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Reviews

Cardiac Involvement in Acquired Immunodeficiency Syndrome—A Review to Push Action

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Summary: As more effective therapies have produced longer survival times for human immunodeficiency virus (HIV)-infected patients, new complications of late-stage HIV infection including HIV-related heart disease have emerged. Almost any agent that can cause disseminated infection in patients with acquired immunodeficiency syndrome (AIDS) may involve myocardium, but clinical evidence of cardiac disease is usually overshadowed by manifestations in other organs, primarily the brain and lungs. Cardiac abnormalities are found at autopsy in two-thirds of patients with AIDS, and more than 150 reports of cardiac complications have been published. Cardiac involvement in HIV disease includes pericardial effusion, myocarditis, dilated cardiomyopathy, and/or endocardial involvement at any stage of the disease. This review deals with all the cardiac manifestations of AIDS and serves to highlight two problems and one indication. First of all, there are very few clinical studies. Current knowledge is based almost exclusively on echocardiography and autopsy studies. Observational or clinical trials would be useful. Second, there exists very poor information on the impact of treatment; and epidemiologic and clinicopathologic studies are mandatory for obtaining detailed data concerning the mechanisms of myocardial damage in AIDS. Finally, because cardiac complications are often clinically inapparent or subtle in the initial stages, periodic screening of HIV-positive patients by electrocardiogram and echocardiogram is probably indicated. In addition, AIDS may also provide the opportunity to gain insights into the pathogenesis of little understood cardiac diseases such as lymphocytic myocarditis and dilated cardiomyopathy.

Key words: acquired immunodeficiency syndrome, myocarditis, cardiomyopathy, human immunodeficiency virus, myocardial dysfunction

Introduction

From 1981 through 1990, 100,777 deaths among persons with acquired immunodeficiency syndrome (AIDS) were reported by local, state, and territorial American health departments; almost a third of these during 1990.[1] In 1991, based on current trends, human immunodeficiency virus (HIV) infection/AIDS is likely to rank among the five leading causes of death in this population.[1,2]

In recent years, there has been an evolving understanding of AIDS as a dynamic viral infection. An appreciation of the complex nature of this infection is essential to comprehending the challenges involved in the treatment of HIV-1 infected persons.

The heart is often the unrecognized target of AIDS-associated lesions even in the initial phase of AIDS outbreak (1981–1989).[3]

It was estimated that in the United States as many as 5,000 patients per year may have cardiac complications resulting from HIV infection;[4] however, similar data from South American countries are still lacking. This has encouraged the formation of a committee for the study of cardiac involvement in AIDS, with members from South American (Argentinian) and European (Italian) laboratories. This association has been proven operative in other fields of cardiology.[5]

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The present review is an attempt to bring together pertinent information and push investigation on the subject in developing countries.

Limited information with only domestic diffusion was issued recently demonstrating that echocardiographic systolic involvement of the left ventricle is a marker of poor prognosis in the short-term follow-up of HIV patients (Conterjnic and Cahn 1997; personal communication).

Clinical Background and Treatment

The new knowledge about HIV replication shows that monotherapy with antiretroviral agents seems to produce viral diversity and resistance if the agent is not capable of suppressing viral replication.[6]

Major advances in the treatment of HIV infection have clearly changed prognoses out of all recognition in the last 2 years. Drugs available for treating HIV infection impair viral replication and therefore postpone immunodeficiency and its clinical sequel.[7] Following activation within cells, nucleoside analogues inhibit reverse transcriptase and terminate development of the viral DNA chain. Protease inhibitors prevent viral maturation. Non-nucleoside reverse transcriptase inhibitors bind to and inhibit the reverse transcriptase of HIV-1, but not that of HIV-2.[7]

In patients infected with HIV, a combination of two or three anti-HIV drugs can reduce the viral replication, delay disease progression, and prolong survival, while limiting development of viral resistance. Triple-therapy combinations that include a protease inhibitor appear particularly effective, although published confirmatory clinical end point data are still required for some regimens.[7]

Since anti-HIV drugs became widely available, median survival in those with HIV infection but initially free of AIDS has increased by 8–14 months depending on the patient's initial disease stage.[8,9] In a recent study, median survival following diagnosis of AIDS was about 20 months which, again, is longer than previous estimates.[10]

However, the possibility of cardiac hypersensibility or toxicity from nucleoside analogs and pentamidine has been suggested.[11] Pentamidine therapy in HIV-infected patients has been associated with prolongation of the QT interval and a high risk for potentially lethal ventricular arrhythmias, especially torsade de pointes, hypotension, and bradycardia.[12]

Monitoring for rate-corrected QT interval prolongation using a serial 12-lead electrocardiogram (ECG) during therapy (baseline and then daily for the first week of treatment) has been proposed as an adequate method of guarding against the complications. However, inhalatory pentamidine does not prolong the QT interval and does not induce an increased risk of torsade de pointes.[13]

Cardiac complications of HIV infection were initially unrecognized or recognized late by clinicians because of a lack of awareness of cardiac diseases in patients with AIDS and the tendency of cardiac disease to mimic clinically the far more common respiratory complications.

The longer survival times led to the appearance of new complications of late-stage HIV infection, including HIV-related heart disease.[14,15] Because of this, cardiac involvement in HIV infection that was previously believed to be an unusual manifestation of the disease is now being described with increasing frequency.

Cardiac Involvement in Acquired Immunodeficiency Syndrome: General Considerations

Although cardiac disease can occur at any stage of HIV infection, cardiac morbidity and mortality are more common in advanced stages.[16]

Almost any agent that can cause disseminated infection in patients with AIDS may involve the myocardium, but clinical evidence of cardiac disease is usually overshadowed by manifestations in other organs, primarily the brain and lungs. As a consequence, the number of patients with AIDS with cardiac involvement at autopsy greatly exceeds the number with significant cardiac disease during life.

Cardiac abnormalities are found at autopsy in two-thirds of patients with AIDS,[17] and more than 150 reports of cardiac complications have been published. Cardiovascular disease occurs in approximately 6.5–6.8% of HIV-infected persons.[18]

It is estimated that by the year 2000, 10 million children will be HIV-positive with the greatest numbers in Africa, South and Southeast Asia, and South America.[19] Longitudinal follow-up of children infected with HIV by vertical transmission reveals that the cardiovascular system can be involved in over 90% of selected patients.[20]

Some prospective studies suggest that over 17,000 HIV-positive patients may develop some form of symptomatic cardiac disease requiring medical intervention. These data are based on symptomatic heart disease occurring at a rate of 5 cases per 100 patient years of follow-up.[21] Only a small subgroup of patients who develop Class III or IV congestive heart failure demonstrate rapid deterioration leading to primary cardiac death. These patients with the most severe form of HIV-related heart disease are likely to have the greatest impact on cardiovascular care in HIV-infected patients.[21]

Early autopsy descriptions of cardiac abnormalities in patients infected with HIV-1 showed nonbacterial thrombotic endocarditis, infectious and serous pericardial effusions, myocarditis secondary to opportunistic organisms, and neoplastic heart disease, particularly Kaposi's sarcoma and lymphoma.[21,22]

Cardiac involvement in HIV disease may be a well-characterized cardiac disease occurring coincidentally in a patient with AIDS, a complication of AIDS or its treatment, or possibly a direct result of HIV infection of the heart,[23] and cardiac involvement in HIV disease includes pericardial, myocardial, and/or endocardial involvement at any stage of the disease (see below).

Pericardial tamponade and/or constriction may be related to lymphoma and Kaposi's sarcoma, infections, or nonspecific effusions.[24]

Myocardial dysfunction may result from specific neoplastic infiltration or myocarditis. Although cardiac malignant lymphomas are rare, recently an increasing number of patients with AIDS and cardiac lymphoma has been reported.[25, 26]

Opportunistic organisms, such as *Toxoplasma gondii* and *Cryptococcus neoformans*, which rarely cause myocarditis in immunocompetent hosts, are common pathogens in AIDS myocarditis.

Particularly intriguing is the role of HIV-1 in nonspecific myocarditis and dilated cardiomyopathy (potentially lethal arrhythmia) that occurs in patients with AIDS. It was suggested that myocarditis could progress to cardiomyopathy in some patients (see below).[15]

As in other debilitating conditions, patients with AIDS can present with nonbacterial thrombotic endocarditis and/or infective myocarditis, including right heart valve endocarditis associated with intravenous drug use[4, 14, 15, 27] or the increasingly widespread use of indwelling venous catheterization.

As previously mentioned, most patients with AIDS have no overt clinical evidence of cardiac disease.[28, 29] When cardiac dysfunction does develop, the signs and symptoms are often misinterpreted to be the result of noncardiac causes (pulmonary failure or infection) that can mimic heart failure.[4, 15, 30] Although cardiac symptoms (dyspnea and chest pains), signs (pulsus paradoxus and murmurs), or ECG or roentgenogram manifestations of AIDS may be significant, they are not generally helpful in establishing a clinical diagnosis.[30]

HIV infection is associated with cardiac abnormalities in 45 to 50% of HIV-infected patients,[3, 24, 31, 32] and cannot be detected easily by clinical evaluation alone; echocardiography is the most appropriate way to detect heart involvement,[26, 29, 33–39] even in asymptomatic patients with early impairment of systolic and diastolic function.[33] However, other studies report higher incidences of cardiac involvement in patients with AIDS, such as 90% of 73 patients[36] or 74% of 574 HIV-positive patients.[30]

In a study to assess the prevalence of cardiac involvement in a large selected population of patients who had died of AIDS, Barbaro *et al.* found ECG alterations in 85.3% of patients, whereas echocardiographic morphofunctional alterations were documented in 95.1% of patients.[33] In another echocardiographic study, 67% of the patients presented with left ventricular dysfunction detected only by echocardiogram without any other clinical sign.[40]

Ventricular hypertrophy and nonspecific ECG abnormalities such as ST-T wave changes have been observed in patients with ventricular hypertrophy (left or right ventricular hypertrophy, 21–50%; rhythm disturbances, 2–24%; ventricular ectopy, 30%). In addition to atrial and ventricular arrhythmias, sinus arrhythmia and first- and second-degree heart block have also been described.[41]

In a prospective survey of 157 acutely ill HIV-positive patients in a hospital in Zimbabwe,[40] echocardiographic abnormalities were noted in 50% of patients. The most common pathologies were left ventricular dysfunction (22%) and pericardial disease (19%).

The hearts of HIV-infected patients are commonly infected in the later stages of the disease by different opportunistic microorganisms such as cytomegalovirus, *T. gondii*,[10, 42] *C. neoformans*, and other fungi.[43–45] However, no correlation could be found between the opportunistic infections and the cardiac abnormalities, with the single exception of infective endocarditis and drug addiction, but this is largely known and independent of HIV infection.[31]

As mentioned, myocardial dysfunction may also result indirectly via immunological mechanisms or by the action of drugs such as zidovudine, pentamidine, or ganciclovir, or it may be caused by selenium deficiency (malnutrition).[15]

Pericardial Effusion

Cardiac involvement in HIV infection in Africa has been attributed mainly to pericardial disease, which is the index presentation of patients with AIDS.[40] Many reports have concluded that HIV-associated pericardial effusions are seen frequently, accounting for 63% of all cardiac lesions in one series;[46] their clinical spectrum is broad,[47] and the effusion is usually small and without hemodynamic consequence, but may be large and cause cardiac tamponade.[18, 24, 48]

Most cases of pericardial effusions are idiopathic, but in some cases the etiology can be established. Infections, lymphoma, Kaposi's sarcoma, myocardial infarction, fibrinous exudate, and myocarditis or endocarditis were described as possible etiologies and are frequently associated with advanced stages of infection and left ventricular dysfunction and right ventricular dilatation.[49]

Kovacs *et al.*[50] detected HIV within macrophages in the pericardium, suggesting that HIV itself may play a role in the pathogenesis of pericardial effusion in infected patients.

Within infections, tuberculosis is being observed in increasing amounts with involvement of the pericardium, and consequently effusions are seen increasingly. In fact, pericardial disease in HIV-infected patients in Africa has been shown to be largely due to tuberculosis.[40]

As has been stressed, echocardiograms and a heightened degree of clinical suspicion have proven useful in detecting cardiac dysfunction and life-threatening cardiac tamponade.[30]

In a study involving 14 patients with pericardial effusion associated with HIV infection, the probable etiology was established in four cases and included two with endocarditis, one with lymphoma, and one with myocardial infarction.[47] In another study, pericarditis with effusion was found in the 27.7% of the patients.[32]

Myocarditis

Usually, the etiology of myocarditis has remained idiopathic; however, a few reports[15, 31] have suggested a direct cytopathologic effect of HIV. In spite of this, an intriguing unanswered question is whether HIV directly infects myocardial fibers and causes myocardial damage. HIV, its protein components, or both, have been demonstrated by culture, in situ hybridization, and Southern blot tests in hearts of patients with AIDS with and without cardiac abnormalities. Initially, studies found evidence of HIV only in inflammatory cells. HIV-1

DNA has been identified in the hearts of three patients with AIDS by Southern blot.[51]

More recently, HIV proteins (p17, p24, and gp120/160) have been detected in myocardial fibers of nine patients.[17] Six of these patients died from cardiac complications and all them had large amounts of viral proteins.

One study reported evidence by HIV virus itself,[52] using the technique of in situ DNA hybridization applied to myocardiums obtained at autopsy. The authors concluded that the presence of HIV nucleid acid sequences may represent a preclinical marker of impending AIDS-associated myocardial disease.[52]

Common viruses such as coxsackie B and cytomegalovirus with inclusions have also been reported.[53, 54] The interpretation of these findings is complicated by the fact that cytomegalovirus may be present without necessarily being the cause of pathologic changes that are present.

Nearly all viral complications of AIDS in adults are DNA viruses that have reactivated from latency. Indeed, patients with end-stage AIDS handle RNA viruses relatively normally from an immunological perspective. Evidence other than sporadic isolation is needed to suggest that a specific virus is relevant.

In a few cases of lymphocytic myocarditis, an associated pathogen is found. Microorganisms reported to involve the heart in cases of AIDS include cytomegalovirus, cryptococcus, *Candida, Toxoplasma gondii*, sarcosporidium, *Histoplasma capsulatum*, and bacterial infection including tuberculosis, coxsackie virus and *Aspergillus*.[16] In most cases, opportunistic infection of the heart is associated with systemic infection of the organism.

Far more common in AIDS than infectious myocarditis is nonspecific lymphocytic myocarditis that, according to clinico-pathologic studies,[55] is present in more than 40% of autopsy cases in some series. In 80% of those patients no etiologic agent is identified. This pathologic finding is believed to be related to a specific pathogenic action of HIV on myocardial tissue. Of note, ventricular arrhythmias have been described in 15–30% of patients with lymphocytic interstitial myocarditis.[55]

Lymphocytic myocarditis was the most frequent of the abnormalities in patients with AIDS[16] reported in 52% in one series of 71 patients who died from AIDS.[56] Although biventricular abnormalities are found in many cases, isolated right ventricular hypertrophy or dilatation also occurs but is usually associated with pulmonary disease rather than with intrinsic cardiac disease.[16]

Lymphocytic myocarditis has rarely been diagnosed during the clinical course by endomyocardial biopsy.[16] In one study, the HIV genome was directly detected in purified cardiac myocytes from endocardial biopsies of patients with and without cardiac dysfunction. However, the authors found no evidence supporting a direct role of HIV in myocardial dysfunction. Dendritic cells were increased in number and harbored HIV more often than the myocytes, suggesting that they may be involved in the development of cardiac dysfunction.[57] Thus, myocarditis is a frequent finding at necropsy in patients with AIDS and may contribute to the development of biventricular dilation.[56]

The incidence of myocarditis found at autopsy ranged from 2 to 50%;[31] these discrepancies might be due to the different diagnostic criteria employed.

In 100 sequential autopsies, cardiac lesions were present in the myocardium in 47% of cases, 38% displayed signs of active myocarditis, and opportunistic agents such as toxoplasma, cytomegalovirus, mycobacteria, and fungi were commonly found. *P. carinii* spared the heart, although it was present in the lungs of 47% of the patients.[3]

In 60 consecutive autopsies,[58] myocarditis according to the Dallas criteria was seen in 42% of the cases, and in 7 of these cases a probable pathogen (*Toxoplasma gondii*, cytomegalovirus, fungi) was demonstrated. Diffuse myocardial fibrosis was observed in 67% of the cases and was considered to be partly due to repair after myocyte necrosis/myocarditis; and in 38% there was dilation and/or hypertrophy of the right ventricle.[58]

In a further 34 consecutive autopsies,[59] the total frequency of focal lymphocytic infiltrates with and without myocyte necrosis was 26.4 and 32.3%, respectively. In six control cases, these infiltrates were absent. The number of infiltrative foci per section, their wall distribution, number of leukocytes per focus, and cell phenotype were similar in cases with and without myocyte necrosis. In inflammatory foci associated with necrosis, CD45+/CD68+ monocytes prevailed as a possible manifestation of nonspecific reparative process. In addition, in both patients with AIDS and in HIV-negative drug abusers, a population of CD68+ dendritic monocytes (histiocytes) characterized by a restricted CD45 expression (PanLeu-/9.4+) was found dispersed in the interstitium, with a significantly higher frequency in the subendocardial layer. Histologic evidence of myocardial virus infections was not observed. Cytomegalovirus antigens, however, were found in frozen sections of five of six cases with lymphocytic infiltrates, suggesting that this virus might be one of the possible causes of myocarditis in AIDS. Moreover, in two of these cytomegalovirus-positive cases, a concomitant expression of HIV-1 antigens in isolated intramyocardial leukocytes was also observed.[59]

In our experience, four cases of myocarditis from *Toxoplasma gondii* were observed at autopsy among 18 consecutive cases of AIDS.[60] All cases showed spotty inflammatory myocardial infiltration, consisting mainly of T lymphocytes and, to a lesser extent, of B lymphocytes, histiocytes, mastocytes, and eosinophilic granulocytes, with presence of *T. gondii* in the cytoplasm of a few myocardial cells. The incidence of toxoplasmic myocarditis in heart involvement in AIDS was 22%, manifoldly higher than in preceding reports from the literature. This suggests that cardiac toxoplasmosis is far from rare in patients with AIDS.[60]

Hansen[58] proposed that the myocardium is weakened by myocarditis and by repair with resulting fibrosis. There might be some degree of compensatory hypertrophy, but there is a risk of heart failure/dilation when the functional demand is increased. The heart failure is usually right-sided since the major pathologic changes are pulmonary.

Dilated Cardiomyopathy

Dilated cardiomyopathy, with or without clinical manifestations of cardiac disease, is one of the most common cardiac complications of HIV infection, and the survival of the patients affected by myocardial dysfunction is extremely low.[14, 61-64] Dilated cardiomyopathy accounts for approximately one-third of HIV-related deaths.[18] Echocardiographic findings of dilated cardiomyopathy have been reported in 30 to 40% of patients with AIDS[31] and in another study it was found in 16.9% of patients.[32]

Dilated cardiomyopathy occurs late in the course of HIV infection and is usually associated with a significantly reduced CD4 cell count[64] and with symptoms and signs that are attributed to other disease processes.[15] The pathogenesis is uncertain; in some cases myocarditis was involved as the cause of cardiac enlargement and dysfunction.

Only sporadically have HIV and coxsackie B virus been demonstrated in the myocardium in HIV-affected patients. Therefore, no causative relation with the development of cardiomyopathy has been established; however, it was suggested that there was a direct or indirect cytopathogenic effect caused by the AIDS virus itself[52] or by other viral infection. HIV has been detected within myocardial cells by in situ hybridization, immunohistochemistry, polymerase chain reaction (PCR), and culture,[50, 57, 65, 66] suggesting that the virus itself may be the cause of cardiomyopathy and lymphocytic myocarditis in some patients. Other possible factors include pulmonary disease, nutritional deficiency, anemia, cardiotoxic drug effect, and immunologic factors.

Dworkin *et al.*[67] have demonstrated low selenium levels in the cardiac tissue of eight patients who died from AIDS. In a retrospective study of 137 HIV-infected children, it was found that cardiomyopathy was 8.4 times more likely to occur in children who had been given zidovudine previously.[68] Immunologic factors involving cytokines such as TNF,[16] as well as autoimmunity as suggested by increased antiheart antibody titers, may be involved in the pathogenesis of the myocarditis observed in AIDS-associated cardiomyopathy.[69]

The following processes may be involved in the immunopathologic mechanisms of myocardial injury: (1) viral infection of myocytes that may injure them irreversibly, eliciting a nonspecific inflammatory response; (2) CD8+ T cell response to virus-infected myocytes expressing endogenous viral peptides in association with MCH class I antigens and resulting in myocyte lysis and myocarditis; (3) induction of an aberrant autoimmune response against autoantigenic peptides complexed to self-MCH molecules expressed on myocytes and resulting in further injury; (4) autoimmune responses that target normal as well as infected myocardial cells and produce myocarditis[21] and its associated cardiomyopathy.

Endocarditis

Endocarditis in patients with AIDS is relatively uncommon and is usually nonbacterial; infective endocarditis usually occurs in drug addicts and is almost exclusively of bacterial origin.[18, 22, 70] Nonbacterial thrombotic endocarditis is usually an incidental finding without clinical symptomatology, but rarely the vegetations embolize and cause symptoms of ischemia.

Because salmonellal bacteremia is common in HIV-infected patients and because salmonella have a propensity to adhere to endothelial cells, these patients are at risk of endocarditis and endarteritis.[71] Infectious forms of AIDS-associated heart disease with *M. tuberculosis*, cardiac cryptococcosis, and *Salmonella typhimurium* were diagnosed and successfully treated.[72]

Wall Motion and Wall Thickening Abnormalities

Without concurrent coronary artery disease, the pathogenesis of segmental abnormalities of left ventricular function and subclinical myocardial dysfunction[63, 73] occurring in some patients with HIV remains unknown.

Impairment of left ventricular contractility as assessed from fractional shortening appears to be the most common echocardiographic finding, followed by left ventricular wall thinning, pericardial effusion, and eventually by cavity dilation. This evolution is suggestive of myocardial damage and supports the hypothesis that progressive dilated cardiomyopathy may be a cardiac complication of AIDS.[74]

In a prospective series of 31 pediatric patients with AIDS, Lipshultz *et al.*[75] found frequent conduction defects and arrhythmias. Inflammatory changes of the conduction system were found in three of four histologically examined cases.

Coronary Artery Abnormalities

Coronary artery abnormalities are relatively uncommon findings in patients with AIDS, but significant coronary lesions were found in eight HIV-positive adults who had no other risk factors for coronary disease. All were found suddenly dead, and autopsy showed severe eccentric coronary atherosclerosis with no vasculitis or calcifications. The authors suggest that atherosclerosis may be related to a viral infection, given the absence of other cardiovascular risk factors.[76]

Malignancies

Kaposi's sarcoma involving the heart is relatively common in patients with AIDS and is usually metastatic. Primary lymphomas of the heart are extremely rare; secondary spread to the heart is far more frequent. Lymphomas are usually unsuspected clinically and may present with cardiac symptoms including congestive heart failure, pericardial effusion, and heart block.[16]

Endomyocardial Biopsy in Acquired Immunodeficiency Syndrome

In spite of the importance of endomyocardial biopsy as a tool for diagnosis of myocardial disease,[77-80] this study

has been rarely used in cardiac involvement in AIDS.[16,21,81,82] Barbeau *et al.*[81] evaluated the findings in 19 patients with AIDS. Histopathologic, unsophisticated, endomyocardial biopsy studies exhibited no opportunistic infections but showed a specific myocarditis in half of the patients. In another case report,[82] some data, using virologic and immunopathologic studies, suggested the possible involvement of HIV in the pathogenesis of cardiomyopathy.

However, these studies are completely insufficient from the modern technical point of view, as well as from the small number of patients studied.[16,21]

Conclusion

Although it is evident that the diagnosis of AIDS-associated heart disease is becoming routine, its treatment has not been reported except in anecdote.[72] This results from a lack of epidemiologic studies with a large number of patients that stress the characteristics of heart involvement in AIDS as well as from the absence of an adequate clinico-pathologic correlationship.

This review deals with all the cardiac manifestations of AIDS and serves to highlight two problems and one indication. First of all, there are very few clinical studies. Current knowledge is based almost exclusively on echocardiography and autopsy studies. Observational or clinical trials based on syndromes of heart failure, tamponade, and so forth, would be useful. Second, there exists very poor information on the impact of treatment. Clinicians have assumed that conventional treatment is appropriate for patients with heart failure and AIDS; however, there is some anecdotal evidence, based upon a low peripheral vascular resistance due to sepsis, that these patients tolerate angiotensin-converting enzyme inhibitors poorly.

As a consequence, it is mandatory for epidemiologic and clinicopathologic studies to obtain detailed data concerning the mechanisms of myocardial damage in AIDS. Finally, because cardiac complications are often clinically inapparent or subtle in the initial stages, periodic screening of HIV-positive patients by ECG and echocardiogram is probably indicated. The use of routine ECG and echocardiogram for asymptomatic patients with HIV infection is controversial. The ECG is much less expensive than an echocardiogram; it lends itself well to repeat serial assessment and was recommended for monitoring treatment with agents such as pentamidine that affect the conduction system.[12]

Girgis *et al.* observed that these alterations are not as frequent as has been reported and concluded that routine continuous telemetry monitoring would probably not add significantly to serial ECG monitoring.[83] On the other hand, echocardiographic examination is more informative and sensible than ECG monitoring. Indeed, echocardiography appears to be the most appropriate way to detect heart involvement during HIV infection; it allows for early diagnosis and thus provides time to find the most suitable way of treating cardiac abnormalities, even in the early asymptomatic phase of the disease.[31]

Prompt recognition and treatment is important because palliative therapy with diuretics and vasodilators can be worthwhile: mild global left ventricular dysfunction appears to be reversible in many patients, and a subgroup progresses to symptomatic heart failure without treatment.

It appears prudent to perform a careful cardiac examination at the time of diagnosis of HIV to obtain a baseline functional assessment. An ECG and an echocardiogram should be performed if there are signs of heart disease, chronic lung disease, or an acute exacerbation of lung disease not responsive to routine therapy. Of note, the presence of left ventricular dysfunction on a single echocardiogram does not necessarily imply a poor prognosis.[15]

Ideally, viral load assays and CD4 T-cell counts should be used together with a careful clinical examination, with measurements and ECG usually being made about every 3 months. Left ventricular dysfunction appears to be increased in patients with low CD4 counts, although other clinical markers of susceptibility have not yet been well defined.[11] In this connection, echocardiographic control seems advisable every 6 months.

The aim of the Italian-Argentine committee is to study the prevalence of heart involvement through cooperative cardiovascular noninvasive studies (i.e., echocardiogram, echo-Doppler) and to obtain endomyocardial biopsies in a selected number of patients with abnormal clinical tests. These endomyocardial biopsies will be useful, first to obtain adequate diagnosis and to improve treatment, and second to apply sophisticated techniques (in situ hybridization techniques, immunohistochemistry, PCR, etc.) for obtaining information about the etiology and physiopathogenesis of the disease and, as a consequence, to improve the treatment of the causal mechanism of the cardiovascular complication, since it is difficult to isolate the specific cause of the problem (the HIV virus itself, the drugs used to treat the HIV infection, the opportunistic infections, etc.).

In all patients who died a full autopsy is being carried out, and, particularly for the heart, the same studies as for endomyocardial biopsies are being performed.

In addition, AIDS may also provide insights into the pathogenesis of poorly understood cardiac diseases such as lymphocytic myocarditis and dilated cardiomyopathy.

References

1. Anonymous: Mortality attributable to HIV infection/AIDS in the USA, 1981–1990. *MMWR* 1991;40:41–44
2. Schulhafer EP, Verma RS: Acquired immunodeficiency syndrome: Molecular biology and its therapeutic intervention. *In Vivo* 1989; 3:61–78
3. Buhler JA, Schneider J: Heart and AIDS. *Schweiz Med Wochenschr/J Suisse Med* 1994;124:1326–1333
4. Kaul S, Fishbein MC, Siegel RJ: Cardiac manifestations of acquired immune deficiency syndrome: A 1991 update *Am Heart J* 1991;122:535–544
5. Milei J: Young labs (South American) associates to old tradition (Italian) in cardiovascular pathology. *Cardiovasc Pathol* 1997;6: 299

6. Falus JD: Los inhibidores de proteasa: Un paso crítico en el tratamiento de VIH. *Medico Interamericano* 1996;15:233–258
7. Anonymous: Major advances in the treatment of HIV-1 infection *Drug Ther Bull* 1997;35:25–29
8. Enger C, Graham N, Peng Y, Chmiel JS, Kingsley LA, Detels R, Muñoz A: Survival from early, intermediate, and late stages of HIV infection. *J Am Med Assoc* 1996;275:1329–1334
9. Monsuez JJ, Vittecoq D, Kinney EL: Increased survival of AIDS patients with heart disease within 10 years? *Circulation* 1996;94: 2312–2313
10. Mocroft A, Youle M, Morcinek J, Sabin CA, Gazzard B, Johnson MA, Phillips AN: Survival after diagnosis of AIDS: A prospective observational study of 2625 patients. *Br Med J* 1997;314:409–413
11. Herskowitz A, Choou Wu T, Willoughby SB, Vlahov D, Anasari AA, Beschorner WE, Baughman KL: Myocarditis and cardiotropic viral infection associated with severe left ventricular dysfunction in late-stage infection with human immunodeficiency virus. *J Am Coll Cardiol* 1994;24:1025–1032
12. Izquierdo Patron M, La Fuente C, Haro Estarriol M, Arévalo González M: Sinus bradycardia secondary to systemic pentamidine. *Rev Esp Cardiol* 1996;49:919–920
13. Cardoso JS, Mota Miranda A, Conde C, Moura B, Rocha Goncalves F, Lecour H: *Int J Cardiol* 1997;59:285–289
14. Herskowitz A: Cardiomyopathy and other symptomatic heart diseases associated with HIV infection. *Curr Opin Cardiol* 1996;11: 325–331
15. Jacob AJ, Sutherland GR, Bird AG, Brettle RP, Ludlam CA, McMillan A, Boon NA: Myocardial dysfunction in patients infected with HIV: Prevalence and risk factors. *Br Heart J* 1992;68: 549–553
16. Voytek TM, Joshi V: Cardiac pathology of pediatric HIV infection. *Prog Pediatr Cardiol* 1997;7:7–18
17. Cotton P: AIDS giving rise to cardiac problems. *J Am Med Assoc* 1990;263:2149
18. Anderson DW, Virmani R: Emerging patterns of heart disease in human immunodeficiency virus infection. *Hum Pathol* 1990;21: 253–259
19. Weniger BC, Brown R: The march of AIDS through Asia. *N Engl J Med* 1996;335:343–344
20. Kaplan S: Evolving epidemiology of human immunodeficiency viral (HIV) infection. *Prog Pediatr Cardiol* 1997;7:1–6
21. Herskowitz A, Willoughby SB, Vlahov D, Baughman KL, Ansari AA: Dilated heart muscle disease associated with HIV infection. *Eur Heart J* 1995;16(suppl O):50–55
22. Roldan EO, Moskowitz L, Hensley GT: Pathology of the heart in acquired immunodeficiency syndrome. *Arch Pathol Lab Med* 1987;111:943–946
23. Patel RC, Frishman W: Cardiac involvement in HIV infection. *Med Clin North Am* 1996;80:1493–1512
24. Thuesen L, Moller A: Heart involvement in HIV infection. *Nord Med* 1994;109:298–299
25. Aftabuddin M, Islam N, Alimuzzaman M, Koiralla TR, Hori Y: Cardiac malignant lymphoma in severe combine immunodeficient mice. *Indian Heart J* 1996;48:368–370
26. Denis J, Hery B, Crepin V, Guillemot L, Guerzider P: Malignant tumoral lymphoma of the heart in human immunodeficiency virus infection: Diagnosis by echocardiography. *Arch Mal Coeur Vaiss* 1995;88:507–510
27. Francis CK: Cardiac involvement in AIDS. *Curr Probl Cardiol* 1990;15:569–639
28. Feneley MP: Managing HIV. Part 5: Treating secondary outcomes. 5.9 HIV-related cardiovascular disease. *Med J Aust* 1996;164:482
29. Guillemot L, Denis J, Caille G, Migeon J, Nouel JF, Linder F: X-ray computed tomographic diagnosis of primary cardiac malignant lymphoma in AIDS. *J Radiol* 1996;77:45–48
30. Nyamathi A: AIDS-related heart disease: A review of the literature. *J Cardiovasc Nurs* 1989;3:65–76
31. De Castro S, Migliau G, Silvestri A, D'Amati G, Giannantoni P, Cartoni D, Kol A, Vullo V, Cirelli A: Heart involvement in AIDS: A prospective study during various stages of the disease. *Eur Heart J* 1992;13:1452–1459
32. Longo Mbenza B, Tonduangu K, Muvova D, Phuati MB, Seghers KV, Kestelot H: A clinical study of cardiac manifestations related to AIDS in Kinsaha. *Arch Mal Coeur Vaiss* 1995;88:1437–1443
33. Barbaro G, Barbarini G, Di Lorenzo G: Early impairment of systolic and diastolic function in asymptomatic HIV-positive patients: A multicenter echocardiographic and echo-Doppler study. The Gruppo Italiano Per lo Studio Cardiologico dei Pazienti Affetti da AIDS. *AIDS Res Hum Retroviruses* 1996;12:1559–1563
34. Casalino E, Laissy JP, Soyer P, Bouvet E, Vachon F: Assessment of right ventricle function and pulmonary artery circulation by cine-MRI in patients with AIDS. *Chest* 1996;110:1243–1247
35. Coudray N, de Zuttere D, Force G, Champetier de Ribes D, Pourny JC, Antony I, Lecarpentier Y, Chimla D: Left ventricular diastolic function in asymptomatic and symptomatic human immunodeficiency virus carriers: An echocardiographic study. *Eur Heart J* 1995;16:61–67
36. Kinney EL, Brafman D, Wright RJ: Echocardiographic findings in patients with acquired immunodeficiency syndrome (AIDS) and AIDS-related complex (ARC). *Cathet Cardiovasc Diagn* 1989;16: 182–185
37. Lassaigne D, Greder A, Hedoire F, Grollier G, Potier JC, Bazin C: Myocardial involvement in AIDS. Echographic study in 85 human immunodeficiency virus infected patients. *Ann Med Interne Paris* 1991;142:205–208
38. Akhras F, Dubrey S, Gazzard B, Noble MI: Emerging patterns of heart disease in HIV infected homosexual subjects with and without opportunistic infections: A prospective colour flow Doppler echocardiographic study. *Eur Heart J* 1994;15:68–75
39. Gouello JP, Chennebault JM, Loison J, Bovachour G, Tirot P, Achard J: Echocardiographic abnormalities in the stage IV of HIV infection. *Presse Medic* 1993;22:712–716
40. Hakim JG, Matenga JA, Siziya S: Myocardial dysfunction in human immunodeficiency virus infection: An echocardiographic study of 157 patients in hospital in Zimbawe. *Heart* 1996;76: 161–165
41. Starc T: Heart failure and cardiac disease in children with HIV infection. *Prog Pediatr Cardiol* 1997;7:45–50
42. al Kassab AK, Habte Gabr E, Mueller WF, Azher Q: Fulminant disseminated toxoplasmosis in an HIV patient. *Scand J Infect Dis* 1995;27:183–185
43. Mertens RB, Didier ES, Fishbein MC, Bertucci DC, Rogers LB, Orenstein JM: *Encephalitozoon cuniculi microsporidiosis*: Infection of the brain, heart, kidneys, trachea, adrenal glands, and urinary bladder in a patient with AIDS. *Mod Pathol* 1997;10:68–77
44. Yachnis AT, Berg J, Martinez Salazar A, Bender BS, Diaz L, Rojiani AM, Eskin TA, Orenstein JM: Disseminated microsporidiosis especially infecting the brain, heart, and kidneys. Report of a newly recognized pansporoblastic species in two symptomatic AIDS patients. *Am J Clin Pathol* 1996;106:535–543
45. Escamilla R, Hermant C, Petureau F, Voigt JJ, Krempf M: Disseminated aspergillosis with pulmonary and cardiac localization in an HIV-infected patient. *Rev Mal Respir* 1995;12:380–382
46. Lewis W: AIDS: Cardiac findings from 115 autopsies. *Prog Cardiovasc Dis* 1989;32:207–215
47. Eisenberg MJ, Gordon AS, Schiller NB: HIV-associated pericardial effusions. *Chest* 1992;102:956–958
48. Heidenreich PA, Eisenberg MJ, Kee LL: Pericardial effusions in AIDS. Incidence and survival. *Circulation* 1995;92:3229–3234
49. Moreno R, Villacastin JP, Bueno H, López de Sa E, López Sendón JL, Bobadilla JF, Garcia Fernández MA, Delcan JL: Clinical and echocardiographic findings in HIV patients with pericardial effusion. *Cardiology* 1997;88:397–400
50. Kovacs A, Hinton DR, Wright D, Xu J, Rasheed S, Hofman F: Human immunodeficiency virus type 1 infection of the heart in three infants with acquired immunodeficiency syndrome and sudden death. *Pediatr Infect Dis J* 1996;15:819–824

51. Flomenbaum M, Soeiro R, Udem SA, Kress Y, Factor SM: Proliferative membranopathy and human immunodeficiency virus in AIDS hearts. *J AIDS* 1989;2:129–135
52. Grody WW, Cheng L, Lewis W: Infection of the heart by the human immunodeficiency virus. *Am J Cardiol* 1990;66:203–206
53. Wink K, Schmitz H: Cytomegalovirus myocarditis. *Am Heart J* 1980;100:667–672
54. Wilson R, Morris T, Rossel RJR: Cytomegalovirus myocarditis. *Br Heart J* 1982;34:856–858
55. Barbaro G, DiLorenzo G, Grisorio B, Barbarini G: 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* 1996;41:1199–1207
56. Anderson DW, Virmani R, Reilly JM, O'Leary T, Cunnion RE, Robinowitz M, Macher AM, Punja U, Villaflor ST, Parrillo JE, *et al.*: Prevalent myocarditis at necropsy in the acquired immunodeficiency syndrome. *J Am Coll Cardiol* 1988;11:792–799
57. Rodriguez ER, Nasim S, Hsia J, Sandin RL, Ferreira A, Hilliard BA, Ross AM, Garrett CT: 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* 1991;68:1511–1520
58. Hansen BF: Pathology of the heart in AIDS. A study of 60 consecutive autopsies. *APMIS* 1992;100:273–279
59. Parravicini C, Baroldi G, Gaiera G, Lazzarin A: Phenotype of intramyocardial leukocytic infiltrates in acquired immunodeficiency syndrome: A postmortem immunohistochemical study in 34 consecutive cases. *Mod Pathol* 1991;4:559–565
60. Matturri L, Quattrone P, Varesi C, Rossi L: Cardiac toxoplasmosis in pathology of acquired immunodeficiency syndrome. *Panminerva Med* 1990;32:194–196
61. Kaminski HJ, Katzman M, Wiest PM, Gifford DR, Rackley R, Iskandar SS, Lederman MM: Cardiomyopathy associated with the acquired immune deficiency syndrome. *J Acquir Immune Defic Syndr* 1988;1:105–110
62. Cetta F, Michels VV: The natural history and spectrum of idiopathic dilated cardiomyopathy, including HIV and peripartum cardiomyopathy. *Curr Opin Cardiol* 1995;10:332–338
63. Webb JG, Chan Yan C, Kiess MC: Cardiac dysfunction associated with the acquired immunodeficiency syndrome (AIDS). *Clin Cardiol* 1988;11:423–426
64. Currie PF, Jacob AJ, Foreman AR, Elton RA, Brettle RP, Boon NA: Heart muscle disease related to HIV infection: Prognostic implications. *Br Med J* 1994;309:1605–1607
65. Bagasra O, Bobroski LE, Pestaner JP, Seshamma T, Pomerantz RJ: Localization of HIV-1 in cardiac tissue utilizing in situ PCR. *Cell Vision* 1996;3:6–10
66. Calabrese LH, Proffitt MR, Yen Lieberman B, Hobbs RE, Ratliff NB: Congestive cardiomyopathy and illnes related to the acquired immunodeficiency syndrome (AIDS) associated with isolation of retrovirus from myocardium. *Ann Intern Med* 1987;107:691–692
67. Dworkin BM, Antonecchia PP, Smith F: Reduced cardiac selenium content in AIDS. *J Parent Ent Nutr* 1989;13:644–647
68. Domanski MJ, Sloas MM, Follmann DA: Effect of zidovudine and didanosine treatment on heart function in children infected with human immunodeficiency virus. *J Pediatr* 1995;127:137–146
69. Beschorner WE, Baughman K, Turnicky RP: HIV-associated myocarditis. Pathology and immunopathology. *Am J Pathol* 1990;137:1365–1371
70. Jaques AK, Arroja I, Araujo C, Azevedo J, Borges A, Santos I, Cabral A, Campos MJ, Masinho K, Borges F: Sindrome de inmunodeficiencia adquirida, miocardiopatia hipertrofica e endocardite infecciosa multivalvular. Aproposito de um caso clinico. *Rev Port Cardiol* 1995;14:53–58
71. Fernandez Guerrero ML, Torres Perea R, Gomez Rodrigo J, Nunez Garcia A, Jusdado JJ, Ramos Rincon JM: Infectious endocarditis due to non-typhi salmonella in patients infected with human immunodeficiency virus: Report of two cases and review. *Clin Infect Dis* 1996;22:853–855
72. Kinney EL, Monsuez JJ, Kitzis M, Vittecoq D: Treatment of AIDS-associated heart disease. *Angiology* 1989;40:970–976
73. Hecht SR, Berger M, Van Tosh A, Croxson S: Unsuspected cardiac abnormalities in the AIDS. An echocardiographic study. *Chest* 1989;96:805–808
74. Corallo S, Mutinelli M, Moroni M, Lazzarin A, Celano V, Repossini A, Baroldi G: Echocardiography detects myocardial damage in AIDS: Prospective study in 102 patients. *Eur Heart J* 1988;9:887–892
75. Lipshultz SE, Chanock S, Sanders SP, Colan SD, Perez Atayde A, McIntosh K: Cardiovascular manifestations of human immunodeficiency virus infection in infants and children. *Am J Cardiol* 1989;63:1489–1497
76. Paton P, Tabib A, Loire R, Tete R: Coronary artery lesions and human immunodeficiency virus infection. *Res Virol* 1993;144:225–231
77. Ferrans VJ, Roberts WC: Myocardial biopsy: A useful diagnostic procedure or only a research tool? *Am J Cardiol* 1978;41:965–967
78. Mason JW, O'Connell JB: Clinical merit of endomyocardial biopsy. *Circulation* 1989;79:971–979
79. Milei J, Bortman G, Fernández Alonso G, Grancellli H, Beigelman R: Immunohistochemical staining of lymphocytes for the reliable diagnosis of myocarditis in endomyocardial biopsies. *Cardiology* 1990;77:77–85
80. Milei J, Fernandez Alonso JG, Vanzulli S, Storinio R, Matturri L, Rossi L: Myocardial inflammatory infiltrate in human chronic Chagasic cardiomyopathy: Immunohistochemical findings. *Cardiovasc Pathol* 1996;5:209–219
81. Barbeau P, Pellegrin JL, Labouyne E, Brossard G, Rispal P, Lasseur C, Leng B: Intérêt et limites de la biopsie endomyocardique au cours de l'infection par le VIH. *Rev Med Interne* 1993;14:1032
82. Cenacchi G, Re MC, Furlini G, La Placa M, Binetti G, Rapezzi C, Alampi G, Magnani B: Human immunodeficiency virus type 1 antigen detection in endomyocardial biopsy: An immunopathological study. *Microbiologica* 1990;13:145–149
83. Girgis I, Gualberti J, Langan L, Malek S, Mustaciuolo V, Costantino T, McGinn TG: A prospective study of the effect of IV pentamidine therapy on ventricular arrhythmias and QTc prolongation in HIV-infected patients. *Chest* 1997;112:646–653