated cardiac troponin I (cTnI) and myoglobin levels with or without increased levels of myocardial fraction of creatine kinase (CK-MB). A clinical diagnosis of myocarditis or congestive heart failure in an HIV-infected patient may be difficult to make due to the masking of symptoms by concomitant bronchopulmonary disease and/or wasting syndromes. Differentiating myocarditis from myocardial infarction may also be difficult. A careful clinical history and physical examination, electrocardiogram (ECG) review, and analysis of traditional risk factors expanded to include HIV-specific therapies (i.e., PIs in the context of HAART regimens) may direct the diagnosis.

Myocardial enzyme testing will help to detect myocardial injury rapidly with high sensitivity and specificity. Markers of cardiac injury should be interpreted in relation to the timing of the onset of the patient's symptoms. An elevation of myoglobin in the absence of an elevated cTnI level in subsequent samples may be related to an inflammatory muscle disease. Myositis is more likely to occur in HIV-infected patients, making myoglobin a much less specific marker for cardiac injury.

An isolated positivity of cTnI suggests a minimal myocardial damage of small areas of the myocardium (micronecrosis). In HIV-positive patients, micronecrosis may be caused by an inflammatory process secondary to myocarditis or pericarditis with extended epicarditis (perimyocarditis) or secondary to autoimmune mechanisms induced by infections or antiviral drugs. In case of a positive CK-MB and/or cTnI in patients with a nondiagnostic ECG (e.g., presence of left bundle branch block, chronic ischemic alterations), clinical skills and echocardiography should help guide the differential diagnosis of myocarditis (absence or reversible hypokinesia) or acute myocardial infarction (with or without ST-segment elevation). However, endomyocardial biopsy represents the gold standard in the diagnosis of myocarditis. According to the Dallas criteria, myocarditis is defined as "a process characterized by a lymphocytic infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease" [3].

Intravenously administered immunoglobulins may be useful in improving the clinical outcome and the echocardiographic measurements of cardiac mass and function. The apparent efficacy of immunoglobulin therapy may be the result of immunoglobulins inhibiting cardiac autoantibodies (i.e., anti-α-myosin autoantibodies) by competing for *Fc* receptors or dampening the secretion or effects of cytokines and cellular growth factors [4]. Serial therapy in children has been shown to improve fractional shortening and left ventricular mass and to stabilize the disease process. Immunomodulatory therapy may be helpful in HIV-infected adults and children with declining left ventricular function, but further study is needed to evaluate the efficacy of this therapy and its impact on mortality.

Infective Endocarditis

The diagnosis of infective endocarditis is based on clinical, echocardiographic, and bacterial culture data. HIV-infected patients usually present with fever, sweats, weight loss, coexisting pneumonia, and/or meningitis. Among intravenous drug addicts, the tricuspid valve is most frequently

affected (Fig. 1). Vegetations may form on the tricuspid or pulmonic valves with resultant pulmonary embolism and consequent septic pulmonary infarcts that appear as multiple opacities on chest radiograms. Systemic emboli may involve the coronary arteries, spleen, bowel, extremities, and central nervous system. Cardiac rhythm alterations (i.e., atrioventricular block) may suggest the presence of an abscess in proximity to the atrioventricular node. Peripheral pulses must be examined for signs of embolic occlusion or pulsating mass suggesting mycotic aneurysm. Mycotic aneurysms may occur in the intracranial arteries potentially leading to intracranial hemorrhage.

Echocardiographic findings in endocarditis include mobile echodense masses attached to the inflow side of the valvular leaflets or mural endocardium. Pericardial effusion is frequently associated. Transthoracic echocardiography (TTE) is useful for detecting relatively large valvular mass(es); however, perivalvular abscess, leaflet perforation, or rupture of the valvular chordae are better assessed by transesophageal echocardiography (TEE). Both TTE and TEE, which may be performed in the ED, are also useful in guiding the duration of antibiotic therapy and evaluating the timing for surgery when necessary.

Assessment of infective endocarditis in an HIV-infected patient should include at least four sets of blood cultures separated by 30 min. Empiric broad-spectrum antibiotic therapy should be started within a maximum of 2–3 h from admission of the patient to the ED (after blood culture sets are obtained). According to our clinical experience, combination regimens including vancomycin 15 mg/kg i.v. (maximum 1 g) every 12 h, ampicillin 2 g i.v. every 4 h, and gentamycin 1 mg/kg i.m. every 8 h have significant bactericidal activity and cover methicillin-resistant *Staphylococcus aureus* [1].

Nonbacterial thrombotic endocarditis, also known as marantic endocarditis, is most common in patients with HIV wasting syndrome [1]. The incidence of marantic endocarditis and systemic embolization from marantic endocarditis is a rare cause of death in AIDS patients receiving HAART regimens. On the contrary, its frequency is increasing in developing countries (about 10%), where HAART availability is scanty, with a high mortality rate for systemic embolization [5].

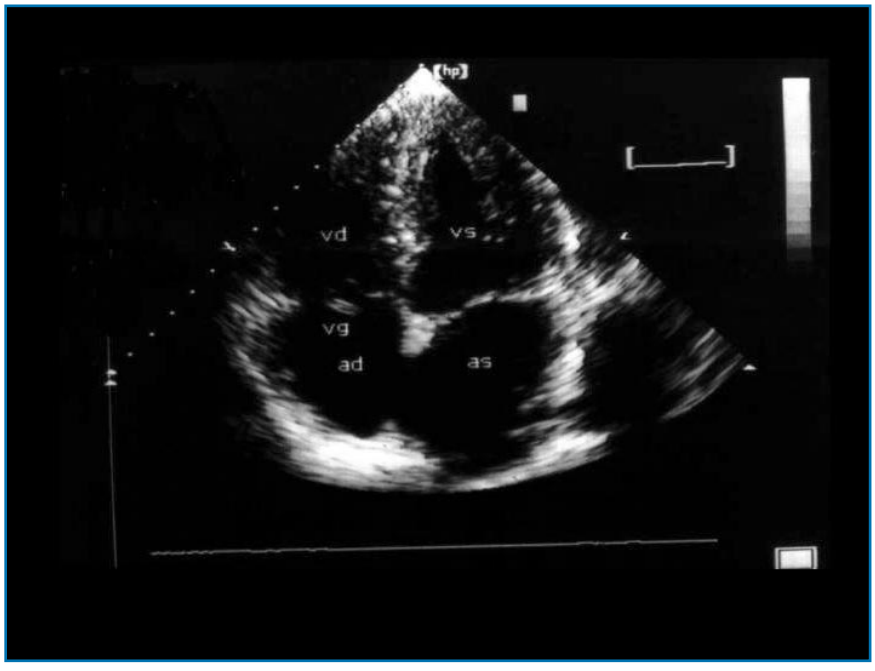

Fig. 1. Echocardiographic finding of *Candida* endocarditis in an intravenous heroin user suffering from AIDS. A vegetation (*vg*) is attached to the anterior leaflet of the tricuspid valve (apical four-chamber view). *AD*, right atrium; *AS*, left atrium; *VD*, right ventricle; *VS*, left ventricle. (From [1] with permission from Elsevier)

Pericardial Effusion

Pericardial effusion in HIV disease is generally related to opportunistic infections (*Mycobacterium tuberculosis, Mycobacterium avium intracellulare, Staphylococcus aureus, Nocardia asteroides, Rhodococcus equi, Listeria monocytogenes, Chlamydia trachomatis,* coxsackievirus, Epstein-Barr virus, cytomegalovirus, adenovirus, herpes virus, *Histoplasma capsulatum, Cryptococcus neoformans,* and *Toxoplasma gondii*), or to malignancy (Kaposi's sarcoma, non-Hodgkin's lymphoma), but most often a clear etiology is not found. Fever, chest pain radiating to the left shoulder (often dull), aggravated by supine posture and often decreased by sitting up and leaning forward, and pericardial friction rub (over the left sternal border, usually accentuated by sitting up and leaning forward) should suggest acute pericarditis. Pericardial effusion is suggested by absence or weakness of the apical impulse with an apparent increase in the area of dullness to percussion over the left chest and over the hepatocardiac angle as well as by muffled heart sounds, diffuse low-voltage ECG, electrical alternans of QRS complexes, and increased cardiac opacity on chest radiographs. Echocardiography confirms clinical suspicion by showing the pericardial effusion (Fig. 2A, B). An M-mode technique may help to demonstrate characteristic signs of cardiac tamponade: right atrial compression and diastolic right ventricular collapse. These echocardiographic signs precede pulsus paradox or severe dyspnea related to the hemodynamic effects of cardiac tamponade. CT scans can easily demonstrate pericardial effusion and help analyze the thickness of the pericardium and reveal signs of constrictive pericarditis (Fig. 3).

Pericardial effusion may resolve spontaneously in up to 42% of HIV-positive patients [1]. Pericardiocentesis is currently recommended only in large or poorly tolerated effusions, for diagnostic evaluation of systemic illness, or in the presence of cardiac tamponade [1].

Congestive Heart Failure

In HIV-infected patients, symptoms of heart failure may be masked by concomitant illness such as diarrhea or malnutrition, or may be disguised by bronchopulmonary infection. Echocardiography is the only sensitive and specific method for the evaluation of ventricular function and pericardial effusion in this population and should be considered early in a patient with a change in clinical status (Fig. 4).

Standard heart failure treatment regimens are generally recommended for HIV-infected patients with dilated cardiomyopathy and congestive heart failure, even though these regimens have not been

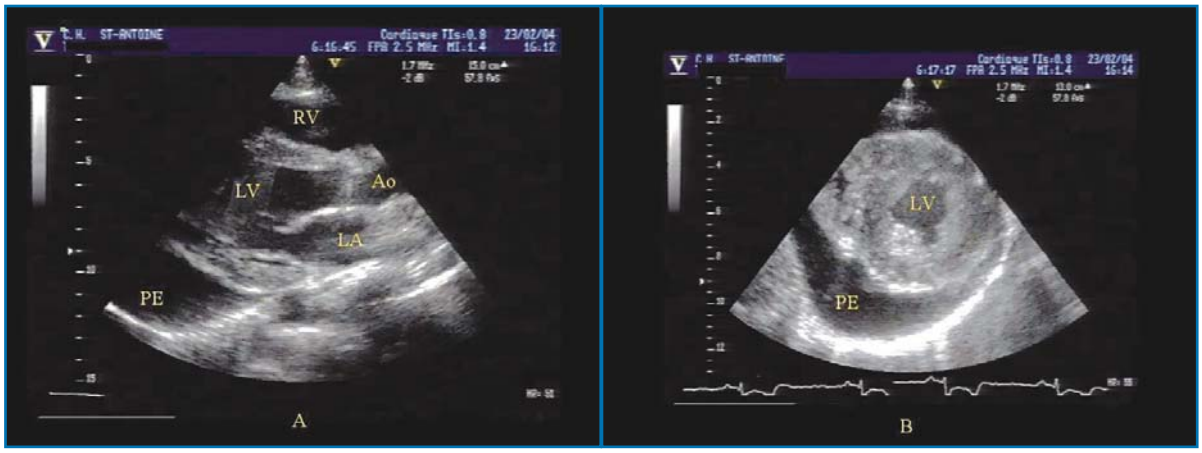

Fig. 2. Echocardiographic finding of posterior pericardial effusion in an AIDS patient. **A** Parasternal long-axis view. **B** Parasternal short-axis view. *LV*, left ventricle; *RV*, right ventricle; *Ao*, aorta; *LA*, left atrium; *PE*, pericardial effusion

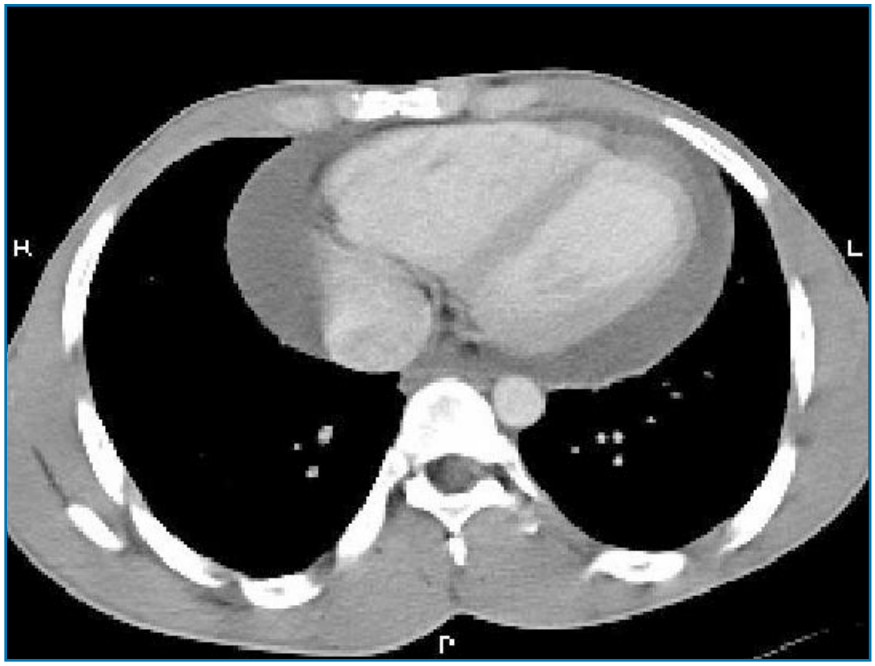

Fig. 3. CT scan finding of a large and circumferential pericardial effusion in an HIV-infected patient with *Mycobacterium tuberculosis* infection

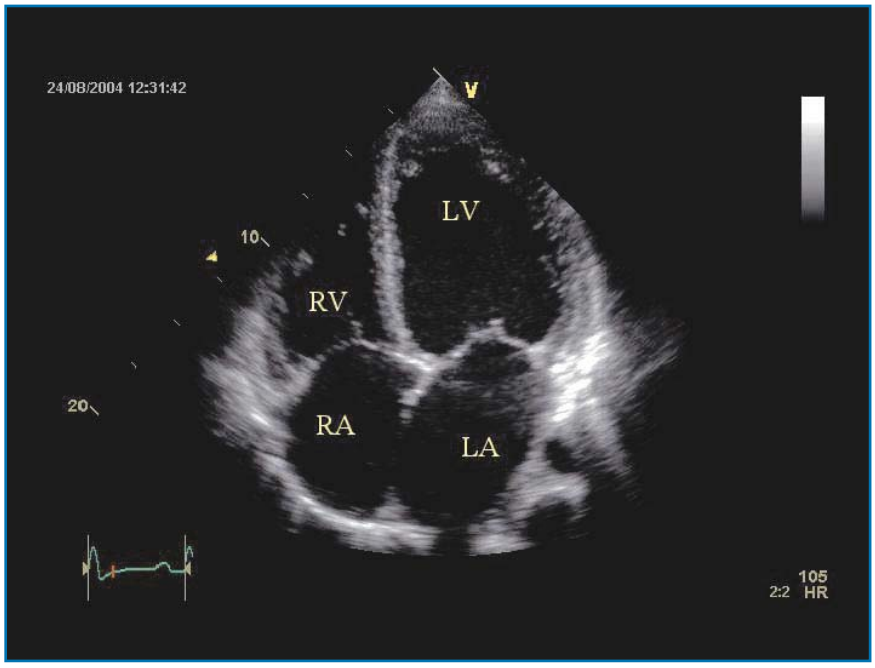

Fig. 4. Dilated cardiomyopathy in an HIV-infected patient (four-chamber apical view). Left ventricualr ejection fraction: 25%. Note the dilatation of both left and right cardiac chambers. *RA*, right atrium; *RV*, right ventricle; *LA*, left atrium; *LV*, left ventricle

tested in this specific population. Patients with systolic dysfunction and symptoms of fluid retention should receive a loop diuretic and an aldosterone antagonist as well as an angiotensin-converting enzyme (ACE) inhibitor. ACE inhibitors are recommended on the basis of general heart failure studies, but may be poorly tolerated due to low systemic vascular resistance from diarrheal disease, infection, or dehydration. Digoxin may be added to the therapy regimen of patients with persistent symptoms or rapid atrial fibrillation. When the patient is euvolemic, a beta-blocker (e.g., carvedilol, meto-

prolol, and bisoprolol) may be started because of its beneficial effects on circulating levels of inflammatory and anti-inflammatory cytokines.

Arrhythmias

Both tachy- and bradyarrhythmia may be observed in HIV-infected patients in relation to:

Structural alterations of the endocardium (infective endocarditis), of the myocardium (myocarditis, dilated cardiomyopathy), and of the pericardium (infective and neoplastic pericarditis and myopericarditis). In HIV-infected patients with myocarditis, the most frequent arrhythmias are ventricular ectopic beats. Bradycardias (e.g., left bundle branch block and/or atrioventricular block) may be observed in patients with HIV-associated dilated cardiomyopathy as a consequence of fibrous degeneration of the conduction system [6].

Side effects of both antiretroviral drugs or drugs used in the treatment and/or prophylaxis of opportunistic infections and neoplasms. Ganciclovir, amphotericin B, cotrimoxazole (trimethoprim-sulfamethoxazole), and pentamidine may cause torsades de pointes (TdP) that can degenerate into ventricular fibrillation and sudden cardiac death (Fig. 5). TdP is related to prolongation of the ventricular action potential duration (QTc interval of the electrocardiogram >0.45 s) and it has been described also with the administration of macrolide antibiotics (erythromycin, clarithromycin). Uncorrected electrolyte alterations (e.g., hypokalemia, hypomagnesemia, hypocalcemia) related to malnutrition and/or to chronic diarrhea or electrolyte imbalances induced by diuretics are also associated. These alterations, which should be evaluated and treated as early as possible, may further contribute to prolonging the QTc interval.

Use of central nervous system stimulant drugs (e.g., cocaine, amphetamines). Cocaine abuse has been associated with myocarditis, myocardial infarction, and dilated cardiomyopathy even in HIV-negative subjects, possibly because of intermittent microvascular spasm resulting from catecholamine surges associated with a high risk of ventricular arrhythmia.

Particularly in the ED, the first line of therapy for TdP is to stop medications suspected of prolonging the QT interval and to correct electrolyte imbalances. Intravenously administered magne-

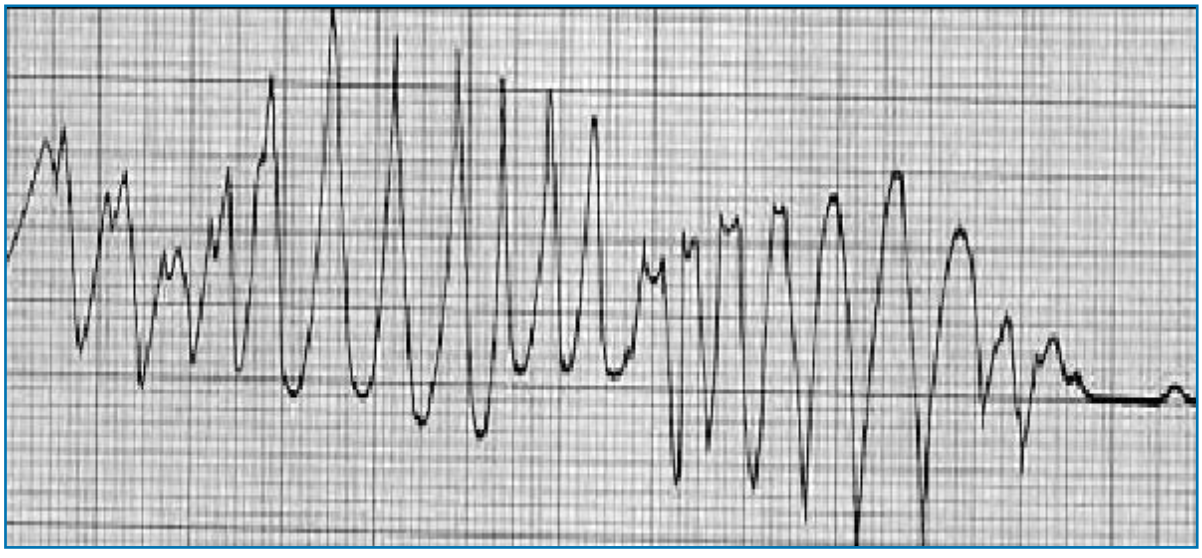

Fig. 5. Run of torsade de pointes in an HIV-infected subject receiving pentamidine as prophylaxis for *Pneumocystis carinii* pneumonia during Holter electrocardiographic monitoring (lead CM5). Note the prolongation of the QT interval of the QRS complex following the arrhythmic run (0.50 s). (From [1] with permission from Elsevier)

sium sulfate is immediately indicated (loading dose of 1–2 g, mixed in 50–100 ml of saline, over 5–10 min followed by a continuous infusion of 1.0–2.0 g/h over 4–6 h), whereas i.v. infusion of isoproterenol (0.01–0.02 mcg/kg per minute) in the absence of known or suspected coronary artery disease may accelerate the heart rate and suppress ventricular arrhythmias while temporary ventricular pacing (overdrive pacing) is initiated [1].

In HIV-infected patients, hemodynamically stable sustained monomorphic wide-QRS complex tachycardia is another diagnostic challenge for the emergency physician, as ventricular tachycardia (VT) must be distinguished from supraventricular tachycardia (SVT). In particular, SVT with an accessory pathway, preexisting bundle-branch block or rate-dependent bundle-branch block should be considered. SVT with aberrant conduction is frequently observed in HIV-infected patients with dilated cardiomyopathy and histological diagnosis of myocarditis [1] (Fig. 6). In patients that are hemodynamically stable with no symptoms or clinical evidence of tissue hypoperfusion or shock, initial management should proceed under the presumption that the arrhythmia is VT, and electric cardioversion is the preferred therapy. If electrical cardioversion is not possible, empiric pharmacological therapy may be necessary with agents such as procainamide or amiodarone, which possess efficacy against VT and SVT and are also acceptable in patients with accessory pathway conduction [1].

Procainamide is administered in an infusion of 20 mg/min until the arrhythmia is suppressed or hypotension ensues, or when a total of 17 mg/kg of the drug has been given. Amiodarone is administered as 150 mg over 10 min, followed by 150 mg over the next 30 min, and then 1 mg/min infusion for 6 h followed by 0.5 mg/min, to a maximum daily dose of 2 g. If the patient is in shock or in congestive heart failure (hemodynamically unstable), a wide-QRS complex tachycardia should be presumed to be VT that requires immediate termination with synchronized cardioversion [1].

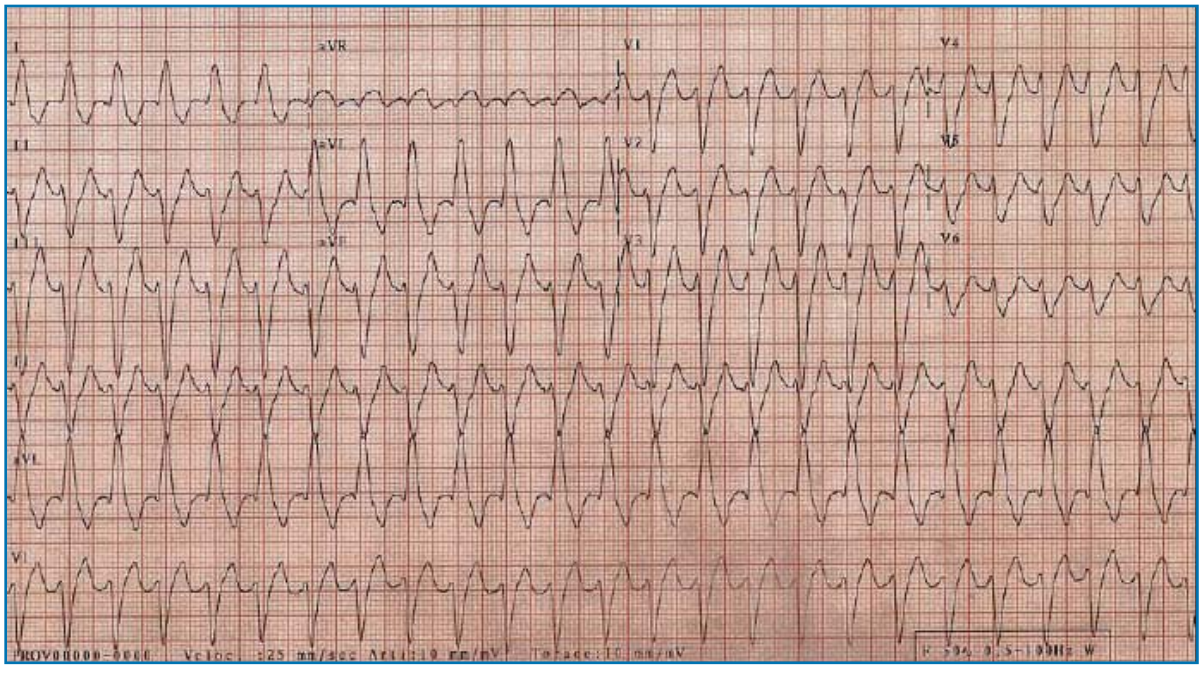

Fig. 6. Wide-QRS complex supraventricular tachycardia in HIV-infected patients with echocardiographic diagnosis of dilated cardiomyopathy (left ventricular ejection fraction: 30%) and diagnosis of myocarditis confirmed by histological examination of endomyocardial biopsy specimens

Coronary Heart Disease

Contraindications to thrombolytic therapy in HIV-infected patients with acute coronary syndrome include acute pericarditis, infective endocarditis, active cavitating pulmonary tuberculosis, and thrombocytopenia. Primary percutaneous transluminal coronary angioplasty, if feasible, seems the most appropriate treatment in some HIV-infected patients. In patients presenting with unstable angina or non-Q-wave myocardial infarction without specific therapeutic contraindications, the best approach may be medical therapy (i.v. nitroglycerin, aspirin, low-molecular-weight heparin, IIb/IIIa platelet inhibitor, beta-blockers). Patients with unstable angina at high risk (recent severe angina, elevated cTnI, ischemic ECG changes, hypertension, elevated cholesterol, diabetes, active smokers) or with myocardial infarction without ST-segment elevation should undergo coronary angiography to define their anatomy and optimize treatment to prevent ischemic injury and sudden death. Cardiac revascularization has been shown to be beneficial in the treatment of HIV-infected patients with coronary artery disease [7]. Indeed, the extraordinary fruits of a massive research effort have made it reasonable to perform elective surgery and to offer major surgery to patients independently of their immunologic status, and the concern that the surgical team would be exposed to a significant risk of acquiring HIV infection during surgery has proved to be unfounded. Cardiac surgeons should have a hightened awareness for the possiblity of successful surgical treatment of HIV-infected patients with a definitive clinical diagnosis of coronary artery disease [7].

HIV-Associated Pulmonary Hypertension and Right Ventricular Dysfunction

In HIV-positive patients with risk factors for pulmonary embolism (cancer, lower limb fractures, prolonged immobilization, recent surgery, infective endocarditis of the right-sided heart valves), the onset of acute paroxysmal dyspnea with jugular venous distension and normal physical examination of the chest, with an ECG not suggestive of acute myocardial infarction and chest radiograms negative for acute pulmonary infiltrate, pulmonary embolism should be considered. The onset of hemoptysis days after dyspnea, associated with fever, stabbing chest pain (exacerbated by deep inspiration and coughing), and pleural friction rub, should suggest pulmonary infarction (see the chapter on HIV-associated pulmonary hypertension by G. Barbaro, this volume).

Oxygen and steroids are generally used in the ED for HIV-infected patients with pulmonary hypertension, with conflicting results. Calcium channel blockers (e.g., nifedipine and diltiazem), epoprostenol, and nitric oxide have been suggested in the treatment of HIV-associated pulmonary hypertension; however, controlled clinical trials have not been performed to confirm their efficacy [8, 9]. Studies on the effects of HAART therapy on pulmonary artery endothelial cells have shown contradictory results [10, 11]. Further information about the treatment of HIV-associated pulmonary hypertension is reported in a separate chapter of this volume.

Conclusions

Often, symptoms of congestive heart failure or pericardial effusion in HIV-infected patients are nonspecific and may be attributed to generalized illness or coinfection. Echocardiography noninvasively and accurately aids diagnosis during any change in clinical status and it also directs therapy. Patients will usually respond to early therapy for left ventricular dysfunction and increased left ventricular mass. Treatment based on these findings may prolong the quality and duration of life, and may also direct further patient evaluation.

The role of the ED cardiologist in the evaluation and treatment of patients with HIV infection should therefore be expanded to include patients who are being evaluated for or who are receiving HAART regimens, especially those with underlying risk factors, since the HAART-associated metabolic syndrome may increase the risk of acute coronary syndromes and stroke. Careful clinical and echocardiographic evaluation is required also

for HIV-infected patients who receive drugs with a recognized cardiotoxic action (doxorubicin, interferon alpha, pentamidine), since they may worsen the clinical outcome of HIV-associated cardiomyopathy and increase the risk of potentially fatal arrhythmias [1].

References

1. Barbaro G, Fisher SD, Giancaspro G, Lipshultz SE (2001) HIV-associated cardiovascular complications: a new challenge for emergency physicians. Am J Emerg Med 19:566-574
2. Morris A, Huang L (2004) Intensive care of patients with HIV infection: HAART warming improvement but beware of future HAART (and heart) attacks. Chest 15:1602-1604
3. Aretz HT (1987) Myocarditis: the Dallas criteria. Hum Pathol 18:619-624
4. Lipshultz SE, Orav EJ, Sanders SP, Colan SD (1995) Immunoglobulins and left ventricular structure and function in pediatrics HIV infection. Circulation 92:2220-2225
5. Nzuobontane D, Blackett KN, Kuaban C (2002) Cardiac involvement in HIV-infected people in Yaounde, Cameroon. Postgrad Med J 78:678-681
6. Barbaro G, Di Lorenzo G, Grisorio B, Barbarini G (1996) Clinical meaning of ventricular ectopic beats in the diagnosis of HIV-related myocarditis: a retrospective analysis of Holter electrocardiographic recordings, echocardiographic parameters, histopathological and virologic findings. Cardiologia 41:1199-1207
7. Frater RW, Sisto D, Condit D (1989) Cardiac surgery in human immunodeficiency virus (HIV) carriers. Eur J Cardiothorac Surg 3:146-150
8. Aguilar RV, Farber HW (2000) Epoprostenol (prostacyclin) therapy in HIV-associated pulmonary hypertension. Am J Respir Crit Care 162:1846-1850
9. Klings ES, Farber HW (2001) Current management of primary pulmonary hypertension. Drugs 61:1945-1956
10. Pellicelli AM, D'Ambrosio C, Vizza CD et al (2004) HIV-related pulmonary hypertension. From pathogenesis to clinical aspects. Acta Cardiol 59:323-330
11. Zuber JP, Calmy A, Evison JM et al (2004) Pulmonary arterial hypertension related to HIV infection: improved hemodynamics and survival associated with antiretroviral therapy. Clin Infect Dis 38:1178-1185

Guidelines for the Prevention of Cardiovascular Risk in HIV-Infected Patients Treated with Antiretroviral Drugs

D. Scevola, G. Barbarini, G. Barbaro

Introduction

Highly active antiretroviral therapy (HAART) has decreased by two-thirds [1] the lethality of AIDS and opportunistic infections. However, the improved survival of HIV patients receiving HAART has become associated with lipid abnormalities [2–14] that increase cardiovascular morbidity, compromising the patient's quality of life and the efficacy of HAART. AIDS is changing from a "slim disease" to a "lipodystrophic disease" as a consequence of prolonged survival and the direct effect of HAART. The risk of cardiovascular disease in HIV patients is increased two- to threefold by disturbances in fat metabolism. New strategies addressed to prevent and manage such emerging disorders [15, 16] are needed. Moreover, coronary heart disease (CHD) is the leading cause of death and a common cause of morbidity in Western countries. Approximately 14 million Americans have CHD, according to NHANES III data [17]. Annually, about 1.1 million of them experience a heart attack and about 500,000 die from CHD (Fig. 1).

The objective proposed by various health authorities for the year 2010 is to reduce CHD

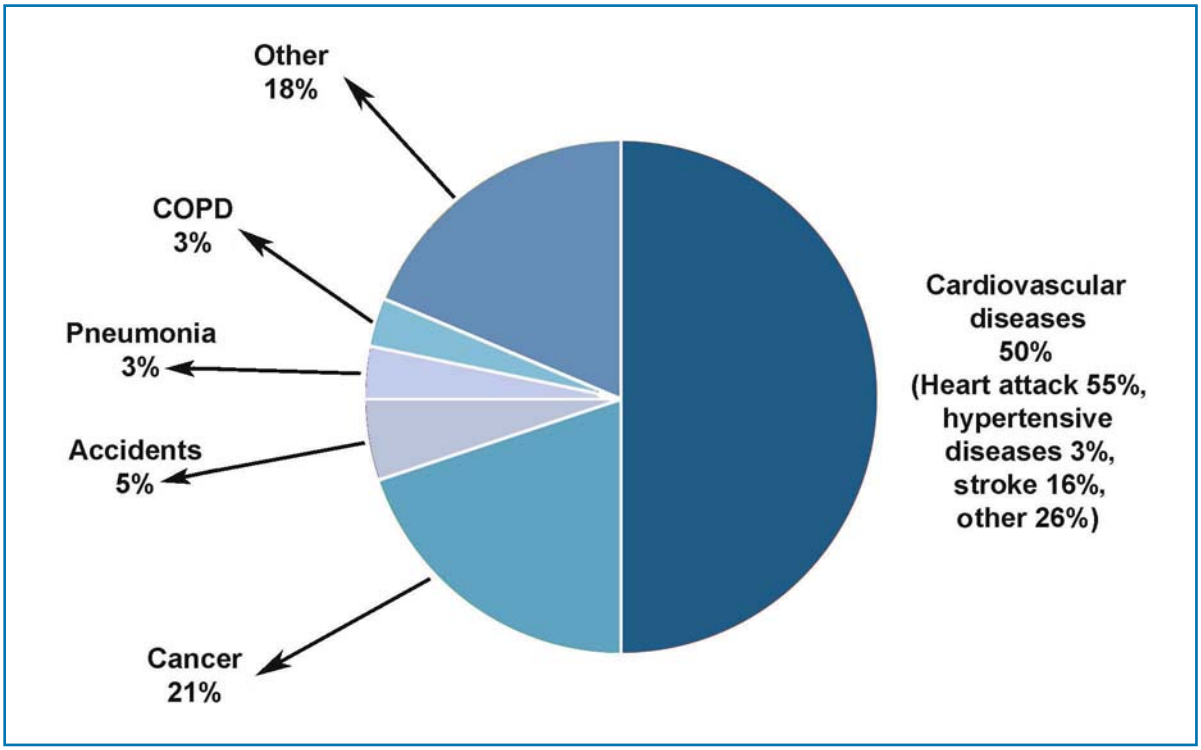

Fig. 1. Cardiovascular diseases account for 50% of the total deaths in the United States. *COPD*, chronic obstructive pulmonary disease

deaths to no more than 51 in 100,000, "enhancing the cardiovascular health and quality of life of all Americans through improvement of medical management, prevention and control of risk factors, and promotion of healthy lifestyle behaviors" [18].

In light of this policy also adopted by the European Union, particular attention must be devoted to HIV-infected individuals, who in the near future could represent an emerging population at a more elevated risk of CHD due to the prolonged life expectancy and/or metabolic disturbances induced by therapy [19–22]. Elevated triglycerides (TG), low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, and reduced levels of high-density lipoprotein (HDL) cholesterol are associated with visceral fat accumulation, peripheral lipodystrophy/lipoatrophy, and CHD. It has been reported that 5%–75% of HIV patients receiving HAART experience a worse lipid metabolism and body fat distribution after 10–12 months of therapy.

Our guidelines, based on our own and others' experience [23–28], meet the intervention criteria defined by the American National Cholesterol Education Program (NCEP) [29], including evaluation criteria, diet prescription, drug and exercise treatment – preliminary discussion included in The Pavia Consensus Statement, October 2001 [30, 31] – and the recommendations of the HIV Medicine Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group (AACTG) [32].

Patient Evaluation Criteria

Patients at risk of CHD must be routinely evaluated for risk factors (Fig. 2) such as family history, smoking, hypertension, hormonal status, obesity, physical activity (Fig. 3), alcohol abuse, hypogonadism, hypothyroidism, diabetes, and renal or hepatic disease.

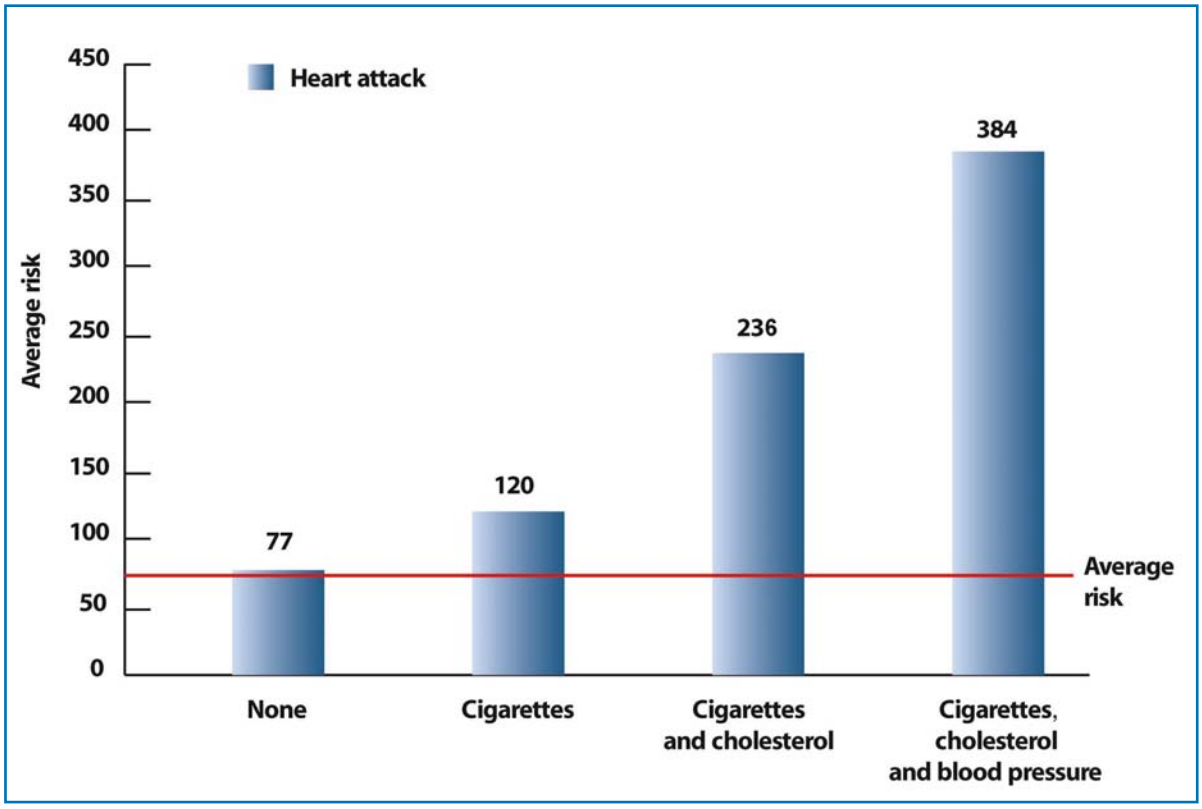

Fig. 2. People with combinations of three risk factors for coronary heart disease have a five times higher probability of heart attack than persons without risk factors. Physical inactivity is an additional risk factor

Fig. 3. Changes in physiologic functions with age and physical activity. The functional capacity of organs (e.g., cardiac index, breathing capacity, nerve conduction velocity, liver, kidneys, brain activity) declines with age and inactivity

Guidelines include the measurement of total cholesterol, HDL, LDL, and VLDL cholesterol, TG, lactate [30–32], the measure of body compartments, body circumferences and skinfolds [22], and resting metabolic rate (RMR; as a measure of the energy expended for maintenance of physiologic functions) that generally represents the largest portion of daily energy expenditure (60%–75%) [23–25]. We use the WHO equations for body weights and heights [26] along with bioimpedance analysis (BIA) and indirect calorimetry to predict the RMRs and energy expenditure for different age and sex groups [27, 28]. Energy production is estimated by measuring O_2 consumption and CO_2 production using a special calorimeter (e.g., Datex-Engstron Division Instrumentarium Corp. Helsinki, Finland; type MBM-200-23-01). RMR values normally range between 0.7 and 1.6 kcal/min according to the subject's body composition, gender, and level of training.

Intervention Criteria

Nutritional and Pharmacological Approach

No universally accepted guidelines exist for the nutritional treatment of lipid matabolism disturbances in HIV patients, but according to NCEP [19, 29] and our own as well as other authors' studies [15, 22, 28, 30–33], in patients *with preexisting CHD* we counsel dietary intervention when the LDL cholesterol level ranges between 100 mg/dl and 130 mg/dl, adding drug therapy if LDL cholesterol exceeds 130 mg/dl. Among patients *without CHD, but presenting two or more risk factors* (Fig. 2), dietary intervention is strongly indicated when LDL cholesterol is between 130 mg/dl and 160 mg/dl. Drug therapy must be added when LDL exceeds 160 mg/dl. With *fewer than two risk factors,* dietary modifications should be recommended when LDL levels range between 160 mg/dl and 190 mg/dl. Drug therapy should be

considered with LDL levels over 190 mg/dl. For patients with very high TG levels (>400 mg/dl) the AACTG [30] suggests a dietary intervention when total cholesterol is higher than 240 mg/dl or HDL cholesterol is lower than 35 mg/dl. Patients with isolated hypertriglyceridemia (fasting serum levels >200 mg/dl) should follow an adequate diet and physical exercise program. If levels exceed 1,000 mg/dl, pharmacological therapy should be strongly suggested because of the risk of pancreatitis. The same indication is mandatory for patients with a history of pancreatitis having TG levels over 500 mg/dl.

To reduce hypercholesterolemia, dietary and exercise treatments are recommended before pharmacological intervention. In patients suffering from wasting and lipid disturbances, it seems preferable to treat the wasting first [28, 34, 35].

For each patient, the guidelines for nutritional intervention must consider RMR, gut functions, concomitant diseases, hormonal status, appetite, and social conditions, as previously described [22, 30, 32]. At the first sign of malnutrition, suitable nutritional treatment is advised [28] because of the positive effect on the infection and on the quality of life. A balanced supply of *n*-6 and *n*-3 polyunsaturated fatty acids (PUFA) including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA; the main components of fish oil) may modulate cytokine production. EPA, as a direct suppressant of lipid mobilization factor, counteracts weight loss, lipolysis, and protein catabolism [36]. Amino acids (1.5–2 g/kg per day) must be administered to block protein loss. A quote of them (<0.7 g/kg per day) should include essential amino acids. Branched chain amino acids are useful in hepatic encephalopathy. An early and aggressive nutritional treatment of wasting and lipid metabolism disturbances improves the general clinical status, reducing the length of hospital stay. Unfortunately, the National Health Services do not support nutritional therapy programs.

Pharmacological intervention on appetite and metabolic pathways with drugs, such as cyproheptadine [37], progestin derivatives [34, 38–40], insulin-like growth factor-1 [41], steroids, and growth hormone [22, 42, 43], contributes to the success of any nutritional program.

Drugs Lowering Lipids

Because only 40% of patients [19] treated with diet and physical exercise have reduced lipid levels, therapy with statins and/or fibrates for hypercholesterolemia and/or hypertriglyceridemia becomes necessary [30]. In the group of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, pravastatin 10–40 mg PO q.i.d. or atorvastatin 10–40 mg PO q.i.d. are preferred because they are the least susceptible to interactions with protease inhibitors. Fluvastatin 20–80 mg PO b.i.d. is an alternative. In the group of fibrates, clofibrate 1 g PO b.i.d., gemfibrozil 600 mg PO b.i.d. before meals, and fenofibrate 54–160 mg PO q.i.d. with meals are the first-line choice for isolated hypertriglyceridemia or mixed hypercholesterolemia plus hypertriglyceridemia. Because of the high risk of pancreatitis, an isolated increase of TG levels over 1,000 mg/dl, with normal HDL values, needs treatment with statin or fibrates and replacement of saturated fats with nonsaturated fats. In combined disorders (high cholesterol, high TG), statins and fibrates together may control lipid metabolism, but can also cause muscle damage (rhabdomyolysis). In some patients, gemfibrozil (600 mg b.i.d.), atorvastatin (10 mg q.i.d.), or their combination (G+A) reduces total cholesterol by 32%, 19%, and 30%, respectively, and TG by 59%, 21%, and 60%. The antilipidemic drugs pose a risk of toxicity because the majority of them (atorvastatin, lovastatin, simvastatin, bezafibrate, ciprofibrate, fenofibrate, gemfibrozil) are metabolized by the same CYP3A liver enzymes as protease inhibitors and other drugs taken by HIV-infected patients. Pravastatin and fluvastatin, on the contrary, have other mechanisms of excretion. Protease inhibitors, macrolides, and imidazole derivatives have an inhibitory effect on CYP3A and can raise statin levels by 10- to 20-fold, potentially leading to increased muscle and liver toxicity. CHD due to lipid metabolism alterations takes 5–10 years to develop, while heart attacks seen after a few weeks or months of HAART are attributed to thrombosis and not to artheriosclerosis. The use of metformin can reduce central fat and insulin resistance [44], but it also reduces general body fat and muscle mass. Troglitazone (Rezulin), which is

active on glucose levels without effects on lipids and body fat [45], was removed from the market because of liver toxicity. Rosglitazone (Avandia) and pioglitazone (Actos) are related compounds with a lower risk of hepatic toxicity. In spite of a confirmed improvement of insulin resistance, contrasting findings have been reported on the use of glitazones in the treatment of HIV-associated lipodystrophy/lipoatrophy [46]. Growth hormone [42, 43, 47] reduces abdominal fat without having an influence on peripheral fat loss and lipids. Androgenic anabolic steroids (oxandrolone, nandrolone decanoate) increase muscular body mass without changes in lipids and body fat [48]. Niacin 50–100 mg PO b.i.d./t.i.d. and bile acid sequestring agents may have side effects, while fish oil 3–5 g PO q.i.d. is well tolerated [49]. We usually administer fish oil and/or vegetable derivative PUFAs [22, 48, 50], associated with L-carnitine, in order to increase the beta-oxidative processes of long-chain fatty acids and we replace saturated fats with polyunsaturated fats.

In patients without other risk factors, such as smoking, preexisting cardiovascular diseases, or dyslipidemia, "wait and see" may be an appropriate strategy [14].

Physical Exercise

Exercise has been extensively studied in patients with known coronary artery disease. It has been shown to induce a beneficial adaptation in the cardiovascular system as well as the peripheral musculature [28, 51, 52, 53–55] (Table 1, Fig. 4).

Aerobic exercise and resistance exercise are the most popular methods of preventing or treating sarcopenia and increasing muscular performance [56].

In our experience, both aerobic and anaerobic exercise associated with a personalized training diet improve muscular endurance and body composition in HIV patients, in accordance with results obtained by Stringer [57] and Smith [52].

For developing complete muscular strength, three exercise methods are commonly used: weight training, isometric training, and isokinetic training.

The neck, arms, and shoulders; the chest, abdomen, and back; and the buttocks and legs can be conditioned separately by specific exercises. All our exercise programs include progressive resistance training of the major muscle groups.

Table 1. Beneficial effects of muscular exercise

Increases
> Resistance to fatigue
> Elasticity and flexibility
> Muscular mass and strength
> Respiratory capacity
> Appetite
> Intestinal functions
Decreases
< Stress and insomnia

HDL levels may be favorably increased in sedentary people who engage in aerobic training. Concurrently, the LDL levels are lowered so that the net result is a considerably improved ratio of HDL to LDL or HDL to total cholesterol. This exercise effect appears to be independent of whether or not the diet is low in fat or whether or not the exerciser is overweight. The effect of regular endurance-type exercise on the blood lipid profile is certainly a strong argument for incorporating vigorous physical activity into a total program of health maintenance in HIV patients receiving HAART. It is well know that exercise improves myocardial circulation and metabolism and enhances vascularization, cardiac glycogen stores, and glycolitic capacity that protects the heart from hypoxic stress [55]. Mechanical and contractile properties of the myocardium are improved, enabling the conditioned heart to maintain or increase contractility during a specific challenge. Heart rate and blood pressure are favorably reduced so the work of the myocardium is significantly reduced at rest and during exercise.

Exercise reduces the symptoms and medication doses needed and it corrects the nutritional imbalances and side effects of drugs and altered diet. Many clinical signs and symptoms are responsive to exercise: atrophy of muscle and bone, postural hypotension, joint stiffness, reflexes, cardiovascular deconditioning, anorexia, gastrointestinal motility, insomnia, and depression. Exercise is the way to stimulate the muscles not only to move the body

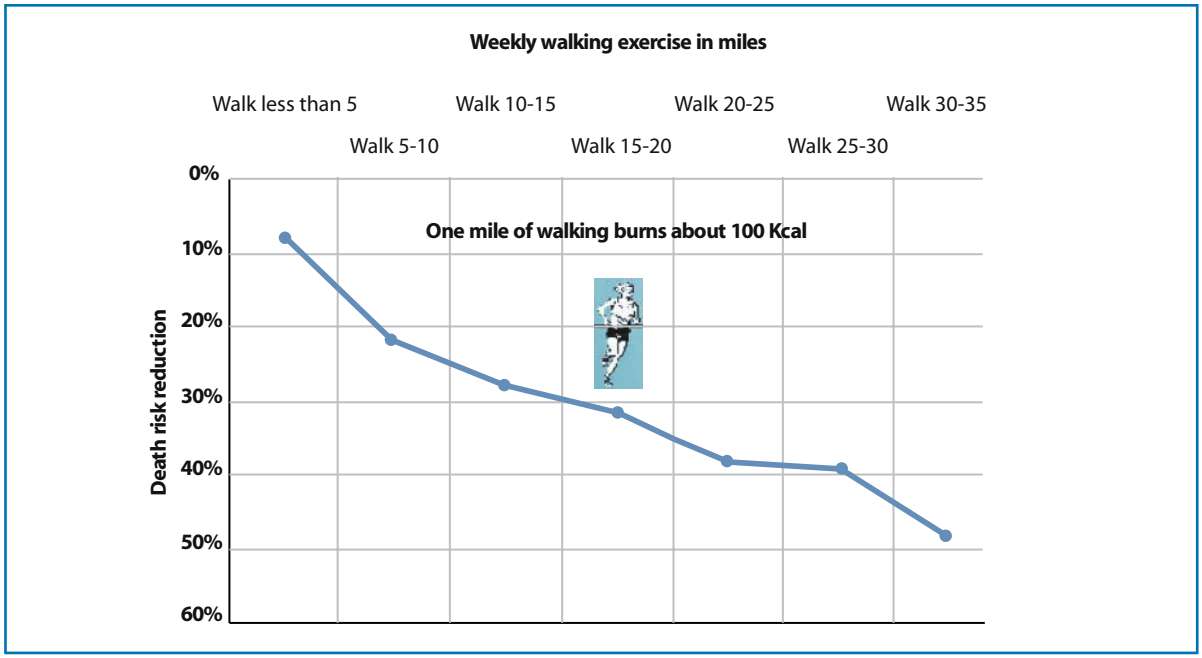

Fig. 4. Regularly walking/jogging more than 3 miles a day proportionally reduces the risk of death. No additional benefits are obtained with energy expenditure beyond 3,500 kcal per week

better but also to increase biochemical reactions devoted to energy production. The predominant energy pathways required in physical activities are the ATP-CP system, the lactic acid system, and the oxygen or aerobic system that are often operative simultaneously (Fig. 5). However, their relative con-

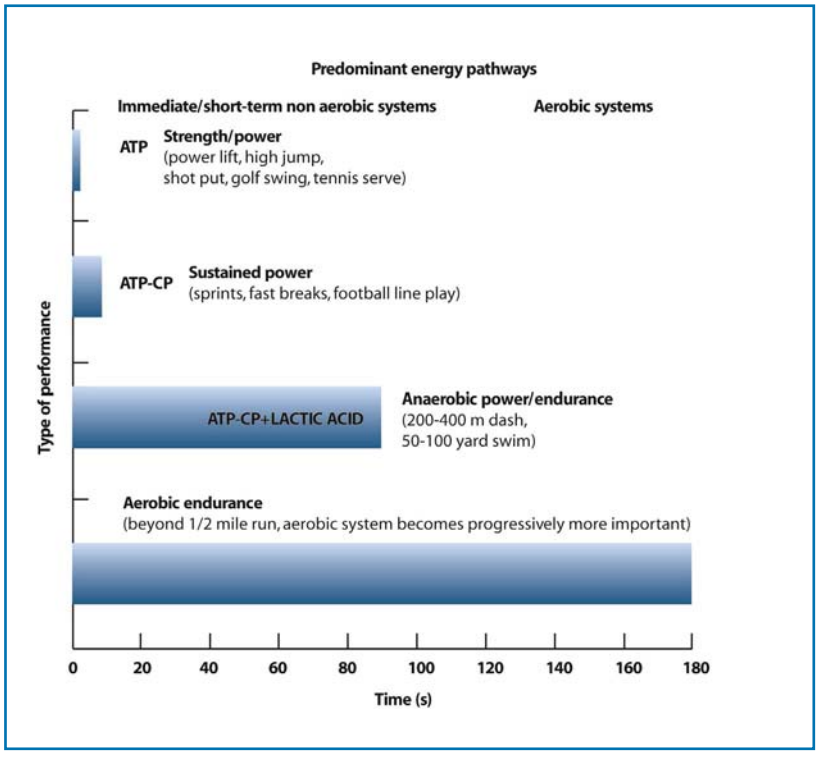

Fig. 5. The three energy systems (ATP-CP system, lactic acid system, aerobic system) involved in some physical activities. In exercises with an intense, short burst of energy, the energy is provided anaerobically almost exclusively by the stored reserve of ATP and CP. In performances lasting between 10 and 90 s, the energy from lactic acid production becomes an important source. After 2–4 min of continuous activity, the energy is released almost exclusively from aerobic reactions

tributions to the total energy requirement during an exercise may differ markedly. This contribution is related directly to the length of time and intensity that a specific activity is performed.

Anaerobic Conditioning

During intense, maximal bursts of energy lasting no more than 6 s, the energy is provided anaerobically almost exclusively by the stored high-energy molecules of phosphates – ATP and CP. Overload of the ATP-CP pool can be achieved by engaging specific muscles in maximum bursts of effort for 5 or 10 s. In physical activities chosen to enhance the ATP-CP energy capacity of specific muscles, the subject must perform numerous bouts of intense, short-duration exercise. The energy for performances lasting between 10 and 90 s is still supplied predominantly by anaerobic reactions, but lactic acid becomes a more important source of energy. To improve the lactic acid energy system, the training program must be of sufficient intensity and duration to stimulate lactic acid production as well as to overload the ATP-CP energy system. An effective way to increase near-maximum levels and overload the lactic acid system is repeat bouts of up to 1 min of extreme running, swimming, or cycling, stopped 30–40 s before exhaustion. The exercise bout should be repeated several times after 1–2 min of recovery. Recovery time from the exercise can be considerable when large amounts of lactic acid are produced (Fig. 5).

Aerobic Conditioning

After 2–4 min of continuous exercise, any physical activity becomes progressively more dependent on aerobic energy for the resynthesis of the phosphates. Under aerobic conditions, pyruvic acid from carbohydrate metabolism and molecules from fat and protein are transformed into various intermediate substances with the final formation of CO_2, H_2O, and large amounts of energy. If O_2 supply and utilization are adequate, lactic acid does not accumulate and fatigue is absent. We can reach a condition of endurance or aerobic fitness in which the body's ability to generate ATP aerobically exceeds the energy produced from anaerobic reactions. To have a practical measure of cardiovascular capacity of the subject, we use the step-up test (Fig. 6) that provides the heart rate response to aerobic exercise: a low heart rate during exercise and a small increment with more intense exercise reflect a high level of cardiovascular fitness. A simple method to recover heart rates for evaluation of relative fitness for aerobic exercise is the Tecumseh step test [52].

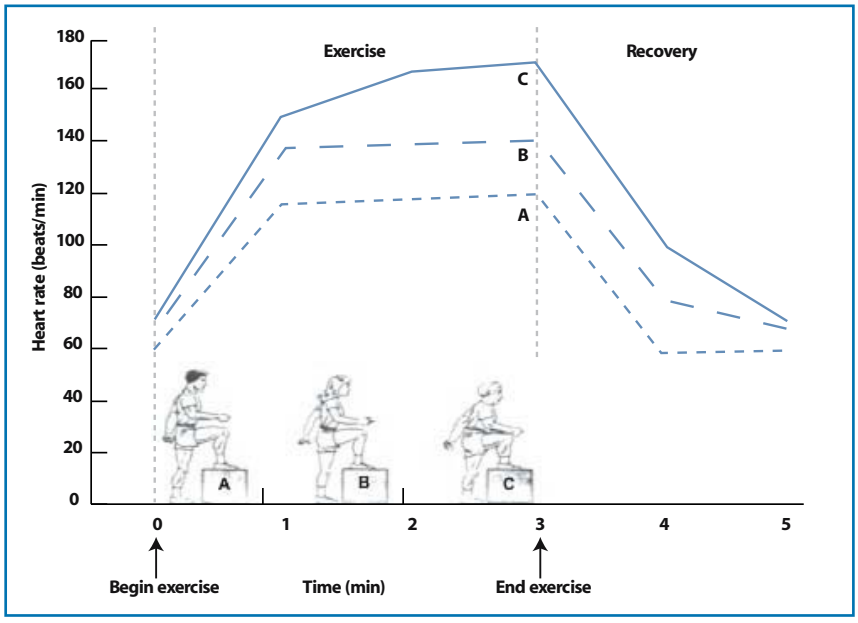

Fig. 6. Step-up exercise to evaluate the cardiovascular capacity: the different heart rate response of three individuals during 3 min of regular stepping. The subjects are basically conditioned differently: *A* is a professional football player and at the end of 3 min reaches a heart rate of 115 beats per minute; for *B*, a gym-trainer, the heart rate is 140 beats per minute, while *C*, a sedentary young person, reaches 170 beats per minute. Heart rate recovery is complete 2 min after the end of exercise

The stepping cadence must be 22 steps per minute for women and 24 for men, with a stepping height of 20 cm. After 3 min of stepping and exactly 30 s after stopping, the subject must measure the pulse for 30 s in a standing position. The number of pulse beats, from the 30-s to the 1-min postexercise period, is the heart rate score (Fig. 7). By means of special equations and the recovery heart rate, the maximal O_2 consumption can be calculated [53].

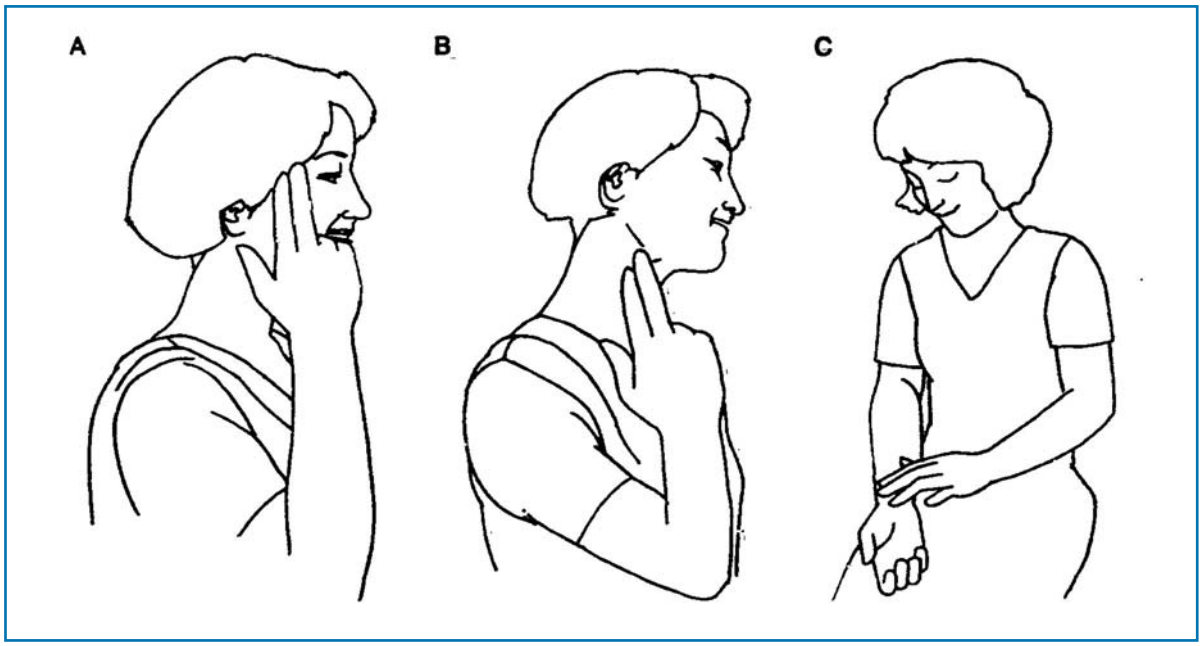

Fig. 7. Pulse rate self-taken at the (**A**) temporal, (**B**) carotid, and (**C**) radial arteries

Determination of Frequency, Duration, and Intensity of Training

The intensity of training is the most critical factor that influences successful aerobic conditioning and can be expressed in diffent ways: as calories consumed, as a percentage of maximal O_2 consumption, as heart rate or percentage of maximum heart rate, or as multiples of RMR required to perform the work. The exercise must be sufficient to produce an increase in heart rate to at least 130–140 beats per minute, equivalent to about 50%–55% of the maximum aerobic capacity or about 70% of the maximum exercise heart rate (Fig. 8).

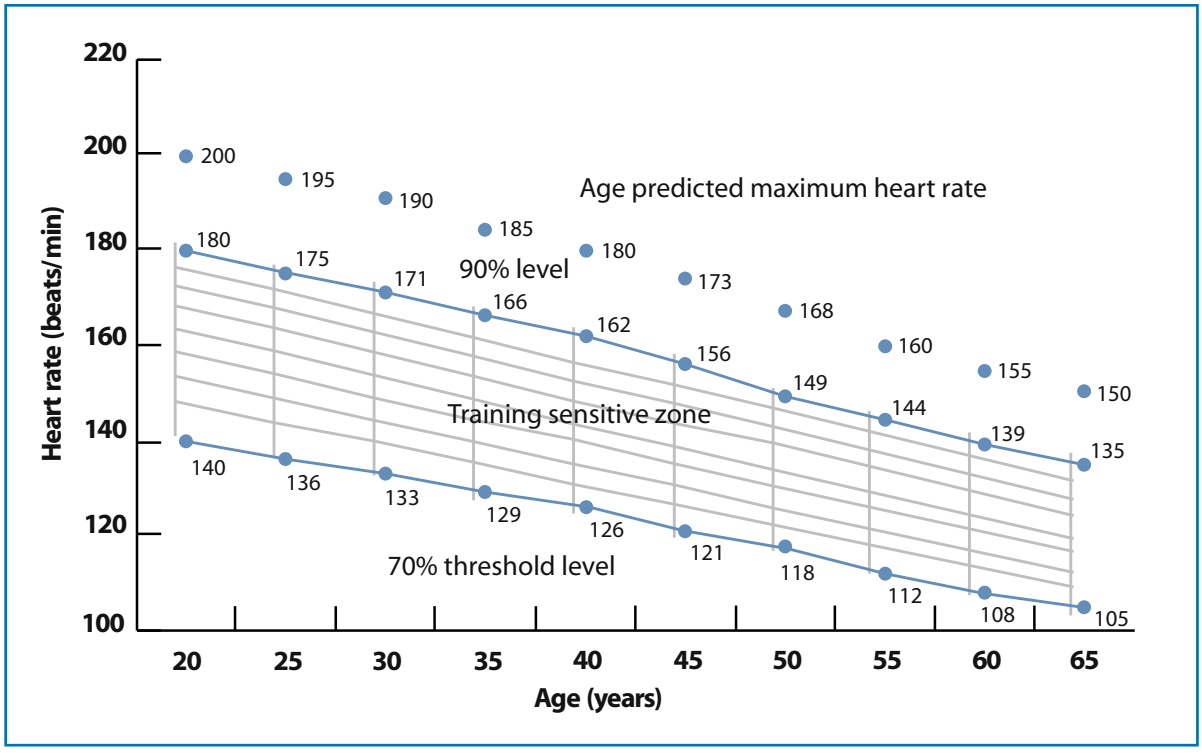

Fig. 8. The diagram shows the percentages (70%–90%) of maximal heart rate (included in the depicted training zone) required to train aerobic systems of energy production in different age groups. The subject must exercise for 3–5 min in order to obtain a desired pulse rate, counting for 10 s after stopping. For example, a training heart rate equal to 70% of the age-related maximal value for a man of 40 years can be calculated using the formula (0.70×180=126 beats per minute). Exercise must be performed at least for 20 min. A training response occurs if an exercise is performed two or preferably three times each week for at least 6 weeks. Both continuous as well as intermittent overload are effective in improving aerobic capacity. A single 3 to 5 min of vigorous exercise performed three times a week improves aerobic capacity as much as a less exhausting but steady-state exercise for 20 min. Our aerobic training program is conducted 3 days a week utilizing 20–30 min of continuous exercise of sufficient intensity to expend about 300 kcal. For example, subjects trained on a bicycle ergometer 20–30 min a day (~300 kcal), three times a week for 8 weeks, with a training intensity of 85% of maximum heart rate improved maximal O_2 uptake by 7.8% [30]

References

1. Palella FJ, Delaney KM, Mooreman AC et al (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 338:853-860
2. Dubè MP, Sattler FR (1998) Metabolic complications of antiretroviral therapies. AIDS Clinical Care 10:41-44
3. Sullivan AK, Nelson MR (1997) Marked hyperlipidaemia on ritonavir. AIDS 11:938-939
4. Hengel RL, Watts NB, Lennox JL (1997) Benign symmetric lipomatosis associated with protease inhibitors. Lancet 350:1596
5. Miller KD, Jones E, Yanovski JA et al (1998) Visceral abdominal-fat accumulation associated with use of indinavir. Lancet 351:871-875
6. Carr A, Samaras K, Burton S et al (1998) A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 12:F51-F58
7. Lo JC, Mulligan K, Tai VW et al (1998) "Buffalo hump" in men with HIV-infection. Lancet 351:867-870
8. Carr A, Samaras K, Chisholm DJ, Cooper DA (1998) Pathogenesis of HIV-1-protease inhibitor-associated peripheral liopdystrophy, hyperlipidemia, and insulin resistance. Lancet 352:1881-1883
9. Rosenberg HE, Mulder J, Sepkowitz K et al (1998) "Protease-paunch" in HIV+ persons receiving protease inhibitor therapy: incidence, risks and endocrinologic evaluation. Fifth Conference on

Retroviruses and Opportunistic Infections, Chicago, February 1998, abstract 408
10. Kotler DP, Rosenbaum KB, Wang J et al (1998) Alterations in body fat distribution in HIV-infected men and women. Twelfth World AIDS Conference, Geneva, Switzerland, June–July 1998, abstract 32173
11. Engelson ES, Kotler DP, Tan YX et al (1998) Altered body fat distribution in HIV infection: regional body composition measurements by whole body MRI and DXA scans. Twelfth World AIDS Conference, Geneva, Switzerland, June–July 1998, abstract 32181
12. Boyle BA (1999) Lipodystrophy: A new phenomeneon? AIDS Reader 9:15-17
13. Gervasoni C, Ridolfo AL, Trifirò G et al (1999) Redistribution of body fat in HIV-infected women undergoing combined antiretroviral therapy. AIDS 13:465-471
14. Bernasconi E (1999) Metabolic effects of protease inhibitor therapy. AIDS Reader 9:254-269
15. Scevola D, Di Matteo A, Uberti F et al (2000) Reversal of cachexia in patients treated with potent antiretroviral therapy. AIDS Reader 10:365-375
16. Henry K, Zackin R, Dube M et al (2001) Metabolic status and cardiovascular disease risk for a cohort of HIV-1-infected persons durably suppressed on an indinavir-containing regimen(ACTG 372A). Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections. February 4–8, 2001, Chicago, Illinois, abstract 656
17. Adams PF, Marano MA (1995) Current estimates from the National Health Interview Survey, 1994, National Center for Health Statistics. Vital Health Statistics 10:193
18. Anonymous (1999) Department of Health and Human Services, Healthy People 2010, Draft for Public Comment
19. Henry K, Melroe H, Huebesh J et al (1999) Experience with the National Cholesterol Education Program (NCEP) guidelines for the identification and treatment of protease inhibitor related lipid abnormalities: results of a prospective study. Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, Illinois, 1999, abstract 671
20. Grunfeld C, Feingold KR (1992) Metabolic disturbances and wasting in the acquired immunodeficency syndrome. N Engl J Med 5:329-337
21. Lonergan JT, Havlir D, Barber E, Mathews WC (2001) Incidence and outcome of hyperlactatemia associated with clinical manifestations in HIV-infected adults receiving NRTI-containing regimens. Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections, February 4–8, 2001, Chicago, Illinois, abstract 624
22. Scevola D, Bottari G, Oberto L, Faggi A (1996) AIDS cachexia: basics and treatment. In: Ruf B, Pohle HD, Goebel FD, L'age M (eds) HIV-Infektion, Pathogenese, Diagnostik und Therapie. Socio-Medico Verlag, Graefelfing, pp 281-327
23. Melchior JC, Salmon D, Rigaud D et al (1991) Resting energy expenditure is increased in stable, malnourished HIV-infected patients. Am J Clin Nutr 53:437-441
24. Grunfeld C, Pang M, Shimizu L et al (1992) Resting energy expenditure, caloric intake and short-term weight change in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. Am J Clin Nutr 55:455-460
25. Shevitz AH (2000) Resting energy expenditure in the HAART era. AIDS Reader 10:539-544
26. WHO (1986) Working group on the use and interpretation of anthropometric indicators of nutritional status. Bull WHO 64:929-941
27. Kotler DP, Rosenbaum K, Wang J, Pearson RN (1999) Studies of body composition and fat distribution in HIV-infected and control subjects. J Acquir Immune Defic Syndr Hum Retrovirol 20:228-237
28. Scevola D (1993) La cachessia nelle malattie infettive e neoplastiche. Edizioni Medico Scientifiche, Pavia
29. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001) Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 285:2486-2497
30. Scevola D, Di Matteo A, Lanzarini P et al (2003) Effect of exercise and strength training on cardiovascular status in HIV-infected patients receiving highly active antiretroviral therapy. AIDS 17(S1):S123-S129
31. Volberding PA, Murphy RL, Barbaro G et al (2003) The Pavia consensus statement. AIDS 17(S1):S170-S179
32. Dubé MP, Stein JH, Aberg JA et al (2003) Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medicine Association of the Infectious Disease Society of America and the Adult AIDS clinical trials group. Clin Inf Dis 37:613-627
33. Barrios A, Blanco F, Garcìa-Benayas T et al (2002) Effect of dietary intervention on highly active antiretroviral therapy-related dyslipemia. AIDS 16:2079-2081
34. Von Roenn JH (1994) Management of HIV-related body weight loss. Drugs 47:774-783

35. Scevola D, Bottari G, Zambelli A et al (1992) Trattamento dietetico ed ormonale dei deficit nutrizionali nell'AIDS. Clin Dietol 19:127-140
36. Tisdale M, Beck SA (1991) Inhibition of tumour induced lipolysis in vitro and cachexia and tumour growth in vivo by eicosapentaenoic acid. Biochem Pharmacol 41:103-107
37. Kardinal CG, Loprinzi CL, Schaid DJ et al (1990) A controlled trial of cyproheptadine in cancer patients with anorexia and/or cachexia. Cancer 65:2657-2662
38. Scevola D, Zambelli A, Bottari G et al (1991) Appetite stimulation and body weight gain with medroxyprogesterone acetate in AIDS anorexia and cachexia. Farmaci e Terapia 3:77-83
39. Scevola D, Parazzini F, Negri C, Moroni M (1995) Efficacy and safety of high-dose MPA treatment of AIDS cachexia: the Italian multicentre study. Fourth Congress of the European Association for Palliative Care. Barcelona, December 6–9, 1995, abstracts book, pp 443-447
40. Scevola D, Bottari G, Oberto L et al (1995) A double-blind-placebo controlled trial of megestrol acetate on caloric intake and nutritional status in AIDS cachexia. Fourth Congress of European Association for Palliative Care. Barcelona, December 6–9, 1995, abstracts book, pp 427-437
41. Rondanelli M, Solerte SB, Fioravanti M, Scevola D et al (1997) Circadian secretory pattern of growth hormone, insulin-like growth factor type I, cortisol, adrenocorticotropic hormone, thyroid-stimulating hormone, and prolactin during HIV infection. AIDS Res Hum Retroviruses 14:1243-1249
42. Scevola D, Bottari G, Oberto L et al (1995) Megestrol acetate (MA) and growth hormone (rHGH) as combined therapy for AIDS cachexia. Fourth Congress of European Association for Palliative Care. Barcelona, December 6–9, 1995, abstracts book, pp 438-442
43. Wanke C, Gerrior J, Kantaros J et al (1999) Recombinant human growth hormone improves the fat redistribution syndrome (lipodystrophy) in patients with HIV. AIDS 13:2099-2103
44. Saint-Marc T, Touraine JL (1999) Effects of metformin on insulin resistance and central adiposity in patients receiving effective protease inhibitor (PI). Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, Illinois, abstract 672
45. Walli RK, Michl GM, Bogner JR et al (1999) Effects of the PPAR-Activator troglitazone on protease inhibitor associated peripheral insulin resistance. Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, Illinois, abstract 673
46. Carr A, Workman C, Carey D, Rogers G, Martin A, Baker D et al (2004) No effect of rosiglitazone for treatment of HIV-1 lipoatrophy: randomised, double-blind, placebo-controlled trial. Lancet 363:429-38
47. Torres R, Unger K (1999) The effect of recombinant human growth hormone on protease-inhibitor-associated fat maldistribution syndrome. Sixth Conference on Retroviruses and opportunistic Infections, Chicago, Illinois, abstract 675
48. Strawford A, Barbieri T, Parks E et al (1999) Resistance exercise and supraphysiologic androgen therapy in eugonadal men with HIV-related weight loss. JAMA 281:1282-1290
49. Scevola D, Oberto L, Bottari G, Faggi A (1995) Lipidi e Malattie Infettive. Abstracts Book XII Congresso Nazionale ADI. Torino, 16-18/11, p 187
50. Scevola D, Bottari G, Oberto L, Faggi A, Venturino P (1996) Problemi nutrizionali del paziente AIDS e strategie terapeutiche. Quaderni di Cure Palliative (S1):51-64
51. Amsterdam EA (1997) Exercise in cardiovascular health and disease. Yorke Medical Books, New York
52. Smith BA, Neidig JL, Nickel JT et al (2001) Aerobic exercise: effects on parameters related to fatigue, dyspnea, weight and body composition in HIV-infected adults. AIDS 15:693-701
53. Montoye HJ (1975) Physical activity and health: an epidemiologic study of an entire community. Prentice-Hall, Englewood Cliffs
54. Katch FI, Freedson PS, Jones CA et al (1985) Evaluation of acute cardiorespiratory responses to hydraulic resistance exercise. Med Sci Sports Exerc 17:168-173
55. Crow RS, Rantahargiu PM, Prineas RJ et al (1986) Risk factors, exercise fitness and electrocardiographic response to exercise in 12,866 men at risk of symptomatic coronary heart disease. Am J Cardiol 57:1075-1082
56. Pollock M, Gaesser G, Butcher J et al (1998) The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness and flexibility in healthy adults. Med Sci Sports Exerc 30:975-991
57. Stringer WW, Berezovskaya M, O'Brien WA et al (1998) The effect of exercise training on aerobic fitness, immune indices, and quality of life in HIV+ patients. Med Sci Sports Exerc 30:11-16

Appendix 1

Cardiovascular Monitoring of HIV-Infected Subjects and Cardiovascular Risk Stratification and Primary Prevention of Cardiovascular Disease in Patients Receiving HAART According to the Pavia Consensus Statement

Cardiovascular Monitoring in HIV-Infected Patients [1]

Diagnostic test	Clinical application
Electrocardiogram (ECG)	Routine ECG or Holter monitoring of HIV-infected patients may not be indicated. However, it may be useful for HIV-infected patients with palpitations, syncope, unexplained stroke, or known autonomic dysfunction, and for those who are starting or receiving medications known to be arrhythmogenic or to affect repolarization with prolongation of electrocardiographic QTc interval (e.g., pentamidine). For this latter subset of patients, ECG should be performed at least every 6 months.
Echocardiography	Baseline and serial echocardiographic monitoring may be essential in detecting early disease and targeting patients who would benefit from early intervention and aggressive early antiretroviral therapy. Echocardiography should be repeated every 1-2 years if the patient is asymptomatic and every 6 months if symptomatic. Diastolic dysfunction or other process (e.g., pericardial effusion, valvular heart disease, endocarditis) should be considered to explain clinical signs and symptoms. Echocardiography should also be considered in patients with unexplained or persistent pulmonary symptoms and in those with viral coinfection (e.g., cytomegalovirus, Epstein-Barr virus, or adenovirus). Echocardiography is useful in assessing for increased left ventricular mass in patients with systemic hypertension or in assessing right ventricular pressure in patients with suspected pulmonary hypertension.
Blood pressure monitoring	Routine assessment of blood pressure in HIV-infected patients is important because these patients seem to be at higher risk of developing hypertension and of developing it at a younger age than the general population. Predisposing conditions including vasculitis, acquired glucocorticoid resistance, acute and chronic renal failure, and drug interactions (e.g., the interaction between indinavir and stavudine-phenylproanolamine) should be carefully assessed. Some reports indicate that elevated blood pressure may be related to protease inhibitor-induced

	lipodystrophy and metabolic disorders, especially to fasting triglyceride levels with a prevalence of hypertension in up to 74% of patients with HAART-associated metabolic syndrome.
Blood tests	In patients with unexplained heart failure, the following tests should be performed: a complete blood count to determine anemia and other hematologic abnormalities, serum electrolytes for hypocalcemia, hypophosphatemia, hyponatremia, and hypokalemia, and albumin, thyroid-stimulating hormone measurements for hypothyroidism; measurement of serum iron and ferritin; measurement of serum angiotensin 1-converting enzyme activity; antinuclear antibody measurements; vanillylmandelic acid measurements for pheochromocytoma; tests of amyloid, blood urea nitrogen, and creatinine, with urinalysis for renal failure; and assessment for hypogonadism and hepatic disease.
Cardiac catheterization and endomyocardial biopsy	For HIV-infected patients with congestive heart failure of unclear etiology that has not responded to 2 weeks of anticongestive therapy, cardiac catheterization with possible endomyocardial biopsy may be indicated. The finding of cytomegalovirus inclusions or other histologic evidence of infection (e.g., by polymerase chain reaction or in situ hybridization) may direct therapy. The presence of myocarditis may suggest immunomodulatory therapy. Angiography may be indicated for patients with suspected coronary heart disease.
Cardiovascular side effects of common HIV therapy	Cardiovascular side effects and interactions of common HIV therapy should be carefully assessed while monitoring HIV-infected patients. Because of medication interactions and side effects, HIV-infected patients should receive individualized therapy.

Cardiovascular Risk Stratification of HIV-Infected Patients Receiving HAART [1]

1. All HIV-infected patients should have cardiovascular risk factors evaluated according to the Framingham score before receiving HAART. The use of Framingham scores and other noninvasive investigations of cardiovascular risk may help in the decision regarding the use of antiretrovirals and other treatment. Lipid profiles and other blood tests for preventive cardiology should be routine before and during HAART.

2. Before HAART is started, lipid profiles should be measured after an 8–12-h fast to establish a baseline, and the measurements should be repeated routinely during the HAART therapy. Serum glucose and hemoglobin A1C measurements are especially indicated for patients on HAART.

3. Fasting lipids and glucose should be measured before the initiation of protease inhibitors and at regular 3–6-month intervals thereafter. For patients with elevated triglyceride levels at baseline, lipid measurements should be repeated within 1–2 months of starting HAART. If fasting triglyceride levels are above 400 mg/dl, then the calculated LDL cholesterol level will be unreliable.

4. The routine evaluation of coagulation parameters is probably not advisable until the benefit of widespread screening is assessed in prospective studies. However, clinicians should be aware of the increased risk of coagulative disorders in patients on HAART, especially in those with HAART-associated metabolic syndrome, and they should check coagulative parameters (D-dimer, plasminogen activator inhibitor-1, tissue-type plasminogen activator antigen, protein S, protein C and antithrombin III) at least once a year in they patients on HAART.

5. An elevated plasma homocysteine level is recognized as an independent factor for atherosclerosis and cardiovascular disease. It is caused by genetic variants [homozygous mutations (*C677T* and *A1298C*) of the *MTHFR* gene], malnutrition, drugs, or renal failure. Especially when above 10 µmol/l, it can be treated with dietary supplementation of folic acid, vitamin B_6, and vitamin B_{12}. The plasma homocysteine level should be checked at least once a year in HIV-infected patients with at least two major cardiovascolar risk factors and in those who receive protease inhibitors.

Primary Prevention of Cardiovascular Disease in HIV-Infected Patients Receiving HAART [1]

1. HIV-infected patients receiving HAART should be encouraged to perform physical activity. Regular exercise programs decrease rates of cardiovascular disease and improve immunologic parameters (improvement of natural killer cell function, immunoglobulin production, lymphocyte activation).

2. The patients should be encouraged to follow a healthy diet (rich in fruits and vegetables); a daily potassium supplement of about 60 mmol; fish oil supplementation in large doses of 3 g/ay; possibly calcium supplementation; possibly magnesium supplementation; smoking cessation and checking blood pressure at least once a week.

3. Protease inhibitors should be used with caution in patients with increased risk for cardiovascular disease, especially in those who have at least two major cardiovascular risk factors, independently of age, gender, and stage of HIV disease.

4. Because pharmacologic treatment to reduce cholesterol in HIV-infected patients is complicated by drug interactions, nondrug therapies such as modification of risk factors should be emphasized according to the National Cholesterol Education Program (NCEP) guidelines (www.nhlbi.nih.gov). The NCEP guidelines define low HDL cholesterol as less than 40 mg/dl and LDL cholesterol less than 100 mg/dl as optimal. Because LDL cholesterol calculated values are unreliable in patients with a serum triglyceride level above 400 mg/dl, for these patients a total cholesterol level above 240 mg/dl or an HDL cholesterol level below 35 mg/dl should prompt dietary interventions.

5. Statin therapy may prove useful in patients undergoing protease inhibitor treatment. According to the US-based Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group, for protease inhibitor-treated HIV-infected patients with hypercholesterolemia, treatment with low-dose pravastatin (initial dosage 20 mg/day), fluvastatin (initial dosage 20 mg/day) or atorvastatin (10 mg/day) is recommended. Pravastatin and fluvastatin are the statins that are least influenced by the CYP3A4 metabolic pathway. Lovastatin or simvastatin therapy should be avoided because of interactions with protease inhibitors or non-nucleoside reverse transcriptase inhibitors and because of the risk of rhabdomyolysis. In patients with established coronary heart disease or total cholesterol above 400 mg/dl, drug therapy with statins should be considered as a concomitant initial therapy along with low-dose aspirin (160 mg/day).

6. When treatment with statins is not appropriate or when patients do not respond to these agents, gemfibrozil (600 mg twice daily) or fenofibrate (200 mg once daily) are reasonable alternatives. Concomitant use of fibrates and statins may increase the risk of skeletal muscle toxicity.

7. Nondrug therapy (diet and exercise) is recommended for patients with fasting serum triglyceride levels of above 200 mg/dl. Severe hypertriglyceridemia requires a very low-fat diet, avoidance of free sugars, and decreased alcohol intake. Omega-3-fatty acids as oil or supplements may be helpful, although not yet tested in this subset of patients.

8. Gemfibrozil or fenofibrate are recommended for patients with hypertriglyceridemia who require drug therapy, and these agents are also considered reasonable initial treatment choices for patients with combined hyperlipidemia. Refractory dyslipidemia may suggest switching from protease inhibitors to non-nuclesoside reverse transcriptase inhibitors with a better metabolic profile (e.g., nevirapine, efavirenz).

9. In HIV-infected patients with hypertension, standard treatment based on guidelines from the Joint National Commission (JNC VII) [2] should be followed as there are no specific subpopulation studies at this time. However, in managing hypertension (blood pressure >140/90 mmHg) in HIV-infected patients receiving HAART, the first-choice drugs are ACE inhibitors or angiotensin II receptor antagonists (if not contraindicated), since these drugs have a good metabolic profile. Calcium channel blockers should be administered at low dosage, since they interact with protease inhibitors. Diuretics and beta-adrenergic blockers should be avoided in patients with "metabolic syndrome." There is no direct evidence on the effects of lowering blood pressure below 140/80 mmHg.

10. In managing glucose abnormalities, it is important to remember that some glitazones are metabolized by cytochrome P4503A4 and so their use with protease inhibitors could increased risks for myositis and hepatitis. In spite of a confirmed improvement of insulin resistance, contrasting findings have been reported about the use of glitazones in the treatment of HIV-associated lipodystrophy/lipoatrophy [3, 4].

References

1. Volberding P, Murphy R, Barbaro G et al (2003) The Pavia Consensus Statement. AIDS 17(S1):S170-S179
2. Chobanian AV, Bakris GL, Black HR et al (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 289:2560-2572
3. Hadigan C, Yawetz S, Thomas A, Havers F, Sax PE, Grinspoon S (2004) Metabolic effects of rosiglitazone in HIV lipodystrophy: a randomized, controlled trial. Ann Intern Med 140:786-794
4. Carr A, Workman C, Carey D et al (2004) No effect of rosiglitazone for treatment of HIV-1 lipoatrophy: randomised, double-blind, placebo-controlled trial. Lancet 363:429-438

Appendix 2

Interactions Between Antiretrovirals and Drugs Commonly Used to Treat Cardiovascular Diseases According to the Pavia Consensus Statement [1]

1. Interactions among protease inhibitors (PIs) and drugs used to treat cardiovascular diseases

PIs	Amprenavir	Indinavir	Lopinavir/ ritonavir	Nelfinavir	Ritonavir	Saquinavir/ atazanavir
Ca^{++} channel blocker	**Bepridil**	None	None	None	**Bepridil**	None
Antiarrhythmics						
Amiodarone	None	None	None	None	*Affected drug*: Amiodarone *Interacting drug*: Ritonavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Use with caution or avoid concomitant use	None
Flecainide	None	None	*Affected drug*: Flecainide *Interacting drug*: Lopinavir/ritonavir *Mechanism*: Potential for increased levels due to inhibition of metabolism *Recommendation*: Avoid concomitant use	None	*Affected drug*: Flecainide *Interacting drug*: Ritonavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Use with caution or avoid concomitant use	None
Propafenone	None	None	*Affected drug*: Propafenone *Interacting drug*: Lopinavir/ritonavir *Mechanism*: Potential for increased levels due to inhibition of metabolism *Recommendation*: Avoid concomitant use	None	*Affected drug*: Propafenone *Interacting drug*: Ritonavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Use with caution or avoid concomitant use	None

cont. →

cont.

Quinidine	None	None	None	None	*Affected drug*: Quinidine *Interacting drug*: Ritonavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Use with caution or avoid concomitant use	None
Statins						
Fluvastatin	*Affected drug*: Fluvastatin *Interacting drug*: Amprenavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	*Affected drug*: Fluvastatin *Interacting drug*: Indinavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	None	*Affected drug*: Fluvastatin *Interacting drug*: Nelfinavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	*Affected drug*: Fluvastatin *Interacting drug*: Ritonavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	None
Lovastatin	*Affected drug*: Lovastatin *Interacting drug*: Amprenavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	*Affected drug*: Lovastatin *Interacting drug*: Indinavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	*Affected drug*: Lovastatin *Interacting drug*: Lopinavir/ritonavir *Mechanism*: Potential for increased levels due to inhibition of metabolism *Recommendation*: Avoid concomitant use	*Affected drug*: Lovastatin *Interacting drug*: Nelfinavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	*Affected drug*: Lovastatin *Interacting drug*: Ritonavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	None
Pravastatin	None	*Affected drug*: Pravastatin *Interacting drug*: Indinavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	*Affected drug*: Pravastatin *Interacting drug*: Lopinavir/ritonavir *Mechanism*: Inhibition of metabolism – atorvastatin AUC increased 33% *Recommendation*: No dose adjustment necessary	*Affected drug*: Pravastatin *Interacting drug*: Nelfinavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	*Affected drug*: Pravastatin *Interacting drug*: Ritonavir *Mechanism*: Pravastatin AUC decreased by median 0.5-fold in patients receiving RTV/SQV *Recommendation*: No dosage change necessary	None

cont. →

cont.

Simvastatin	*Affected drug*: Simvastatin *Interacting drug*: Aprenavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	*Affected drug*: Simvastatin *Interacting drug*: Indinavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	*Affected drug*: Simvastatin *Interacting drug*: Lopinavir/ritonavir *Mechanism*: Potential for increased levels due to inhibition of metabolism *Recommendation*: Avoid concomitant use	*Affected drug*: Simvastatin *Interacting drug*: Nelfinavir *Mechanism*: Inhibition of metabolism – AUC increased 5-fold *Recommendation*: Avoid concomitant use	*Affected drug*: Simvastatin *Interacting drug*: Ritonavir *Mechanism*: Inhibition of metabolism – simvastatin AUC increased 31.6-fold in patients receiving RTV/SQV *Recommendation*: Avoid simvastatin in patients on ritonavir/saquinavir	None
Atorvastatin	*Affected drug*: Atorvastatin *Interacting drug*: Aprenavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	*Affected drug*: Atorvastatin *Interacting drug*: Indinavir *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	*Affected drug*: Atorvastatin *Interacting drug*: Lopinavir/ritonavir *Mechanism*: Inhibition of metabolism – atorvastatin AUC increased 5.8-fold *Recommendation*: Use with caution - start at low doses and monitor	*Affected drug*: Atorvastatin *Interacting drug*: Nelfinavir *Mechanism*: Induction of metabolism – AUC increased 74% *Recommendation*: Use with caution - start at low doses and monitor	*Affected drug*: Atorvastatin *Interacting drug*: Ritonavir *Mechanism*: Inhibition of metabolism – atorvastatin AUC increased 4.5-fold in patients receiving RTV/SQV *Recommendation*: Use atorvastatin with caution in patients on ritonavir/saquinavir	None
Anticoagulants						
Warfarin	*Affected drug*: Warfarin *Interacting drug*: Amprenavir *Mechanism*: Inhibition of metabolism – potential for increased risk of bleeding *Recommendation*: Monitor INR closely or avoid concomitant use	None	None	*Affected drug*: Warfarin *Interacting drug*: Nelfinavir *Mechanism*: Induction of metabolism – decreased anticoagulation and risk of blood clot or embolus *Recommendation*: Monitor INR closely or avoid concomitant use	*Affected drug*: Warfarin *Interacting drug*: Ritonavir *Mechanism*: Induction of metabolism – decreased anticoagulation and risk of blood clot or embolus *Recommendation*: Monitor INR closely or avoid concomitant use	None

Light red shadowing indicates major interactions; yellow shadowing indicates moderate interactions; light blue shadowing indicates minor interactions.
AUC, area under the curve; INR, International Normalized Ratio

2. Interactions among nucleoside reverse transcriptase inhibitors (NRTI) and nucleotide reverse transcriptase inhibitors (NtRTI) and drugs used to treat cardiovascular diseases

NRTI/NtRTI	Abacavir	Zidovudine	Lamivudine	Zalcitabine	Stavudine	Didanosine	Tenofovir
Ca^{++} channel blocker							None
Antiarrhythmics							
Amiodarone	None	None	None	None	None	None	None
Flecainide	None	None	None	None	None	None	None
Propafenone	None	None	None	None	None	None	None
Quinidine	None	None	None	None	None	None	None
Statins							
Fluvastatin	None	None	None	None	None	None	None
Lovastatin	None	None	None	None	None	None	None
Pravastatin	None	None	None	None	None	None	None
Simvastatin	None	None	None	None	None	None	None
Atorvastatin	None	None	None	None	None	None	None
Anticoagulants							
Warfarin	None	None	None	None	None	None	None

3. Interactions among non-nucleoside reverse transcriptase inhibitors (NNRTI) and drugs used to treat cardiovascular diseases

NNRTI	Delavirdine	Nevirapine	Efavirenz
Ca^{++} channel blocker	None	None	None
Antiarrhythmics			
Amiodarone	None	None	None
Flecainide	None	None	None
Propafenone	None	None	None
Quinidine	None	None	None
Statins			
Fluvastatin	*Affected drug*: Fluvastatin *Interacting drug*: Delavirdine *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	None	None

Lovastatin	*Affected drug*: Lovastatin *Interacting drug*: Delavirdine *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	None	None
Pravastatin	*Affected drug*: Pravastatin *Interacting drug*: Delavirdine *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	None	None
Simvastatin	*Affected drug*: Simvastatin *Interacting drug*: Delavirdine *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	None	None
Atorvastatin	*Affected drug*: Atorvastatin *Interacting drug*: Delavirdine *Mechanism*: Inhibition of metabolism – potential for increased levels and toxicity *Recommendation*: Potential for hypolipidemic toxicity (dizziness, headache, GI side effects). Monitor patient closely and consider dose reduction	None	None
Anticoagulants			
Warfarin	*Affected drug*: Warfarin *Interacting drug*: Delavirdine *Mechanism*: Inhibition of metabolism – potential for increased risk of bleeding *Recommendation*: Monitor INR closely or avoid concomitant use	*Affected drug*: Warfarin *Interacting drug*: Nevirapine *Mechanism*: Induction of metabolism – decreased anticoagulation and risk of blood clot or embolus *Recommendation*: Monitor INR closely or avoid concomitant use	*Affected drug*: Warfarin *Interacting drug*: Efavirenz *Mechanism*: Induction of metabolism – decreased anticoagulation and risk of blood clot or embolus *Recommendation*: Monitor INR closely or avoid concomitant use

Light red shadowing indicates major interactions; yellow shadowing indicates moderate interactions; light blue shadowing indicates minor interactions.
AUC, area under the curve; INR, International Normalized Ratio

Reference

1. Volberding P, Murphy R, Barbaro G et al (2003) The Pavia Consensus Statement. AIDS 17(S1):S170-S179

Subject Index

(f, figures; t, tables)