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CARDIAC MANIFESTATIONS OF HIV

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1. ABSTRACT

Cardiac disease in the setting of HIV/AIDS has only recently been appreciated. The pathogenesis is multifactorial including direct toxic effects, viruses, autoimmunity, nutritional deficiencies and drugs. The clinical manifestations include pericardial, myocardial and valvular heart disease. Lipodystrophy, caused by anti-retroviral therapy is common and may be a risk factor in ischemic heart disease. The treatment of lipodystrophy is reviewed in detail.

2. INTRODUCTION

HIV is known to involve multiple organ systems. The heart is one of the major organs to be targeted by the direct effects of HIV infection and by secondary opportunistic infections caused as a result of the acquired immunodeficiency. Moreover, antiretroviral therapy has tremendous effects on the cardiovascular system that impact seriously upon the survival of patients infected with HIV. Accordingly, this chapter will address the epidemiology and pathogenesis of HIV related heart disease. In addition, the clinical manifestations of HIV-related heart disease and lipodystrophy will be discussed.

3. EPIDEMIOLOGY

Cardiac involvement is a well known complication of HIV/AIDS. It is being identified more frequently not only at autopsy but also clinically. The prevalence of HIV related heart disease reported in the literature ranges between 25 and 75 percent. In the US alone, about 5,000 patients per year are noted to have cardiac complications arising from HIV infection (1-6). Estimates of the rate of HIV related heart disease are derived from various retrospective and prospective studies. These studies were either based on clinical diagnosis, cardiac investigations or autopsy results. The first small prospective study involved 12 HIV infected patients and found that 50 percent of them had abnormal cardiac function or pericardial effusions and 75 percent of patients had electrocardiographic abnormalities including low voltage QRS complexes (7). Another prospective study based on serial echocardiography in 429 HIV infected patients revealed that 21 percent of them subsequently developed new cardiac abnormalities that included LV dilatation in 22 patients, diastolic dysfunction in 9 patients, LV dilatation and hypokinesis in 8 patients, isolated pericardial effusion in 8 patients, left ventricular hypertrophy in 3 patients, intracardiac mass in 2 patients

Table 1. Probable mechanisms involved in pathogenesis of HIV induced cardiac disease

1. Intracellular HIV in cardiac myocytes causes myocarditis and cardiomyopathy
2. Cardiotropic opportunistic viral infection – coxsackie group B virus, Epstein-Barr virus, CMV etc.
3. Autoimmune processes involving MHC class I molecules, anti alpha-myosin autoantibodies and cytokines such as TNF-α and iNOS
4. Nutritional deficiencies – selenium, carnitine and thiamine
5. Cardiotoxic drug use – antiretrovirals, interferon alpha, doxorubicin, other antiviral and antifungal drugs

and right heart dilation in 1 patient (8). An autopsy study of 440 patients that died of AIDS related causes found that 19 percent of them had cardiac abnormalities. These included pericardial effusions in 53 patients, lymphocytic interstitial myocarditis in 30, infective endocarditis in 28, dilated cardiomyopathy in 12 patients, myocardial Kaposi sarcoma in 2 and myocardial B-cell immunoblastic lymphoma in 1 patient (9). The prevalence of dilated cardiomyopathy in HIV positive patients is about 8 percent, with almost all of them in NYHA functional classes III and IV.

4. PATHOGENESIS

The mechanism by which HIV induces cardiac disease is not completely clear although there are a lot of hypotheses. Some of the possible mechanisms include direct toxic effects of the HIV on cardiac myocytes, other co-existing cardiac opportunistic infections, autoimmunity, drug related cardiotoxicity and nutritional deficiencies (Table 1).

4.1. Direct toxic effects

HIV can be readily identified by culture, southern blotting or in-situ hybridization in the myocardial cells of patients infected with HIV who suffer from dilated cardiomyopathy. Slightly more than half of HIV positive patients with positive hybridization signal have documented active myocarditis. Only one fourth of patients with active myocarditis had other opportunistic viral infections of their myocardium. This demonstrates that HIV probably exerts direct toxic effects on the cardiac myocytes (10). However, the mechanism by which the HIV virus enters CD4 receptor negative myocytes is unclear. The myocardial dendritic cells may play an important role in the mechanism of entry of the virus into the myocytes. Approximately 85 percent of patients diagnosed with dilated cardiomyopathy have a histologic diagnosis of myocarditis. This suggests that there might be a pathogenetic role for HIV induced myocarditis in the development of dilated cardiomyopathy.

4.2. Cardiotropic viruses

Cardiotropic viruses such as coxsackie group B virus and Epstein-Barr virus could also play a minor role in the pathogenesis of heart disease in HIV infected patients. In a study that assessed cardiac involvement by performing autopsies on patients that died of AIDS, it was noted that about 6 percent of patients had infective endocarditis, 12 percent had pericardial effusions and only a small fraction of patients had evidence of coinfection with Coxsackie group B virus, Epstein-Barr virus and cytomegalovirus (11). This suggests that coinfection with other cardiotropic viruses may play a minor role in the pathogenesis of cardiac disease in HIV patients.

4.3. Autoimmunity

Immunohistologic studies reveal increased expression of myocardial MHC class I molecules in HIV positive patients with severe left ventricular dysfunction (12), suggesting the presence of an active immune process within the myocardium. Both cell mediated and humoral immunity are thought to be involved in the process of causing HIV-1 induced cardiomyopathy. A study that assessed the frequency of circulating cardiac specific autoantibodies in HIV positive patients with and without echocardiographic evidence of left ventricular dysfunction revealed that cardiac autoantibodies detected by immunoflourescence were more common in HIV positive patients than in the HIV negative controls. It was noted that the autoantibodies were particularly more common in the subset of HIV positive patients with heart disease, suggesting a possible role for these cardiac autoantibodies in the pathogenesis of HIV related heart disease. Specifically, anti alpha myosin autoantibody detected by ELISA were found more often in HIV positive patients with heart disease than in HIV positive patients with normal hearts or in HIV negative controls. On follow up, 50 percent of HIV positive patients with normal echocardiograms but raised autoantibody concentrations died with left ventricular abnormalities at necropsy suggesting that cardiac autoantibodies may be markers of the development of left ventricular dysfunction in HIV positive patients with normal hearts (13). The inflammatory cell infiltrate in HIV positive patients with dilated cardiomyopathy is predominantly composed of CD3 and CD8 lymphocytes, whereas patients with idiopathic dilated cardiomyopathy have predominantly CD4 and B lymphocytes (14).

The mechanism of development of cardiac autoimmunity is obscure in HIV patients. One possible theory is that cardiotropic viruses could modify surface antigens or expose other hidden epitopes on the cell surface of cardiac myocytes, thus facilitating the onset of an anomalous autoimmune response against endogenous antigenic peptides associated with the HLA molecules (15).

Cytokines such as tumor necrosis factor-alpha (TNF-α) and inducible nitric oxide synthase (iNOS) are thought to be involved in the pathogenesis of HIV related cardiomyopathy. Myocardial samples of patients with HIV related cardiomyopathy were found to have a greater intensity of TNF-α and iNOS staining when compared with samples from patients with idiopathic dilated cardiomyopathy or those infected with coxsackie virus B3

or adenovirus (16). The intensity of staining was inversely correlated with CD4 counts, ejection fractions and with left ventricular end-diastolic volume index as assessed by echocardiography, suggesting that severe immunodeficiency may enhance the inflammatory response and increase the expression of toxic cytokines. The proinflammatory cytokines and iNOS could then stimulate the production of NO which could affect both the heart and the central nervous system. This is a possible mechanism that explains the well-documented relationship between dilated cardiomyopathy and encephalopathy in HIV infected patients. Another clinical trial of HIV infected patients with dilated cardiomyopathy who were also diagnosed with encephalopathy revealed that they had worsening cardiac function following the diagnosis of encephalopathy and a higher mortality rate when compared to patients without encephalopathy (17). The mortality rate attributed to congestive heart failure was 73 percent in patients with encephalopathy and 12 percent in patients without encephalopathy. Another study noted that dilated cardiomyopathy was diagnosed in 30 percent of HIV positive children with encephalopathy compared to only 2 percent of children without encephalopathy (18).

4.4. Nutritional deficiencies

Nutritional deficiencies can also contribute to the pathogenesis of cardiac disease in HIV infected patients. Deficiencies of selenium, carnitine and thiamine are known to impair ventricular function (19). Selenium deficiency is found to be common in HIV positive children, but not in adults. It is a component of glutathione peroxidase, which plays a role in the antioxidant response in various cells and tissues. Selenium deficiency could be responsible for the cardiotoxic effects of opportunistic cardiotropic viruses and is known to be associated with congestive cardiomyopathy and skeletal-muscle disorders in non HIV infected patients. However, studies of selenium deficient mice did not substantiate the relationship between selenium deficiency and cardiomyopathy. Conversely, selenium supplementation resulted in clinical and echocardiographic improvement in a very small cohort of HIV positive patients. Therefore, the role of selenium and other micronutrients in the development of cardiac disease in HIV patients is unclear at this point (19a). Further investigations are needed to assess the role of micronutrients in the development of cardiomyopathy in HIV positive patients.

4.5. Drug related cardiotoxicity

Drugs that are used to treat HIV positive patients may also contribute to cardiac disease. The effects of antiretroviral agents on lipid and glucose metabolism are discussed in detail in a latter portion of this chapter. Other drugs that might play a role in the pathogenesis of cardiomyopathy include interferon-alpha and doxorubicin which are used to treat patients with Kaposi's sarcoma and foscarnet sodium which is used to treat patients with cytomegalovirus disease. Use of amphotericin B, ganciclovir, trimethoprim-sulphamethoxazole, ketoconazole, terfenadine, cisapride and pentamidine is known to be associated with cardiac arrythmias.

5. CLINICAL MANIFESTATIONS OF HIV INDUCED HEART DISEASE

As the survival of HIV infected patients improved with antiretroviral therapy, late effects of cardiac involvement are being seen more frequently. HIV is known to affect, directly or indirectly, every structural aspect of the heart including the pericardium, myocardium, endocardium and the coronary vessels.

5.1. Pericardial disease

Pericardial involvement is common in HIV infected patients and could result in pericardial effusion, pericarditis, cardiac tamponade or constrictive pericarditis. Approximately 20 percent of AIDS patients have pericardial effusion (20). In HIV infected patients, pericardial effusions occur almost exclusively in those with AIDS. A study that evaluated the incidence of pericardial effusions in HIV infected patients found that there were no cases of pericardial effusions in asymptomatic HIV patients and an 11 percent per year incidence in patients with AIDS (21). Most of them are small and clinically asymptomatic. The incidence of pericardial effusions that are large has ranged from about seven to thirty percent (22-25).

Causes of pericardial effusion in AIDS patients include infection with *Staphylococcus aureus*, *Mycobacterium tuberculosis*, *Streptococcus pneumoniae, Cryptococcus neoformans* as well as other microorganisms. Adenocarcinoma, Kaposi's sarcoma and lymphoma may also cause pericardial effusion in HIV infected patients (26-30). However, in the majority of cases, a specific cause of the effusion cannot be identified. Several theories exist to explain the pathogenesis of these idiopathic effusions. They include "capillary leak syndrome", cytokines such as interleukin-2 and tumor necrosis factor which are elevated in end-stage AIDS and the direct effect of the HIV virus itself.

AIDS patients with pericardial effusion tend to have a lower CD4 count than those without pericardial effusion and those with pericardial effusion also tend to have a shortened survival (36 percent mean 6 month survival vs 93 percent) independent of albumin levels and CD4 counts (21). The size of the effusion had no significant impact on the survival time. The mere presence of pericardial effusions can be considered as a marker of end-stage HIV infection, but they are rarely the cause of death (31).

Most small pericardial effusions are asymptomatic, but the large effusions could cause dyspnea (75 %), tachycardia, (43%), increased jugular venous pressure (30%), paradoxical pulse (20%) and pedal edema (23%) (24). Any HIV patient presenting with the above symptoms should be further evaluated by echocardiography for the presence of effusions. Pericardial drainage should be considered for those patients with large effusions and those with tamponade. An attempt should be made to determine the cause of the effusion and appropriate therapy should be

instituted. Surgical intervention is not likely to be very helpful (26).

5.2. Myocardial and valvular disease

The prevalence of myocardial disease in HIV patients, derived from clinical and autopsy reports varies from 25 percent to 75 percent and includes dilated cardiomyopathy, myocarditis, ischemic heart disease and neoplastic invasion from lymphoma or Kaposi's sarcoma. Right ventricular involvement can also stem from HIV related pulmonary disease.

Transgenic mice that express HIV-1 in ventricular cardiac myocytes demonstrated pathologic left ventricular hypertrophy and abnormal mitochondria, suggesting that HIV virus could cause structural changes in the myocardium that could in turn lead to clinical cardiac disease (32). Electrocardiographic abnormalities such as low voltage QRS complexes are known to occur in 75 percent of HIV infected patients. This provides further evidence that the HIV virus could cause structural changes in the myocardium.

5.2. Myocardial disease

5.2.1. Cardiomyopathy

Dilated cardiomyopathy in AIDS patients is strongly associated with depressed CD4 cell count [33-34]. About 8 percent of HIV positive patients are known to have significant left ventricular dysfunction. Eighty four percent of those are in New York Heart Association class III and 16 percent are in class IV (33). Mortality is increased in HIV positive patients with cardiomyopathy and is independent of age, sex and CD4 cell counts. At a similar infection stage, the median survival to AIDS-related death was 101 days in patients with left ventricular dysfunction and 472 days in patients with a normal heart (35). Compared to ischemic or idiopathic cardiomyopathy, HIV related cardiomyopathy has an extremely poor prognosis (36).

5.2.2. Myocarditis

Myocarditis is a common cause of left ventricular dysfunction. In HIV patients, it could be caused by the cytotoxic action of the HIV virus itself or by accompanying opportunistic infections such as cytomegalovirus, coxsackie virus, Adenovirus, *Candida albicans*, *Cryptococcus neoformans* or *Toxoplasma gondii*. A specific cause of myocarditis can only be identified in about 20 percent of cases of HIV infected patients. In autopsy studies, lymphocytic myocarditis was identified in 52 percent of patients who died of AIDS (37). Three types of histological features were commonly noted: lymphocytic infiltrate with necrosis of myocardial fibers, lymphocytic infiltrate without necrosis of myocardial fibers, and focal and mild myocarditis with a mononuclear infiltrate.

5.2.3. Ischemic heart disease

Ischemic heart disease is rising in prevalence in HIV infected patients. This is likely due to the increasing life span of HIV infected adults in combination with the untoward side effects of HAART on lipid and glucose metabolism. Eccentric fibroatherotic plaques of coronary arteries with varying degrees of chronic inflammatory infiltrates have been noted on pathologic examination of hearts of patients that died of AIDS (38). The etiology of coronary artery disease in HIV patients is unclear at this time, but it is thought to be as a result of atherogenesis caused by virus infested monocyte-macrophages, possibly through altered adhesion or angiitis. A detailed description of lipodystrophy will follow later.

5.2.4. Infectious endocarditis

Infectious endocarditis is another condition that is quite common in HIV patients, especially in those that acquired HIV as a result of intravenous drug abuse. In one series, HIV was noted to be the most common underlying condition in patients admitted to a teaching hospital with infectious endocarditis (39). Thirty three percent of patients admitted with infective endocarditis had underlying HIV infection. In HIV infected patients, endocarditis usually involves the right side (tricuspid valve), but the clinical presentation is no different than in non-HIV infected patients. *Staphylococcus aureus* was noted to be the most common etiologic agent. Patients with advanced HIV were noted to have a higher mortality rate than non-HIV infected patients.

5.2.5. Pulmonary hypertension

Pulmonary hypertension is also being recognized as a serious complication of HIV infection. It could occur both in the early and late stages of HIV infection and is not related to the degree of immunosuppression. To date there are no identifiable risk factors for development of pulmonary hypertension in HIV infected patients. Patients present with progressive shortness of breath, effort intolerance, exertional dyspnea, pedal edema, non productive cough, fatigue, syncope or chest pain. Examination reveals increased intensity of P2, with P2 being louder than A2, right sided S3 and S4 gallop, murmurs of tricuspid and pulmonary regurgitation, increased jugular venous pressure and peripheral edema (40). Diagnosis of HIV related pulmonary hypertension is made after ruling out all secondary causes of pulmonary hypertension such as left sided cardiac valvular disease, myocardial disease, congenital heart disease, connective tissue disease, chronic thromboembolic disease, use of cocaine and use of appetite suppressing drugs. Investigations that help support the diagnosis are chest X-ray, electrocardiogram and echocardiography. Chest X-ray generally reveals enlarged central pulmonary arteries and clear lung fields, but could be entirely normal in early stages of the disease. Electrocardiogram is usually significant for right axis deviation and right ventricular hypertrophy with tall P waves in leads II, III and aVF, tall R waves in V1 and abnormal S waves in V5 and V6. Complete or incomplete right bundle branch block may also be present. Transthoracic echocardiography usually reveals systolic flattening of the interventricular septum, enlarged right atrium and ventricle and a reduction in both left ventricular systolic and diastolic dimensions. Patent foramen ovale and pericardial effusion are also common findings. The gold standard test for diagnosis of pulmonary hypertension however is cardiac catheterization which demonstrates increase pulmonary artery pressure to three times above normal, elevated right atrial pressure and

decreased cardiac output. Left sided chamber pressures and pulmonary capillary wedge pressure are usually normal. Pulmonary function tests reveal a mild restrictive pattern with low diffusion capacity in patients with severe HIV related pulmonary hypertension. Treatment of pulmonary hypertension is not different in HIV patients and is as unsatisfactory as in non HIV infected patients. Vasodilators such as calcium channel blockers are the mainstay of therapy. Other medications that could be used are orally active prostacyclin, beraprost sodium, carvedilol and anticoagulants. Pulmonary hypertension tends to be more aggressive in HIV patients than in those without HIV. The median survival of HIV infected patients diagnosed with pulmonary hypertension is only about 1.3 years (41).

5.2.6. Congenital heart disease

Congenital heart disease occurring in infants born with HIV infection has also been described. The P2C2 HIV study revealed that fetuses born to HIV positive mothers have abnormal cardiovascular structure and function as demonstrated by fetal echocardiography, irrespective of the HIV status of the infant. The congenital cardiovascular malformations noted included atrial and ventricular septal defects, patent ductus arteriosus, tricuspid valve prolapse, valvar pulmonary stenosis, mitral valve prolapse, subaortic stenosis and single coronary artery system (42). The rates of congenital malformations in HIV infected infants however is not statistically different from HIV uninfected infants (43).

6. LIPODYSTROPHY

HIV infected patients, in addition to having the traditional coronary risk factors such as age and gender, also tend to have a higher prevalence of cigarette smoking, cocaine use, hyperglycemia and hypertriglyceridemia. As a result, HIV infected patients are at a higher risk of sustaining myocardial infarctions than the general non HIV infected population. Moreover, there are several studies that demonstrated that the coronary risk in HIV patients is augmented further by the use of potent antiretroviral therapy. In one cohort of 5,000 HIV infected patients, the incidence of acute myocardial infarction per 1,000 patient-years increased from 0.59 to 3.41 following the introduction of HAART (44). An analysis of four phase III clinical trials revealed that the risk was increased not only by using protease inhibitor containing antiretroviral regimens, as was previously thought, but also by using protease inhibitor sparing antiretroviral regimens (45).

Lipodystrophy caused by antiretroviral therapy is a syndrome characterized by peripheral fat loss from face, limbs and buttocks, and central fat accumulation in abdomen, breasts and over the dorso-cervical spine. Metabolic features associated with the syndrome include hypertriglyceridemia, hypercholesterolemia, insulin resistance and type 2 diabetes mellitus. It is thought to be highly prevalent in HIV infected patients receiving antiretroviral therapy, especially those receiving protease inhibitors. One large study that used a combination of self reports by patients and data from physical examinations and dual energy X-ray absorptiometry revealed an 83 percent prevalence of lipodystrophy in patients after 21 months of antiretroviral therapy (46). The overall incidence of new-onset diabetes mellitus in HIV infected patients treated with HAART is only about 1 to 6 percent. The incidence of patients with abnormal oral glucose tolerance tests, however, is much higher, ranging around 60 percent (47). Elevated triglyceride and cholesterol levels were found in upto 74 percent of patients treated with protease inhibitors. The increase was associated with use of all of the available protease inhibitors (48). However, the risk of hypertriglyceridemia was highest in patients receiving ritonavir: patients receiving ritonavir were 19.6 times more likely to develop hyperlipidemia than PI-naïve patients whereas the risk was 8.5 times with nelfinavir and 3.8 times with indinavir (49).

Several risk factors have been identified for the development of lipodystrophy and they include white race, age, CD4 nadir below 200 cells/microliter, cumulative time on stavudine, protease inhibitor use and being NNRTI naïve (50-51).

The cause of HAART associated lipodystrophy is unknown, but several theories exist. One hypothesis is that protease inhibitors can inhibit lipid and adipocyte regulatory proteins that have partial homology to the catalytic site of the HIV-1 protease (52). Insulin resistance as a cause of the lipodystrophy syndrome stemmed from observations of longitudinal studies that revealed that insulin resistance often precedes lipodystrophy, but this causal relationship has never been proven and they might be largely independent phenomena (53-54). The fact that patients receiving NRTI therapy and suffering from lipodystrophy exhibit a depletion of mitochondrial DNA in their subcutaneous fat led some investigators to believe that mitochondrial toxicity may play a role in the pathogenesis of HAART induced lipodystrophy (55). More recent studies have revealed that protease inhibitors and to a lesser extent reverse transcriptase inhibitors could modulate adipocyte differentiation and/or cause reduction in the intracellular degradation of cellular proteins, that in turn could lead to alteration in lipid metabolism (56-60). Immune reconstitution (61), altered cytokine production (62-63) and hormonal interferences (64-65) are also thought to play a role in the pathogenesis of HAART associated lipodystrophy syndrome.

HAART induced lipodystrophy can increase the risk of coronary artery disease about three to four fold. Other coronary risk factors such as age and smoking, if present could make that risk worse (66). Increase in the thickness of the carotid artery wall as measured by an ultrasonogram is thought to be predictive of an increased risk of myocardial infarction in patients receiving antiretroviral therapy (67).

6.1. Treatment of lipodystrophy

Treatment of HAART induced lipodystrophy includes the following:

- Lifestyle changes – patients should be encouraged to follow a low fat diet and exercise regularly. Unfortunately, lifestyle changes alone have not been proven to be a viable option in the treatment of

lipodystrophy caused by HAART. This is partly due to difficulty in achieving compliance with the diet and exercise regimens. The difficulty is more pronounced in HIV infected population because of the emphasis that was placed on gaining weight until more recently. In addition, strict compliance with low fat diet and exercise regimens may not be adequate, however, as a sole mode of therapy.

Modification of other existing risk factors such as smoking cessation, increasing physical activity and better control of diabetes mellitus and hypertension should be stressed.

- Necessity of antiretroviral therapy should be carefully reconsidered. Since the parameters of initiating antiretroviral therapy have changed so frequently in the recent past, all patients with lipodystrophy should be re-evaluated for the need to continue antiretroviral therapy and those that do not meet the current guidelines should be given the option of discontinuing therapy.

- Drug holidays or structured treatment interruptions could be considered if deemed appropriate.

- Switching antiretroviral therapy from protease inhibitor containing to protease inhibitor sparing regimens may result in an improvement in triglyceride and total cholesterol levels (68-71). A recent study suggests that there may be some improvement in lipoatrophy caused by regimens containing stavudine and zidovudine when they are substituted with abacavir, without any resultant loss of antiretroviral potency (72).
- Lipid lowering therapy is commonly needed. Fibric acid analogues such as gemfibrozil and fenofibrate are known to work effectively in reducing triglyceride levels by inhibiting triglyceride synthesis and increasing lipoprotein lipase activity. They also have a favorable drug interaction profile. The other class of drugs used is the HMG-coenzyme A reductase inhibitors, which are effective in reducing the total cholesterol levels. However, they are not very effective in reducing triglyceride levels and have a greater potential for drug interaction with antiretroviral medications. A combination of both classes of drugs has been studied in a small trial that revealed a drop in total cholesterol and triglyceride concentrations by 30 percent and 60 percent respectively over 6 months (73). This approach however is riddled with problems with polypharmacy, compliance issues, side effects and major drug interactions.

7. SUMMARY

In conclusion, as the prevalence of HIV is increasing worldwide and advances in the treatment of HIV are being implemented, cardiac disease resulting from HIV is also becoming more common. The mechanism of HIV induced cardiac disease is unclear but it may include direct toxic effects of HIV on the myocardial cells, coinfection with cardiotropic opportunistic viruses, autoimmune processes and the concomitant use of cardiotoxic drugs. Clinicians have to be familiar with the diverse cardiovascular presentations of HIV, including opportunistic infections and neoplastic conditions that may involve the heart in this population of patients. In fact, HIV is being recognized as one of the leading causes of pericardial effusions, myocarditis, and cardiomyopathy. The prevalence of coronary artery disease is increasing in HIV positive patients as a result of longer survival and the use of potent antiretroviral medications. In light of the growing evidence of HAART related lipodystrophy and the resulting increased coronary risk, every HIV infected patient should be carefully evaluated, preferably early in the course of HIV disease to identify and focus on coronary disease risk factors. Behavior modification leading to risk reduction should be stressed.

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REFERENCES

1. Corallo S, M.R. Mutinelli, M Moroni, A Lazzarin, V. Celano, A. Repossini, G. Baroldi: Echocardiography detects myocardial damage in AIDS: prospective study in 102 patients. *EUR Heart J* 9(8), 887-92 (1988)

2. Himelman R, W.S. Chung, D.N. Chesnoff: Cardiac manifestations of human immunodeficiency virus infection: a two dimensional echocardiographic study. *J Am Coll Cardiol* 13, 1030-1036 (1989)

3. Lipshultz S, S. Chanock, S.P. Sanders, S.D. Colan, A. Perez-Atayde, K. McIntosh: Cardio-vascular manifestations of human immunodeficiency virus infection in infants and children. *Am J Cardiol* 63,1489-1497 (1989)

4. Jacob A, G.R. Sutherland, A.G. Bird, R.P. Brettle, C.A. Ludlam, A. McMillan, N.A. Boon: Myocardial dysfunction in patients infected with HIV: prevalence and risk factors. *Br Heart J* 6, 549-553 (1999)

5. Herskowitz A, D. Vlahov, S. Willoughby, R.E. Chaisson, S.P. Schulman, D.A. Neumann, K.L. Baughman: Prevalence and incidence of left ventricular dysfunction in patients with human immunodeficiency virus infection. *Am J Cardiol* 71, 955-957 (1993)

6. DeCastro S, G. Migliau, A. Silvestri, G. D'Amati, P. Giannantoni, D. Cartoni, A. Kol, V. Vullo, A. Cirelli: Heart Involvement in AIDS: a prospective study during various stages of the disease. *Eur Heart J* 13, 1452-1459 (1992)

7. Raffanti S, A.J. Chiaramida, P. Sen, P. Wright, J.R. Middleton, S. Chiaramida: Assessment of cardiac function in patients with the acquired immunodeficiency syndrome. *Chest* 93, 592-594 (1988)

8. Hsia J, L.B. McQuinn: AIDS Cardio myopathy. *Resid Staff Physician:* 39, 1-24 (1993)

9. Fisher S, S. Lipshultz: Epidemiology of Cardiovascular Involvement in HIV disease nd AIDS, HIV-Associated Cardiovascular Disease. *Annals of NY Academy of Sciences* 246, 13-23 (2001)

10. Barbaro G, G. DiLorenzo, B. Grisorio, . Barbarini: Cardiac involvement in the cquired immunodeficiency syndrome: a ulticenter clinical-pathological study. *NEJM* 339 (16), 1093-1099 (1998)

11. Barbaro G, G. DiLorenzo, B. Grisorio, G. Barbarini:Cardiac involvement in the acquired immunodeficiency syndrome: a multicenter clinical –

pathological study Gruppo Italiano per lo Studio Cardiologico dei pazienti affetti da AIDS Investigative. AIDS Res Hum Retroviruses: 14 (12), 1071-1077 (1998)
12. Herskowitz A, T.C. Wu, S.B. Willoughby, D. Vlahov, A.A. Ansari, W.E. Beschorner, K.L. Baughman: 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 (1994)
13. Currie P, J.H. Goldman, A.L. Caforio, A.J. Jacob, M.K. Baig, R.P. Brettle, A.J. Haven, N.A. Boon, W.J. McKenna: Cardiac autoimmunity in HIV related heart muscle disease. *HEART* 79(6), 599-604 (1998)
14. Barbaro G, G. Dilorenzo, M. Soldini, G. Giancaspro, B. Grisorio, A. Pellicelli, G. Barbarini: The intensity of myocardial expression of inducible nitric oxide synthase influences the clinical course of human immunodeficiency virus associated cardiomyopathy. *Circulation* 100, 633-639 (1999)
15. Herskowitz A: Cardiomyopathy with other symptomatic heart diseases associated with HIV infection: *Curr Opin Cardiol* 11(3),325-31 (1996)
16. Barbaro G, G. DiLorenzo, M. Soldini, G. Giancaspro, B. Grisorio, A. Pellicelli, G. Barbarini: The intensity of myocardial expression of inducible nitric oxide synthase influences the clinical course of human immunodeficiency virus associated cardiomyopathy. *Circulation* 100:633-639 (1999)
17. Barbaro G, G. DiLorenzo, G. Soldini, et al: Clinical course of cardiomyopathy in HIV infected patients with or without encephalopathy related to the myocardial expression of TNF-α and INOS. Gruppo Italiano per lo Studio Cardiologico dei pazienti affetti da. *AIDS* 14, 827-838 (2000)
18. Cooper E, C. Hanson, C. Diaz, H. Mendez, R. Abboud, R. Nugent, J. Pitt, K. Rich, E.M. Rodriguez, V. Smeriglio: 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 (1998)
19. Miller T, E. Orav, S.D. Colan, S.E. Lipshultz: Nutritional status and cardiac mass and function in children infected with the human immunodeficiency virus. *Am J Clin Nutr* 66, 660-664 (1997)
19a. Barbaro G, S.E. Lipshultz: Pathogenesis of HIV associated Cardiomyopathy. HIV-Associated Cardiovascular Disease. *Annals of NY Acad Sci:* 946, 57-81.
20. Fink L, N. Reichek, M.G. Sutton: Cardiac abnormalities in acquired immune deficiency syndrome. *Am J Cardiol* 54,1161-1163 (1984)
21. Heidenreich P, M. Eisenberg, L. Kee, C.A. Somelofski, H. Hollander, N.B. Schiller, M.D. Cheitlin: Pericardial Effusions in AIDS: Incidence and Survival, *Circulation* 92 (11) 3229-3234 (1995)
22. Anderson D, R. Virmani: Emerging patterns of heart disease in human immunodeficiency virus infection. *Hum Pathol* 21, 253-259 (1990)
23. Thuesen L, A. Moller: Heart involvement in HIV infection. *Nord Med* 109, 298-299 (1994)
24. Chen Y, D. Brennessel, J. Walters, M. Johnson, F. Rosner, M. Raza: Human immunodeficiency virus associated pericardial effusion: report of 40 cases and review of the literature. *Am Heart J* 137, 516-521(1995)
25. Barbaro G, G. DiLorenzo, B. Barbarini: AIDS Res Hum Retroviruses. 14 (12):1071-1077 (1998)
26. Flum, D.R., J.T. McGinn, D.H. Tyras: The role of the "pericardial window" in AIDS. *Chest* 107, 1522-1525 (1995)
27. Decker C, C.U. Tuazon: Staphylococcus aureus pericarditis in HIV infected patients. *Chest* 105, 615-616 (1994)
28. Karve M, M.R. Murali, H.M. Shah, K.R. Phelps:Rapid evolution of cardiac tamponade due to bacterial pericarditis in two patients with HIV-1 infection. *Chest* 101, 1461-1463 (1992)
29. Sunderam G, R.J. Maniatis, J. Oleske, R. Kapila, L.B. Reichman: Tuberculosis as a manifestation of the acquired immunodeficiency syndrome. *JAMA* 256, 362-366 (1986)
30. Zuger A, E. Louie, R.S. Holzman, M.S. Simberkoff, J.J. Rahal: Cryptococcal disease in patients with the acquired immunodeficiency syndrome:diagnostic features and outcome of treatment. *Ann Intern Med* 104, 234-240 (1986)
31. Rerkpattanapipat P, N. Wongpraparut, L.E. Jacobs, M.N. Kotler: Cardiac manifestations of acquired immunodeficiency syndrome. *Arch Intern Med* 160, 602-608 (2000)
32. Lewis W: AIDS cardiomyopathy: physiological, molecular, and biochemical studies in the transgenic mouse. *Ann NY Acad Sci* 946, 46-56 (2001)
33. Barbaro G, G. DiLorenzo, B. Grisorio, G. Barbarini: Incidence of Dilated cardiomyopathy and detection of HIV in myocardial cells of HIV positive patients. *N Engl J Med* 339, 1093-1099 (1998)
34. Lipshultz S, K.A. Easley, E.J. Orav, S. Kaplan, T.J. Starc, J.T. Bricker, W.W. Lai, D.S. Moodie, K. McIntosh, M.D. Schluchter, S.D. Colan: Left ventricular structure and function in children infected with HIV. *Circulation* 7, 1246-1256 (1998)
35. Currie P, A.J. Jacob, A.R. Foreman, R.A.Elton, R.P. Brettle, N.A. Boon: Heart muscle disease related to HIV infection: prognostic implications, *Br Med J* 309, 1605-1607 (1994)
36. Felker G, R.E. Thompson, J.M. Hare, R.H. Hruban, D.E. Clemetson: Underlying causes and long term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 342, 1077-1084 (2000)
37. Anderson D, R. Virmani, J.M. Reilly, t. O'Leary, R.E. Cunnion, M. Robinowitz, A.M. Macher, U. Punja, S.T. Villaflor, J.E. Parrillo: Prevalent myocarditis at necropsy in AIDS. *J Am Coll Cardiol*; 11, 792-799 (1988)
38. Paton P, A. Tabib, R. Loire, R. Tete: Coronary artery lesions and human immunodeficiency virus infection. *Res Virol* 144, 225-231 (1993)
39. Bouza E, A. Menasalvas, P. Munoz, F.J. Vasallo, M. del Mar Moreno, M.A. Garcia Fernandez: *Medicine*: 80 (5); 298-307 (2001)
40. Mehta, N, I.A. Khan, R.N. Mehta, D.A. Sepkowitz: HIV related pulmonary hypertension. Analytic review of 131 cases. *Chest* 118, 1133-1141 (2000)
41. Pellicelli P, F. Palmieri, S. Cicalini, N. Petrosillo Fabrizio, S. Cicalini: Pathogenesis of HIV-related Pulmonary Hypertension, HIV Associated Cardiovacular Disease, *Ann NY Acad Sci* 946, 82-94 (2001)
42. Hornberger L, S.E. Lipshultz, K.A. Easley, S.D. Colan, M. Schwartz: Cardiac structure and function in fetuses of

mothers infected with HIV: the prospective P2C2 HIV multicenter study. *Am Heart J* 140, 575-84. (2000)
43. Lai W., S.E. Lipshultz, K.A. Easley, T.J. Starc, S.E. Drant, J.T. Bricker, S.D. Colan, D.S. Moodie, G. Sopko, S. Kaplan: Prevalence of congenital cardiovascular malformations in children of human immunodeficiency virus infected women. *J Am Coll Cardiol* 32(6), 1749-1755 (1998)
44. Rickerts V, H. Brodt, S. Staszewski, W. Stille: Incidence of myocardial infarction in HIV infected patients between 1983 and 1998: The Frankfurt HIV-Cohort Study. *Eur J Med Res* 5:329-333 (2000)
45. Coplan P, et al: No association observed between indinavir therapy for HIV/AIDS and myocardial infarction in 4 clinical trials with 2,825 subjects. Presented at the 6th Conference on Retroviruses and Opportunistic Infections, Chicago IL, USA Abstract 658 (1999)
46. Carr A, K. Samaras, A. Thorisdottir, G.R. Kaufmann, D.J. Chisholm, D.A. Cooper: Diagnosis, prediction and natural course of HIV-1 protease inhibitor associated lipodystrophy, hyperlipidemia and diabetes mellitus: a cohort study. *Lancet* 353, 2093-2099 (1999)
47. Walli R, O. Herfort, G.M. Michl, T. Demant, H. Jager, C. Dieterle, J.R. Bogner, R. Landgraf, F.D. Goebel: Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1 infected patients. *AIDS* 12, F167-F173 (1998)
48. Carr A, K. Samaras, D.J. Chisholm, D.A. Cooper: Pathogenesis of HIV-1 protease inhibitor associate peripheral lipodystrophy, hyperlipidemia and insulin resistance. *Lancet* 351, 1881-1883 (1998)
49. Periard D, A. Telenti, P. Sudre, J.J. Cheseaux, P. Halfon, M.J. Reymond, S.M. Marcovina, M.P. Glauser, P. Nicod, R. Darioli, V. Mooser: Atherogenic dyslipidemias in HIV infected individuals treated with protease inhibitors. Swiss HIV Cohort Study. *Circulation* 100, 700-705 (1999)
50. Mauss S, M. Wolf, Corzillius, et al: Prevalence and risk factors for HIV associated lipodystrophy syndrome in patients being 3 years on ART. Presented at the 40th Interscience Conference on Antimicrobial agents and chemotherapy, Toronto, Ont., Canada. Abstract 1287 (1997)
51. Mallal S, M.John, C.B.Moore, I.R. James, E.J. McKinnon: Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. *AIDS* 14, 1309-1316 (2000)
52. Carr A, K. Samaras, D.J. Chisholm, D.A. Cooper: Pathogenesis of HIV-1 protease inhibitor associated peripheral lipodystrophy, hyperlipidemia and insulin resistance. *Lancet* 351, 1881-1883(1998)
53. Mulligan K, C. Grunfeld, V.W. Tai, H. Algren, M. Pang, D.N. Chernoff, J.C. Lo, M. Schambelan: Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection. *J. Acquir Immune Defi Synd* 23, 35-43 (2000)
54. Hadigan C, J.B. Meigs, C. Corcoran, P. Rietschel, S. Piecuch, N. Basgoz, B. Davis, P. Sax, T. Stanley, P.W. Wilson, R.B. D'Agostino, S. Grinspoonl: Metabolic abnormalities and cardiovascular risk factors in adults with human immunodeficiency virus infection and lipodystrophy. *Clin Infect* Dis 32, 130-139 (2001)
55. Walker U, et al: Decrease of mitochondrial DNA content in adipose tissue of HIV-1 infected patients treated with NRTI's. *Antiviral Ther* 5 (Suppl.5) 5 (2000)
56. Caron M, M. Auclair, C. Vigouroux, M. Glorian, C. Forest, J. Capeau: The HIV-protease inhibitor indinavir impairs adipocyte differentiation and induces insulin resistance by probably altering ADD1/SREBP-1 maturation. *Antiviral Ther* 5(Suppl 5) 4 (2001)
57. Parker R, D.S. Myers, B.A. Andrews, et al: Effects of nucleoside reverse transcriptase inhibitors and HIV protease inhibitors on adipogenesis and adipocyte metabolism. *Antiviral Ther*. 5 (Suppl 5), 4 (2000)
58. Liang J, O.Distler, D.Cooper, et al: HIV protease inhibitors increase secretion of apolipoproteins from hepatoma cells by preventing protesomal degradation. *Antiviral Ther* 5 (Suppl 5), 12 (2000)
59. Distler O, J.Liang, D.Cooper et al.:Direct effects of protease inhibitors on lipid metabolism in cultured mammalian cells. *Antiviral* Ther 5 (Suppl 5), 13 (2000)
60. Nguyen A, A.M. Gagnon, J.B. Angel, J.B., A. Sorisky.:Ritonavir increases the level of active ADD-1/SREBP-1protein during adipogenesis. *AIDS* 14, 2467-2473. (2000)
61. Wurtz R, Ceaser. S: Adipose redistribution in human immunodeficiency virus serpositive patients: association with CD4 response. *Clin Infect Dis* 31,1497-1498 (2000)
62. Ledru E, N. Christeff, O. Patey, P. de Truchis, J.C. Melchior, M.L. Gougeon: 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 (2000)
63. Clerici M, M. Galli, S. Bosis, C. Gervasoni, M. Moroni, G. Norbiato: Immunoendocrinologic abnormalities in human immunodeficiency virus infection. *Ann N.Y.Acad.Sci* 917, 956-961 (2000)
64. Yanovski J, K.D. Miller, T. Kino, T.C. Friedman, G.P. Chrousos, C. Tsigos, J. Falloon: Endocrine and metabolic evaluation of human immunodeficiency virus infected patients with evidence of protease inhibitor associated lipodystrophy. *J Clin Endocrinol Metab* 84, 1925-1931 (1999)
65. Christeff N, J.C. Melchior, P. de Truchis, C. Perronne, E.A. Nunez, M.L. Gougeon:
Lipodystrophy defined by a clinical score in HIV infected men on highly active antiretroviral therapy: correlation between dyslipidemia and steroid hormone alterations. *AIDS* 13, 2251-2260 (1999)
66. Egger M: Collected abstractsof 40th Interscience Conference on Antimicrobial Agents and Chemotherapy (Toronto, Ontario, Canada), no. 1374. American Society for Microbiology.
67. Maggi P, G. Serio, G. Epifani, G. Fiorentino, A. Saracino, C. Fico, F. Perilli, A. Lillo, S. Ferraro. M. Gargiulo, A. Chirianni, G. Angarano, G. Regina, G. Pastore: Premature lesions of the carotid vessels in HIV-1 infected patients treated with protease inhibitors. *AIDS* 14, F123-F128. (2000)
68. Goebel F. & R.K. Walli for the CNA30017 Study team. A novel use of abacavir to simplify therapy in PI experienced patients successfully treated with HAART: CNA30017. Presented at the 7th conference on Retroviruses

and Opportunistic Infections, San Francisco, CA, USA. Abstract 51. (2000)
69. Carr A, D.A. Cooper: A randomized multicenter study of protease inhibitor substitution in aviremic patients with antiretroviral lipodystrophy syndrome. Presented at the 7th conference on Retroviruses and Opportunistic Infection, San Francisco, CA, USA. Abstract 205. (2000)
70. Barreiro P, V. Soriano, F. Blanco, C. Casimiro, J.J. de la Cruz, J. Gonzalez--Lahoz: Risks and benefits of replacing protease inhibitors by nevirapine in patients under long-term successful triple combination therapy. *AIDS* 14, 807-812. (2000)
71. Hoffman C, E. Jaegel-Guedes, E. Wolf, et al: PI to Efavirenz switch effect on lipids in HIV positive patients. Presented at the XIIIth International AIDS conference, Durban, South Africa Abstract WePeB4185 (2000)
72. Carr A, C. Workman, D. Smith, J. Hoy, J. Hudson, N. Doong, A. Martin, J. Amin, J. Freund, M. Law, D.A. Cooper: Abacavir substitution for Nucleoside analogs in patients with HIV Lipotrophy. *JAMA* 288, 207-215 (2002)
73. Henry K, H. Melroe, J. Huebesch, J. Hermundson, J. Simpson: Atorvastatin and gemfibrozil for protease inhibitor-related lipid abnormalities. *Lancet* 352, 1031-1032 (1998)

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