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HIV-Associated Cardiomyopathy

Etiopathogenesis and Clinical Aspects

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Key Words:
Human immunodeficiency virus · Acquired immunodeficiency syndrome · Cardiomyopathy · Myocarditis · Cytokines · Tumor necrosis factor-α

Herz 2005;30:486–92

DOI 10.1007/s00059-005-2728-z

Abstract

Human immunodeficiency virus (HIV) disease is recognized as an important cause of dilated cardiomyopathy. Myocarditis and myocardial infection with HIV-1 are the best-studied causes of cardiomyopathy in HIV disease. HIV-1 virions appear to infect myocardial cells in a patchy distribution with no direct association between the presence of the virus and myocyte dysfunction. Myocardial dendritic cells seem to play a significant pathogenetic role by activating multifunctional cytokines (i.e., tumor necrosis factor-α) and the inducible form of nitric oxide synthase that contribute to progressive and late myocardial tissue damage. Coinfection with other viruses (usually, coxsackievirus B3 and cytomegalovirus) may also play an important etiopathogenetic role.

The introduction of highly active antiretroviral therapy (HAART) has significantly reduced the incidence of myocarditis in HIV-infected patients living in developed countries. By contrast, in developing countries, where the availability of HAART is scanty and greater is the pathogenetic role of nutritional factors, the incidence of HIV-associated myocarditis and cardiomyopathy is increasing with a high mortality rate for congestive heart failure.

A clinical diagnosis of myocarditis or congestive heart failure may be difficult in an HIV-infected patient due to masking of symptoms by concomitant bronchopulmonary disease and/or wasting syndromes, especially in a more advanced stage of HIV disease. Immunomodulatory therapy (intravenous immunoglobulins) may be helpful in adults and children with HIV-associated myocarditis and declining left ventricular function. Data on the role of HAART in the treatment of HIV-associated myocarditis and cardiomyopathy are lacking.

HIV-assoziierte Kardiomyopathie. Ätiopathologie und klinische Aspekte

Schlüsselwörter:
Kardiomyopathie · Herzinsuffizienz · HIV · HAART

Zusammenfassung

Die Infektion mit dem humanen Immundefizienzvirus (HIV) ist als eine relevante Ursache für die Ausbildung einer dilatativen Kardiomyopathie erkannt worden. Die Myokarditis sowie die myokardiale Infektion mit HIV-1 sind die bisher am besten untersuchten Ursachen für die Ausbildung einer Kardiomyopathie bei HIV-positiven Personen. HIV-1-Virionen verursachen eine verstreute Infektion myokardialer Zellen ohne direkte Beziehung zwischen der Präsenz des Virus und der Funktion des Myozyten. Hierbei scheinen dendritische Zellen im Myokard eine signifikante pathogenetische Rolle zu spielen. Dies geschieht mittels Aktivierung multifunktionaler Zytokine wie z.B. Tumor-Nekrose-Faktor-α und der induzierbaren Form der Nitroxid-Synthetase (iNOS), die zur myokardialen Gewebsschädigung beitragen. Koinfektionen mit anderen Viren, wie häufig Coxsackie-Virus B3 und Zytomegalievirus, können ebenfalls eine bedeutende ätiopathologische Rolle spielen.

Mit Einführung neuer antiretroviraler Therapiekonzepte (HAART) hat sich die Inzidenz von Myokarditiden in den Industrienationen deutlich reduziert. Im Gegensatz dazu steigt die Inzidenz HIV-assoziierter Myokarditiden und Kardiomyopathien in Entwicklungsländern, wo der Zugang zu effektiver Medikation begrenzt ist und der Ernährungssituation eine höhere pathogenetische Rolle zukommt.

Die klinische Diagnose der Myokarditis oder Herzinsuffizienz ist bei HIV-positiven Personen, insbesondere im fortgeschrittenen Stadium der Erkrankung, nicht zuletzt aufgrund gleichzeitiger Symptome bronchopulmonaler Erkrankungen und/oder eines Wasting-Syndroms erschwert. Eine immunmodulatorische Therapie, wie sie durch die intravenöse Gabe von Immunglobulinen erreicht wird, kann bei Erwachsenen und Kindern mit HIV-assoziierter Myokarditis und reduzierter Pumpfunktion einen positiven Effekt aufweisen. Erkenntnisse über die Rolle der antiretroviralen Therapie in der Behandlung der HIV-assoziierten Myokarditis und Kardiomyopathie fehlen bisher.

Introduction

Human immunodeficiency virus (HIV) disease is recognized as an important cause of dilated cardiomyopathy, with an estimated annual incidence of 15.9/1,000 before the introduction of highly active antiretroviral therapy (HAART) [1]. The importance of cardiac dysfunction is demonstrated by its effect on survival in acquired immunodeficiency syndrome (AIDS). Median survival to AIDS-related death is 101 days in patients with left ventricular dysfunction and 472 days in patients with a normal heart by echocardiography at a similar infection stage [1]. The unadjusted hazard ratio for death in HIV-related cardiomyopathy compared to idiopathic cardiomyopathy is 4.0; the ratio adjusted after multivariate analysis is 5.86 [1]. The introduction of HAART regimens, by preventing opportunistic infections and reducing the incidence of myocarditis, has reduced the prevalence of HIV-associated cardiomyopathy by about 30% in developed countries [5, 30]. However, the median prevalence of HIV-associated cardiomyopathy is increasing in developing countries (about 32%), where the availability of HAART is scanty and greater is the pathogenetic impact of nutritional factors [27].

Pathologic Features

Pathologic features of AIDS-associated cardiomyopathy are similar to those observed in HIV-uninfected patients. At autopsy, the heart shape is modified, because of ventricular dilation and apical rounding. Heart weight is generally increased, owing to fibrosis and myocyte hypertrophy [2, 15]. On average, long-term survivors have significantly heavier hearts than those dying after a brief disease course. The epicardium is usually normal and coronary arteries do not show significant atherosclerosis. The myocardium is rather flabby and the ventricular wall usually collapses on section [2, 15]. On cut surface, the ventricles show an eccentric hypertrophy, that is, a mass increase with chamber volume enlargement. Although hypertrophy is demonstrated by the increase in cardiac weight, this is not always grossly evident owing to ventricular dilation; the free wall width may be normal, or even thinner than normal, as happens in short-term survivors. Endocardial fibrosis is a common finding, as well as mural thrombi, mainly located at the apex. Dilated cardiomyopathy can be associated with pericardial effusion or infective endocarditis, especially in intravenous drug abusers [2, 15]. On histology, myocytes show variable degrees of hypertrophy and degenerative changes, such as myofibril loss, causing hydropic changes within the myocell. An increase in interstitial and endocardial fibrillar collagen is a constant feature in HIV-associated cardiomyopathy [2, 15].

Etiopathogenesis

Animal Models

Simian immunodeficiency virus (SIV) infection in rhesus macaques is a valuable model in understanding the pathogenesis of cardiac injury associated with retroviral infection in a relevant nonhuman primate model of AIDS [32]. Chronic SIV infection resulted in depressed left ventricular systolic function and an extensive coronary arteriopathy suggestive of injury due to cell-mediated immune response [32]. Two thirds of chronically infected macaques that died of SIV had related myocardial effects. Lymphocytic myocarditis was seen in 9/15 and coronary arteriopathy in 9/15 (six alone and three in combination with myocarditis) upon necropsy. In infected macaques, coronary arteriopathy was extensive, with evidence of vessel occlusion and recanalization, and related regions of myocardial necrosis in four macaques. On necropsy, two animals had marantic endocarditis and one had a left ventricular mural thrombus. Macaques with cardiac pathology were emaciated to a greater extent than macaques with SIV and similar periods of infection who did not experience cardiac pathology [32].

Myocarditis

Myocarditis is still the best-studied cause of dilated cardiomyopathy in HIV disease. According to the author's clinical and pathologic experience, HIV-associated myocarditis may be defined as *"a process characterized by a lymphocytic infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease in subjects infected by HIV with or without evidence of opportunistic infective agents"* [2]. Myocarditis has been documented at autopsy in 40–52% of patients who died of AIDS before the introduction of HAART [15]. In the Gruppo Italiano per lo Studio Cardiologico dei pazienti affetti da AIDS (GISCA) autopsy series histological diagnosis of myocarditis was made in 30 of 82 patients (37%) with cardiac involvement [2]. Of twelve autopsy patients with dilated cardiomyopathy, ten (83%) had active myocarditis at histological examination of myocardial tissue specimens [2].

Histological findings in HIV-infected patients with myocarditis do not substantially differ

from those observed in HIV-uninfected patients. Lymphocytes, along with fewer macrophages, are distributed diffusely as single cells or in small clusters. Autopsy studies of AIDS patients dead of acute left ventricular dysfunction almost invariably show a marked inflammatory infiltrate [2]. However, mild and focal mononuclear infiltrates are frequently observed in hearts of AIDS patients, irrespective of the presence of cardiac symptoms [2]. The intracardiac conduction system is sometimes affected in AIDS patients, generally as a complication of myocarditis. Primary involvement of the conduction system is possible as a consequence of opportunistic infections, drug cardiotoxicity, or primary location of HIV-1 in the specific conduction tissue [2]. Histological examination of myocardium specimens at autopsy may show mononuclear infiltration of the intracardiac conduction tissue, which is frequently associated with vasculitis and fragmentation of the bundles with lobulation and fibrosis. These findings are generally associated with electrocardiographic conduction abnormalities. Among them, the most common are left anterior hemiblock, left bundle branch block, and first-degree atrioventricular block [2]. In the GISCA autopsy series 5/12 patients (42%) with cardiomyopathy also had intracardiac conduction system alterations on histological examination. Two of them had lymphocytic infiltration of the conduction tissue as complication of active myocarditis, and the remaining three had fragmentation and fibromatous degeneration of the left bundle [2].

Nonviral myocarditis. The most common opportunistic infectious agent associated with myocarditis in AIDS is *Toxoplasma gondii*, observed as often as 12% in one autopsy series with deaths from AIDS between 1987 and 1991 [16]. There may be regional differences in the incidence of *T. gondii* myocarditis, perhaps because the natural reservoir of organisms persists more easily in humid environments. Elevation of myocardial fraction of creatine kinase (CK-MB) may commonly occur with myocardial toxoplasmosis. *T. gondii* organisms can produce a gross pattern of patchy irregular white infiltrates in myocardium similar to non-Hodgkin's lymphoma. Microscopically, the myocardium shows scattered mixed inflammatory cell infiltrates with polymorphonuclear leukocytes, macrophages, and lymphocytes. *T. gondii* can produce quite variable inflammation along with myocardial fiber necrosis. The three microscopic patterns of involvement by *T. gondii* include acute diffuse myocarditis, focal myocarditis, and presence of organisms without significant inflammation or necrosis [15, 16]. In *Toxoplasma* myocarditis, true *T. gondii* extracellular cysts, or pseudocysts within myocardial fibers, both of which contain the small 2-µ-sized bradyzoites, are often hard to find, even if inflammation is extensive. Immunohistochemical staining may reveal free tachyzoites, the organisms that are found outside of cysts. Otherwise, it is difficult with routine hematoxylin and eosin staining to distinguish these free tachyzoites from fragments of inflammatory cells or myocytes that have undergone necrosis within the areas of inflammation [15, 16].

Fungal opportunistic infections of the heart occur infrequently in HIV-infected patients. They are often incidental findings at autopsy, and cardiac involvement is probably the result of widespread dissemination, as exemplified by *Candida* sp. and by the fungi *Cryptoccocus neoformans, Coccidioides immitis*, or *Histoplasma capsulatum* [2, 15, 16]. Fungal lesions are characterized grossly by the appearance of multiple small rounded white plaques. They may have a hemorrhagic border, particularly lesions caused by *Aspergillus* that can be angioinvasive. Microscopically, fungal lesions have variable inflammatory infiltrates and necrosis, and a specific diagnosis is made by identifying yeast forms or hyphae of specific organisms, aided by standard histological stains such as Gomori methenamine silver or periodic acid Schiff [2, 15, 16]. The near absence of an inflammatory infiltrate accompanying fungal organisms is a manifestation of immune system failure with progression of AIDS to a late stage when opportunistic infections are more likely to be widely disseminated to organs such as the heart [2, 15, 16].

Patients living in endemic areas for *Trypanosoma cruzi* may rarely develop a pronounced myocarditis [28, 31]. *Mycobacterium avium*-complex infection can be widely disseminated and involve the heart with microscopic lesions characterized by clusters of large macrophages filled with numerous acid-fast rod-shaped organisms [2, 15, 16].

Pneumocystis carinii can involve the heart in cases with widespread dissemination of this organism [16]. Grossly, the epicardium and cut surfaces of the myocardium may have a sandpaper-like quality due to the presence of multiple pinpoint foci of calcification. Microscopically, this calcification is not accompanied by significant inflammatory cell infiltrates, but there may be deposits of amorphous granular pink exudate similar to that seen in alveoli with *Pneumocystis carinii* pneumonia [15, 16]. The cysts may be difficult

to recognize, even with Gomori methenamine silver stain, and diagnosis is aided by immunohistochemical staining [15, 16].

Viral myocarditis. Histology and immunohistochemistry rarely detect the presence of viruses in the myocardium [2]. However, in situ hybridization or polymerase chain reaction studies reveal a high frequency of either cytomegalovirus or HIV-1 or both, in AIDS patients with lymphocytic myocarditis and severe left ventricular dysfunction [2, 13]. These data support the hypothesis that, at least in a subset of patients, HIV-1 has a pathogenetic action and possibly influences the clinical evolution toward dilated cardiomyopathy.

Herskowitz et al. detected a positive hybridization signal for HIV-1 in endomyocardial biopsy specimens from 15 of 37 patients (40%) with left ventricular dysfunction. Histological and immunohistological techniques documented that most of these patients had myocarditis [13]. HIV-1 nucleic acid sequences were detected at autopsy by in situ DNA hybridization in 35% of the GISCA patients with cardiac involvement; 86% of them had active myocarditis at histological examination. Among patients with myocarditis, coinfection with coxsackievirus B3 was documented in 32%, with Epstein-Barr virus in 8%, and with cytomegalovirus in 4% [2]. In autopsy biopsy samples, myocytes with a positive hybridization signal were sparse, usually only one to four cells per section [2]. Although about 70% of patients with positive hybridization signals had active myocarditis at histological examination, most myocytes with positive hybridization signal were not surrounded by inflammatory cells [2]. In the GISCA autopsy series, HIV-1 was documented by in situ hybridization in 83% of patients with myocarditis [2].

Coinfection with other viruses seems to have an important etiopathogenetic role. The GISCA autopsy records show that 83% of patients with myocarditis and 50% of those with dilated cardiomyopathy were coinfected with cardiotropic viruses (usually, coxsackievirus B3 and cytomegalovirus) [2]. Herskowitz et al. used in situ hybridization to detect myocardial cytomegalovirus infection in 48% of HIV-positive patients with myocarditis and left ventricular dysfunction who underwent endomyocardial biopsy [13]. Bowles et al. used polymerase chain reaction and found that 42% of HIV-positive patients with cardiomyopathy had cytomegalovirus or adenovirus in the myocardial tissue [6]. Some patients with adenovirus coinfection had congestive heart failure but not myocarditis, suggesting that the virus may be virulent without associated inflammatory response [6].

Myocardial Cytokine Expression as a Factor in Cardiomyopathy

Myocardial dendritic cells may play a role in the interaction between HIV-1 and the cardiac myocyte and in the activation of cytotoxic cytokines [3]. Recently, it has been demonstrated that HIV-1 invades the myocardium through endothelial cells by micropinocytosis and infects perivascular macrophages, which produce additional virus and cytokines, such as tumor necrosis factor-(TNF-)α. The virus produces cardiomyocyte apoptosis either by signaling through CCR3, CCR5 or CXCR4, by entry intro cardiomyocytes (after binding to ganglioside GM1), or through TNF-α [11, 34]. It is also possible that HIV-1-associated protein gp 120 may induce myocyte apoptosis through a mitochondrion-controlled pathway by activation of inflammatory cytokines [34].

In HIV infection, dendritic cells can initiate the primary immunologic response and present the antigen to T-lymphocytes. The interaction between dendritic cells and T-lymphocytes, particularly CD8 cells, could promote a local elevation in the multifunctional cytokine TNF-α, which can also be produced and secreted by infected macrophages [23, 25]. TNF-α produces a negative inotropic effect by altering intracellular calcium homeostasis, possibly by inducing nitric oxide (NO) synthesis, which also reduces myocyte contractility [12, 35].

Myocarditis and dilated cardiomyopathy are associated with markedly elevated cytokine production, but the elevations may be highly localized within the myocardium, making peripheral cytokine levels uninformative [3]. When myocardial biopsies from patients with HIV-associated cardiomyopathy are compared to samples from patients with idiopathic dilated cardiomyopathy, the former stain more intensely for both TNF-α and inducible nitric oxide synthase (iNOS). Staining is particularly intense in samples from patients with a myocardial viral infection and correlated with CD4 count, independent of antiretroviral treatment [3]. Staining is also more intense in samples from patients with HIV-associated cardiomyopathy coinfected with coxsackievirus B3, cytomegalovirus, Epstein-Barr virus or adenovirus [3]. Moreover, staining for iNOS is more intense in samples from patients coinfected with HIV-1 and coxsackievirus B3 or cytomegalovirus

than in samples from patients with idiopathic dilated cardiomyopathy and myocardial infection with coxackievirus B3 or who had adenovirus infection alone [3]. In patients with HIV-associated dilated cardiomyopathy and more intense iNOS staining, the survival rate was significantly lower: those whose samples stained more than 1 optical density unit had a hazard ratio of mortality of 2.57 (95% confidence interval: 1.11–5.43). Survival in HIV-infected patients with less intense staining was not significantly different from survival in patients with idiopathic dilated cardiomyopathy [3].

Autoimmunity as a Contributor to Cardiomyopathy

Cardiac-specific autoantibodies (anti-α-myosin autoantibodies) are more common in HIV-infected patients with dilated cardiomyopathy than in HIV-infected patients with healthy hearts. Currie et al. reported that HIV-infected patients were more likely to have specific cardiac autoantibodies than were HIV-negative controls [10]. Those with echocardiographic evidence of left ventricular dysfunction were particularly likely to have cardiac autoantibodies, supporting the theory that cardiac autoimmunity plays a role in the pathogenesis of HIV-related heart disease and suggesting that cardiac autoantibodies could be used as markers of left ventricular dysfunction in HIV-positive patients with previously normal echocardiographic findings [10]. In addition, monthly intravenous immunoglobulin in HIV-infected pediatric patients minimizes left ventricular dysfunction, increases left ventricular wall thickness, and reduces peak left ventricular wall stress, suggesting that both impaired myocardial growth and left ventricular dysfunction may be immunologically mediated [20]. These effects may be the result of immunoglobulins inhibiting cardiac autoantibodies by competing for Fc receptors, or they could be the result of immunoglobulins dampening the secretion or effects of cytokines and cellular growth factors [20]. These findings suggest that immunomodulatory therapy might be helpful in adults and children with declining left ventricular function, although further study of this possible therapy is needed.

Relationship between HIV-Associated Cardiomyopathy and Encephalopathy

HIV-infected patients with encephalopathy are more likely to die of congestive heart failure than are those without encephalopathy (hazard ratio: 3.4) [9, 19]. Cardiomyopathy and encephalopathy may both be traceable to the effects of HIV reservoir cells in the myocardium and the cerebral cortex. These cells may hold HIV-1 on their surfaces for extended time periods even after antiretroviral treatment, and they may chronically release cytotoxic cytokines (TNF-α, interleukin-6, and endothelin-1), which contribute to progressive and late tissue damage in both systems. Since the reservoir cells are not affected by treatment, the effect is independent of whether the patient receives HAART.

Nutritional Deficiencies as a Factor in Left Ventricular Dysfunction

Nutritional deficiencies are common in HIV infection and may contribute to ventricular dysfunction independently of HAART. Malabsorption and diarrhea can both lead to trace element deficiencies which have been directly or indirectly associated with cardiomyopathy [26]. Selenium replacement may reverse cardiomyopathy and restore left ventricular function in selenium-deficient patients [26]. HIV infection may also be associated with altered levels of vitamin B_{12}, carnitine, growth hormone, and thyroid hormone, all of which have been associated with left ventricular dysfunction [26].

Left Ventricular Dysfunction Caused by Drug Cardiotoxicity

Studies of transgenic mice suggest that zidovudine is associated with diffuse destruction of cardiac mitochondrial ultrastructure and inhibition of mitochondrial DNA replication [17, 18]. This mitochondrial dysfunction may result in lactic acidosis, which could also contribute to myocardial cell dysfunction. However, in a study of infants born to HIV-positive mothers followed from birth to age 5, perinatal exposure to zidovudine was not found to be associated with acute or chronic abnormalities in left ventricular structure or function [21]. Other nucleoside reverse transcriptase inhibitors, such as didanosine and zalcitabine, do not seem to either promote or prevent dilated cardiomyopathy. In AIDS patients with Kaposi's sarcoma, reversible cardiac dysfunction was associated with prolonged, high-dose therapy with interferon α [33]. High-dose interferon α treatment is not associated with myocardial dysfunction in other patient populations, so it has been proposed that it may have a synergistic effect with HIV infection [33]. Doxorubicin (adriamycin), which is used to treat AIDS-related Kaposi's sarcoma and non-Hodgkin's lymphoma, has a

dose-related effect on dilated cardiomyopathy [7], as does foscarnet sodium when used to treat cytomegalovirus esophagitis [8].

Clinical and Therapeutic Approach

In HIV-infected patients symptoms of heart failure may be masked by concomitant illness such as diarrhea or malnutrition, or may be disguised by bronchopulmonary infection. Echocardiography is the only sensitive and specific method in the evaluation of ventricular function and pericardial effusion in this population and should be considered early in a patient with a change in clinical status [4]. Standard heart failure treatment regimens are generally recommended for HIV-infected patients with dilated cardiomyopathy and congestive heart failure even though these regimens have not been tested in this specific population by controlled clinical studies. Patients with systolic dysfunction and symptoms of fluid retention should receive a loop diuretic and an aldosterone antagonist as well as an angiotensin-converting enzyme inhibitor (ACEI). ACEIs are recommended based on general heart failure studies, but may be poorly tolerated due to low systemic vascular resistance from diarrheal disease, infection, or dehydration. Digoxin may be added to therapy for patients with persistent symptoms or rapid atrial fibrillation. When the patient is euvolumic, a β-blocker (e.g., carvedilol, metoprolol, and bisoprolol) may be started for its beneficial effects on circulating levels of inflammatory and anti-inflammatory cytokines [29].

Suspecting acute myocarditis in HIV-infected patients is important, as this condition may evolve and include life-threatening congestive heart failure and arrhythmias. Fever and infection of the upper respiratory tract or flu-like symptoms may precede exertional dyspnea by as little as hours or days. Signs and symptoms may occur at rest and include palpitations, atypical chest pain, and electrocardiographic alterations. Laboratory alterations may include elevated cardiac troponin I (cTnI), myoglobin with or without elevated levels of CK-MB [4]. Differentiating myocarditis from myocardial infarction may also be difficult. A careful clinical history and physical examination, electrocardiogram (ECG) review, and analysis of traditional risk factors expanded to include drug use (i.e., cocaine) and/or HIV-specific therapies (i.e., use of protease inhibitors in the context of HAART regimens) may direct the diagnosis [4]. The state of immunocompetence of the patients should be carefully assessed by CD4 count. In spite of the recent description of immune reconstitution inflammatory disease in HIV-infected patients receiving HAART [14], a CD4 count < 200/mm^3 has still to be considered a marker of increased risk for myocardial opportunistic infections. Markers of cardiac injury should be interpreted in relation to the timing of the onset of the patient's symptoms. An elevation of myoglobin in the absence of an elevated cTnI in following samples may be related to an inflammatory muscle disease. Myositides are more likely to occur in HIV-infected patients making myoglobin much less specific as a marker for cardiac injury [4].

An isolated positivity of cTnI suggests a minimal myocardial damage of small areas of myocardium (micronecrosis). In HIV-infected patients, micronecrosis may be caused by an inflammatory process secondary to myocarditis or pericarditis with extended epicarditis (perimyocarditis) or to autoimmune mechanisms induced by infections or antiviral drugs (mainly nucleoside reverse transcriptase inhibitors). In case of elevated levels of CK-MB and/or cTnI in HIV-infected patients with a non-diagnostic ECG (i.e., presence of left bundle branch block, chronic ischemic alterations), clinical skills and echocardiography should help guide the differential diagnosis of myocarditis (absence or reversible hypokinesia) or acute myocardial infarction (with or without ST segment elevation). In spite of the fact that magnetic resonance scan is increasingly utilized to screen for myocarditis [24], data on the role of this procedure in the diagnosis of HIV-associated myocarditis are lacking. Cardiac catheterism with endomyocardial biopsy still represents the gold standard in the diagnosis of HIV-associated myocarditis [4].

No prospective controlled clinical studies have investigated the efficacy of specific therapeutic regimens for HIV-associated myocarditis other than intravenous immunoglobulins [22]. Data on the role of HAART in the treatment of HIV-associated myocarditis are lacking.

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