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INCIDENCE OF DILATED CARDIOMYOPATHY AND DETECTION OF HIV IN MYOCARDIAL CELLS OF HIV-POSITIVE PATIENTS

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ABSTRACT

Background Human immunodeficiency virus (HIV) infection is increasingly recognized as an important cause of dilated cardiomyopathy. However, the pathogenesis of the heart-muscle disease in the acquired immunodeficiency syndrome is unclear.

Methods We performed a prospective, long-term clinical and echocardiographic follow-up study of 952 asymptomatic HIV-positive patients to assess the incidence of dilated cardiomyopathy and to analyze the clinical variables associated with the development of cardiomyopathy. All patients with an echocardiographic diagnosis of dilated cardiomyopathy underwent endomyocardial biopsy for histologic, immunohistologic, and virologic assessment.

Results During a mean (\pm SD) follow-up period of 60 ± 5.3 months, an echocardiographic diagnosis of dilated cardiomyopathy was made in 76 patients (8 percent), with a mean annual incidence rate of 15.9 cases per 1000 patients. The incidence of dilated cardiomyopathy was higher in patients with a CD4 count of less than 400 cells per cubic millimeter (as compared with a CD4 count of ≥ 400 cells per cubic millimeter) and in those who received therapy with zidovudine. A histologic diagnosis of myocarditis was made in 63 of the patients with dilated cardiomyopathy (83 percent). Inflammatory infiltrates were predominantly composed of CD3 and CD8 lymphocytes, with staining for major histocompatibility complex class I antigens in 71 percent of the patients. In the myocytes of 58 patients, HIV nucleic acid sequences were detected by in situ hybridization, and active myocarditis was documented in 36 of the 58. Among these 36 patients, 6 were also infected with coxsackievirus group B (17 percent), 2 with cytomegalovirus (6 percent), and 1 with Epstein-Barr virus (3 percent).

Conclusions Dilated cardiomyopathy may be related either to a direct action of HIV on the myocardial tissue or to an autoimmune process induced by HIV, possibly in association with other cardiotropic viruses. (N Engl J Med 1998;339:1093-9.)

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THE acquired immunodeficiency syndrome (AIDS) represents a unique opportunity to study the relation between myocarditis and dilated cardiomyopathy.¹⁻⁸ Current hypotheses concerning the pathogenesis of cardiomyopathy associated with infection with the human immunodeficiency virus (HIV) include infection of myocardial cells with HIV type 1 (HIV-1) or coinfection with other cardiotropic viruses, postviral cardiac autoimmunity, autonomic dysfunction, and cardiotoxicity from illicit drugs and pharmacologic agents (such as nucleoside analogues and pentamidine).¹⁻¹⁰ HIV-1 genomic material has been demonstrated within cardiac myocytes in patients with congestive cardiomyopathy at autopsy and biopsy.⁸⁻¹⁰ Nevertheless, the pathogenesis of the heart-muscle disease in HIV infection is still unclear.¹¹ We report the results of a five-year follow-up study of a large, selected population of asymptomatic HIV-positive patients in which we evaluated the incidence of dilated cardiomyopathy echocardiographically over time, correlating the clinical features with immunologic and virologic data.

METHODS

Selection of Patients

In this prospective, long-term clinical study HIV-positive patients in New York Heart Association (NYHA) functional class I and Centers for Disease Control and Prevention (CDC) stage II¹² were eligible. The study protocol was approved by the institutional review board of the coordinating center of the study (Department of Infectious and Tropical Diseases, University of Pavia, Pavia, Italy). The research was carried out in accordance with the Declaration of Helsinki. The study protocol was explained to all the patients, and all the patients selected for the study gave their informed consent.

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The following were reasons for exclusion from the study: an age of less than 18 years; a CD4 count of less than 400 per cubic millimeter; use of illicit drugs or previous treatment with experimental drugs known to have a definite cardiotoxic action; previous treatment with antiretroviral or immunomodulating drugs or both; the presence of serious diseases not specifically related to HIV infection (diabetes, hypertension, rheumatic disease, and neoplastic diseases); a family history of cardiovascular diseases; a previous congenital or acquired heart disease (including mitral-valve prolapse); an ejection fraction, assessed by echocardiography, of less than 50 percent; and inability to provide informed consent.

During the follow-up period, antiretroviral treatment could be given if the CD4 count dropped below 400 cells per cubic millimeter. Zidovudine was given first. If patients showed signs of intolerance of zidovudine within one week after they began taking it, they were assigned to receive didanosine or zalcitabine. Similarly, pentamidine could be administered as prophylaxis against *Pneumocystis carinii* pneumonia if required. HIV infection was confirmed by two enzyme-linked immunosorbent assays and Western blot analysis. The diagnosis of AIDS was based on the CDC criteria.¹² An indirect immunofluorescence assay with monoclonal antibodies (Ortho Diagnostic Systems, Raritan, N.J.) was used for the CD4 count.

End Points and Data Collection

The incidence of dilated cardiomyopathy assessed by echocardiography and the detection of HIV in the myocardial cells of the patients with dilated cardiomyopathy were the end points of the study. Data regarding both clinical features and echocardiographic measurements were reported on the charts of the subjects selected for the study. Each chart was provided with a computer-generated identification code. All data from the centers affiliated with the Gruppo Italiano per lo Studio Cardiologico dei Pazienti Affetti da AIDS (GISCA) were filed by a centralized computerized system, and the data were then analyzed with use of a computerized data base by an independent investigator who was unaware of the subjects' status.

Clinical and Echocardiographic Studies

Clinical examination and a CD4 count were performed every three months, whereas electrocardiographic and echocardiographic examinations were performed every six months. Patients' functional classes were defined in accordance with the NYHA criteria. Heart failure was considered to be present if the patient met the NYHA criteria for functional class III or IV. Twelve-lead electrocardiographic recordings were made with a Hewlett-Packard PageWriter (model XLI M1705A, Hewlett-Packard, Palo Alto, Calif.). A Hewlett-Packard Sonos 500 (model 77020A) with either a 3.5-MHz or 5.0-MHz transducer was used for M-mode and B-mode echocardiographic and cardiac Doppler examinations. M-mode measurements were performed according to the recommendations of the American Association of Echocardiography.¹³ The average thickness of the left ventricular wall during diastole and left ventricular mass were calculated with use of a truncated ellipsoid formula.¹⁴ According to this formula, the left ventricular mass index in a normal man is 71 g per square meter, and the upper limit of the normal range is 94 g per square meter. Left ventricular volumes and ejection fractions were measured with a modification of Simpson's rule.^{15,16} With the use of this technique, the mean left ventricular end-diastolic volume index in a normal man is 58 ml per square meter, and the upper limit of the normal range is 80 ml per square meter. Echocardiographic Doppler measurements were based on standard procedures that have been described previously.¹¹

Echocardiographic Definition of Dilated Cardiomyopathy

Dilated cardiomyopathy was defined as the presence of diffuse left ventricular hypokinesia (ejection fraction, <45 percent) and dilatation (left ventricular end-diastolic volume index, >80 ml per square meter).¹⁶

Endomyocardial Biopsy

Biopsy specimens of right ventricular endomyocardium were obtained through the right internal jugular vein, under fluoroscopic control, with a Caves-Schultz biptome (Millar Instruments, Houston), with use of the Stanford technique.¹⁷ Five to eight samples measuring 1.5 to 3 mm³ were obtained from the middle-to-distal portion of the right ventricular septum.

Histologic and Immunohistologic Studies

The endomyocardial-biopsy samples were fixed in 10 percent buffered formalin and embedded in paraffin. Six serial sections were cut with a microtome (thickness, 4 to 5 μ m) and stained with hematoxylin and eosin. Specific stains (e.g., Gram's, Ziehl-Neelsen, and periodic acid-Schiff) were used to identify bacteria, fungi, and mycobacteria. Histologic findings were interpreted by two independent pathologists who were unaware of the patients' status. Immunoperoxidase staining of serial sections of the same paraffin-embedded tissue used for histologic analysis was performed with monoclonal antibodies to the leukocytes CD45 (CLA, Dako, Glostrup, Denmark), MB1 (pan-B cells, Clonelab, Denville, N.J.), and CD57 (Leu-7, Becton Dickinson, San Jose, Calif.). Frozen sections were used to identify other lymphocyte and antigen markers, including monoclonal antibodies to CD45 (HLe1, Becton Dickinson), CD3 (Ortho Diagnostics), CD2 (OKT11, Ortho Diagnostics), CD4 (Leu-3A, Becton Dickinson), CD8 (Leu-2, Becton Dickinson), CD11 (OKM1, Ortho Diagnostics), CD16 (Leu-11b, Becton Dickinson), and CD25 (interleukin-2 receptor, Becton Dickinson), and major histocompatibility complex (MHC) classes I and II (Becton Dickinson). The immunoperoxidase technique was performed according to the method of Beschorner et al.¹⁸

Definition of Myocarditis

A histologic diagnosis of active or borderline myocarditis was defined according to the Dallas criteria.¹⁹ In accordance with Beschorner et al.,¹⁸ a lymphocytic infiltrate was defined as a finding of more than 10 lymphocytes per high-power field (magnification, $\times 400$) with use of a microscope with wide-field, 10 \times eyepieces (diameter, 550 μ m; area, 2.4 μ m by 105 μ m; Olympus, Hamburg, Germany).

Microbiologic Study

Two to three endomyocardial-biopsy samples were not fixed in formalin and were processed for bacteriologic, mycologic, and virologic examination. Bacteriologic and mycologic examinations were performed according to conventional techniques.²⁰ The samples were assessed for cytomegalovirus by centrifugation culture (shell-vial assay) according to the method described by Woods et al.²¹ The samples were assessed for other cardiotropic viruses (coxsackievirus, adenovirus, herpesvirus, and Epstein-Barr virus) with the use of conventional cell cultures and specific enzyme immunoassays.²⁰

Detection of HIV in Myocardial Tissue

In situ DNA hybridization (with a mixture of ³⁵S-labeled RNA probes encompassing the entire HIV genome) was used to detect the presence of HIV in the myocardial tissue, according to the method described by Grody et al.⁹ Negative controls were derived from myocardial specimens obtained at autopsy from 25 HIV-negative patients without known heart disease. Positive controls were derived from HIV-infected lymphocyte cultures.

Statistical Analysis

Continuous data are expressed as means \pm SD. The chi-square test with Yates' correction and Fisher's exact test (for expected frequencies of less than 5) were used for analysis of categorical data.²² All computations were performed with Epi Info software (version 6, CDC, Atlanta).²³ All P values were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Characteristics of the Patients and Duration of Follow-up

The enrollment of patients began in January 1992. At that time, data on 2350 patients were recorded in the files of the study centers. Among them, 1328 were intravenous drug users and had symptoms of HIV infection (112 were in CDC stage III, 1201 were in CDC stage IVa, and 15 were in CDC stage IVd) and were thus excluded from the study. Another 70 patients did not fulfill the selection criteria because of preexisting cardiovascular or systemic diseases. A total of 952 HIV-positive subjects who were in CDC stage II fulfilled the selection criteria and were enrolled in the study. The general characteristics of these patients and their base-line echocardiographic measurements are given in Table 1. The executive committee decided to stop the study in May 1997. The mean duration of follow-up was 60 ± 5.3 months.

Clinical Evolution of HIV Disease

During the clinical follow-up, a CD4 count of less than 400 cells per cubic millimeter was documented in 181 patients a mean of 28 ± 12.1 months after enrollment. Ninety-one patients showed signs of intolerance of zidovudine (500 mg per day orally) within one week after they began taking it. Therefore, 46 were assigned to receive didanosine (4 mg per kilogram of body weight every 12 hours) and 45 were assigned to receive zalcitabine (0.75 mg every 8 hours). These patients did not switch to other antiretroviral treatments during the follow-up period. The other 90 patients continued the treatment with zidovudine until the end of follow-up.

In accordance with the CDC criteria, a diagnosis of AIDS was made in 12 patients (9 homosexual and 3 heterosexual). The mean time from the date of enrollment to the diagnosis of AIDS was 46.8 ± 7.8 months in these patients. Among them, two homosexual patients, without an echocardiographic diagnosis of dilated cardiomyopathy, died of *P. carinii* pneumonia 52 and 55 months after enrollment.

Incidence of Dilated Cardiomyopathy and Clinical Findings

During the follow-up period, an echocardiographic diagnosis of dilated cardiomyopathy was made in 76 patients, for a mean annual incidence rate of 15.9 cases per 1000 patients. In these patients, the diagnosis of dilated cardiomyopathy was made a mean of 28 ± 10.3 months after enrollment. Sixty-four patients were in NYHA functional class III, whereas 12 patients were in class IV. Patients with dilated cardiomyopathy had four-chamber enlargement and diffuse left ventricular hypokinesia at echocardiography, with a mean ejection fraction of 41 ± 2.1 percent (range, 38 to 44), an end-diastolic volume index of 95 ± 5.3 ml per square meter, an end-systolic volume index of 54 ± 8.7 ml per square

TABLE 1. GENERAL CHARACTERISTICS AND BASE-LINE ECHOCARDIOGRAPHIC FINDINGS OF THE 952 PATIENTS.

CHARACTERISTIC	VALUE*
Male sex — no. (%)	681 (71.5)
Mean age — yr	28
Age range — no.	
19–23 yr	456
24–37 yr	496
Homosexual — no.	322
Heterosexual — no.	317
Blood transfusion recipient — no.	313
CD4 count — cells/mm ³	670 ± 51.1
Mean duration of documented seropositivity — mo	12 ± 2.3
Left ventricular end-diastolic volume index — ml/m ²	57 ± 15
Left ventricular end-systolic volume index — ml/m ²	22.8 ± 12
Left atrial volume index — ml/m ²	37 ± 10
Average diastolic left ventricular wall thickness — cm	1.0 ± 2.5
Left ventricular mass index — g/m ²	73 ± 22
Left ventricular ejection fraction — %	55 ± 5.2
E wave:A wave ratio	1.1 ± 0.3
Integral of E-wave area — cm/sec ²	7.2 ± 1.2
Integral of A-wave area — cm/sec ²	4.3 ± 1.1
Integral of A-wave area/total area — cm/sec ²	0.31 ± 0.02
Isovolumetric relaxation time — msec	73 ± 15

*Plus-minus values are means \pm SD.

meter, a left ventricular mass index of 103 ± 22 g per square meter, and an isovolumetric relaxation time of 115 ± 12.7 msec. Seven patients showed slight-to-moderate pericardial effusion without symptoms or signs of cardiac tamponade. On electrocardiography, inverted P waves in lead V₁ indicative of left atrial enlargement were documented in 32 patients, ventricular ectopic beats in 17 patients, QRS voltage indicative of left ventricular hypertrophy with an inverted T wave in 12 patients (the J point was 1.5 mm or less in 8 patients and more than 1.5 mm in 4 patients), and left bundle-branch block in 8 patients.

Of the 12 patients who were given a diagnosis of AIDS, 4 had dilated cardiomyopathy. Of the 12 patients who were in NYHA functional class IV, 5 died of congestive heart failure a mean of 9 ± 2.1 months after the diagnosis of cardiomyopathy.

Histologic and Immunopathological Findings

All 76 patients with an echocardiographic diagnosis of dilated cardiomyopathy underwent endomyocardial biopsy within 1 month (range, 13 to 35 days) after the demonstration of cardiomyopathy. A histologic diagnosis of myocarditis was made in 63 patients (36 with active myocarditis and 27 with border-

line myocarditis) (Fig. 1). In the other 13 patients, microscopical study revealed areas of interstitial and perivascular fibrosis without an inflammatory-cell infiltrate. The inflammatory-cell infiltrates were predominantly CD3 lymphocytes in 12 patients and CD8 lymphocytes in 64 patients. Intense staining limited to MHC class I molecules was found in myocytes from 54 patients, whereas aberrant MHC class II staining was observed in 22 patients. CD57 cells were documented in 23 patients, whereas CD25 cells, B lymphocytes, natural killer cells, and monocytes were documented in 1 patient.

Microbiologic Findings

The cultures of endomyocardial-biopsy samples were negative for bacteria, fungi, adenovirus, and herpesvirus for all 63 patients with myocarditis. The cultures were positive for coxsackievirus group B in 15 patients (6 with active and 9 with borderline myocarditis), for cytomegalovirus in 4 patients (2 with active and 2 with borderline myocarditis), and for Epstein-Barr virus in 4 patients (1 with active and 3 with borderline myocarditis). In the 13 patients with no evidence of an inflammatory-cell infiltrate, the cultures were negative for bacteria, fungi, and viruses.

Detection of HIV in the Myocardial Cells of Patients with Dilated Cardiomyopathy

HIV was readily identified by in situ hybridization in the positive controls (HIV-infected lymphocyte

cultures). None of the negative controls (heart specimens obtained at autopsy from HIV-negative patients) showed a specific hybridization signal within myocytes and interstitial cells. A positive hybridization signal was detected in the myocytes of 58 study patients. In most cases, the staining was isolated, with one to four positive cells per section (Fig. 2). In 36 of 58 patients with a positive hybridization signal, active myocarditis was documented, although the positive myocytes were not surrounded by inflammatory cells. Among these 36 patients, 6 were also infected with coxsackievirus group B, 2 with cytomegalovirus, and 1 with Epstein-Barr virus.

Factors Associated with the Development of Dilated Cardiomyopathy

The extent of the immunodeficiency of the patients had a major role in the development of cardiomyopathy. In fact, an echocardiographic diagnosis of dilated cardiomyopathy was made in 5 patients with CD4 counts of at least 400 cells per cubic millimeter and in 71 patients with CD4 counts of less than 400 cells per cubic millimeter ($P < 0.001$). In 27 patients the CD4 count ranged from 300 to 399 cells per cubic millimeter, whereas in 44 it ranged from 200 to 299 cells per cubic millimeter ($P = 0.007$). Among patients with a CD4 count of less than 400 cells per cubic millimeter, the incidence of dilated cardiomyopathy was greater among those who received zidovudine. The use of other drugs with a potentially cardio-

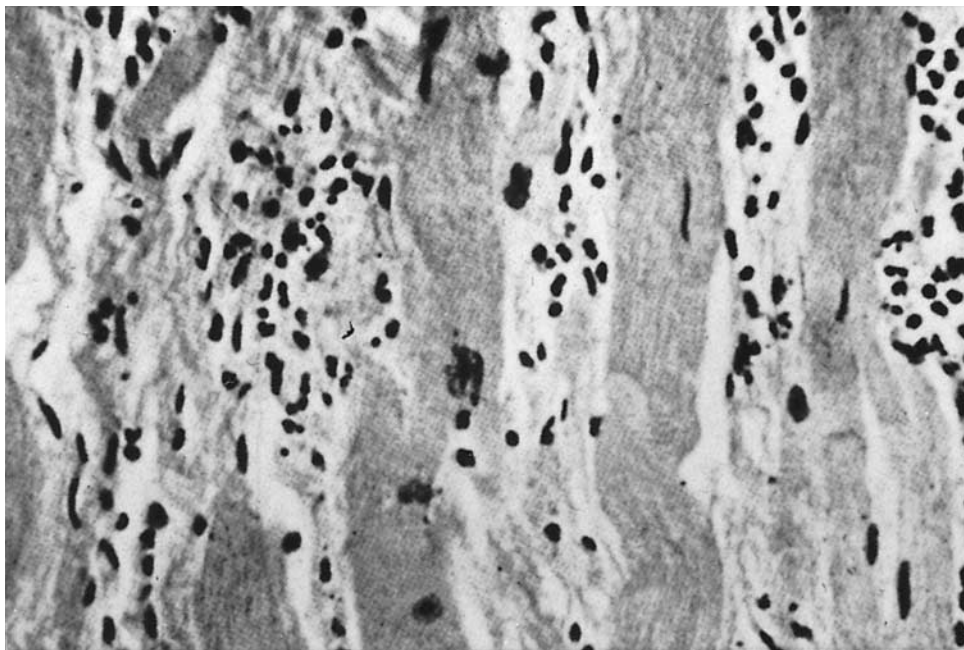


Figure 1. Light Photomicrograph of an Endomyocardial-Biopsy Specimen Demonstrating Active Myocarditis. A lymphocytic inflammatory infiltrate is present along with myocellular necrosis (hematoxylin and eosin, $\times 400$).

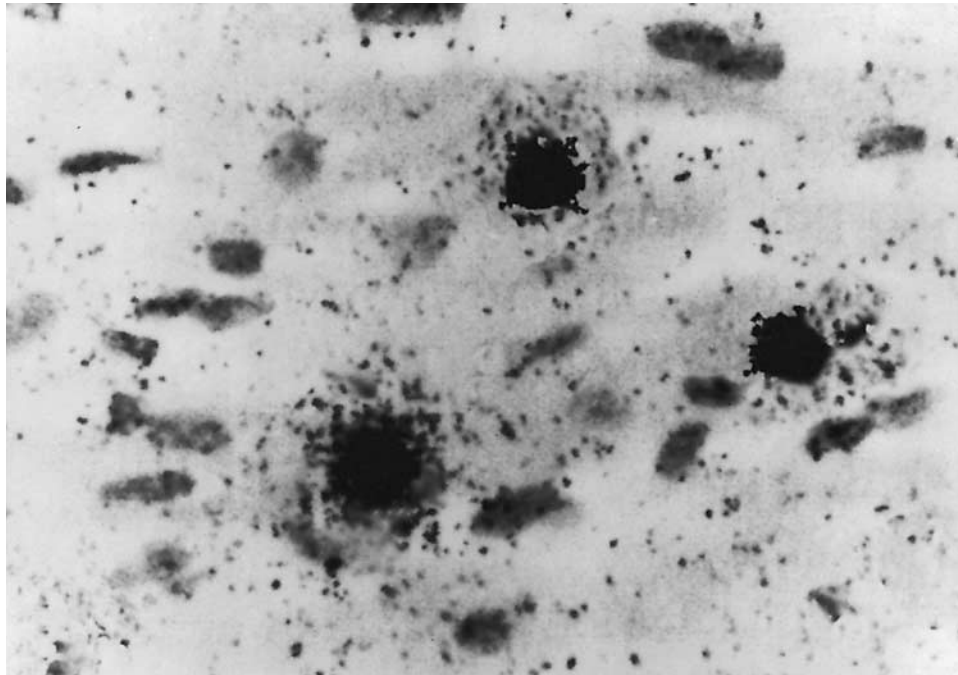


Figure 2. In Situ Hybridization of an HIV RNA Probe in a Section of Myocardial Tissue Obtained by Endomyocardial Biopsy in a Patient with Myocarditis.

There is intense staining within three myocytes that are not surrounded by inflammatory cells (hematoxylin and eosin, $\times 400$).

toxic action (e.g., pentamidine) did not significantly influence the incidence of dilated cardiomyopathy. In fact, of 12 patients with AIDS who received pentamidine as prophylaxis against *P. carinii* pneumonia, 3 patients, who also received zidovudine, had dilated cardiomyopathy. The demographic characteristics and risk factors for HIV infection of the patients with an echocardiographic diagnosis of dilated cardiomyopathy according to the CD4 count are shown in Table 2.

DISCUSSION

Several investigators have reported on the association between AIDS and dilated cardiomyopathy in clinical and pathological studies.^{5-8,10,24} In our long-term echocardiographic follow-up, the diagnosis of dilated cardiomyopathy was made in 8 percent of the subjects selected for the study. All patients with dilated cardiomyopathy were in NYHA functional class III (84 percent) or IV (16 percent).

The extent of immunodeficiency of the patients, as assessed by the CD4 count, influenced the incidence of dilated cardiomyopathy, with a higher incidence among patients with a CD4 count of less than 400 cells per cubic millimeter. Although some authors have described an association between the use of antiretroviral therapy with zidovudine and the development of cardiomyopathy,^{25,26} we believe that the extent of immunodeficiency has a major role in the development of cardiomyopathy. In fact, among

the patients who received zidovudine, the incidence of cardiomyopathy was greater in those with a CD4 count of less than 300 cells per cubic millimeter. Similarly, the difference observed in the incidence of dilated cardiomyopathy among the risk groups was influenced more by the extent of immunodeficiency than by the type of antiretroviral treatment.

The role of myocarditis in the development of dilated cardiomyopathy has not been fully characterized.^{4-8,20} Lymphocytic myocarditis can be found at autopsy in 46 to 52 percent of patients with AIDS, as reported in a review of the literature.⁶ In our study, a histologic diagnosis of myocarditis was made in 83 percent of the patients with dilated cardiomyopathy.

The presence of HIV in cardiac tissue has been documented by culture, Southern blotting, and in situ hybridization.^{8-10,20} Grody et al. detected HIV nucleic acid sequences in cardiac-tissue sections from 27 percent of the patients who were examined and who had died of AIDS.⁹ Herskowitz et al. detected positive hybridization signals for HIV-1 and cytomegalovirus in 15 percent and 48 percent, respectively, of patients with left ventricular dysfunction who underwent endomyocardial biopsy. The majority of them were found to have myocarditis on histologic and immunohistologic examination.⁸ We detected HIV nucleic acid sequences in 76 percent of the patients with dilated cardiomyopathy and in 57 percent of the patients with a histologic diagnosis of myocarditis.

TABLE 2. DEMOGRAPHIC CHARACTERISTICS AND RISK FACTORS FOR HIV INFECTION OF THE 76 PATIENTS WITH AN ECHOCARDIOGRAPHIC DIAGNOSIS OF DILATED CARDIOMYOPATHY, ACCORDING TO THE CD4 COUNT.*

VARIABLE	NO. OF PATIENTS	≥400 CD4 CELLS/mm ³	300–399	200–299
			CD4 CELLS/mm ³	CD4 CELLS/mm ³
			no. (%)	
Sex				
Male	47	4 (9)	17 (36)	26 (55)
Female	29	1 (3)	10 (34)	18 (62)
Age				
19–28 yr	39	3 (8)	13 (33)	23 (59)†
29–37 yr	37	2 (5)	14 (38)	21 (57)
Risk factors for HIV infection				
Homosexuality	49	4 (8)	21 (43)	24 (49)‡
Heterosexuality	25	1 (4)	5 (20)	19 (76)§
Blood transfusion	2	0	1 (50)	1 (50)
Antiretroviral treatment				
Zidovudine	51	0	19 (37)	32 (63)¶
Didanosine	11	0	4 (36)	7 (64)
Zalcitabine	9	0	4 (44)	5 (56)

*The P values are for significant differences in the incidence of cardiomyopathy both within each of the two groups of patients with a CD4 count of less than 400 cells per cubic millimeter and between these groups. All the P values for the differences in the incidence of cardiomyopathy between these two groups of patients and the group of patients with a CD4 count of ≥400 per cubic millimeter had an α level of less than 0.05 for the comparisons within each demographic and risk group. Because of rounding, not all percentages total 100.

†P=0.041 for the comparison with patients with a CD4 count of 300 to 399 cells per cubic millimeter.

‡P=0.048 for the comparison with heterosexuals with a CD4 count of 200 to 299 cells per cubic millimeter.

§P<0.001 for the comparison with heterosexuals with a CD4 count of 300 to 399 cells per cubic millimeter.

¶P=0.017 for the comparison with patients with a CD4 count of 300 to 399 cells per cubic millimeter who received zidovudine.

In view of the fact that we found myocarditis in 83 percent of the patients with dilated cardiomyopathy on histologic examination and that we found a positive hybridization signal in 57 percent of the patients with myocarditis, we believe that HIV has a direct action in inducing myocarditis and that there is a pathogenetic relation between myocarditis and dilated cardiomyopathy. Nevertheless, we did not detect a specific hybridization signal in 43 percent of the patients with myocarditis and we did not find myocarditis on histologic examination in 17 percent of the patients with dilated cardiomyopathy. Furthermore, in most cases the myocytes with a positive hybridization signal were sparse and were not surrounded by inflammatory cells. It has been suggested that the cardiac disease may be related either to a direct action of HIV on the myocardial tissue or to an autoimmune process induced by HIV, sometimes in association with other cardiotropic viruses.^{8,9,18,20,27} In fact, some cardiotropic viruses seem to have an important pathogenic role, since we detected other vi-

ruses (particularly, coxsackievirus group B) in 36.5 percent of the patients with myocarditis and in 15.5 percent of the patients with a positive hybridization signal. With the progression of HIV disease, the advanced state of immunodeficiency may enhance the pathogenic action of both HIV and other cardiotropic viruses and influence the clinical manifestations of the cardiomyopathy. Both cell-mediated and humoral immunity have been postulated to have a pathogenetic role in the initiation and progression of the viral cardiomyopathic process.²⁸ The presence of viral hybridization and increased myocardial expression of MHC class I molecules strongly suggest the presence of an active immune process within the myocardium. These findings are consistent with those previously reported by Herskowitz et al.⁸

The increasing occurrence of HIV-associated cardiomyopathy detected by autopsy studies and by echocardiographic findings strongly suggests that a careful cardiologic evaluation should be made to detect early involvement of the heart in HIV-positive patients.¹¹ Conventional treatment with digoxin, diuretics, and converting-enzyme inhibitors may help improve cardiac function, even in asymptomatic HIV-positive patients.¹¹ Further efforts should be made to elucidate the pathogenesis of HIV-associated cardiomyopathy and myocarditis. Studies of patients with AIDS and heart disease may also have important implications for patients with myocarditis and cardiomyopathy that are not caused by HIV.²⁹

APPENDIX

In addition to the authors, the members of the Gruppo Italiano per lo Studio Cardiologico dei Pazienti Affetti da AIDS were as follows (all in Italy): *University La Sapienza, Rome* — G. Giancaspro, M. Soldini, M. Ribersani, F. De Rosa; *Aurelia Hospital, Rome* — F. D'Andrea; *Polliclinico S. Matteo, Pavia* — W. Calderon, F. Cadario, G. Filice; *AIDS Center, Pavia* — M. Viani; *AIDS Center, Gorgonzola* — A. Lucchini, R. Vitali; *AIDS Center, Sesto S. Giovanni* — F. Leder; *AIDS Center, Magenta* — G. Monolo, E. Gola; *AIDS Center, Voghera* — G. Del Buono, P. Sambartolomeo, A. Salamone; *AIDS Center, Vigevano* — S. Edo, F. Barbieri; *AIDS Center, Abbiategrasso* — S. Lopez; *General Hospital, Novara* — G. Rizzo; *AIDS Center, Foggia* — B. Caccianotti, G. Salandra; and *AIDS Center, Lucera* — A. Catanzaro.

REFERENCES

1. Acierno LJ. Cardiac complications in acquired immunodeficiency syndrome (AIDS): a review. *J Am Coll Cardiol* 1989;13:1144-54.
2. Bestetti RB. Cardiac involvement in the acquired immune deficiency syndrome. *Int J Cardiol* 1989;22:143-6.
3. Levy WS, Simon GL, Rios JC, Ross AM. Prevalence of cardiac abnormalities in human immunodeficiency virus infection. *Am J Cardiol* 1989;63:86-9.
4. Reilly JM, Cunnion RE, Anderson DW, et al. Frequency of myocarditis, left ventricular dysfunction and ventricular tachycardia in the acquired immune deficiency syndrome. *Am J Cardiol* 1988;62:789-93.
5. Anderson DW, Virmani R, Reilly JM, et al. Prevalent myocarditis at necropsy in the acquired immunodeficiency syndrome. *J Am Coll Cardiol* 1988;11:792-9.
6. Kaul S, Fishbein MC, Siegel RJ. Cardiac manifestations of acquired immune deficiency syndrome: a 1991 update. *Am Heart J* 1991;122:535-44.
7. Baroldi G, Corallo S, Moroni M, et al. Focal lymphocytic myocarditis in acquired immunodeficiency syndrome (AIDS): a correlative morphologic and clinical study in 26 consecutive fatal cases. *J Am Coll Cardiol* 1988;12:463-9.
8. Herskowitz A, Wu T-C, Willoughby SB, et al. Myocarditis and cardiotropic viral infection associated with severe left ventricular dysfunction in

- late-stage infection with human immunodeficiency virus. *J Am Coll Cardiol* 1994;24:1025-32.
9. Grody WW, Cheng L, Lewis W. Infection of the heart by the human immunodeficiency virus. *Am J Cardiol* 1990;66:203-6.
 10. Calabrese LH, Proffitt MR, Yen-Lieberman B, Hobbs RE, Ratliff NB. Congestive cardiomyopathy and illness related to the acquired immunodeficiency syndrome (AIDS) associated with isolation of retrovirus from myocardium. *Ann Intern Med* 1987;107:691-2.
 11. 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. *AIDS Res Hum Retroviruses* 1996;12:1559-63.
 12. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. *MMWR Morb Mortal Wkly Rep* 1987;36:Suppl 1:3S-15S.
 13. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978;58:1072-83.
 14. Byrd BF III, Wahr DW, Wang YS, Bouchard A, Schiller NB. Left ventricular mass and volume/mass ratio determined by two-dimensional echocardiography in normal adults. *J Am Coll Cardiol* 1985;6:1021-5.
 15. Wahr DW, Wang YS, Schiller NB. Left ventricular volumes determined by two-dimensional echocardiography in a normal adult population. *J Am Coll Cardiol* 1983;1:863-8.
 16. Himelman RB, Chung WS, Chernoff DN, Schiller NB, Hollander H. Cardiac manifestations of human immunodeficiency virus infection: a two-dimensional echocardiographic study. *J Am Coll Cardiol* 1989;13:1030-6.
 17. Caves PK, Stinson EB, Billingham ME, Shumway NE. Percutaneous transvenous endomyocardial biopsy in human heart recipients: experience with a new technique. *Ann Thorac Surg* 1973;16:325-36.
 18. Beschoner WE, Baughman KL, Turnicky RP, et al. HIV-associated myocarditis: pathology and immunopathology. *Am J Pathol* 1990;137:1365-71.
 19. Aretz HT, Billingham ME, Edwards WD, et al. Myocarditis: a histopathologic definition and classification. *Am J Cardiovasc Pathol* 1987;1:3-14.
 20. Barbaro G, Di Lorenzo 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;41:1199-207.
 21. Woods GL, Young A, Johnson A, Thiele GM. Detection of cytomegalovirus by 24-well plate centrifugation assay using a monoclonal antibody to an early nuclear antigen and by conventional cell culture. *J Virol Methods* 1987;18:207-13.
 22. Armitage P, Berry G. *Statistical methods in medical research*. 3rd ed. Oxford, England: Blackwell Scientific, 1994.
 23. Dean AG, Dean JA, Coulombier D, et al. *Epi Info, version 6: manual: a word processing program for public health on IBM-compatible microcomputers*. Atlanta: Centers for Disease Control and Prevention, 1994.
 24. Cohen IS, Anderson DW, Virmani R, et al. Congestive cardiomyopathy in association with the acquired immunodeficiency syndrome. *N Engl J Med* 1986;315:628-30.
 25. Herskowitz A, Willoughby SB, Baughman KL, Schulman SP, Bartlett JD. Cardiomyopathy associated with antiretroviral therapy in patients with HIV infection: a report of six cases. *Ann Intern Med* 1992;116:311-13.
 26. Domanski MJ, Sloas MM, Follmann DA, et al. Effect of zidovudine and didanosine treatment on heart function in children infected with human immunodeficiency virus. *J Pediatr* 1995;127:137-46.
 27. Herskowitz A, Willoughby S, Wu T-C, et al. Immunopathogenesis of HIV-1-associated cardiomyopathy. *Clin Immunol Immunopathol* 1993;68:234-41.
 28. Woodruff JF. Viral myocarditis: a review. *Am J Pathol* 1980;101:425-84.
 29. Factor SM. Acquired immune deficiency syndrome: the heart of the matter. *J Am Coll Cardiol* 1989;13:1037-8.

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