The implications of HIV infection on the management of valvular heart disease in Southern Africa

D.P. Naidoo* and K. Shein#

*Department of Cardiology, University of KwaZulu-Natal
#Department of Cardiology, Inkosi Albert Luthuli Central Hospital

Address for correspondence:
Dr Kyi Shein
Department of Cardiology
Inkosi Albert Luthuli Central Hospital
Private Bag X03
Mayville
4058
South Africa

Email:
Naidood@ukzn.ac.za
kyishe@ialch.co.za

ABSTRACT

There is very limited information on the disease profile and treatment approaches in HIV patients with valvular heart disease (VHD) in developing countries. HIV infection impacts on patients with VHD in three settings: HIV/Aids as a comorbid disease in patients with underlying valve disease, infective endocarditis secondary to immunosuppression, and non-infective valve involvement from myocardial failure or from marantic endocarditis.

The clinical presentation of infective endocarditis does not differ between HIV and non-HIV patients, with the exception that intravenous drug abuse is a common cause in specific populations. While peri-operative mortality and morbidity is high in acute infective endocarditis, surgical interventions do not increase the postoperative risk for complications or death and should therefore not be withheld. There is also little evidence to suggest that HIV or antiretroviral drugs increase the rate of cardiac-related pregnancy complications or that pregnancy may alter the course of HIV infection.

Since antiretroviral therapy has been associated with considerable improvement in clinical status prior to surgery, as well as in long term outcomes, all patients with valve disease in whom intervention is likely should undergo HIV testing and staging so that highly active antiretroviral treatment (HAART) may be instituted timeously.

Conclusion: The high prevalence of HIV in our population makes consideration of this comorbidity an essential facet in the routine evaluation and management of patients with VHD. There is solid evidence that these patients do no worse than non-HIV patients undergoing medical treatment or percutaneous/surgical intervention – open-heart surgery may be offered safely to patients with HIV if proper precautions are taken. SAHeart 2009; 6:64-74

INTRODUCTION

South Africa has one of the most rapidly growing human immune deficiency virus (HIV) epidemics in the world with an estimated 5.7 million HIV positive people.[1] Of the 6 800 new HIV infections that occurred per day in the world in 2007, more than two out of three adults (68%) and nearly 90% of children infected with HIV live in Sub-Saharan Africa.[1] Although 18% of these infections occurred in young adults (15-49 years) little attention has been paid to the comor bidity associated with HIV seropositivity. In fact, except for tuberculosis and opportunistic infections, there are no specific guidelines that are available for the management of different comorbid diseases in these patients that demand attention in their own right.

Most decision-making regarding management in HIV patients is influenced by immune status, often taking the CD4 count into consideration. However, it is not infrequent that arbitrary decision-making approaches are adopted, and intervention/surgery turned down on the basis of HIV seropositivity alone. This review addresses the management of valvular heart disease in HIV patients, and the issues surrounding diagnosis and treatment in the South African context.

CARDIAC DISEASE IN HIV

The nature and pattern of cardiovascular involvement in HIV/Aids have been extensively investigated[2,3] and reviewed in western literature.[4,5,6] Cardiac involvement in patients with HIV/Aids (Table I) is relatively common and associated with increased

TABLE 1: Cardiac disease associated with HIV and Aids

Pericarditis and Pericardial effusion (TB)
Dilated cardiomyopathy/myocarditis with global LV dysfunction
Endocarditis
Infective
Marantic
Pulmonary hypertension
Vasculitis
Increased risk of coronary artery disease
Abnormal lipid metabolism and lipodystrophy syndrome
Insulin resistance and impaired glucose metabolism
Cardiac arrhythmias
Neoplasms
Kaposi's sarcoma
Non-Hodgkin lymphoma

morbidity and mortality. The spectrum ranges from pericardial disease with effusion, to myocardial disease, as well as involvement of the valve endocardium. With the advent of highly active antiretroviral therapy (HAART), coronary artery disease and dyslipidaemia, drug-related cardiotoxicity and cardiac autonomic dysfunction have begun to emerge and are becoming increasingly prevalent.[7]

MYOCARDIAL INVOLVEMENT IN HIV

Little change in cardiac function has been documented in ambulatory HIV positive patients.[8,9] Diastolic abnormalities have been reported in patients without clinical evidence of cardiac disease.[10] Advanced systolic dysfunction is more common in the patients classified as having Aids,[8] but there has been a decline in cardiomyopathy with the advent of HAART in the developed countries.[11] In contrast heart involvement in developing countries is dominated by pericardial tuberculosis, often accompanied by impairment of left ventricular function due to associated myocarditis.[12,13,14]

In prospective cross sectional studies in Africa which have included patients with Aids, the prevalence of dilated cardiomyopathy has been reported to vary from 15% to 35%[15,16,17] compared to the 15% overall reported in a western series by Currie.[18] A study from Cameroon evaluated cardiac involvement in 75 African patients according to the clinical stage of the disease and the immunological status of the patients.[15] This study found that dilated cardiomyopathy occurred in 7/30 (23.33%) of Aids patients, 1/24 (4.17%) HIV positive non-Aids patient, but in none of the HIV negative subjects. In this study dilated cardiomyopathy occurred in six (31.58%) of the patients with a CD4 cell count ≦ 100 cells/microlitre and in two (6.06%) with CD4 counts > 100 cells/microlitre (chi2 = 4.02, p = 0.03). This association of cardiomyopathy with more advanced immunosuppression and lower CD4 counts is consistent with international experience.[18] Global left ventricular dysfunction is typically found in the late stages of HIV infection. The clinical picture of dilated cardiomyopathy is strongly associated with CD4 counts < 100 cells/microlitre.

ACUTE INFECTION AND LV DYSFUNCTION

The cause of heart muscle disease in patients with HIV infection is not clear. Autopsy studies document a high prevalence of myocarditis (46%), but in over 80% of cases no specific aetiology has been found. Many cases seem to be related to a lymphocytic myocarditis directly related to the HIV infection, while opportunistic infection accounts for the remaining 20% (examples being cytomegalovirus/toxoplasma gondii infection).[18] Other potential pathogenic factors include nutritional deficiencies, the cardiotoxic effects of antiretroviral drugs and other opportunistic infections.

Regardless of its aetiology the presence of impaired left ventricular function in these subjects is an independent adverse prognostic factor; it is associated with very low CD4 counts and with reduced survival compared to those with normal hearts, 18 which poses serious challenges in the medical and surgical treatment of valve-related disease.

VALVE INVOLVEMENT IN HIV

To date most reports on valvular heart disease (VHD) in HIV infected patients have focused on infective endocarditis (IE) in drug addicts.[19,20,21,22,23] If, as Levy suggested, the risk of developing IE in HIV positive patients is related to the degree of immune paresis[3] then one would expect low CD4 counts to increase the risk of bacteremia, and subsequent seeding on the valve tissue would predispose to infective endocarditis, particularly in subjects with a predisposing valve/cardiac lesion.[3] Bacteremia is indeed common in the HIV positive patients, due to the numerous immunologic defects present in this disease.[24] IE is reported to be common in advanced HIV patients, and mortality increases with a decreasing CD4 count.[19,25] The rise in staphylococcal infections, and the immune paresis associated with Aids pose diagnostic challenges, and they also have important implications for management in these patients.[25] Furthermore infection may be caused by unusual organisms, such as bartonella, salmonella and listeria.[26,27]

Although infective endocarditis is the most common cardiac complication of HIV/Aids in the Western world,[20] the clinical outcome in these patients appears to depend more on the valve affected and the virulence of the organism rather than the HIV serostatus.[20]

In a large series of 263 cases of definite IE (Dukes criteria), including a 100 cases in HIV positive patients, over a 13- year period in intravenous drug users between 1986 and 1999 in the pre-HAART era De Rosa found no major differences in outcome between HIV negative and HIV positive patients.[21] In another large series of 493 cases of native valve endocarditis (220 cases in intravenous drug users) diagnosed from 1985 to 1999 Martin-Davila analysed 13 variables, including HIV serostatus and CD4 cell count < 200 cells/microlitre, and showed that the main prognostic factors of in-hospital mortality in right-sided IE were large vegetations > 2 cm and fungal etiology.[28] As with cardiomyopathy it is reported that IE rates have decreased in the current HAART era from 20.5 to 6.6 per 1 000-person-years[29] accompanied by an appearance of noninfective valvular disease (marantic and rheumatic causes NIVD) and coronary artery disease (CAD) in HIV patients.[5,30] In multivariate regression an increased risk of IE occurred in intravenous drug users (odds ratio 8.71), those with CD4 counts <50 cells/microlitre, and those with HIV-1 RNA >100 000 copies/ml.[29] The most common aetiologic organism was Staphylococcus aureus (40 (69%) of these 11 (28%) were methicillin resistant). Within 1-year, 16% had IE recurrence and 52% died. Also a new pattern of IE in IVDA is emerging, characterised by more frequent left heart involvement (61.5%), a severe clinical course, and a need for surgery in the active phase.[22]

HIV ASSOCIATED INFECTIVE ENDOCARDITIS IN AFRICA

There are few reports of infective endocarditis in HIV/Aids from developing countries.[31,32] Despite the high prevalence of rheumatic heart disease it is distinctly uncommon in our environment, probably due to the low prevalence of mainline drug addiction. A 3-year survey of IE at our centre found that the clinical profile in the HIV positive patient was similar to the HIV negative patient, and was characterised by fever, clubbing, murmurs and severe valve regurgitation with similar responses to therapy.[32] The CD4 counts in 4/17 HIV infected patients who demised were 139, 135, 149 and 249 cells/microlitre^3. This is in contrast to the findings of the Emory group who suggested that there was no correlation between the mortality and the degree of immunosuppression.[24,33] The most common underlying predisposing abnormality in our series is rheumatic heart disease. Although S.aureus and S.viridans are the common infecting organisms,[20] a high rate of culture negativity has been reported[31,32] probably related to prior antibiotic therapy, and in the absence of microbiological indices the sensitivity of the modified Duke criteria is diminished.[34] The lack of specificity in echocardiographic criteria becomes apparent when diagnosing IE in the HIV population, as these patients often have elevated ESR and CRP levels due to anaemia or non-valvular infection. Furthermore it is also being increasingly recognised that non-bacterial thrombotic endocarditis (NBTE) may be the cause when blood culture is negative.[35] NBTE is characterised by the presence of friable vegetations on cardiac valves, which consist

of fibrin and platelet aggregates and is being increasingly recognised as a potentially life-threatening source of thrombo-embolism. NBTE occurs in 3 to 5% of Aids patients, mostly in patients with extreme wasting. It is often difficult to diagnose and one has to rely on strong clinical suspicion. Even with an established diagnosis, treatment of NBTE is difficult. In the non-HIV patients anticoagulation has been instituted although there are no prospective randomised studies to support this strategy. There are also no guidelines for surgical intervention in patients with NBTE. Systemic embolisation from marantic endocarditis in the Aids patient is a rare cause of death in the HAART era. In haemodynamically stable patients surgical intervention is generally not recommended unless the patient develops severe valve damage with resultant heart failure.

EFFECTS OF IMMUNE SUPPRESSION ON CLINICAL MANIFESTATIONS AND OUTCOME

It is not clear to what extent HIV may alter the clinical picture of underlying valvular heart disease, or worsen the progression of the disease and the haemodynamic changes such as pulmonary hypertension. In HIV patients with IE abscess formation with paravalvular extension has been reported, which could be related to the advanced stage of immune deficiency, but the numbers are too few to draw firm conclusions.[32,36] In Nel's series four out of seventeen HIV positive patients with infective endocarditis had advanced immunodeficiency with a mean CD4 count <100 cells/microlitre. When the HIV positive patients were stratified into 2 groups: CD4 counts <200 cells/microlitre; and >200/mm^3, Nel did not find any differences in the clinical features, nor were there any differences in the infecting organism between the groups. There were four known deaths amongst the HIV positive patients (23.6%), and fourteen deaths amongst the HIV negative patients (23.3%) (p = ns).

Significant morbidity was present in these patients, such as anaemia, concomitant TB and dialysis-requiring renal failure.[26] Nosocomial infection leading to prosthetic valve and catheter-related endocarditis poses serious challenges in management because of the emergence of antibiotic resistance among causative organisms.[29]

IMPACT OF HIV SEROSTATUS ON UNDERLYING VALVULAR HEART DISEASE:

Information from a cardiac disease in pregnancy cohort

Women of reproductive age are the fastest growing population with HIV, and in developing countries rheumatic heart disease (RHD) is a major cause of maternal morbidity[37] and mortality.[38,39] Recent reviews have not focused on the impact of HIV serostatus in these patients.[40,41] Two studies have shown that HIV serostatus does not modify the treatment effects in patients with cardiac disease during pregnancy.[42,43] In a one year review of 95 patients with cardiac disease in pregnancy during 2003.[43] At our institution (Inkosi Albert Luthuli Central Hospital, Durban) Nqayana et al. found 31 (33%) patients to be HIV positive; 46 tested negative and the remaining 18 declined testing. Rheumatic heart disease was the commonest aetiology (81%). There were 22 patients with isolated mitral stenosis, and 11 were New York Heart Association (NYHA) III-IV. Four patients had undergone balloon mitral valvuloplasty (BMV) prior to pregnancy. Eight patients (4 HIV positive) required intervention, and percutaneous valvuloplasty was accomplished successfully during pregnancy. Cardiac complications were mainly related to rhythm disturbances and heart failure while bleeding from over-anticoagulation accounted for the majority of the non-cardiac complications (Table 3). Maternal morbidity and adverse fetal outcomes were associated with late presentation and problems with anticoagulation, not with HIV serostatus.

Outcome measures were similar in HIV-infected and non-infected groups (Table 5). The mean CD4 count was 463 cells/microlitre (range 79-1419). The ejection fraction was normal in all patients except for three with cardiomyopathy (Table 2). Of note Nqayana found that HIV infected women did not have a higher wound infection rate, puerperal sepsis rate, nor was there a higher neonatal infection rate compared to non-HIV infected women. Nor did there appear to be any difference in outcome in the 3 women who had advanced disease with low CD4 counts (< 200 cells/microlitre). The provision of antiretrovirals for maternal health had just begun and the standard of care at the time of this study was the provision of single dose of nevirapine given to the

TABLE 2: Impact of HIV serostatus on pregnancy-associated heart disease

Parameter	HIV (n=31)	Non HIV (n=46)
Demographics		
Age (years)	18 - 39	15 - 45
Parity: P0	12	19
Preterm	13	14
CD4 count <200 cells/microL	3	-
Balloon mitral valvuloplasty	4	4
Mitral valve replacement	1	-
Normal delivery	8	21
Caesarean section	21	25
Outcome		
Haematoma	2	1
Stillbirth	2	2
Birth weight (<2.5 kg)	9	13

Modified from Nqayana et al.[43]
MVR = mitral valve replacement. NVD = normal vaginal delivery. C/S = caesarean section

mother at the time of birth, and to the baby within 24 hours of delivery, for the prevention of mother to child HIV transmission. The limited evidence to date suggests that HIV infection or antiretroviral drugs do not increase the rate of cardiac-related pregnancy complications nor does pregnancy alter the course of HIV infection.[44]

IMPACT OF HIV SEROSTATUS AND COMORBIDITY IN PATIENTS UNDERGOING CARDIAC VALVE SURGERY

To date, most valve surgery has been in patients with infective endocarditis related to intravenous drug use (Table 3). Recently[45] Blyth et al. reviewed the records of 49 HIV infected non-IVDA patients (65% female), undergoing surgery over a nine-year period (1995-2003) at our centre. Of these 45 patients had

TABLE 3: Cardiac surgery in HIV patients

Studies, year country	Surgery	No. of patients (surgeries)	Mean age	Follow up (months) (mean)	Mean CD4 pre-op	Mortality rate (%)	Comment
Aris A, et al. 1993 Spain	Mainly valve	40 85% IVDA	30	4-72 (21)	NA	20 early 25 late	Aids not accelerated by CPB pathologies related to IVDA are causes of poor prognosis
Chong T, et al. 2003 US	Valve	22 73% IVDA	38	Up to 96	NA	45 late	Low operative risk Poor late result associated with IVDA
Mestres CA, et al. 2003 Spain	Valve, coronary	31(35) 19% IVDA	35	2-171	278	22.6 early 37.5 late	Increase in HIV pts requiring cardiac surgery Decrease in acute IE Late death not related to AIDS
Trachiotis GD, et al. 2004 US	Valve, coronary	37 Few IVDA	41	84	360 >300 selected	2.7 early	Acceptable risk and outcomes of cardiac surgery in selected HIV pts
Filsoufi F, et al. 2006 US	Valve, coronary	25 68% IVDA	47	2-90 (44)	440 12.5 late	4 early	Survival rate of 86% at 3 years Surgeons should not hesitate to perform major surgeries
Blyth DF, et al.* 2006 South Africa	Mainly valve	49 (50) No IVDA	33	2-70 (23)	685 >400 selected	6 early 17.3 late	Surgery worthwhile in selected HIV pts No evidence that CPB accelerated progression to Aids

**Not on HAART*

rheumatic valvular heart disease and 44 underwent cardio-pulmonary bypass. Absence of clinical Aids and a CD4 count above 400 cells/microlitre, were the criteria used in selecting patients fulfilling the usual criteria for surgery. All but one of the patients improved their functional class. Blyth concluded that surgery in HIV positive patients with CD4 counts >400 cells/microlitre is likely to have a similar early outcome when compared with the HIV negative patients.[45] The outcome of surgery in patients with CD4 counts >400 cells/microlitre has been reported by Filsoufi[46] et al. who found a 86% 3-years survival in 25 patients undergoing cardiac surgery with CD4 count of 51-1 050 (mean 440). Of these ten patients had CD4 count < 400/microlitre. These findings support our contention that surgeons should not hesitate to perform major surgical procedures in patients with AIDS or HIV infection per se, whenever they are indicated.

The issue of the timing of surgery in these patients arises when there is comorbid infection, particularly tuberculosis (TB). In South Africa it is estimated that >60% of TB patients have HIV co-infection. These patients are not infrequently referred for cardiac surgery, resulting in three confounding factors in therapeutic decision making i.e. initiation of anti-tuberculous therapy; timing of surgery; and the introduction of HAART. Drug interactions between current HAART and anti-TB medications, as well as the immune reconstitution syndrome associated with initiation of HAART during TB treatment impose therapeutic challenges in the timing of treatment regimens and surgical intervention. The World Health Organisation's (WHO) guidelines suggest that individuals with TB who have CD4 count <200 cells/microlitre should initiate HAART 2 to 8 weeks after starting TB treatment. In those with CD4 counts >200 cells/microlitre HAART may be delayed until the initial intensive phase of TB treatment is complete. The timing of surgery in these patients will depend on urgency of the procedure. We have adopted a pragmatic approach with at least 2 weeks of anti-TB treatment before commencing HAART in those with CD4 <200 who are in need of urgent surgery.

ISSUES RELATED TO CARDIAC SURGERY (TABLE 4)

While it is recognised hospital mortality and pneumonia in HIV patients are higher than in uninfected cases in some series,[47,48] a retrospective analysis of patients undergoing general surgical procedures has shown that other operative outcomes were comparable for HIV infected and non-HIV infected patients.[48] Hospital mortality and complications in Blyth's series were acceptably low (6% and 34.7% respectively) in a selected group of patients (CD4 count >400 cells/microlitre). Furthermore, except for undiagnosed preoperative infection (Tuberculosis1 and infective endocarditis1) he did not find a higher wound infection rate in his patients; even the commonest early complication, pericardial

TABLE 4: Issues/challenges in the management of valve disease in HIV

Effects of immune suppression on clinical parameters : Hb, Platelets, albumin
Procedural risks
Blood sampling in HIV patients
TEE and use of sheath
Intervention/surgery
Bleeding complications and anticoagulant therapy in HIV patients
Treatment response and the effects of HIV on healing process
Emerging challenges
Emergence of prosthetic valve and pacemaker-related endocarditis increase in antibiotic resistance among aetiologic organisms e.g. MRSA
Increase in comorbid disease eg atherosclerosis, diabetes, dialysis-dependent renal failure, and drug abuse.[8]
Acute phase reactants (CRP and ESR often related to opportunistic infection, anaemia)
High prevalence of tuberculosis co-infection
Simultaneous anti-tuberculous therapy and HAART
HAART in the peri-operative period
Issues in surgical management
Prioritising against surgery in the HIV patient:
• Perception that surgery may accelerate the disease process
• Perceived diminution in life expectancy
• Quality of life vs life prolongation
• Perceived contribution to society
Prioritising due to limited resources:
• Limited access to aftercare and antiretroviral therapy
• Elective vs emergency care
• Delaying surgery in HIV positive patients

effusion, was not related to bacterial infection. There is evidence that viral load of 30 000 copies per milliliter or more was associated with increased complications (adjusted odds ratio, 2.95; P=.007), but a CD4 cell count less than 200 cells/microlitre was not associated with poorer outcomes following general surgery.[48]

PROGRESSION OF HIV INFECTION

Surgeons have been reluctant to operate in the belief that HIV-related immune supppression would lead to poor surgical outcomes and progression of disease. Blyth documented eight late deaths during follow-up of 43 cases, mostly from Aids Concern about the effects of bypass surgery, which have been allayed since it has now been shown that transient changes in the CD4 count during CPB is not associated with disease progression even when counts are low.[30,52,53] Also the recurrence of endocarditis in patients operated upon during the phase of active infection[54,55] has been found to be related to continuing intravenous drug abuse, and not due to the HIV status. Since the report by Mellors et al.[51] that viral load increases as Aids develops it has become established that viral load influences disease progression. Access to HAART is therefore critical in halting the progression to Aids and thereby late complications related to surgery .

HAART in peri-operative period needs special attention. There are no specific guidelines for the initiation or the continuation of HAART in the peri-operative period. The timing of initiation depends on the urgency of surgery and clinical stage of the disease. The major issues to consider include the potential toxicity and the possibility of drug interactions associated with HAART, and the emergence of drug resistance should treatment be withheld in the peri-operative period. Until further studies emerge, it is reasonable to continue HAART until operation and to administer medication post-operataively via nasogastric tube where possible.

ISSUES RELATED TO THE MANAGEMENT OF VALVE DISEASE (TABLE 5)

1. The role of echocardiography

The HIV patient with VHD presents unique challenges in management: in addition to the evaluation of disease severity the clinician is faced with the comorbidities arising from HIV serostatus. These include unsuspected abnormalities such as pericardial effusion, cardiomyopathy, pulmonary hypertension and infective endocarditis.

A baseline echocardiographic evaluation at the time of HIV diagnosis with follow up scans every 2 years has been recommended in subjects with VHD.[56] Lipshultz suggests that annual scans should be performed in symptomatic patients with referral to the cardiologist when cardiovascular abnormalities are detected. Clearly this recommendation is not appropriate in Southern Africa where rheumatic heart disease is endemic and there is a high rate of HIV infection. In our setting, while the indication for echocardiography should be symptom-driven, a full clinical evaluation of the symptomatology is mandatory before referral for echocardiography.

TABLE 5: Treatment principles in guiding percutaneous intervention/ surgery

HIV is a chronic viral illness
HIV infection should be regarded as a comorbidity factor like HbsAg
There is no scientific basis to:
• deny any intervention because of HIV infection;
• discriminate in favour of non-HIV status; and
• refuse to operate because of the risk of exposure.
Operative/interventional outcomes are similar for HIV infected and non-HIV infected patients
Surgical treatment decisions should be the same as for non-HIV patient
Preoperative preparation in VHD
Address comorbidity prior to surgery
Exclude active pulmonary infection
Accurately determine ventricular function
Determine the operative risk of anaesthesia and surgery
Peri-operative HAART therapy
Timing of surgery if CD4 count < 200/microL or "Aids defining illness (Kohli)
6 weeks of HAART before urgent surgery
3 to 6 months of HAART before elective surgery

2. The patient with acute dyspnoea

Many patients with HIV/Aids develop multiple opportunistic infections, and present with persistent or unexplained pulmonary symptoms, so that dyspnoea is often presumed to be of pulmonary origin. Echocardiography is an essential tool in the evaluation of acute dyspnoea of hospitalised patient with HIV/Aids, especially when the shortness of breath is out of proportion to the pulmonary involvement. With the recognition that HIV cardiomyopathy is often silent (see above), measurement of left ventricular function should also be considered in the evaluation of unexplained dyspnoea in these patients, since the management in these instances is clearly different. The detection of left ventricular dysfunction calls for greater care in the management of comorbid infections since careful attention needs to be paid to fluid and volume status in these patients.

3. Assessment of haemodynamic status and ventricular function

Of importance is a determination of the possible cause and severity of ventricular dysfunction when it is present. HIV related myocarditis consists of a cell-mediated injury of the myocytes and phenotypically appears identical to a subgroup of non-HIV positive patients.[57] There is therefore little to be gained by performing myocardial biopsies in these patients prior to surgery. Furthermore, no prospective studies have evaluated the treatment regimens in HIV associated cardiomyopathy.

A decline in the incidence of HIV associated cardiomyopathy that has been documented in the post HAART era, suggests that the administration of HAART prevents opportunistic infection and could, in this way, reduce the incidence of pericardial effusion and myocardial involvement in these patients.[11]

The development of severe pulmonary hypertension in the patient with valve disease may present a diagnostic dilemma. It may be secondary to left-sided valve disease or it may be due to the HIV itself. HIV associated pulmonary hypertension is a well-described entity with an incidence 1/200.[4] It presents with dyspnoea in young patients and in contrast to cardiomyopathy, shows no correlation with opportunistic infections or the CD4 count. Plexogenic pulmonary arteriopathy is the most frequent pathologic finding and the prognosis is poor: half the patients are dead within a year. HIV associated pulmonary hypertension should only be diagnosed when other causes (thromboembolism, airway disease, valvular disease) have been excluded.

It should be considered when the pulmonary hypertension is clearly out of proportion to the severity of valve involvement.

4. Increased atherosclerotic risk

The administration of HAART has been associated with an increase in the incidence of coronary heart disease in patients receiving protease inhibitors.[58] Recent reports also indicate that the metabolic changes associated with these drugs is accompanied by elevation in blood pressure in up to 74% of patients with metabolic syndrome. Careful screening is therefore essential in patients who are receiving HAART, especially in those with risk factors for coronary disease, as the atherogenic effect of treatment may accelerate this risk.

5. Effects of antiretroviral therapy

The improved survival of patients with HIV infection who have access to HAART has resulted in HIV becoming a chronic viral disease with a growing disease burden. The 5-year survival after surgery has improved from 48%[59] to 64.9% at one year[30] and in another study has been documented to be over 80% at 3 years[46,52] in the post-HAART era. The marked improvement in mortality with the use of ARVs reported by Palella[59] supports the contention that all patients should be offered surgery where it is indicated.

6. Ethical issues

Although surgeons are prepared to operate on HIV carriers most are still are reluctant to operate on patients with Aids[54,60] despite the low risk of accidental skin injury. Legal and ethical issues arise when patients are denied appropriate care without adequate grounds for such decisions being clear and documented. In the US[61] two surgeons are being sued by Ronald Flowers, a patient with HIV who was denied open-heart surgery at the George Washington University Hospital. The patient had suffered

two transient strokes secondary to a vegetative growth on his aortic valve. The surgeons felt that open-heart surgery on a HIV positive patient posed too great a risk for the surgical team, and the patient was transferred to another hospital where the surgery was successfully completed. This case draws attention to the ethics of withholding appropriate treatment when there is adequate literature to support surgery in HIV patients with valvular heart disease, taking the necessary precautions in those who test positive or who decline testing. Mestres noted that their unit is now more frequently referred HIV patients for surgery, possibly due to a greater acceptance of improved results.[30] They now accept all referrals, regardless of Centre of Disease Control classification.

CURRENT APPROACH AND SUGGESTED GUIDELINES

There are several complexities in the clinical decision-making in the individual HIV infected patient, with a lack of data to support clear guidelines. Blyth's retrospective review only included patients with CD4 counts >400. We do not know what the outcome of the patients with lower CD4 counts (200-400) would have been. Horberg found that a viral load ≥ 30 000 copies/ml was associated with increased complications (adjusted OR 2.95; p=0.007).[48] Viral suppression to fewer than 30000 copies/ml reduced surgical complications. However, in this study Horberg pointed out that a CD4 count <200 was not associated with poorer outcomes.

Although there was a higher rate of complications, Blyth found no increase in infections in his study. He therefore felt that patients with low counts could be placed on a waiting list while receiving HAART. It has been well described that six months after starting HAART, the achieved CD4 cell count and viral load, but not values at baseline, are strongly associated with subsequent disease progression. These findings should inform our guidelines on selection for surgery and when to modify HAART in these patients.[65]

We now perform routine voluntary HIV testing for all patients with VHD in whom intervention is imminent. As there are few operative guidelines[63] we base our elective management on immune status, taking the CD4 T-lymphocyte count into consideration. When the CD4 T-cell count exceeds 400 cells/microlitre, patients are managed according to standard protocols appropriate for sero-negative patients. At this level Blyth reported that outcomes are similar to uninfected subjects, and there is no difference in the mortality rate. Where the CD4 count is in the range 200-400 cells/microlitre our treatment approaches are still the same but our surgeons have adopted a conservative alternative to surgery in most instances, recently calling for the introduction of HAART and an estimation of the viral load.[64] Relying on CD4 count and viral load as the only parameters for decision-making is not only too restrictive, but it also this does not take into account the Centers for Disease Control and Prevention (CDC) staging of infection, as was done by Filsoufi et al. Furthermore the CD4 count has wide inter-test variability and shows poor correlation with clinical staging. Wasting used as a CDC indicator is also not reliable since it may be manifestation of cardiac cachexia associated with VHD. What seems to be appropriate is our setting is the patient's general condition and associated comorbidity (Hb, albumin, renal function) and urgency of surgery. If the patient is in good general health, with a low viral load and without serious comorbidity, surgery is offered regardless of the CD4 count.

Where the clinical staging and CD4 count is Aids defining (<200 cells/microlitre), palliative treatment is administered unless surgery is deemed life-saving (e.g. stuck valve, atrial myxoma) and the patient is otherwise in good health.

CONCLUSION

In developing countries IE in HIV patients occurs mainly in patients with underlying RHD. The common infecting organisms are S. aureus and S. viridans. With increasing drug abuse the prevalence of endocarditis in HIV infected subjects in our environment will likely increase, posing further problems in diagnosis. Careful forward planning is essential in patients in whom interventional procedures are imminent. In the absence of an adequate database of information in HIV patients suggested

guidelines (Table 6) may only be tentative, but are critical to appropriate management in our setting. A team involving the physician, cardiologist, virologist, cardio-thoracic surgeon and counsellor should be involved in the care of these patients, especially those requiring intervention/surgery. There are now several reports of successful treatment, including surgical outcomes in HIV infected patients, even when the CD4 counts are low. In addition to the fact that there is very little scientific basis for not offering surgical or percutaneous intervention to HIV infected patients there are serious moral and ethical issues that militate against such an approach.

TABLE 6: Suggested guidelines in the evaluation of VHD HIV testing

All patients under consideration for percutaneous intervention/surgery should undergo voluntary testing (HIV and HBsAg) after adequate pre-test counselling.
Clinical and immunological staging should be applied using appropriate measures (CD4 count/ CD4/8 ratio/ CD 4 % and viral load)
HAART should be initiated without delay where indicated
Evaluation of comorbidity
Estimation of acute phase reactants (ESR, CRP viral vs bacterial) to assess the activity of comorbid disease, including infection and carditis
Where endocarditis is suspected, blood cultures should be taken frequently, and where possible, prior to antibiotic therapy
Aggressive treatment of coexistent infection (tuberculosis), and other comorbidities
Diagnostic evaluation
Careful evaluation of disease severity including transthoracic echo (TTE) to:
• evaluate the severity of valve dysfunction;
• detect evidence of infective endocarditis (vegetations, paravalvular extension, prosthetic valve dehiscence); and
• document ventricular dimensions and ventricular function.
Transesophageal echo should be performed where TTE images are suboptimal, with mechanical prosthetic valves, or if paravalvular infection is suspected:
• adequate sterilisation of the transducer is a critical requirement since the risk of trauma during passage of the scope is likely to be associated with bleeding in the presence of oesophageal candidiasis;
• using a protective sheath and gumguard; and
• observe the usual precautions against needlestick injury - fully equipped crashcart on standby.

REFERENCES

1. UNAIDS, Aids epidemic update, 2008; WHO, Epidemiological fact sheet on HIV/Aids and sexually transmitted infections, Sept 2008.
2. Barbaro G, Lorenzo G, Grisorio B, et al. Cardiac involvement in the Acquired Immunodeficiency Syndrome: A multi-centre clinical-pathological study. Aids Research and Human retroviruses. 1998;14(12):1071-1077.
3. Levy WS, Simon G, Rios J, et al. Prevalence of cardiac abnormalities in HIV infection. Am J Cardiol 1989;63:86-89.
4. Katz A, Sadaniantz. Echocardiography in HIV cardiac disease. Prog Cardiovasc Dis 2003;45(4):285-292.
5. Sani MU, Okeahialam BN. Epidemiology and pathogenesis of Human Immunodeficiency Virus (HIV) related heart disease: a review. Niger J Med. 2005 Jul-Sep;14(3):255-60. Review.
6. Barbaro G. Cardiovascular manifestations of HIV infection. Circulation 2002; 106: 1420-1425.
7. Sudano I, Spieker LE, Noll G, et al. Cardiovascular disease in HIV infection. Am Heart J.2006;151:1147-55.
8. Himelman R, Chung W, Chernoff D, et al. Cardiac manifestations of human immunodeficiency virus infection: a two-dimensional echocardiography study. J Am Coll Cardiol. 1989;13:1930-1936.
9. Thuesen L, Moller A, Kristensen BO, et al. Cardiac function in patients with Human Immunodeficiency Virus infection and with no other active infections. Dan Med Bull. 1994 Feb;41(1):107-9.
10. Longo-Mbenza B, Seghers LV, Vita EK, et al. study. Heart. 1998 Aug; 80(2):184-9.
11. Pugliese A Isnardi D, Saini A, Scarabelli T, et al. Impact of highly active antiretroviral therapy in HIV positive patients with cardiac involvement. J Infect 2000;40: 282-284.
12. Magula N, Mayosi B. Cardiac involvement in HIV-infected people living in Africa: a review. Cardiovasc J South Afr 2003;14(5): 231-237.
13. Ntsekhe M. Impact of HIV infection on cardiovascular disease in Africa. Circulation 2005;112:3602-3607.
14. Makotoko M. The Human Immunodeficiency Virus and cardiovascular disease. Cardiovasc J SA 2003;14(5):222-223.
15. Nzuobontane D, Blackette KN, Kuaban C. Cardiac involvement in HIV infected people in Yaounde, Cameroon. Postgrad Med J. 2002 Nov;78(925):678-81.
16. LongoMbenza B, Seghers KV, Phuati M, et al. Heart involvement and HIV infection in African patients. Int J Card 1998;64:63-73.
17. Hakim JG, Matenga JA and Siziya S. Myocardial dysfunction in human HIV infection: An echocardiographic study of 151 patients in hospital in Zimbabwe. Heart; 1996; 76:161-165.
18. Currie P, Jacob A, Foreman A, et al. Heart muscle disease related to HIV infection: prognostic implications. BMJ 1994;309:1605-1607.
19. MacMurdo C, Sande MA. Infective endocarditis in the 21st century. Infect Dis 2000; 5(1): 1-6.
20. Valencia E, Miro J. Endocarditis in the setting of HIV infection. Aids Rev. 2004 Apr-Jun;6(2):97-106.
21. De Rosa FG, Cicalini S, Canta F, et al. Infective endocarditis in intravenous drug users from Italy: the increasing importance in HIV infected patients. Infection. 2007 Jun; 35(3):154-60.
22. Carozza A, De Santo LS, Romano G. IE in IV drug abusers: patterns of presentation and long-term outcomes of surgical treatment. J Heart Valve Dis. 2006 Jan;15(1):125-31.
23. Cicalini S, Forcina G, De Rosa FG. Infective endocarditis in patients with Human Immunodeficiency Virus infection. Journal of Infection, 2001;42:267-271.

REFERENCES

24. Abraham J, Veledar E, Lerakis S. Comparison of frequency of active infective endocarditis by echocardiography in patients with bacteremia with and without Human Immunodeficiency Virus. AM J Cardiol. 2003;91:1500-1503.
25. Wilson LE, Thomas DL, Astemborski J, et al. Prospective study of infective endocarditis among injection drug users. J Infectious Dis 2002;185:1761-1766.
26. Durack DT. Evaluating and optimizing outcomes of surgery for endocarditis [editorial]. JAMA. 2003; 290(24):3250-3251.
27. Kerlikowske K and Chambers HF. Kingella Kingae endocarditis in a patient with Acquired Immunodeficiency Syndrome. Western J Med 1999;151(5):558-560.
28. Martin-Davila P, Navas E. Analysis of mortality and risk factors associated with native valve endocarditis in drug users: the importance of vegetation size. Am Heart J 2005 Nov150(5):1099-106.
29. Gebo KA, Burkey MD, Lucas GM, et al. Incidence of risk factors for clinical presentation, and 1-year outcomes of IE in an urban HIV cohort. J Acquir Immune Defic Syndr. 2006 Dec 1;43(4):426-32.
30. Mestres CA, Chuquiure JE, Claramont X, et al. Long-term results after cardiac surgery in patients infected with the Human Immunodeficiency Virus type-1 (HIV-1). Eur J Cardiothoracic Surg. 2003;23(6):1007-1016.
31. Koegelenberg CF, Doubell AF, Orth H, et al. Infective endocarditis in the Western Cape province of South Africa: a 3-year prospective study. QJM 2003;96(3): 217-225.
32. Nel SH, Mbizeni M, Pearce A, et al. Echocardiographic features of the complications of infective endocarditis with special reference to patients with HIV. S Afr Med J (abstr) 2006;96(10):1119-1120.
33. Smith DT, Sherwood M, Cristel R. A comparison of HIV positive patients with and without IE. Am J Med Sciences 2004;328(3):145-149.
34. Predergast BD. Diagnostic criteria and problems in infective endocarditis. Heart. 2004; 90:611-613.
35. Asopa S, Patel A, Khan OA, et al. Non-bacterial thrombotic endocarditis. Eur J Cardiothorac Surg. 2007 Nov;32(5):696-701.
36. Letts DP and Lopez-Candales A. Atypical echocardiographic findings in an immuno-compromised patient. Echocardiography 2004;21(8): 715-719.
37. Essop MR, Nkomo VT. Rheumatic and non-rheumatic valvular heart disease: Epidemiology, Management and Prevention in Africa. Circulation 2005;112: 3584-3591.
38. Saving Mothers. A report of the National Committee on confidential enquiries into maternal deaths in South Africa (1999-2001) DOH. Pretoria. pp 162-174.
39. Naidoo DP. Cardiac Causes of maternal death in pregnancy. Cardiovascular J SA 2002;1(4):193-198.
40. Lung B. The valve patient and pregnancy. Expert Rev Cardiovasc Ther. 2008 Oct;6(9):1249-58.
41. Soma-Pillay P, MacDonald AP, Mathivha TM, et al. Cardiac disease in pregnancy: a 4-year audit at Pretoria Academic Hospital. S Afr Med J. 2008 Jul;98(7):553-6.
42. [No authors listed] HIV status does not affect cardiac therapy effectiveness. Cardiovasc J S Afr. 2006 Sep-Oct; 17(5):280.
43. Nqayana T, Moodley J and Naidoo DP. Cardiac disease in pregnancy: Recent experiences in resource-poor settings. Cardiovasc J Afr. 2008 May-Jun;19(3):145.
44. Evron S, Glezerman M, Harow E, et al. Human Immunodeficiency Virus: anesthetic and obstetric considerations. Anesth Analg 2004;98:503-511.
45. Blyth DF, Buckels NJ, Sewsunker RR, et al. An experience with cardiopulmonary bypass in HIV infected patients. Cardiovasc J SA 2006;17(4):178-185.
46. Filsoufi F, Salberg SP, von Harvou KTJ, et al Excellent outcomes of cardiac surgery in patients infected with HIV in the current era. Clin Infect Dis: 2006; 43:532-6.
47. Abad C, Cardenes MA, Jimenez PC, et al. Cardiac surgery in patients infected with Human Immunodeficiency Virus. Texas Heart Inst J 2000;27:356-360.
48. Horberg MA, Hurley LB, Klein DB, et al. Surgical outcomes in Human Immunodeficiency Virus infected patients in the era of highly active antiretroviral therapy. Arch Surg 2006; 141(12):1238-1245.
49. Moss AR, Bacchetti P. Natural history of HIV infection. Aids. 1989 Feb;3(2): 55-61.
50. Kerlikowske KM, Katz MH, Allen S, et al. Beta 2-microglobulin as a predictor of death in HIV infected women from Kigali, Rwanda. AIDS 1994 Jul; 8(7):963-9.
51. Mellors JW, Kingsley LA, Rinaldo CR Jr, et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. Ann Intern Med 1995 Apr 15;122(8):573-9.
52. Trachiotis GD, Alexander EP, Benator D, et al. Cardiac surgery in patients infected with the Human Immunodeficiency Virus. Ann Thorac Surg. 2003 Oct;76(4): 1114-8.
53. Namai A, Sakurai M, Akiyama M. Cardiac surgery in three patients infected with the Human Immunodeficiency Virus. Gen Thorac Cardiovasc Surg. 2008 Sep;56(9):465-7.
54. Chong T, Alejo DE. Cardiac valve replacement in Human Immunodeficiency Virus infected patients. Ann Thoracic Surg 2003; 76(2):478-480.
55. Frater RW, Comacho M, Frymus M, et al. Cardiac surgery in the patient with Human Immunodeficiency Virus. Adv Cardiol 2003; 40:219-25.
56. Lipshultz SE, Fisher SD, Lai WW. Cardiovascular monitoring and therapy for HIV infected patients. ANN NY Acad Sc I 2001;946: 236-273.
57. Beschorner WE, Baughman K, Turnicky RP, et al. HIV associated myocarditis. American Journal of Pathology, Vol. 137, No. 6, December 1990.
58. Rickerts V, Brodt H, Staszewski S, et al. Incidence of myocardial infarctions in HIV infected persons between 1983 and 1998: the Frankfurt HIV cohort study. Eur J Med Res 2000;5:329-333.
59. Aris A, Pomar JL, Saura E. Cardio-pulmonary bypass in HIV positive patients. Ann Thorac Surg. 1993 May;55(5):1104-7.
60. Palella FJ Jr, Baker RK, Moorman AC, et al. HIV outpatient study investigators. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr. 2006 Sep;43(1):27-34.
61. Condit D, Frater RW. Human Immunodeficiency Virus and the cardiac surgeon: a survey of attitudes. Ann Thorac Surg. 1989 Feb;47(2):182-6.
62. [No authors listed] Suit says patient was denied surgery because of HIV Aids policy law. 1997 May 16;12(9):3.
63. Davison SP, Reisman NR, Pellegrino ED, et al. Peri-operative guidelines for elective surgery in the Human Immunodeficiency Virus positive patient. Plast Reconstr Surg. 2008 May;121(5):1831-40.
64. Tran HS, Moncure M, Tarnoff M, et al. Predictors of operative outcome in patients with Human Immunodeficiency Virus infection and Acquired Immunodeficiency Syndrome. Am J Surg. 2000 Sep;180(3):228-33.
65. Chêne G, Sterne JA, May M, et al. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. Lancet 2003 Aug 30; 362(9385):679-86.