A clinical approach for cardiovascular monitoring of HIV-infected patients. Results from an observational cohort study

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Background. **HIV infection is one of the leading causes of acquired heart disease. Because of its high diffusion, systematic echocardiographic monitoring has been proposed to exclude cardiovascular involvement in these patients. The aim of this study was to evaluate an alternative clinical approach by which echocardiographic screening is limited to patients with a clinical suspicion of heart disease.**

Methods. **We studied 2030 consecutive HIV-infected patients admitted to a tertiary referral hospital (group A). History, physical examination, ECG, and chest X-ray were used to screen HIV-infected patients for cardiovascular involvement. Selected patients were extensively studied, first of all by echocardiography. Cardiovascular and non-cardiovascular deaths were recorded.**

Results. **Cardiovascular involvement was clinically suspected in 201 patients (9.9%; group B). Among them a higher extracardiac mortality was found in presence of pericardial disease (odds ratio [OR] 4.27, 95% confidence interval [CI] 2.01-9.09), while a higher cardiovascular mortality was recorded for patients with cardiomyopathy or myocarditis (OR 2.72, 95% CI 1.09-6.81), and right ventricular dysfunction and/or pulmonary hypertension (OR 4.67, 95% CI 1.44-15.2). Compared with group A, patients in group B had a significantly increased cardiac death rate (0.114 vs 0.018, p < 0.001). A positive echocardiogram slightly increased this rate (from 0.114 to 0.164, p = NS), whereas a negative echocardiogram significantly decreased the cardiac death rate (0.015 vs 0.164, p = 0.004).**

Conclusions. **Clinical selection of HIV-infected patients with suspected cardiovascular involvement may help identify patients with higher frequency of cardiovascular involvement. Among these patients, echocardiography may be a useful screening tool in those at high risk for cardiovascular death.**

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Cardiac abnormalities were discovered early, even before the etiologic agent of AIDS, the HIV, was isolated. Patients with AIDS can have cardiac pathology related to primary involvement, opportunistic infections and tumors or secondary to specific treatment for HIV infection.

In the first reported series, cardiac involvement in HIV-infected patients was noted in 25 to 73% of cases according to study methodology (autopsy series or echocardiographic studies), patient selection and disease progression[1-4]. Patients with HIV infection can have a variety of cardiovascular manifestations. The most common clinical manifestation of cardiovascular disease in patients with AIDS is acute pericarditis; other common cardiac manifestations are pulmonary vascular disease and pulmonary hypertension, valvular disease, myocarditis, cardiomyopathy, and increased incidence of coronary artery disease. Most of these patients have AIDS, but echocardiographic anomalies were also reported in asymptomatic HIV-infected patients. Many of the studies of cardiovascular disease were performed before the availability of highly active antiretroviral therapy; thus, the applicability of some of the following observations to current practice is often uncertain. In more recent series[5,6] clinical relevant cardiac involvement was reported in less than 10% of cases.

Nowadays HIV infection is one of the leading causes of acquired heart disease and specifically of symptomatic heart failure. Many believe that with the prolongation of life, thanks to a more aggressive medical management, clinical cardiovascular involvement will become more prevalent[7-9].

Because of the high diffusion of HIV infection, some authors proposed for the care

of HIV-infected adults and children a routine, systematic evaluation including history, cardiac examination and systematic echocardiographic monitoring, since asymptomatic cardiac disease may be fatal and cardiac symptoms can often be confounded by secondary effects of HIV infection[10]. However, cost-efficacy and cost-effectiveness of this approach have not extensively been evaluated. Moreover, another possible approach is to consider history and physical examination as the best screening tools for cardiovascular involvement in HIV-infected patients and to avoid routine echocardiography. Our experience is based on a clinical approach to HIV-infected patients, looking for signs and symptoms of possible cardiovascular involvement. History and physical examination were used to screen HIV-infected patients for cardiovascular involvement and, to this purpose, selected patients were extensively studied first of all by echocardiography.

The aim of this study was to evaluate the validity of this clinical approach without routine echocardiographic screening.

Methods

Patients. From 1993 to 2001 we studied 2030 consecutive HIV-infected patients (group A) admitted to the Amedeo di Savoia Hospital, Regional Infective Disease Center in Turin, Italy. HIV infection was classified according to the 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults[11]. Therefore, AIDS patients were those included into categories C1-C2-C3. The 1993 definition of AIDS includes all the AIDS-indicator diseases in the 1987 version with three additions: recurrent bacterial pneumonia, invasive cervical cancer, and pulmonary tuberculosis. The most relevant change in the classification was the inclusion of all patients with a CD4 cell count < 200/mm^3. A detailed list of AIDS-indicator diseases can be found in the reported 1993 revised classification system[11] (full-text available at www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm). Patients with AIDS were 1370 (67.5%).

Among them CD4+ was 63.28 ± 82.48 cells/μl, while CD4+ was 362.73 ± 150.69 cells/μl in HIV-infected patients ($p < 0.001$).

Cardiovascular monitoring. History, electrocardiographic and physical examinations were used to screen patients for cardiovascular involvement in HIV-infected patients. Patients with suspected cardiovascular disease underwent echocardiography (group B). Exercise stress test and coronary angiography were performed in selected HIV-infected patients with suspected angina pectoris or silent ischemia.

Suspected cardiac involvement was studied by transthoracic echocardiography using Hewlett Packard Sonos 2500 or Philips 5500; transesophageal echocardiography was limited to selected cases with poor transthoracic echocardiographic window. Echocardiographic measurements were performed according to the American Society of Echocardiography criteria. Pulmonary hypertension was identified as a systolic pulmonary arterial pressure > 40 mmHg, which corresponds to a tricuspid regurgitant velocity on Doppler echocardiography of 3.0-3.5 m/s[12,13].

We performed a 6-month follow-up recording cardiac deaths in the whole population of HIV-infected patients (group A) and cardiac involvement, clinical status, cardiovascular and non-cardiovascular deaths in the selected group of HIV-infected patients with a clinical suspicion of cardiovascular involvement (group B). In this group, patients with AIDS were identified as group B1 and patients without AIDS as group B2.

Results are expressed as mean ± SD or proportions. Continuous variables were analyzed using paired Student's t-test, whereas discrete variables were studied using the χ^2 test. Odd ratios (OR) were calculated with 95% confidence intervals (CI).

Results

Patients. We suspected a cardiovascular involvement by history, physical examination, electrocardiography, and chest X-ray in 201 patients (about 10% of all cases) who underwent echocardiography according to our study protocol. Mean age was 35.3 ± 7.6 (range 21-56 years), 131 males (male/female ratio of 1.9), 163 patients (81.0%) were drug users, 124 (61.7%) had AIDS (group B1). Eighty of 201 patients (39.8%) were treated with highly active antiretroviral therapy (HAART): 21 patients were HIV-infected, while 59 had AIDS. In group B1, 87 patients were drug addicts, and sexual transmission was the cause of HIV infection in the others. Moreover we recorded 12 cases (9.7%) of tuberculosis, 24 cases with lymphomas treated with chemotherapy (19.4%).

Cardiovascular monitoring. Main results of the echocardiographic screening of HIV-infected patients with a clinical suspicion of cardiovascular involvement are reported in tables I and II.

In group B pericardial effusion was more frequently detected in patients with AIDS (group B1) than in HIV-infected patients (group B2, 29.8 vs 7.8%, $p < 0.001$); the same observation held true also for frequency of myocardial disease (28.0 vs 10.0%, $p < 0.01$). Eight patients out 43 with pericardial effusion (18.5%) (6 with light effusion) had a history of tuberculosis and 19 (44%) of opportunistic infections. Twelve patients out 43 with myocardial disease (28%) had a history of lymphomas treated with chemotherapy; 27 (63%) had opportunistic infections.

A comparison between patients with AIDS and HIV-infected patients is reported in table III. Treatment with

Table I. Echocardiographic screening of HIV-infected patients with clinical suspicion of cardiovascular involvement.

Normal	67 (33.3%)
Pericardial effusion	43 (21.4%)
Cardiomyopathy	29 (14.4%)
Myocarditis	14 (7.0%)
Infective endocarditis	23 (11.4%)
RV dilation and PH	15 (7.5%)*
Isolated RV dilation	2 (1.0%)
Masses	6 (3.0%)
Valvular disease	32 (15.9%)

PH = pulmonary hypertension; RV = right ventricular. * 9 patients had left ventricular dysfunction.

HAART was mainly undertaken after 1997. In this study this treatment involved a minority of patients and for a limited time. On this basis, although we did not record cases with cardiovascular disease related to HAART, this study was not designed to provide data on this topic.

After a mean follow-up of 6 months, we recorded 36 cardiac deaths (1.8%) in the whole population of HIV-infected patients (group A) and 23 cardiac deaths (11.4%) in the group of HIV-infected patients with a clinical suspicion of cardiovascular involvement (group B, $p < 0.001$); there were no deaths in group B2. Thirteen deaths were recorded in patients not submitted to echocardiographic evaluation. Among them, 2 cases were due to fulminant myocarditis, 1 to sudden cardiac death, and the majority to end-stage heart failure.

Clinical status of HIV-infected patients with a clinical suspicion of cardiovascular involvement according to cardiac disease subgroups is reported in table IV.

After analysis of subgroup mortality we observed a higher extracardiac mortality in the presence of pericardial disease (OR 4.27, 95% CI 2.01-9.09), whereas a higher cardiovascular mortality was recorded for patients with cardiomyopathy or myocarditis (OR 2.72, 95% CI 1.09-6.81) and right ventricular dysfunction and/or pulmonary hypertension (OR 4.67, 95% CI 1.44-15.2).

Compared with group A (Fig. 1), patients in group B had a significantly increased cardiac death rate (0.114 vs 0.018, $p < 0.001$). A positive echocardiogram slightly increased this rate (from 0.114 to 0.164, p = NS), whereas a negative echocardiogram significantly decreased cardiac death rate (0.015 vs 0.164, p = 0.004). The cardiac death rate of patients in group B with a negative echocardiogram is similar to the cardiac death rate found in the general population of HIV-infected patients (0.015 vs 0.018, p = NS).

Table III. Comparison of cardiovascular involvement type between patients with AIDS and HIV-infected patients.

	AIDS (n=124)	HIV-infected (n=77)	p
Normal	37 (29.8%)	30 (39.0%)	NS
Pericardial effusion	37 (29.8%)	6 (7.8%)	< 0.001
Cardiomyopathy or myocarditis	35 (28.0%)	8 (10.0%)	< 0.01
Infective endocarditis	10 (8.1%)	13 (16.9%)	NS
RV dilation and PH	11 (8.9%)	4 (5.2%)	NS
Isolated RV dilation	1 (0.8%)	1 (1.3%)	NS
Masses	5 (4.0%)	1 (1.3%)	NS
Valvular disease	22 (17.7%)	10 (13.0%)	NS

PH = pulmonary hypertension; RV = right ventricular. A p value of < 0.05 was considered statistically significant.

Discussion

Nowadays HIV infection is one of the leading causes of acquired heart disease and specifically of symptomatic heart failure. Cardiac complications tend to occur later and could become more prevalent as therapy and survival improve. Asymptomatic cardiac disease may be fatal and cardiac symptoms can be sometimes confounded by secondary effects of HIV infection[10,14]; thus, some authors recommended a routine systematic cardiac evaluation including history, cardiac examination and systematic echocardiographic monitoring[10].

However, prospective studies for the evaluation of the efficacy and cost-effectiveness of this strategy are lacking. Our clinical approach to cardiac monitoring of

Table II. Highly active antiretroviral therapy (HAART) and associated diseases in group B.

	HAART	Tuberculosis	Lymphomas	Opportunistic infections	Cirrhosis
No cardiovascular involvement (n=67)	33	–	8	21	16
Pericardial effusion (n=43)	16	8 (6 mild)	6	19	6
Cardiomyopathy (n=29)	9	3	6	18	2
Myocarditis (n=14)	3	–	6	9	1
Infective endocarditis (n=23)	7	2	1	5	2
RV dilation and PH (n=15)	9	1	4	9	–
Isolated RV dilation (n=1)	–	–	–	1	–
Masses (n=6)	–	–	–	–	2
Valvular heart disease (n=35)	10	3	6	10	1

PH = pulmonary hypertension; RV = right ventricular.

Table IV. Follow-up in HIV-infected patients with clinical suspicion of cardiovascular involvement and after echocardiography: cardiac disease subgroups.

	Cardiac death (n=23)	Extracardiac death (n=96)	Alive (n=82)
No cardiac involvement	1 (0.5%)	21 (10.5%)	46 (22.9%)
Pericardial disease	6 (3.0%)	32 (15.9%)	5 (2.5%)
Infective endocarditis	2 (1.0%)	4 (2.0%)	17 (8.5%)
Cardiomyopathy and myocarditis	9 (4.5%)	20 (10.0%)	14 (7.0%)
RV dilation and PH	5 (2.5%)	3 (1.5%)	7 (3.5%)
Valve regurgitation	0	13 (6.5%)	19 (9.5%)
Other	0	3 (1.5%)	5 (2.5%)

Percentages are calculated from the total number of patients in this group (n = 201). PH = pulmonary hypertension; RV = right ventricular.

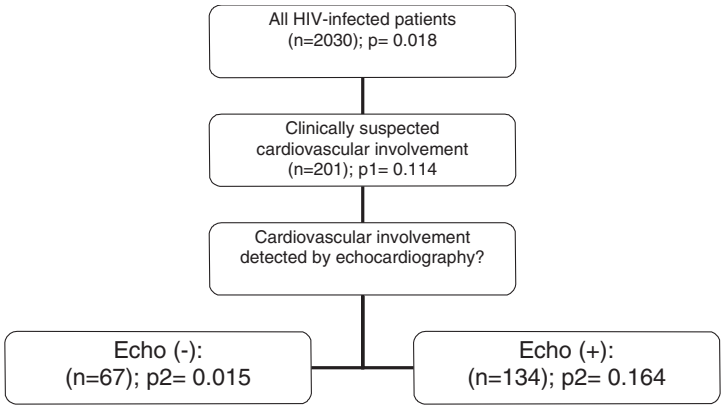

Figure 1. *Cardiac death rate in the general population of HIV-infected patients (p) and in patients with clinically suspected cardiovascular involvement with (p1) and without (p2) echocardiographic screening.*

HIV-infected patients is based on clinical selection of patients with suspected cardiac involvement. These patients are extensively studied first of all by echocardiography.

In our survey this clinical approach selected 201 cases of suspected cardiac involvement (about 10% of all cases) among 2030 HIV-infected patients. Among selected cases we found cardiac involvement in 134 cases (67.0% of selected cases, 6.6% of all cases). In this group the most frequent echocardiographic abnormality was pericardial effusion with or without pericarditis in 21.4% of cases, as already reported in previous studies[15-17]. Pericardial involvement was more frequently observed in patients with AIDS (29.8 vs 7.8%, $p < 0.001$). The development of pericardial effusion was a bad prognostic sign with a higher extracardiac mortality risk (OR 4.27, 95% CI 2.01-9.09). Also in our study pericardial effusion rarely directly contributed to mortality but was a marker of advanced HIV infection[16,18,19].

The second most common cardiac abnormality was dilated cardiomyopathy, which was detected in 14.4% of cases as similarly reported in some studies[14,20]. In our study patients with AIDS had a higher frequency of myocardial disease (28.0 vs 10.0%, $p < 0.01$). Myocardial disease (cardiomyopathy and myocarditis) is associated with higher cardiac mortality (OR 2.72, 95% CI 1.09-6.81) as well as right ventricular dilation with pulmonary hypertension (OR 4.67, 95% CI 1.44-15.2), another well known bad prognostic marker in HIV-infected patients[21].

In the general population of HIV-infected patients (group A) the cardiac death rate was 0.018. Clinical screening of these patients was able to identify a selected group (group B) with an increased cardiac death rate (0.114, $p < 0.001$). In this group echocardiographic screening identified specific cardiovascular involvement in 134 cases with an increased cardiac death rate for this subgroup. Compared with group A (Fig. 1), patients in group B had a significantly increased cardiac death rate (0.114 vs 0.018, $p < 0.001$). A positive echocardiogram was associated with a slight increase in this rate (from 0.114 to 0.164, p = NS), whereas a negative echocardiogram was significantly associated with a decreased cardiac death rate (0.015 vs 0.164, p = 0.004). Cardiac death rate of patients in group B with a negative echocardiogram was similar to the cardiac death rate found in the general population of HIV-infected patients (0.015 vs 0.018, p = NS).

In this study simple clinical screening was able to detect a group of HIV-infected patients at high cardiovascular risk, whereas the subsequent echocardio-

graphic screening was able to detect specific type of cardiovascular involvement or to exclude cardiac abnormalities. Patients without echocardiographic involvement were at very low risk for cardiac death in our study (not different from the general population of HIV-infected patients).

In conclusion, clinical examination is the best screening tool for cardiovascular involvement in HIV-infected patients. There are no advantages in finding subclinical disease. According to this strategy, echocardiography is not indicated routinely and is restricted to a selected group of HIV-infected patients with a clinical suspicion of cardiovascular involvement. Detection of pericardial effusion, myocardial disease or right ventricular dilation with pulmonary hypertension has prognostic implications.

Study limitations. The main study limitation is to be an observational cohort study with the lack of a control group. Although the results of this study are clearly not conclusive, randomized trials are lacking in this field and this is the first study to test a clinical approach to screening of cardiovascular involvement in HIV-infected patients. Future research and a randomized trial on this subject will better reply to the question of how to monitor cardiovascular involvement in HIV-infected patients.

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