Impact of Human Immunodeficiency Virus Infection on Cardiovascular Disease in Africa

Mpiko Ntsekhe, MD; James Hakim, FRCP

Background—Human immunodeficiency virus (HIV) infection is the single greatest health challenge facing Africa today. However, the impact of the HIV epidemic on the cardiovascular system in Africans has received scant attention in the world literature.

Methods and Results—We searched MEDLINE (January 1, 1980, to December 31, 2004) and reference lists of literature on HIV and the heart in Africa and contacted experts in the field. The search for this review yielded 22 articles involving HIV and the cardiovascular system from 8 countries in Africa.

Conclusions—The available information suggests that there are unique features in the etiology, presentation, and spectrum of HIV-associated cardiovascular disorders in people living in Africa. First, pericardial disease may be the initial manifestation of HIV infection in the early stages of the illness. Second, the etiology of cardiac disease tends to reflect the prevalent infectious diseases, such as tuberculosis. Third, unique cardiovascular disorders such as aneurysm of large vessels have been reported in association with HIV infection in several parts of Africa. Finally, the HIV/AIDS pandemic has put pressure on the meager healthcare resources and fragile infrastructure in many African countries, making the diagnosis and treatment of heart disease unrelated to HIV even more difficult. (Circulation. 2005;112:3602-3607.)

Key Words: AIDS ■ cardiomyopathy ■ pericarditis ■ pulmonary heart disease ■ Africa

Africa is home to the majority of the world’s HIV (human immunodeficiency virus)–infected population.3 Despite this, very few of the recent reviews on the cardiovascular manifestation of HIV have systematically examined the African experience.2–9 Much of the work described in the literature was conducted before highly active antiretroviral therapy (HAART) became available. Given that most HIV-infected patients in Africa do not have access to HAART,1 this body of work serves as a useful frame of reference to compare with the African experience of HIV-associated cardiac disease.

This report reviews the epidemiology and clinical spectrum of HIV-associated cardiovascular disease encountered in Africa, with emphasis on areas where the African experience has been different from that described elsewhere; the prognostic implication of HIV-related cardiovascular disease in Africans; and the extent to which HIV has had an impact on the management of non–HIV-related cardiac disease. We searched MEDLINE (January 1, 1980, to December 31, 2004) and reference lists of literature on HIV and the heart in Africa and contacted experts in the field. The search for this review yielded 22 articles involving HIV and the cardiovascular system from 8 countries in Africa (Figure 1). The majority of the articles examined aspects of pericardial disease in HIV-infected African patients.10–18 The remainder described the prevalence, clinical spectrum, and unusual features of cardiac disease in HIV-infected patients.19–32

We review and discuss the available African literature on pericardial disease, cardiomyopathy, and vascular disease. We also address other HIV-associated cardiovascular manifestations, such as endocarditis, pulmonary hypertension, and coronary disease. Finally, we highlight the impact of the HIV epidemic on health services in Africa.

Pericardial Disease

In the pre-HAART era, pericardial effusions were common in people with advanced HIV disease. The annual incidence of pericardial effusions in asymptomatic patients with AIDS was reported as 11%.33 The presence of pericardial effusion conferred a relative risk for mortality of 2.2 compared with CD4-matched controls.33 The cause of pericardial effusion in the majority of HIV-infected patients living in industrialized countries is idiopathic.33 By contrast, in Africa, the majority of pericardial disease in HIV-infected people is caused by treatable microorganisms.8 Mycobacterium tuberculosis (M tuberculosis) has been found to be the cause of pericardial disease in 86% to 100% of HIV-infected patients in Africa.11,13,16 These studies suggest that mycobacteria other than tuberculosis are rarely causative.11,13,16 Important alternative
cardiomyopathy or myopericarditis in HIV-infected patients.15 Niakara et al15 noted that the prevalence of cardiomyopathy in their retrospective analysis of patients hospitalized with pericarditis was 40%. In the pre-HIV era, antituberculosis chemotherapy was associated with a mortality of 8% to 17%, whereas a recent prospective study of patients with tuberculous pericarditis and HIV reported a mortality of 17% to 34%.12 The impact of HIV infection on the clinical course and outcome of tuberculous pericarditis is being explored in the Investigation of the Management of Pericarditis in Africa (IMPI Africa) Registry, which is expected to report its findings in the near future.18

Cardiomyopathy
In the developed world, postmortem and echocardiography studies suggest that the prevalence of HIV-associated cardiomyopathy in the pre-HAART era was 30% to 40%, and the annual incidence was 15.9 per 1000 patients.6 In Africa, cross-sectional echocardiographic studies of outpatient and inpatient HIV-infected patients suggest a prevalence of cardiomyopathy of 9% to 57%.21,29,30,32 Only 1 study followed ambulant patients prospectively,24 and it reported an incidence of 16.9% over 18 months.24 Varying study designs and populations and the lack of a common definition for HIV-associated cardiomyopathy may account in part for the wide range of observed prevalence rates. The fact that left ventricular dysfunction is common in acutely ill patients even outside the setting of HIV may also have distorted the prevalence rates.39

HIV-associated cardiomyopathy has been shown to be associated with more advanced immunosuppression and lower CD4 lymphocyte counts and is independently associated with death. A study from Scotland noted that the median survival to AIDS-related death is 101 days in patients with dilated cardiomyopathy as opposed to the 472 days in their CD4-matched controls.40 Cardiomyopathy was strongly associated with CD4 counts <100×10^6/L. A recent study from Cameroon demonstrated a similar relationship between the degree of immunosuppression and the likelihood of cardiomyopathy.30 Interestingly, a CD4 count of 100×10^6/L proved to be the important threshold in that study as well.30 The prognostic implication of the diagnosis of cardiomyopathy in HIV-infected Africans is not as clear and may be different. Among 133 Congolese patients with cardiomyopathy reviewed retrospectively over a 10-year period, the reported overall mortality was 15% to 20%.32 In a study on the determinants of survival in HIV-positive patients with cardiac involvement from the Democratic Republic of Congo (DRC), cardiomyopathy was associated with a slower progression to AIDS and death.25 The average CD4 count in that study was high (>700×10^6/L) at enrollment, which suggests that the apparent protection against progression to AIDS may have been an epiphenomenon and should be interpreted with caution. In the absence of a carefully conducted study with strict exclusion and inclusion criteria and that is free of any biases that may be present in some of the above studies, it is very difficult to link cardiomyopathy to HIV status or CD4 counts and separate it from comorbid conditions.

There are limited data on the pathogenesis of cardiomyopathy in HIV-infected individuals in Africa. Information on cardiac histology is available from 16 patients from the DRC.25 All 16 patients had histopathological evidence of myocarditis. The cause of the myocarditis was Toxoplasma gondii in 3 (18.75%) of 16, Cryptococcus neoformans in another 3 (18.75%), Mycobacterium avium intracellulare in 2 (12.5%), and direct HIV invasion in the remainder (50%). Although it is difficult to extrapolate these results to larger
Classification of HIV-Associated Vascular Disease

<table>
<thead>
<tr>
<th>Group I</th>
<th>Vasculitides that are well described in the non-HIV population and coincidently occur in HIV-infected people</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group II</td>
<td>Vasculitides related to adverse effects of antiretroviral drugs</td>
</tr>
<tr>
<td>Group III</td>
<td>Vasculitides related to known infectious agents such as cytomegalovirus that are more common in immunosuppression</td>
</tr>
<tr>
<td>Group IV</td>
<td>Vasculitides that appear to have an association with HIV, have unusual clinical presentations that do not fit into previously described disease entities, and have diverse histopathological features that do not represent a single disease entity</td>
</tr>
</tbody>
</table>

populations of patients with HIV cardiomyopathy, it is noteworthy that there was such a significant proportion of opportunistic infectious causes. By contrast, opportunistic infectious diseases were not a common cause of myocarditis in the pre-HAART era in the developed world, where cardiotropic viruses were implicated in the majority of cases.2,4

There has been a significant reduction of HIV-associated cardiomyopathy in the HAART era.41 One Italian study reported the prevalence at 1.8%, an almost 7-fold reduction from the pre-HAART era.41 There is no conclusive evidence that HAART reverses cardiomyopathy, but it does appear that by preventing profound immunosuppression and the development of AIDS, heart muscle remains healthier.41

Vascular Disease

Estimates from outside Africa are that the incidence of HIV-associated vasculitis is less than 1%.42 HIV-associated vascular disease is classified into 4 groups, as outlined in the Table.42 Group IV large-vessel vasculopathy involving the aorta or its major branches is increasingly being recognized in young African patients (mean age 31 years) who have no evidence of atherosclerosis, syphilis, or another cause for vasculitis and occurs at a relatively early stage of HIV disease (median CD4 count 370×10^9/L; Figure 2).26–28,31,43 Typical histological features are a lymphocytic and monocytic inflammatory infiltrate of the endothelium and vasa vasorum, which results in a fibro-occlusive pattern with luminal narrowing and dilatation.20 This pathological process has been described as either an idiopathic focal necrotizing vasculitis associated with aneurysm formation or a granulomatous vasculitis with fibroproliferative vascular occlusion.26

Clinically, the majority of patients present with growing masses that may or may not be painful. Occasionally, patients present due to symptoms related to compression of surrounding tissue with peripheral neuropathies, dysphagia, and abdominal pain.27 A few of the cases also involved the left ventricle.26 Management is conservative, with only the occasional patient requiring surgery.27,28,43

Other Cardiovascular Manifestations: Coronary Artery Disease, Infective Endocarditis, and Pulmonary Hypertension

There is a paucity of literature addressing coronary artery disease, infective endocarditis, and pulmonary hypertension in HIV-infected patients in Africa. However, in view of experience elsewhere in the world, the absence of systematic documentation of the scope of these problems in Africa should not diminish their potential impact or importance.

HIV can affect coronary arteries by several mechanisms. It can initiate an inflammatory response in the coronary vasculature, which may induce endothelial dysfunction and promote atherosclerosis.44 Using in situ hybridization, HIV-1 genomic sequences have been found in the coronary vessels of HIV-infected patients who died of coronary arteritis and acute myocardial infarction.45 Furthermore, there is an association between the use of protease inhibitor antiretroviral drugs and coronary artery events.46 The high background prevalence of conventional risk factors for coronary artery disease where the issue has been addressed has made it difficult to demonstrate a firm link.46 A large prospective, observational study concluded that combination antiretroviral drugs were independently associated with a small but significant increase in coronary events but that the bulk of the attributable risk was related to conventional risk factors.47 Coronary disease is relatively uncommon among black Africans at present, but with the ongoing rapid urbanization of many African societies, this may soon change.48 In light of the much publicized World Health Organization 3×5 initiative, in which by the end of 2005 it is hoped that 3 million people in lower- and middle-income countries will be provided with HAART,1 the issue of coronary disease in HIV-infected individuals receiving HAART may become more important in the near future.

HIV infection is not associated with an increased risk of infective endocarditis. In a South African prospective obser-
vational study that examined the risk factors for infective endocarditis, only 1 of their cohort of 92 patients was HIV seropositive.23 The main risk factors included rheumatic valve disease in 76%, congenital heart disease, the presence of prosthetic valves, and a history of infective endocarditis.23 Of 83 consecutive HIV-infected patients with cardiac disease in the DRC, only 1.2% had infective endocarditis.24 Given the high prevalence of both HIV and rheumatic valvular heart disease in Africa, future prevalence studies may find that a significant proportion of patients with infective endocarditis and underlying rheumatic valvular disease are coincidentally HIV infected.

In regions of the world where the use of intravenous drugs is high (unlike Africa), the prevalence of infective endocarditis has been reported to be as high as 34% in HIV-seropositive cohorts.6 Right-sided valves are most commonly involved, and the predominant organism is Staphylococcus aureus (75% of cases). There may also be a higher incidence of Gram-negative organisms and fungi.59 The prognosis is similar to that in HIV-uninfected patients unless there is involvement of the left-sided valves, the CD4 count is ≤200/µL, or Gram-negative organisms or fungi are involved.40,50 Finally, friable endocardial vegetations known as nonbacterial thrombotic endocarditis were noted in 3% to 5% of patients in Western series in the pre-HAART era.6 The disorder, which has a predilection for patients with the wasting syndrome, has not been described in Africa.

Data from the developed world suggest that HIV-associated pulmonary hypertension has a prevalence of 1/200 compared with 1/200 000 in the general population.9 The few available prevalence studies from Burkina Faso and Zimbabwe suggest rates of 0.6% to 5%. Pulmonary hypertension was much more common in hospitalized as opposed to ambulant patients.21,29 Pulmonary vessel endothelial cell proliferation and vasoconstriction triggered by pleomorphic cytokines (eg, endothelin-1, interleukin-6, and tumor necrosis factor-a) released by HIV-infected pulmonary macrophages and dendritic cells are central to the pathogenesis of HIV-associated pulmonary hypertension.2 None of these cells or cytokines is a potential target for antiretroviral therapy. Despite this, there are studies, such as the Swiss cohort study, that suggest that the use of HAART prolongs survival and reverses the underlying pathophysiology.51 It will be important to document the African experience and epidemiology more systematically, because long-term survival is significantly lower in patients with HIV-associated pulmonary hypertension than in HIV-negative controls, with a median survival of 1.3 versus 2.6 years.51

Impact of HIV on Health Care in Africa
Recent projections suggest that in the African countries with the highest seroprevalence rates, 60% of today’s 15-year-olds will not live to age 60 (Figure 3).52 The mortality rate for HIV-infected 14- to 49-year-olds is 40 times that of their HIV-seronegative age-matched compatriots. Compared with their HIV-positive age-matched counterparts in the developed world, death rates are up to 20 times higher in people living in Africa.1 Given what we know about HIV-associated cardiac disease, a small but significant portion of the morbidity and mortality will be due to cardiovascular disease. For those interested in cardiology, this may represent a major opportunity to both help those in need and learn from well-conducted research of people with potentially unique problems.

The meager healthcare budgets in most African countries have not sufficient to cope with the added burden imposed by the HIV pandemic. In an environment where most people are dependent on government health care, the impact of AIDS has been crippling. In some countries, up to 16% of healthcare workers are HIV seropositive, and it is estimated that between 19% and 53% of all government health employee deaths are AIDS related.53 The result has been a continuous depletion from the healthcare sector of much needed skills and personnel. Despite this, between 1992 and 2002 in some of the areas most affected by HIV, clinic visits increased by as much as 88% and hospital admissions by 81%.53 Overall, the result has been that decades of progress in socioeconomic development, health care, and improvement in life expectancy are rapidly being reversed.1

There is good evidence that HAART significantly reduces the incidence of cardiovascular manifestations of HIV infection.45 However, only 5% of infected adults on the African continent who need HAART receive it.1 African countries are only able to spend 1000 times less on care per HIV-infected patient than the United States.1 There is a glimmer of hope that this vicious circle of severe poverty, high incidence of HIV, poor access to HAART, and high prevalence of HIV-related cardiodisorders will eventually be broken. Several large international funding initiatives have been launched to tackle the HIV/AIDS epidemic in Africa. These include The Global Fund to Fight AIDS, Tuberculosis and Malaria; The Bill and Melinda Gates Foundation; and the World Health Organization’s 3×5 program. These will provide the financing for the much-needed comprehensive treatment programs and other requirements necessary to reverse the impact of

Figure 3. Map of Africa showing estimated seroprevalence rates in high-risk urban populations across the African continent. Reprinted from US Census Bureau, Population Division, International Programs Center, HIV/AIDS Surveillance Data Base, September 2004.52
what Nelson Mandela has described as “a tragedy of unprecedented proportions unfolding in Africa.”

Conclusions
The incidence of opportunistic infections of the heart has increased significantly since the beginning of the HIV epidemic in Africa. Cardiologists and physicians from across the continent are reporting more heart muscle disease, and vascular surgeons have been seeing a larger number of unusual diseases of the aorta and its branches. Unfortunately, to date, most African countries have been unable to deal adequately with the massive healthcare burden the pandemic has created, and despite signs that there is a brighter future ahead, the impact of HIV on this continent will likely be felt for generations to come.

Acknowledgments
The authors acknowledge MESAB (Medical Education for South African Blacks) for their funding through the Don Kennedy Research Grant and the following individuals for their critical comment: Gary Maartens, Patrick Commerford, Graeme Meintjes, and Azeem Latib. A special thanks to Charles Wiysonge and Lucien Bushidi for translating the French articles.

Disclosures
None.

References


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Circulation. 2005;112:3602-3607
doi: 10.1161/CIRCULATIONAHA.105.549220
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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