Echocardiographic features of the complications of Infective Endocarditis with special reference to patients with HIV

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DECLARATION

I hereby declare that this work is original, with assistance from Professor D.P.Naidoo.

The work has not been previously submitted to your, or any other institution.

Signed: .....

Date: 22/08/2008

DEDICATION

To the Almightly Father, through whom, all things are possible.

To my parents, who taught me to always count my blessings instead of my disappointments.

To my family and friends, for their endless support.

To the late Dr Manene Mbizeni, a mentor and a friend.

PRESENTATIONS

The preliminary findings of this project were presented at the following conferences:

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Seventh Annual Congress of the South African Heart Association, Cape Town, 2006.

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PREFACE

Echocardiography plays a vital role in the haemodynamic assessment and structural complications of infective endocarditis. This tool is central to the diagnosis and management of patients with endocarditis, as echocardiographic evidence of an oscillating intracardiac mass or vegetation, an annular abscess, prosthetic valve partial dehiscence, and new valvular regurgitation, are major criteria in the diagnosis of infective endocarditis[5].

By emphasizing the appropriate use of echocardiography, as an essential adjunct to clinical criteria, the practitioner will be guided in early diagnosis of the disease, thereby having substantial prognostic implications on a patient. When this study was planned, it was thought that HIV status influences the patient's predisposition to developing endocarditis. With this study, it was hoped that the prevalence of complications and incidence of infective endocarditis in immunocompromised patients would be determined.

The study protocol was submitted to the Nelson R Mandela Research Ethics Committee, and that committee has granted approval. The study has been structured in accordance with the Declaration of Helsinski (2000), which deals with research involving human subjects.

ABSTRACT

Purpose: The aim was to determine the echocardiographic features of patients with infective endocarditis, and to compare the findings in HIV positive versus HIV negative patients.

Methods: This was a prospective study, conducted over three years using the modified Duke criteria in diagnoses. A control group of age-matched patients with clinical and echocardiographic evidence of valvular regurgitation, who did not satisfy the criteria and who underwent surgery was used in comparison.

Results: During this period 91 patients were screened for infective endocarditis. 77 satisfied the criteria for a definite diagnosis of IE. Blood cultures were positive in 46% cases. The commonest organism was *S. aureus*. Most patients had advanced valve disruption with heart failure and a high peri-operative mortality. The clinical features in the two groups of patients was similar. The incidence of echocardiographic complications was 50.6% in the whole group. Except for leaflet aneurysms in four HIV positive cases, complications were not more frequent in this group.

Conclusion: There was a high rate of culture negative cases in this study, probably related to prior antibiotic usage; in this setting the modified Duke criteria have diagnostic limitations. There was no difference in the clinical presentation of infective endocarditis between HIV positive and HIV negative patients. Leaflet aneurysms were more common in the HIV positive patients.

CHAPTER 1

INTRODUCTION:

1.1 Epidemiology:

Infective endocarditis (IE) is an infection of the endocardial surface of the heart, and is caused by the adherence of organisms to damaged endocardium.[1, 2] It usually refers to microbial, bacterial or fungal infection that occurs as a result of colonization of the endothelium by microorganisms.[3] Major predisposing factors to endocarditis are underlying cardiac structural valvular abnormalities, such as rheumatic heart disease, including the presence of prosthetic heart valves, and central venous access which provide a nidus for the infecting organism.[4] IE is characterised by many clinical features, none of which are specific for the condition, and therefore the diagnosis is determined by the presence of multiple findings, rather than a single test result.[5]

Important developments during the last twenty years have facilitated rapid and accurate diagnosis, and have shown that early aggressive treatment is associated with improved survival.[6] Developments in antibacterial therapy, clinical microbiology, cardiac imaging and cardiac surgery have revolutionized the diagnosis and prognosis of IE.[1] With the introduction of antibiotics, the mortality rate has decreased to 24%, so much so that heart failure from valve damage, rather than uncontrolled infection, has now become the leading cause of death.[7] IE remains a challenging condition however, especially when non-specific clinical features predominate at the time of presentation.[6]

Major trends that have created new challenges include the emergence of prosthetic valve endocarditis, intravascular device-related endocarditis, an increase in antibiotic resistance among aetiologic organisms, increased patient ratio with comorbid conditions such as diabetes, dialysis-dependant renal failure, and drug abuse.[8] From a microbiological standpoint, the rise in *staphylococcal* infections, and the immune status associated with acquired immune deficiency syndrome (AIDS) pose diagnostic challenges that also have important implications for management.[8]

1.2 Predisposing factors:

1.2.1 Underlying cardiac conditions:

The correlation between pre-existing cardiac disease, the presence of bacteremia, and the likelihood of an onset of IE, was first described as early as 1923.[9] IE is higher in patients with existing valvular heart disease, prosthetic cardiac valves or congenital heart disease, and is more common in the male than the female population.[3] There are sparse data available for the developing countries. Even with the introduction of prophylaxis, the incidence of IE is currently estimated between 1.9 and 6.2 infections per 100 000 persons of the general population in the Western countries.[6, 9]

Three main haemodynamic factors predispose a patient to infection, and these are a high-velocity jet stream; flow from a high to a low-pressure chamber; and a narrow orifice that separates two chambers, creating a pressure gradient.[3] These factors are found in patients with valvular heart disease and shunts such as ventricular septal defects (VSD) and patent ductus arteriosus (PDA), which predispose a patient to

developing IE.[3] Mylonakis and Calderwood have risk-stratified cardiac abnormalities that are substrates for IE.[2] Associated high-risk predisposing conditions are previous IE, aortic valve disease, rheumatic heart disease, prosthetic valves, coarctation of the aorta, and complex cyanotic congenital heart disease.[2] Moderate-risk conditions are mitral valve prolapse with valvular regurgitation, leaflet thickening, isolated mitral stenosis, tricuspid valve disease, pulmonary stenosis, and hypertrophic obstructive cardiomyopathy.[2] Low or no-risk conditions are secundum atrial septal defects (ASD), ischaemic heart disease, previous coronary artery bypass, and mitral valve prolapse with thin leaflets and absent regurgitation.[2]

1.2.2 Factors predisposing to infection:

Certain patients, who are at high risk of infection, tend to be at an increased risk of developing IE. These include burn patients, patients undergoing bone marrow transplant, or any other organ transplant patients with arterio-venous (AV) shunts undergoing chronic haemodialysis, as well as those with permanent pacemakers.[10] Poor dental hygiene and diabetes mellitus are also conditions associated with an increased incidence of IE.[2] Intensive care unit (ICU) care predisposes patients to IE by means of surgery, pressure monitoring catheters, and other intravascular devices.[10] There is a high risk of IE with mechanical heart valves during the first three months of surgery, compared to the bioprosthetic valves.[2]

IE is also known to occur in patients with normal valvular structures. In this instance IE usually follows a fulminant infection, such as *staphylococcal* infections. This is

particularly true in right-sided IE. In the setting of normal cardiac valves, IE is also known to occur in patients with chronic alcoholism.[9] This is presumably due to loss of the bacterial filtration of the normal liver.[9] Similarly, the profound immunosuppresion found in AIDS predisposes these patients to multiple opportunistic infections and malignancies, including IE.[11]

According to Levy, et al, the risk of Human Immunodeficiency Virus (HIV) positive patients developing IE is related to their degree of immunodeficiency.[12] The decreased cluster of differentiation counts (CD4) common to HIV patients is likely to increase their risk of developing endocarditis.[12] Very little else is known about the nature of the infecting organisms and the pattern of disease in the immune-suppressed HIV positive patients. Neither is much known about the nature of complicating IE in patients with underlying valvular heart disease who are also HIV positive.

1.3 Diagnosis:

A precise diagnosis of IE is mandatory to guide therapy.[13] Rapid diagnosis, effective treatment and prompt recognition of complications are essential for a good outcome of IE, which carries a high morbidity and mortality rate.[14]

In the presence of bacteremia, valve involvement, peripheral emboli and vascular phenomena, the diagnosis of IE is straightforward.[15] When coexisting diseases mask the features of this disease process, a delay in diagnosis or misdiagnosis is common.[5]

The diagnosis of this disease requires the integration of clinical, laboratory and echocardiographic data.[2]

However, due to the variability in the clinical presentation of this disease, diagnostic criteria need to both sensitive and specific across all forms of the disease.[15] Previously developed strategies were fraught with loopholes, until the advent of the Duke criteria.[15] The Duke criteria surpassed other criteria previously used in the diagnosis of IE, as it emphasised the role of echocardiography, which is the key imaging tool for both diagnosis and assessment of prognosis.[16] The lack of a valid method to classify prognostic severity makes management decisions problematic.[7]

To diagnose IE, the Duke criteria require 2 major, 1 major and 3 minor, or 5 minor criteria. This classification stratifies patients into 3 categories: **definite** cases (proven at surgery), **possible** cases (not meeting definite criteria), and **rejected** (no evidence at surgery).[15] Three criteria used for rejecting a diagnosis of IE are: (1) a firm alternate diagnosis for manifestations of IE, (2) clinical manifestations compatible with IE that resolve $\leq$ 4 days of antibiotic therapy, and (3) no pathologic evidence of IE found at surgery.[17]

Durack, et al modified the Duke criteria for the diagnosis of IE and proposed 4 categories: **definite** (intended to identify patients with a very high probability of having a true-positive diagnosis), **possible** (for cases consistent with IE that fall short of definite by clinical criteria, but are not rejected), **probable** (includes patients who

have received more than 4 days of antibiotic therapy), and **rejected** (where there appears to be resolution of the manifestations of endocarditis, with 4 days or less of antibiotic therapy).[18]

According to the modified criteria, even in the face of negative blood cultures, the presence of 1 major and 2 minor criteria, support a diagnosis of 'definite' IE, provided there are typical echocardiographic findings.[19] A recent scientific statement by the American Heart Association (AHA) recommended that these criteria be used in the clinical evaluation of patients with suspected IE.[16]

Echocardiography is an important diagnostic tool to assess the extent and haemodynamic sequelae of valve damage, cardiac complications and to assist in the management of IE.[20] The usefulness of this modality extends to the detection of complications, evaluation of cardiac size and function, the establishment of a reference point for future observations, and the re-evaluation of patients after intervention.[21] The echocardiographic assessment of structural complications include valvular disruption (commonly seen with vegetations and flail leaflets), aneurysm formation (occurs as a result of regurgitant jets creating secondary sites of infection), perivalvular abscess formation (common in acute endocarditis), fistulae (created by aneurysms and abscess rupture), coronary artery obstruction (due to vegetation fragments embolizing), purulent pericardial effusion, and dehiscence of a prosthetic valve.[15] It also permits assessment of haemodynamic complications which include

valvular regurgitation, premature mitral valve closure, restrictive mitral inflow pattern, valvular stenosis, shunts, congestive heart failure, and systemic embolization.

1.4 Limitations to Diagnosis:

Misdiagnosis or a delayed diagnosis is common and is usually the result of variable clinical presentation.[10] When valvular destruction is severe, patients present with signs and symptoms of pulmonary congestion from heart failure, and the diagnosis is then easily localized to the heart valves. In cases of right-sided endocarditis, pulmonary embolic phenomena and clinical signs of pneumonia predominate, and with left- sided endocarditis, embolised vegetations may present with central nervous system symptoms (e.g.stroke), pleuritic or abdominal pain, thereby directing attention away from the heart.[9]

Furthermore, although fever is a common presenting symptom of IE, it may be absent. Fever varies from very high temperatures associated with rigors, to a prolonged febrile state associated with weakness and loss of weight.[9] Fever may be absent in congestive heart failure, severe debility, chronic renal or liver failure, previous use of antimicrobial drugs, or IE caused by less virulent organsisms.[2] IE in the elderly and in the immunocompromised patient has an atypical presentation since fever is often absent in this group of patients.[22]

Since a defining feature of endocarditis is bacteremia, blood cultures are considered one of the most important tools in making the diagnosis of endocarditis.[23] Positive

blood cultures are considered major diagnostic criteria, and allows for the identification of the aetiologic agent.[24] While true negative cultures rule out the diagnosis of endocarditis, blood cultures alone fail to isolate an aetiologic agent in 2.5% to 31% of cases.[23, 25] New diagnostic approaches which include cultures and microbiological assessment of vegetations yield a better understanding of blood culture negative endocarditis.[2] In other published series, negative blood cultures however, are found in at least 20% of endocarditis patients.[24] Using standard microbiological culture techniques, culture-negative endocarditis is associated with antibiotic use, or the presence of an intracellular pathogen, which is not usually detectable.[23] The *Bartonella*, *Coxiella burnetti*, and *Brucella species* are usually the most commonly identified species associated with culture-negative endocarditis, caused by fastidious organisms.[24] In the presence of toxicity with high fever, a new regurgitant murmur, congestive heart failure (CHF) and evidence of peripheral embolisation, empirical therapy is usually initiated while awaiting the results of blood culture.[10]

In addition to the over-diagnosis that accompanies the above approach, certain illnesses may mimic IE leading to misdiagnosis. These include neoplasias (atrial myxoma, marantic endocarditis, neoplastic disease and carcinoids), autoimmune disease (rheumatic carditis, systemic lupus erythematosus [SLE]), polyarteritis nodosa, and Behcets's), following valvular surgery (intracardiac thrombi, surgical sutures, and fibrin strands), and lastly, miscellaneous causes (eosinophilic heart disease, ruptured mitral chordae, and myxomatous degeneration).[24]

While the presence of risk factors are important in raising the suspicion of IE, they do not contribute to the criteria used by the clinician in making the clinical diagnosis.[26] There have been known cases where fever, symptoms of IE, and positive blood cultures for certain organisms are obtained, and the diagnosis of IE is not made, even though the risk factors are present.[26] Furthermore, in the setting of HIV infection, IE maybe caused by unusual organisms, such as *barbonella*, *salmonella*, and *listeria*.[1] Bacteremia is said to be common in the HIV positive patients, due to the numerous immunologic defects present in this disease.[27] This raises the question whether IE may present differently in HIV positive patients.

1.5 Problem overview:

Until recently, cardiac involvement in HIV infection has received little attention.[12] Studies have confirmed that cardiac abnormalities are more common in HIV-infected people.[28] Many cases of heart muscle disease related to HIV infection seems to be related to an idiopathic lymphocytic myocarditis.[29] Other potential pathogenic factors include nutritional deficiencies, opportunistic infections, and cardiotoxic effects of antiretroviral drugs.[29]

The prevalence of IE in the HIV-infected population is assumed to be similar to patients found in other risk groups, and is estimated at 6.3% to 34%.[30] IE is reported to be common in advanced HIV patients, and mortality increases with a decreasing CD4 count.[10] According to a study by Himelman[31], et al, cardiac lesions were found to be uncommon in ambulatory HIV positive patients, despite prior opportunistic infection,

with the exception of mitral valve prolapse. The study by Himelman[31] further suggests that echocardiographically detectable lesions, especially cardiomyopathy was found to be more common in the patients classified as having AIDS. Many of the cardiovascular findings of AIDS however are still being elucidated.[11] Since not much is known about the pattern of cardiac involvement of IE in patients with HIV, we performed an echocardiographic evaluation to further elucidate this problem.

It is known that the degree of immunosuppression, manifested by a reduced CD4 lymphocyte count, strongly correlates with the presence of echocardiographic abnormalities.[12] An increased risk of IE has not been encountered in children with congenital or acquired immuno-deficiencies.[32] The immunosuppression associated with HIV may alter the clinical picture of valvular heart disease, particularly IE. Therefore, a clearer understanding of the pathogenesis of IE, treatment, and supportive care becomes essential. The documented increase in the prevalence of HIV-associated cardiac disease, supported by echocardiographic studies, calls for a careful cardiological evaluation to determine the pattern of involvement of the heart in the HIV-positive subjects, who develop IE, even in patients in the early phases of the HIV disease.[33]

Regarding IE in HIV positive patients, several issues require further clarification:

1. The echocardiographic characteristics of valve involvement.
2. Whether HIV positive patients have a different clinical presentation.
3. The value of conventional diagnostic criteria.

4. Clinical outcomes of IE in HIV positive patients.

CHAPTER 2

2.1 AIM:

The aim of this study was to compare clinical and echocardiographic features of IE in patients with and without concomitant HIV infection.

2.2 HYPOTHESIS:

It is hypothesized, that infective endocarditis in HIV positive patients is associated with a higher rate of cardiac complications, when compared with HIV negative patients.

2.3 OBJECTIVES:

1. To describe the echocardiographic features of infective endocarditis in HIV positive patients.
2. To compare the type and prevalence of complications of infective endocarditis in HIV positive versus that in HIV negative patients.
3. To determine the outcome of treatment in HIV positive patients.

CHAPTER 3

MATERIALS AND METHODS:

3.1 Research procedure:

The study was prospective in nature and screened a total of ninety-one patients with features of suspected IE between 2004 and 2007. Only patients with a definite diagnosis of IE according to the modified Duke criteria were enrolled for the purpose of the study. Inkosi Albert Luthuli hospital (IALCH) is an eight hundred and forty-two bed, tertiary referral centre, serving a Kwa-Zulu Natal (KZN) population of ten million people, who are of a mixed decent. Patients were excluded if they refused participation in the study, and if they refused HIV testing. One patient refused to participate in the study.

Patients with a clinical diagnosis of IE had an initial examination by transthoracic echocardiography (TTE), to exclude echocardiographic evidence of infection (vegetations, paravalvular extension, prosthetic valve dehiscence), haemodynamic compromise (valvular dysfunction, ventricular dimensions and ventricular function), and to determine the presence of potential risk factors such as congenital, valvular or degenerative heart disease. Leaflet or cuspal thickening, with areas of calcification found at TTE was regarded as suggestion of previous rheumatic heart disease. Where TTE images were suboptimal, such as mechanical prosthetic valves, and if paravalvular extension was suspected, transesophageal echocardiography (TEE) was performed within 24 to 48 hours of admission. (Appendix 1a and 1b are the information leaflets and consent forms used for the purpose of the study, as part of the patient recruitment procedure).

The diagnosis of IE was made by clinical criteria including echocardiography, as well as pathological results (Appendix 2).

3.1.1 Pathological criteria:

Pathological criteria refer to the demonstration of microorganisms in vegetations or abscesses, or pathological lesions with confirmatory histology. The organisms were identified by standard culture practices used in the microbiology laboratory at IALCH. Standard aerobic and anaerobic culture media were used for culturing of all organisms, as the aerobic plus culture medium was not available at this facility. Specimens were incubated for five days to ensure detection of possible fungal infections.

3.1.2 Clinical criteria:

The clinical criteria (modified Dukes) consist of major and minor criteria, which may include 2 major, 1 major and 2 minor or 5 minor criteria.[8] These criteria are as follows:

Major criteria:

1. Positive blood cultures with organisms typical for endocarditis

2. Evidence of endocardial involvement

Minor criteria:

1. Predisposing heart disease

2. Fever > 38 °C

3. Vascular and immunological phenomena

4. Microbiological evidence not meeting major criteria

5. Elevated erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) levels

6. Splenomegaly, clubbing, splinter heamorrhages, and petechiae

7. Central and pheripheral venous access

8. Organisms from metastatic lesions and heamaturia.[34]

After the clinical diagnosis of IE had been made, an echocardiogram was performed on a Sequoia C256 (Acuson, Germany) cardiac ultrasound machine, using a 5MHz transthoracic transducer for TTE, and a 7MHz multiplane transesophageal probe for TEE. The patients were assessed for the presence of vegetations, severity of valvular involvement and evidence of complications. These included annular extension of infection, root abscesses, leaflet aneurysms and tears, fistulae, intracardiac shunts, and pericardial effusions. Adjustment of gain settings and use of the correct transducer frequency was made where necessary to reduce or avoid misdiagnoses. Harmonic imaging (HI) is a modality that is based on the principle of receiving double the emitted ultrasound frequency (second harmonic), and compared with fundamental imaging (FI), HI has a better signal to noise ratio between the cavity and wall, with a reduction in the near field clutter, leading to improved endocardial border delineation and higher image resolution of valve structures.[35] This modality was used during the echocardiographic examinations of all participants, where better delineation of the endocardial borders was thought to enhance the resolution of mobile structures.

3.2 Study participants:

All patients with suspected IE were referred from hospitals in KZN (Appendix 3) to the Department of Cardiology at IALCH. The patients were assessed by clinicians who documented the clinical features of IE. These included pallor; weight loss, splinter hemorrhages (found beneath fingernails and toenails), clubbing of fingers and toes, non-specific joint pain, petechia (small purpuric spots of blood beneath the skin surface) found on the legs and chest, Roth spots (small white spots seen in the retina), Osler's nodes (small, swollen, tender area found on the fingers or toes), and rarely, Janeway lesions, which are raised nodular haemorrhagic lesions that are relatively painless.[4] Blood sampling was performed for estimation of ESR, CRP, serum complement (C3 C4), and blood cultures. Urine was tested for microscopic haematuria. Twelve-lead electrocardiograms were performed on almost all of the patients, to exclude the presence of arrhythmias.

All study participants were tested for HIV (the diagnosis of HIV was determined by an ELISA test), after adequate pre-test counseling by a qualified counselor. If the results were positive, a CD4 count was done. CD4 counts were obtained for all HIV-positive patients. The stage of HIV infection was assessed using both clinical features and the level of CD4 count. A team of physicians, cardiologists, microbiologists, cardio-thoracic surgeons and councilors were involved in the care of these patients, especially those requiring cardiac surgery.

A broad description of the echocardiographic features of IE was documented for the

study population as a whole. Patients were then classified based on their HIV test result and the clinical features, laboratory results and echocardiographic findings compared in the two groups (Appendix 4).

The research study was done on patients who had consented to participate, and who had consented to HIV testing. If patients declined HIV testing, they were excluded from the study. These patients were then referred back to their district level hospitals for appropriate follow-up programs.

3.3 Echocardiographic analysis:

The subsequent paragraphs are a description and elaboration of the echocardiographic features that were used for the purpose of the study.

(i) Vegetation

A vegetation was defined at echocardiography as a discrete echogenic mass seen adherent to a point on the valve leaflet, with distinct characteristics from the leaflet.[36] When identified , vegetations were characterized by four physical properties; (1) **size**; (2) **mobility**, further classified as fixed, fixed at base, pedunculated, or prolapsing; (3) **extent**, determined by single, multiple, involving multiple leaflets, and extention to extravalvular structures; (4) **consistency**, defined as complete calcification, partial calcification, denser than the myocardium without calcium, and consistency equal to the myocardium.[36]

[Figure 1(a), 1(b), 1(c), 1(d) and 1(e)]

(ii) Leaflet aneurysm

An aneurysm, particularly of the mitral valve, was defined as a saccular cavity bulging towards the left atrium in systole, which collapsed during diastole.[9]

[Figure 2(a) and 2(b)]

(iii) Abscess

An abscess was considered to be present when echolucent cavities within the valve annulus or adjacent myocardium were found in the setting of valve infection.[35] The recommended criteria for echocardiographic evidence of aortic root abscesses are:

- prosthetic valve 'rocking'
- aneurysms in the region of the sinus of valsalva
- thickness of the anterior and posterior wall of the aortic root >10mm
- a perivalvular density in the septum >14mm.[37]

[Figure 3 (a) and 3(b)]

(iv) Fistula

Under the influence of systemic intravascular pressures abscesses can progress to fistulous tracts, creating intracardiac shunts.[15] A fistula was considered to be present when colour Doppler showed the presence of abnormal flow communicating a great vessel to the cardiac chambers.[35]

[Figure 3c]

(v) Pericardial effusion

The presence of a pericardial effusion, (an echolucent space between the epicardium and pericardium) the amount and distribution of fluid can be demonstrated on an echocardiogram.[21] When present, the size, and the echogenicity of the effusion was determined.

[Figure 4(a) and 4(b)]

(vi) Leaflet or cuspal perforation

A perforation was considered to be present when an interruption of echoes was recognised along the leaflet, or cuspal surface, as defined by Taams, et al.[38]

(vii) Ruptured chord

The presence of a chordal rupture was recognised by the 'whipping' systolic motion of a leaflet tip, with failure of leaflet coaption.[38]

After the procedure an assessment was made as to whether the patient had echocardiographic indications for surgical intervention. Three echocardiographic features suggesting the potential need for surgery in patients with IE were examined:

(1) **vegetations** – persistent vegetations after systemic embolization, particularly >10mm, showing an increase in size after four weeks.

(2) **valvular dysfunction** – perforation or leaflet rupture, valvular insufficiency with signs of ventricular failure, unresponsive to medical therapy.

(3) **paravalvular extension** - valvular dehiscence; rupture or fistula formation with

new heart block, and large abscesses.[15]

3.4 STATISTICS

This is both a descriptive and an analytical study of the echocardiographic findings in IE. Simple comparisons of the clinical and echocardiographic features were made of the findings in HIV positive and HIV negative patients. Comparisons between HIV positive and HIV negative patients for categorical outcomes (e.g. valvular assessment) were evaluated by means of chi squared tests or Fischer's exact tests. Where the outcome was numerical (e.g. CD4 count) Mann-Whitney tests were used to compare mean ranks in the HIV positive and HIV negative groups. The t test was used to determine the differences between samples. The significance level (p value) was taken at 0.05. Baseline characteristics of all patients were evaluated to identify any underlying risk factors, and to determine the mean age and gender distribution (Appendix 5).

3.5 ETHICS

The study protocol was approved by the Nelson R Mandela Research Ethics Committee (H095/04), and permission for the study received approval from the hospital board, at IALCH. The study has been structured in accordance with the Declaration of Helsinski (2000), which deals with research involving human subjects.

CHAPTER 4

RESULTS:

4.1 Diagnostic Stratification

Of the ninety-one patients screened for suspected endocarditis, a total of seventy-seven patients were classified with a 'definite' diagnosis of IE, nine as 'possible' endocarditis, and five as 'rejected' endocarditis, according to the modified Duke criteria. All consented to HIV testing and inclusion in the study: seventeen were HIV positive, and sixty were HIV negative. The diagnosis and the descriptive features in these patients is based on the modified Dukes and for comparison, the Dukes criteria is shown below (table 1).

Table 1: Duke criteria versus modified Duke criteria

	Duke			**Modified Duke**		
	HIV(+) n=18 (%)	**HIV(-)** n=73 (%)	**Total** 91	**HIV(+)** n=18 (%)	**HIV(-)** n=73 (%)	**Total** 91
Definite	16 (88.9)	47 (64.4)	63	17 (94.4)	60 (82.2)	77
Possible	2 (11.1)	21 (28.8)	23	1 (5.6)	8 (10.9)	9
Rejected	0 (0)	5 (6.8)	5	0 (0)	5 (6.8)	5

Amongst the HIV positive patients, seventeen were classified as 'definite' IE, and the remaining one, as 'possible' IE. This patient had one major criterion (vegetations on the aortic valve) and one minor criterion, which was an elevated ESR level. Twelve patients were lost to follow-up (seven HIV negative, and five HIV positive). Of these ten were classified as 'definite' IE, and two as 'possible' IE. Five of the HIV positive patients underwent surgery, four were 'definite' IE, and one was 'possible' IE. The surgical findings were positive for the four 'definite' cases, while in the remaining HIV

positive patient with 'possible' endocarditis there was no evidence of IE: the valve cusps were normal with failure of coaption.

Amongst the HIV negative patients, sixty were classified as 'definite' IE, and eight as 'possible' IE. Five patients were rejected, because of only one major criterion with no minor criterion (two), or because of only one to two minor criteria (three). These major criteria were vegetations of the mitral valve in one patient, and vegetations of the tricuspid valve in the other patient. Of the thirty-four HIV negative patients referred for surgery, twenty-nine were 'definite' endocarditis, four were 'possible' endocarditis, and one was 'rejected' endocarditis.

From the nine 'possible' endocarditis patients, four had surgery for valve replacements, one had a PDA ligation, and the remaining four had ultimate diagnoses of rheumatic heart disease. Of the five 'rejected' endocarditis patients, one had surgery for a valve replacement, one was diagnosed as an Ebsteins anomaly, and the remaining three diagnoses were rheumatic heart disease.

One patient with definite *staphylococcus aureas* (*S. aureas*) endocarditis, secondary to an infected central venous line, was excluded from initial screening because he declined participation in the study.

4.2 Demographic data

The mean participant age in the whole group was approximately thirty years, and there were no significant differences in age, admission weight (61kg vs. 59kg), and temperature (36.5°C vs. 37°C) between the HIV positive and HIV negative patients. Overall, there was a slight male predominance for the occurrence of IE in both groups of patients, 54.5% (n=42) were male and 45.5% (n=35) were female. Despite the fact four patients had AIDS as defined by the Centre for Disease Control (CDC) criteria at presentation, none of the patients in the HIV positive group had significant weight loss (table 2).

Table 2: Demographic comparison of HIV positive and HIV negative patients

	HIV (+) n=17 (%)	**HIV (-)** n=60 (%)	**P value**
Age	32 (22 – 50)*	31 (12 – 64) *	.867
Gender - male	9 (53)	33 (55)	1.000
- female	8 (47)	27 (45)	
Weight	61 (41 – 82) *	59 (43 – 79) *	.585

*** Mean values with the ranges bracketed.**

4.3 Clinical parameters

Of all the clinical stigmata of IE, clubbing and heart failure were the most common, found in forty-three (55.8%) patients, and thirty-three of (42.9%) patients respectively. In both the HIV positive and HIV negative patients, clubbing was the most common extracardiac feature. Although the presence of fever was found to be higher in the HIV positive patients, only four patients had temperatures above 38^0C. Embolic phenomena

or stroke, occurred in three patients in the HIV positive and six in the HIV negative group; the differences were not statistically significant.

Regurgitant murmurs were documented in all but one patient, who had repeated blood cultures positive for *propriobacterium.* Hepatomegaly mirrored the findings of congestive heart failure and was found in five (29.4%) HIV positive patients, and in twenty-eight (46.7%) HIV negative patients (table 3). First degree heart block was seen in the twelve lead electrocardiograms of fifteen patients, complete heart block was found in one patient, an intraventricular conduction defect was found in five patients, and one patient had a ventricular trigeminal rhythm. The remaining electrocardiograms showed right bundle branch block (n=3), left bundle branch block (n=4), sinus tachycardia (n=5), sinus bradycardia (n=1), left ventricular hypertrophy (n= 10), left atrial enlargement (n= 2), right atrial enlargement (n=1), ventricular extra systoles (n= 5), junctional rhythm (n=1), atrial fibrillation (n=2), and seven patients had normal findings.

Table 3: Clinical features

Parameter	**HIV (+)** n=17 (%)	**HIV (-)** n=60 (%)	**Total** n=77 (%)	**P value**
Fever	4 (23.5)	3 (5)	7 (9.1)	.024
Clubbing	11 (64.7)	32 (53.3)	43 (55.8)	.102
Splinter haemorrhages	2 (11.8)	3 (5)	5 (6.5)	.304
Emboli / stroke	3 (17.6)	6 (10)	9 (11.7)	1.000
Splenomegaly	2 (11.8)	3 (5)	5 (6.5)	
Heart failure	5 (29.4)	28 (46.7)	33 (42.9)	.204

4.4 Laboratory results:

The ESR and CRP were markedly elevated in all patients, the degree of elevation being higher in the HIV positive patients. The haemoglobin level was lower in the HIV positive group but the differences were not statistically significant. Overall, thirty-seven (48%) of the patients had a positive result for rheumatoid factor. The serum complement (C3) was significantly lower in the HIV negative group ($p = 0.001$); this was probably due to the lower serum albumin in this group. There was no difference in the white cell counts between the two groups (table 4). Significantly elevated counts were recorded in fourteen HIV negative and in four HIV positive patients. Markedly elevated counts were recorded in patients infected with *S.aureus* (four HIV negative and one HIV positive), two *staphylococcus epidermis* (*S. epidermis)* (both HIV negative), three *pseudomonas aeruginosa (P. aeruginosa)* (all HIV negative), four *streptococcus viridans* (*S. viridans)* (all HIV negative), one *serratia marcescens* *(S. marcescens)* (HIV negative), and three with negative blood cultures, who were HIV positive.

Table 4: Laboratory results

Lab findings	HIV (+) n=17 (%)	HIV (-) n=60 (%)	P value
White blood count (/l)	7.7 (2.46 – 23.14)	8.7 (4 – 29.4)	.387
Lymphocyte (/l)	2.76 (0.44 – 18.2)	2.93 (0.26 – 6)	.548
Platelets (/l)	273 (123 – 449)	229 (40 – 432)	.675
Haemoglobin (mg/dl)	8.92 (5 – 11.2)	10.76 (6 – 14.2)	.119
Sedimentation rate (mm/Hr)	110.8 (65 – 142)	62.5 (6 – 160)	.024
C-reactive protein (mg/L)	95.19 (0.17 – 265.3)	52.6 (0.02 – 336.4)	.018
Urea(mmol/l)	7.6 (3 – 192)	13.87 (1.4 – 28.3)	.091
Creatinine (mmol/l)	131.6 (57 – 770)	201.42 (43 -851)	.301
Serum albumin (g/dl)	26.94 (18 – 36)	31.35 (0.57 – 49)	.031
Complement 3 (g/l)	1.48 (1.1 – 1.77)	1.09 (0.15 – 1.8)	.001
Complement 4 (g/l)	0.308 (0.13 – 0.46)	0.25 (0.01 – 0.52)	.120
Rheumatoid factor (+)	4 (23.6%)	33 (55%)	.052
Haematuria	3 (17.6%)	19 (31.7%)	

All are mean values with the ranges bracketed, except rheumatoid factor and haematuria

4.5 The Infecting Organism

Thirty-five patients (46.7%) had positive blood cultures; twenty-eight of these were from the HIV negative patients, and seven were from the HIV positive patients.

S. aureus was the most common infecting bacterium for the both groups of patients, and was found overall in sixteen (45.7%) of those with positive cultures. Of these, twelve were HIV negative patients, and four were HIV positive. The second most common infecting bacterium was *S. viridans*; seven patients (20%) were infected with this bacterium. Of these one was in the HIV positive patients, and six in the in the HIV negative patients. Two HIV positive patients were infected with unusual organisms (*propionibacterium* and *streptococcus faecalis [S. faecalis])* (table 5). All patients received appropriate antibiotic treatment at the referring hospitals for infective

endocarditis. The standard treatment in culture negative cases was penicillin plus aminoglycoside administered intravenously. The exact doses could not be retrieved.

Table 5: Infective Organism

Bacterium	**HIV(+) n=17**	**HIV (-) n=60**	**Total**
Staph aureus	4	12	16
Strept viridans	1	6	7
Staph epidermis	-	4	4
Moraxella catarrhalis	-	1	1
Pseudomonas aeruginosa	-	3	3
Serratia marcescens	-	1	1
Propionibacterium	1	-	1
Streptococcus faecalis	1	-	1
Corynebacterium	-	1	1
Culture-negative	10	32	42
Total	17	60	77

The underlying valve morphology was studied carefully to determine whether there was any evidence of previous disease. In most instances the infected valve was thickened, suggesting a rheumatic aetiology. *S. aureus* was the bacterium found to be most common in these cases (table 6). In eighteen cases (ten HIV negative and eight HIV positive) the valve leaflets were thin and mobile, and therefore thought to be normal. The presence of excess valve echoes with prolapse indicated the prolapsing leaflet syndrome in six patients (two HIV positive and four HIV negative).

Table 6: Organisms affecting normal and abnormal valves

	HIV(+)		HIV(-)	
Organism	**Normal valves**	**Thickened valves**	**Normal valves**	**Thickened valves**
S. aureus	2	2	2	10
S. viridans	1	-	-	6
Staph epidermis	-	-	-	4
M. catarrhalis	-	-	1	-
P. aeruginosa	-	-	1	1
Serratia marcescens	-	-	-	1
Propionibacterium	1	-	-	-
S. faecalis	1	-	-	-
Corynebacterium	-	-	1	-
Culture-negative	3	7	5	25
Total	8	9	10	47

Three HIV negative patients had prosthetic IE; one of them had *Pseudomonas aeruginosa IE*

4.6 Echocardiographic findings

All but one patient (n=76) had findings suggestive of infective endocarditis on TTE. These positive findings included the presence of vegetations, root abscesses or leaflet aneurysms. Overall, sixty patients had echocardiographic features suggestive of rheumatic heart disease: of these fifty-one were HIV negative, and nine were HIV positive. These echocardiographic features included thickened valves, failure of leaflet coaption, and leaflet prolapse, which were regarded as possible predisposing factors to infection. Congenital defects were found in five patients, three of whom were patients with VSD (1 HIV positive and 2 HIV negative). Of the remaining 2 patients, 1 had a bicuspid aortic valve, and the other a PDA, both of whom were HIV negative.

Fifty-four (70.1%) patients had a TEE (which was used as an additional confirmatory tool to exclude the presence of cardiac complications), of whom fifty-one had features to suggest IE. The remaining three patients with negative findings at TEE had thickened calcified valves (1), thickened leaflets with chordal rupture (1), and the last one had a normal valve.

4.6.1 Vegetations

Vegetations were the predominant finding in sixty-eight (88.3%) patients at echocardiography (table 7). Vegetations were found in eleven (64.7%) of the HIV positive patients, and in fifty-seven (95%) of the HIV negative patients. The remaining nine patients (six HIV positive and three HIV negative patients) showed no evidence of any vegetation, but had other features suggestive of IE. These were leaflet aneurysms in four and aortic root abscesses in five cases; the remaining patient had a disrupted aortic valve without the presence of vegetations.

Table 7: Echocardiographic Findings

	HIV(+) n=17 (%)	HIV(–) n=60(%)	Total n=77(%)	P value
Vegetations	11(64.7)	57(95)	68 (88.3)	0.447
Leaflet Aneurysm	4 (23.5)	1 (1.7)	5 (6.5)	.008
Abscess	3 (17.6)	3 (5)	6 (7.8)	.118
Regurgitation	16 (94.1)	59 (98.3)	75 (97.4)	
Pericardial effusion	6 (35.3)	26 (43.3)	28 (36.4)	1.000
Chordal rupture/leaflet prolapse	6 (35.3)	20 (33.3)	26 (33.8)	

Overall, vegetations were found mainly on the mitral and aortic valves. Twelve patients had vegetations on both the mitral and aortic valves; one patient with a VSD had

vegetations on the mitral and tricuspid valves. In the HIV negative patients, twenty-one had vegetations on the aortic valves, and twenty-one had vegetations on the mitral valves, compared to the HIV positive cases in whom two had vegetations of the aortic valve, and four had vegetations of the mitral valve. (Figure 1a, 1b, 1c and 1d)

In the six patients with right-sided endocarditis, vegetations were seen on the tricuspid valve in two HIV positive and two HIV negative patients, in the remaining two HIV negative patients vegetations were located on the pulmonary valve and at the tip of the central venous line. (Figure 1e)

In both groups vegetations were either echogenic or homogenous in appearance, with an irregular shape. Thirty-eight patients (49.4%) had a single vegetation, and thirty patients (38.9%) had multiple vegetations (table 8). In the HIV positive patients, the presence of single and multiple vegetations was seen with the same frequency. The HIV negative patients however, were more likely to have a single vegetation, although this was not a significant difference. Vegetation size was found to be slightly increased in the HIV positive patients (11mm), compared to the vegetations seen in the HIV negative patients (10mm) but this was not a significant finding (p value = 0.447). In all cases vegetations were accompanied by significant regurgitation of the affected valve. There was no difference in the severity of regurgitation between the groups. One patient, who was HIV positive, had bacteremia (*propionibacterium*), but had no evidence of vegetations at echocardiography. In this case the diagnosis of IE was based on the presence of bacteremia, early clubbing and an elevated ESR and CRP level

(62mm/Hr and 151mg/L respectively).

There was no relationship between the size of the vegetation and the presence of complications such as abscess formation, aneurysm, stroke or fistula development. Four HIV negative patients with vegetations >10mm had complications, which included an abscess in one, a fistula in another (Figure 3c), and two of whom had strokes. None of the HIV positive patients had complications associated with large vegetations. Large vegetations were seen in four HIV positive patients, and thirteen HIV negative patients.

Table 8: Vegetation characteristics at echocardiography

	HIV (+) n=17	**HIV (–)** n=60	**Total**	**P value**
Site				
Aortic	2 (11.8)	21 (35)	23 (29.9)	.189
Mitral	4 (23.6)	21 (35)	25 (32.5)	.001
Tricuspid	2 (11.8)	1 (1.7)	3 (3.9)	
Other site ***	0 (0)	4 (6.7)	4 (5.2)	
Mixed (aortic + mitral)	3 (17.6)	10 (16.7) **	13 (16.9)	
Mean size (mm)	11(4 – 24) *	10 (3 – 30) *	10(3–30) *	0.447
Vegetation number				
Single	6 (35.3)	32 (51.7)	38 (49.4)	
Multiple	5 (29.4)	25 (41.7)	30 (38.9)	
Total n (%)	11 (64.7)	57 (95)	68 (88.3)	

Values expressed in brackets indicate percentages.

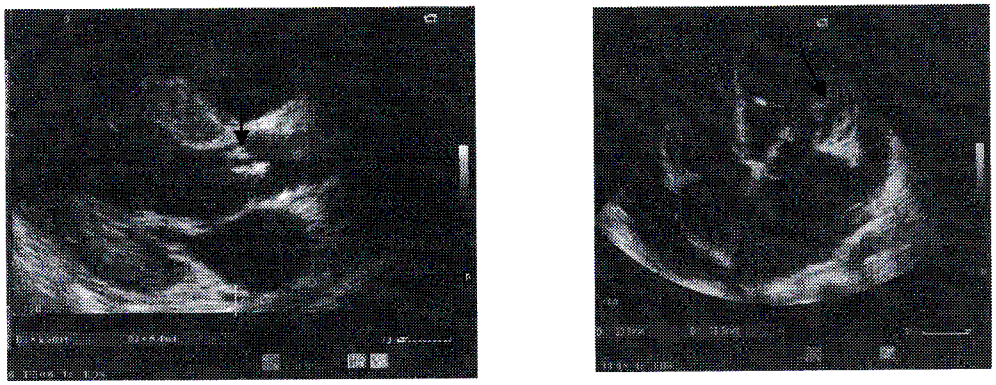
*** Mean values with the ranges bracketed**

**** Includes one patient with a VSD who had mitral and tricuspid valve vegetations**

***** "Other site' refers to central line, pulmonary and prosthesis valves. The left atrial mural endocarditis is included with the mitral valve.**

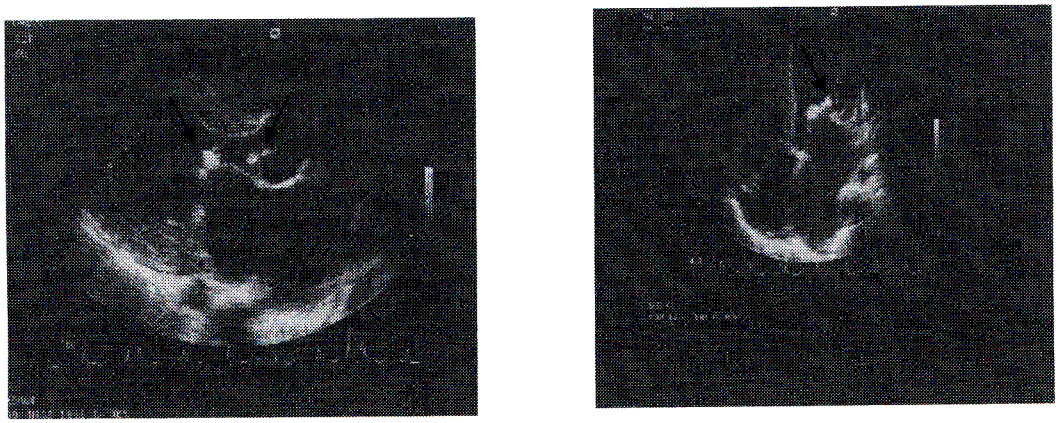
Left sided IE:

HIV positive (Figure1a and 1b)



Vegetations on the aortic valve (left) and mitral valve (right) in a HIV positive patient

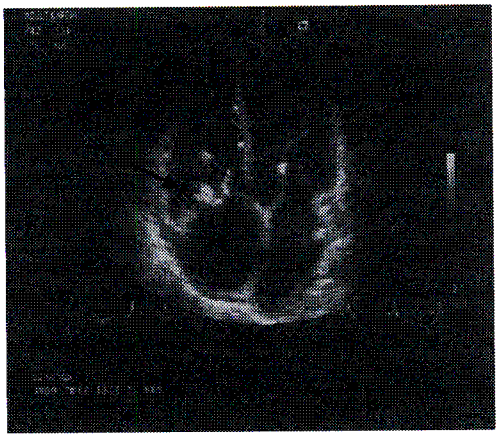
HIV negative (Figure 1c and 1d)



Vegetations on the aortic valve (left) and mitral valve (right) in a HIV negative patient

Right sided IE:

HIV negative (Figure 1e)



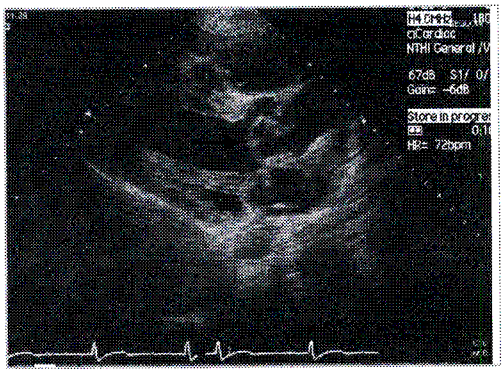
Involvement of the tricuspid valve in the patient with a VSD

4.6.2 Leaflet aneurysms

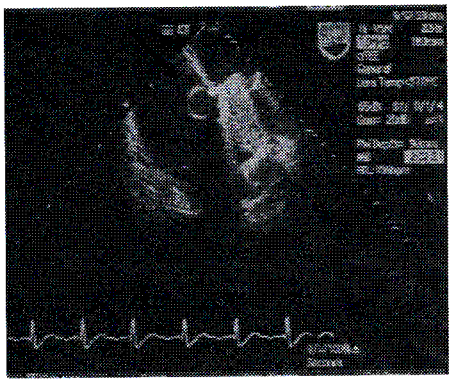
Leaflet aneurysms were found in four of the seventeen HIV positive patients, (23.5%), affecting both the mitral and aortic valves with equal frequency. Among the HIV negative patients, one had a leaflet aneurysm associated with a vegetation <10mm, affecting the mitral valve. The leaflet aneurysms appeared larger in size in the HIV positive patients (0.86cm depth x 0.85cm width), compared to the smaller sized aneurysm in the HIV negative patient (0.21cm depth x 0.3cm width) ($p = .008$).

(table 7) (Figure 2a and 2b)

HIV positive (Figure 2a)



HIV negative (Figure 2b)

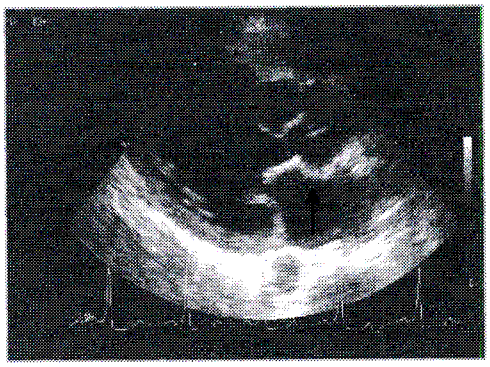


Leaflet aneurysm on the aortic and mitral valves in a HIV positive patient and on the mitral annulus in the HIV negative patient

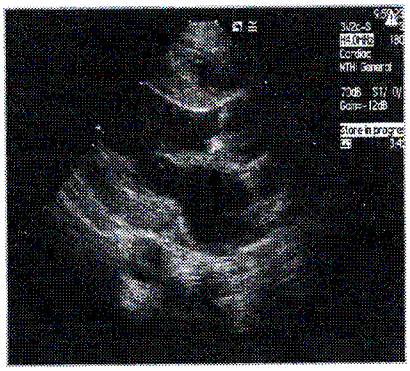
4.6.3 Aortic root abscesses

Aortic root abscesses were found in three of seventeen HIV positive patients (17.6%), and in three HIV negative patients, (5%) (table 7). As in the leaflet aneurysms, the aortic root abscesses were of a larger size on echocardiography in the HIV positive patients (0.73cm depth x 1.2cm width), compared to the HIV negative patients (0.3cm depth x 0.45cm width) ($p = .118$). There was no evidence of myocardial abscess formation. Pericardial effusion associated with a root abscess was found in two HIV negative patients, measuring 1.5cm and 1cm respectively, one of whom had heart failure. Five patients with aortic root abscesses had features of first degree heart block on the electrocardiogram. (Figure 3a and 3b)

HIV positive (Figure 3a)

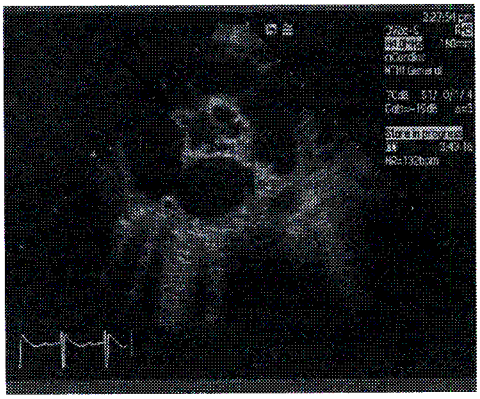


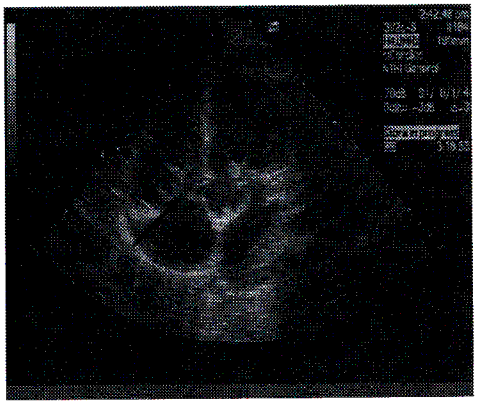
HIV negative (Figure 3b)



Aortic root abscess involving the non coronary cusp of the aortic valve

HIV negative (Figure 3c)





Fistulous connection between a root abscess and the right atrium

4.6.4 Pericardial effusion

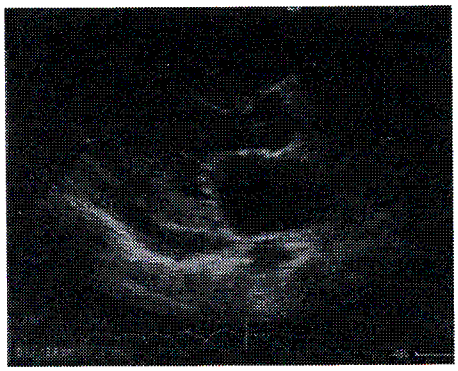
Pericardial effusion was more common in the HIV negative patients, a surprising finding, since it has been reported by Katz[39], et al, that there is generally a strong correlation between pericardial effusions and compromised immune status. It was detected in twenty-six (43.3%) HIV negative patients, compared to six (35.3%) HIV

positive patients (p = ns) (table 7). The effusions were attributed in all but one case to accompanying heart failure, although myocardial abscess formation could not be entirely excluded on echocardiography as the possible aetiology. The average size of the effusion was the same in both groups (1.4cm). Large effusions (>1.5cm) were seen in one HIV positive and nine HIV negative patients. The remaining patients had effusion measuring 1.5cm and less. Most pericardial effusions were simple, without fibrin strands or loculation, except in one HIV negative patient whose 1.2cm effusion demonstrated the presence of fibrin strands. This patient had been treated previously for disseminated tuberculosis (TB). The patient subsequently demised. An autopsy however, was not performed. There was a single case of a pericardial effusion associated with the presence of an aortic root abscess in a HIV negative patient. This patient had a sinus of Valsalva fistula, but there was no evidence of rupture into the pericardial space at echocardiography, or at surgery. At operation the non-coronary cusp was completely eroded, with an aortic root abscess beneath it, with fistulation into the right atrium. The patient demised during surgery, as a result of coronary ostial occlusion.

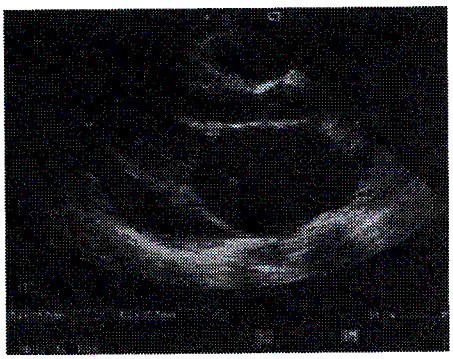
Twenty-two of the twenty-six HIV negative patients with pericardial effusions had severe valvular regurgitation and twelve (46.2%) showed signs of advanced heart failure with fluid overload. All six HIV positive patients with pericardial effusions had severe valvular regurgitation, and two had signs of advanced heart failure. Pericardial effusions were detected in two of the four patients with AIDS, measuring an average size of 1.8cm. These effusions attributed to heart failure in one patient and to

tuberculosis in the other.

HIV negative (Figure 4a)



HIV positive (Figure 4b)



Pericardial effusion in two patients with mitral valve involvement

4.6.5 Left ventricular function:

The ventricular dimensions in the HIV negative patients were slightly increased compared to the HIV positive patients (table 9). Although three patients had ejection fractions <40% (all HIV negative), eleven had an ejection fraction 40 – 50% (one HIV positive and ten HIV negative), and the remaining patients had ejection fraction >50% (sixteen HIV positive and forty-seven HIV negative). Overall, neither group of patients demonstrated reduced ventricular contractility on the echocardiogram. The mean ejection fraction (EF) in the HIV negative patients was 59%, and in the HIV positive patients, 62.9%. The three HIV negative patients who had ejection fractions <40%, had aortic valve regurgitation. None of the HIV positive patients had reduced systolic function.

Table 9: Haemodynamic Parameters and Ventricular systolic function

Mean dimensions	HIV(+)	HIV(-)
End diastolic dimension	62.7mm (41 – 76)	66.5mm (37 – 103)
End systolic dimension	39.6mm (22 – 56)	42.3mm (6 – 74)
Fractional shortening	36.6% (22 -48)	34.6% (21 – 48)
Ejection fraction	62.9% (43 – 75)	59% (35 – 79)
Pulmonary artery pressure	61 (29 - 91)	57 (20 – 110)
Heart failure	5 (29.4%)	28 (46.7)

All are mean values with the ranges bracketed.

Regional wall motion abnormalities (RWMA) were found in seven (11.6%) HIV negative patients, and one HIV positive patient. In the HIV negative patients, the RWMA were due to paradoxical septal wall motion (SPSM) from severe tricuspid regurgitation, except one who had posterior wall hypokinesis. There was no evidence to suggest myocardial infarction. The EF in this group with SPSM was 48% in the HIV negative patients. Of the patients with RWMA, the electrocardiogram findings were complete heart block in one patient, first degree heart block in two patients, left bundle branch block in two patients, intraventricular conduction defect in one patient, and normal findings in two patients. In the HIV positive patient, the EF was 43%.

4.6.6 Underlying valve pathology

At TTE the underlying valve tissue was found to be abnormal (thickened, stenotic valves, failure of leaflet coaption with restricted leaflet motion, and leaflet prolapse) in fifty-seven patients, of whom forty-eight were HIV negative, and nine were HIV

positive. The remaining seventeen patients had normal valves (nine HIV negative and eight HIV positive) Aortic and mitral valve stenosis was seen in both groups of patients, which was most likely due to underlying rheumatic valve disease.

TEE was performed as soon as possible after admission, to confirm the findings on transthoracic imaging, except where it was technically not feasible or the patients judged to be too ill for the procedure. It was also performed if there were changes in the clinical picture, lack of improvement on medical therapy, or if complications were suspected. Fifty-four of the study patients had TEE, of whom fifty-one had findings suggestive of IE. The remaining three patients had thickened calcified valves (n=1), thickened leaflets with chordal rupture (n=1), and normal valves (n=1). Seven of nine patients suspected on transthoracic imaging to have complications such as root abscesses and leaflet aneurysms, had positive findings at TEE; the remaining two did not have the procedure, as they were unable to tolerate the probe.

4.6.7 Complications

Extensive valve disruption was present in both groups, since patients presented at an advanced stage of infection. Except for leaflet aneurysms and root abscesses, which were present in four and three HIV positive patients respectively, there did not appear to be any difference in the prevalence of valve-related complications between the two groups (table 10). Valve disruption due to chordal rupture, and perforated or flail leaflets, were equally distributed in the two groups. There were no striking differences with regards to the shape of vegetations. In both groups ejection fraction as an indicator

of contractility was good, except for three patients in the HIV negative group whose values were below 40% (20, 20, and 35). Clinical heart failure with fluid overload was more frequent in the HIV negative group (table 3).

Table 10: Valve-related Complications

	HIV(+) n=17	**HIV(-)** n=60
Chordal rupture		
Chordal rupture with fluttering	2	4
Flail leaflets	-	1
Leaflet prolapse – aortic - mitral - tricuspid	1 2 1	4 11 -
Leaflet Perforation	1	1
Failure of coaption – aortic - mitral - tricuspid	3 3 -	10 9 1
Regurgitation severity		
mild	1 (5.9)	3 (5)
moderate	3 (17.6)	6 (10)
severe	13 (76.4)	49 (81.7)
Abscess/aneurysm*	7 (41.2)	4 (6.7)

***p value for abscess = .118 *p value for aneurysm = .008**

Echocardiographic features indicating a potential need for surgery were satisfied by at least 90% (n=70) of the patients. There was frequent overlap of these features in some patients (seven in the HIV positive, and fourteen HIV negative patients had an overlap of these features) (table 11). There did not appear to be any differences between the groups

Table 11: Echocardiographic features predictive of surgery

Features	HIV(+) n=17(%)	HIV(-) n=60 (%)	Total
Vegetations			
Persistence after stroke	1 (5.9)	-	1
>10mm	4 (23.5)	13 (21.7)	17
Increase in size	-	1 (1.7)	1
Valve dysfunction			
Perforated leaflets	1 (5.9)	1 (1.7)	2
Valve regurgitation	16 (94.1)	55 (91.7)	71
Impaired LV Function	-	3 (5)	3
Not responding to antibiotics	-	1 (1.7)	1
Paravalvular extension			
Rupture/fistulae	-	1 (1.7)	1
Abscess/aneurysm	7 (41.2)	4 (6.7)	11

4.6.8 HIV stage and Echocardiographic features

The mean CD4 count in the HIV positive patients was 189/mm^3. Four HIV positive patients had advanced immunodeficiency with a mean CD4 count <100/mm^3 (table 12). To determine any association with the stage of infection the echocardiographic findings were examined in the HIV positive patients, stratified into 3 groups: CD4 counts <100/mm^3; 100 to 200/mm^3; and >200/mm^3. No striking differences emerged between the groups. Three of the four patients in the group with AIDS had vegetations, and the fourth, an aortic root abscess. Leaflet aneurysms were found in four patients all with CD4 counts of >100/mm^3. The commonest infecting bacterium was *S. aureus*, found in four patients; all had CD4 counts between > 100/mm^3.

Table 12: Echocardiographic features in HIV positive patients (as per CD4 tertiles)

	CD4<100/mm³ (n=4)	CD4 ≤100-200/mm³ (n=6)	CD4 >200/mm³ (n=7)
Vegetations	n= 3	n=2	n=6
Mean vegetation size	14mm (5 – 24mm) *	10mm (6 – 11mm) *	12mm (4 – 18mm) *
Predominant valve			
mitral	2	-	4
aortic	1	4	1
tricuspid	-	1	1
pulmonary	-	-	-
mitral/aortic	1	-	1
none		1	-
Single	2	2	2
Multiple	1	-	4
Abscess	1	1	1
Aneurysm: mitral		1	-
aortic		1	2
Pericardial effusion	2	2	2
Organisms	S. viridans (1)	S. aureus (2) Propionibacterium(1)	S. aureus (2) S. faecalis (1)

***p value for vegetation size = 0.739**

4.7 Surgical Findings

Thirty-nine patients (thirty-four HIV negative and five HIV positive) underwent valve replacement surgery. Fewer HIV positive patients had surgery since the decision to operate was based on a CD4 count >200/mm³ by the surgeon. At surgery the underlying valve pathology was considered to be rheumatic in origin in thirty-seven cases (95%). In the two remaining cases, the valves were normal.

The diagnosis of IE was confirmed at surgery in 28 out of the 39 cases yielding a high

sensitivity for the modified Dukes, but a low positive predictive value (table 14). In the remaining eleven patients the surgical findings ranged from fibrotic valves to chronic rheumatic valvulitis. Evidence of active rheumatic valvulitis was present in seven patients who also had infective endocarditis.

At surgery vegetations detected on echocardiography were confirmed in 23 out of 37 cases, yielding a sensitivity of 92% and a positive predictive value of 62% (table 13). The detection of aneurysm (n=1/2), abscess formation (n=2/4) and leaflet / cuspal perforations (n=1/7), was suboptimal with echocardiography when compared to the findings at surgery. Echocardiography however, proved accurate in the diagnosis of chordal ruptures, and the presence of a fistula.

Table 13: Echocardiographic findings versus surgical findings

	Echocardiography n=39	**Surgery** n=39
Vegetations	37	23
Abscess	2	4
Fistula	1	1
Aneurysm	1	2
Perforation	1	7
Chordal rupture	4	4

Screening [95% CI]			
Prevalence	:	0.64	[0.47, 0.78]
Sensitivity	:	0.64	[0.43, 0.81]
Specificity	:	0.00	[0.01, 0.27]
Accuracy	:	0.41	[0.26, 0.58]
Predictive value of +ve result	:	0.53	[0.35, 0.71]
Predictive value of -ve result	:	0.00	[0.01, 0.37]

Table 14: Accuracy of Modified Duke Criteria in the diagnosis of Infective Endocarditis using surgical findings as the gold standard

Modified Duke Criteria	Surgery		Total
	Positive	Negative	
Positive	28	11	39
Negative	0	0	0
Total	28	11	39

Screening [95% CI]

Prevalence	:	0.72	[0.55, 0.84]
Sensitivity	:	1.00	[0.85, 1.00]
Specificity	:	0.00	[0.01, 0.32]
Accuracy	:	0.72	[0.55, 0.84]
Predictive value of +ve result	:	0.72	[0.55, 0.84]
Predictive value of -ve result	:	****	[****, ****]

Table 15: Accuracy of vegetation detection by echocardiography using the surgical findings as the gold standard

Vegetations	Surgery		Total
	Positive	Negative	
Positive	23	14	37
Negative	2	0	2
Total	25	14	39

Screening [95% CI]

Prevalence	:	0.64	[0.47, 0.78]
Sensitivity	:	0.92	[0.72, 0.99]
Specificity	:	0.00	[0.01, 0.27]
Accuracy	:	0.59	[0.42, 0.74]
Predictive value of +ve result	:	0.62	[0.45, 0.77]
Predictive value of -ve result	:	0.00	[0.05, 0.80]

4.8 Surgical Outcome

In all patients medical therapy with appropriate antibiotics had been instituted and continued for a total period of six weeks One patient, HIV positive, was referred for emergency surgery. The remaining 38 had urgent surgery in the ensuing weeks. Three

patients demised after surgery (one demised in theatre, one at day seven [HIV positive] and one at day eight post surgery [see mortality below]).

Amongst the HIV negative patients, fifteen had impaired ejection fraction due largely to paradoxical septal motion one week after surgery. At six weeks after surgery two had significant prosthetic leaks and three patients showing impaired ventricular contractility. At the six months follow-up visit one patient had a moderate leak, and two had impaired ventricular contractility. One patient had a stroke nine months post surgery, due to over anticoagulation. At two years follow-up, four patients had mild prosthetic leaks, and one had impaired contractility of the left ventricle.

Amongst the HIV positive patients four had impaired contractility of the left ventricle and one patient had a mild prosthetic leak one week after surgery. One patient demised at day 35 post surgery. At six months and three years follow-up, there was normalisation of the ejection fraction, and the prosthetic leak remained mild. There were no instance of stroke.

4.9 Mortality:

Eighteen (23.4%) patients (fourteen HIV negative and four HIV positive) demised during the course of the study. Six (7.8%) had chronic renal failure. Four of these patients were receiving haemodialysis at the time of diagnosis.

Of the fourteen HIV negative deaths three died in the hospital shortly after surgery (at

surgery, day 7 and day 8). At operation there was fibrinous material covering the prosthetic valve with an aneurysm of the ascending aorta in one patient, severe aortic regurgitation with and abscess and fistula formation in the second, and the remaining patient had a valve completely destroyed by endocarditis, with a mass of vegetations on the aortic valve. The patient who demised at surgery had occlusion of the coronary ostia; the patient who demised on day seven was documented as cardiogenic shock, and the last patient had an intraventricular haemorrhage. The remaining eleven patients died after discharge from hospital. No exact cause of death could be determined.

Of the four HIV positive patients who demised, one died 35 days after surgery whilst in hospital, as a result of methicillin resistant staphylococcal (MRSA) septicaemia, acquired postoperatively. The remaining three patients died after discharge from hospital.

CHAPTER 5

DISCUSSION:

This is one of the first echocardiographic studies of IE comparing HIV positive and HIV negative patients in a cohort of seventy-seven patients seen over a three year period (2004 to 2007). Few data have been published on the clinical characteristics and outcome of IE in patients with HIV infection. Even fewer data exist on the echocardiographic findings in these patients. To date, IE in HIV infected individuals Western series has been described almost exclusively in intravenous drug users, and has been reportedly rare in other HIV infected subjects. In this report we have described the echocardiographic features of IE in HIV positive subjects and related them to the clinical findings.

In contrast to Western series the most common underlying predisposing abnormality observed in our study was rheumatic heart disease. The mitral and aortic valves were predominantly affected, mostly by the presence of a single vegetation. Certain differences emerged in that the size of the vegetations were slightly larger in the HIV positive patients (11mm compared to 10mm of the HIV negative patients) ($p = 0.447$), a finding that was more predominant in the patients classified as having AIDS. Leaflet aneurysms and aortic root abscesses occurred more frequently in the HIV positive patients, but the numbers are too few to draw firm conclusions.

With the exception of fever which was significantly more common the HIV positive patients (23.5%), the clinical profile of IE in the HIV positive patient was similar to the HIV negative patient, and was characterized by clubbing, murmurs and severe valve regurgitation. Echocardiography revealed severe valve damage, often with abscess formation, consequent upon advanced infection. Although ventricular contractility, as assessed by EF was similar in both groups, ventricular dimensions were increased (albeit not significantly) in the HIV negative patients. This was associated with the presence of pericardial effusions. Furthermore, more than half (62%) the patients with pericardial effusion had failure of leaflet or cuspal coaption. These findings are in keeping with the fact that HIV negative patients had a higher rate of overt heart failure. None of the effusions were thought to be due to tuberculosis, although in one patient (HIV negative) there was fibrin stranding within the effusion, with other evidence to indicate tuberculosis.

5.1 Bacteremia:

S. aureus was the most common infecting bacterium (20.8%) found in this series, followed by *S. viridans* (9.1%). Like Jaffe[40], et al, in Seattle, Washington, these organisms accounted for the majority of the culture positive cases. *S. aureus* was found in four HIV positive (23%) patients, and twelve HIV negative (20%) cases in our series. In a study similar to ours Abrahams[27] found that *S. aureus* was the causative organism for bacteremia in almost half of all patients in both groups. These findings are in contrast to a local series *by* Koegelenberg[41], et al, in the Western Cape, who showed

that *S. viridans* is still the most common of bacteria in their group of HIV positive patients.

In western series *S. aureus* is the most common causative organism causing IE in HIV-positive patients; it is reported largely in intravenous drug users and had a predilection for the tricuspid valve. None of the patients recruited in our study were intravenous ("mainline") drug users. Right-sided IE was found in five patients (6.8%, all HIV negative) and occurred in those with congenital abnormalities (such as patent ductus arteriosus and ventricular septal defects). The incidence of left-sided involvement with *S. aureus* was similar in both HIV positive and HIV negative patients; it was found in three (17.6%) HIV positive and nine (15%) HIV negative patients.

Petzsch[20] suggests that persistence of *S. aureus* in the blood cultures should raise suspicion of valve abscesses or possible metastases to other organs. Only one patient in our study, who had multiple positive blood cultures, had a root abscess secondary to *S. aureus* infection. Infective endocarditis due *to S aureus* is a fulminant infection associated with higher rates of stroke, systemic embolization, persistent bacteremia, and a high mortality (25% to 40%).[24] Six of our eighteen deaths were due to *S. aureus* infection, (two HIV positive).

The majority of patients in our study had underlying rheumatic heart disease as a predisposing factor. In five patients IE occurred in the setting of haemodialysis (n=4) and pacemaker infection (n=1). The underlying valve morphology was thought to be

normal in three patients with *S. aureus* infection; two were HIV positive and one was HIV negative. None of the three (3.9%) patients with prosthetic valve endocarditis (all HIV negative) had *S. aureus* infection. In all three cases the infection occurred long after surgery (10yr, 10yr and 5 months) and was due to *corynebacterium* and *pseudomonas aeruginosa;* the remaining patient had a negative blood culture. These patients had peri-prosthetic leaks, but there was no evidence of other complications such as ring abscesses, fistulae, conduction defects or purulent pericarditis.[9]

We tried to ascertain whether the size of vegetations was related to certain groups of organisms, and found that the majority of patients with vegetations >10mm were in fact culture negative IE (n=12). The high rate (54.5%) of culture negativity in this series is worrying and probably related to prior antibiotic therapy and poor culture techniques. In this setting, the sensitivity of the Duke criteria is diminished, as it relies heavily on microbiological indices.[16] In our study, forty-two patients had negative blood cultures, an occurrence which is likely due to the setting of our study, which is a tertiary referral centre receiving patients who are already on antibiotics. In febrile patients with elevated ESR clinicians at base hospitals feel obliged to administer antibiotic therapy prior to the completion of a basic evaluation. Hence the large number of 'culture-negative' IE cases.[41] This has serious implications for treatment, especially in HIV positive patients, since the ESR is often elevated from non-valvular infection. Recent literature suggests that a marked reduction in the incidence of bacteremia is also seen in patients receiving antiretroviral therapy. Only three patients in our study were on highly active

antiretroviral therapy (HAART) treatment, and a positive blood cultures was found in one of the three patients (*S. aureus).*

Cardiovascular disease patterns in HIV-infected people have been reported to be similar in Europe, North America, and Africa.[42] The difference exists in the causative organisms implicated in these conditions.[42] Bacteremia is common in patients who are HIV positive and is due to the numerous immunologic defects present in this disease.[27] We did not find the unusual causative organisms reported in the West such as *barbonella, salmonella,* and *listeria*, but we did have two instances of rare organisms, (*propionibacterium and corynebacterium).*

5.2 Nonbacterial thrombotic endocarditis

Slightly more HIV positive patients in our study, ten (58.8% vs. 50%) were shown to have negative blood cultures, thereby raising the possibility of nonbacterial thrombotic endocarditis (NBTE) in these cases. Initially known as thromboendocarditis, NBTE refers to the fibrin deposition on the cardiac valves.[43] It is commonly found in patients with a variety of malignancies, and is known to complicate fulminant acute diseases such as septicemia or burns.[43] Underlying rheumatic heart disease is thought to be an important aetiologic factor in NBTE.[43] It is thought that both valvular deformation and hypercoagulable states are important in the genesis of NBTE.[43] The deformed valve is exposed to blood platelets, which adhere to collagen, resulting in nonbacterial thrombotic vegetations, with an absence of inflammatory reaction.[43] Direct valvular damage could lead to verrucae formation.[43] It is said that the presence of vegetations

with a noninfectious aetiology can also produce a clinical picture similar to that of culture-negative endocarditis. Although large embolisation associated with NBTE is rare[11], small embolisation is more frequent as the vegetations are assumed to be quite friable and embolise easily[43]. There are no particular symptoms and signs, which suggest a diagnosis of NBTE, but serial negative blood cultures should alert the clinician to the possibility of NBTE which is reportedly common in HIV positive patients.[41]. Neurological events are the most common manifestation of NBTE.[43] Of interest, three of our HIV positive patients had strokes, (two culture negative) thereby suggesting the possibility of NBTE in the latter cases. Because of the absence of an inflammatory reaction in NBTE a low rate of positive rheumatoid factor levels is expected. In our study we did have a lower rate, 23.4% (n=4) in HIV positive, compared to 55% (n=33) in the HIV negative patients. In one HIV positive patient, who had a CD4 count >200/mm^3, we found a "vegetation" along the free wall of the left atrium, below the left atrial appendage. This was not thought to be a thrombus, because it satisfied the criteria for a vegetation and occurred in the region of the high velocity jet.[44]

5.3 Role of echocardiography in IE

5.3.1 Vegetations

Vegetations were found in 88.3% (n=68) of our patients. They were attached to the heart valves, chordae or the mural endocardium and were also found in association with septal defects. Vegetations on the mitral and aortic valves were found to occur with the same frequency in both HIV positive and negative patients. Vegetation size was

slightly bigger in the HIV positive patients (11mm versus 10mm in the HIV negative patients) ($p = 0.447$). Patients with CD4 counts $<100/mm^3$, were shown to have larger vegetations (14mm) than the remaining HIV positive patients (11mm) ($p = 0.739$).

It is said the absence of echocardiographically visualised vegetations identifies patients with lower morbidity and mortality, since these patients are likely to have fewer embolic events, less congestive heart failure, and require surgery less frequently. In our study we found that only one HIV positive patient who had no endocardial involvement, but six HIV positive patients had extensive valve damage from the infective process without vegetations. It is possible that in these cases vegetations may have embolised. The total disappearance of vegetations has been previously observed in a study by O'Brien[45], et al during the treatment period, without clinical evidence of systemic embolization. We noticed this in one HIV positive patient in our study, who, at day 41, showed a disappearance of the vegetation. In another patient (HIV negative) the vegetation appeared smaller and denser on the echocardiogram after one month of medical treatment. Serial evaluation of changes in vegetation size and morphology depends on the ability of the observer to reproduce both transducer position and gain setting, so that the size and density data may be compared.[45] By increasing the gain setting it is possible to make a lesion appear larger, and vice versa.[45] Proper standardization of technique is an important aspect in evaluating the natural history of vegetations.[45] This has clinical significance since a vegetation has to be 2-3mm before it can be detected by the imaging system.

The high rate of negative blood cultures raises the possibility that vegetations were the result of disease processes other than infection. Therefore clinical correlation with echocardiographic findings is necessary, since echocardiography (both TTE and TEE), is unable to differentiate between septic and aseptic vegetations such as that seen in NBTE, neither is it able to distinguish between present and past infection.[48] The verrucae of rheumatic carditis could also be the cause of false-positive findings when small vegetations are detected at echocardiography. Indeed many of our patients were young (fourteen of the patients were below twenty years of age), and could have had recrudescent rheumatic carditis. This accounts for the fact that histological evidence of carditis was present in seven of the thirty-nine patients who had valve replacement surgery.

Several studies[15, 36, 38], et al, have shown a higher complication rate, particularly stroke, in patients with vegetations over 10 mm. Of the nine patients who had a stroke in our study, only one was found to have vegetations over 10mm in size. Among the risk factors associated with embolic events (age, vegetation size, prothrombin activity, serum albumin, and CRP) [46] we noted an elevated CRP level in our patients who developed strokes. CRP has been shown to be an important marker of bacterial infection, and also possible complications in patients with IE.[46] It is thought that CRP induces the inflammatory response, with direct effect on platelets, thereby resulting in more friable lesions that are at risk for embolization.[46] Caball's study showed no correlation between vegetation size and cerebral embolisation[46] and he therefore suggested that an elevated CRP is independently associated with thromboembolic

events The highest CRP levels in our series were documented in two HIV positive patients with stroke (135 and 142mg/L).

Cabell[46], et al, have reported that at least 37% of patients with definite IE demonstrate evidence of thromboembolic events. Embolisation can occur before the diagnosis of IE, during therapy, and after therapy is completed.[24] In our study seven patients were referred with stroke, one patient experienced a stroke while on treatment, and another had a stroke post surgery. These nine accounted for 10.4% with a clinically overt embolic episode, all on native valves; three were HIV positive. Baddour[24], et al suggests that there is an increased incidence of embolisation amongst patients infected with *S. aureus, Candida, (Haemophilus parainfluenzae, Haemophilus aprophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae, sutonella) HACEK* and *abiotrophia* organisms. We isolated *S. viridans* in two of the nine patients with stroke. We did not routinely perform CT scans on our patients, and so cannot comment on the prevalence of occult cerebral embolisation. Computerised tomographic (CT) scans (n=14), showed infarcts in half (n=7), brain atrophy in four, and in the remaining three found no abnormalities. Two of the patients were HIV positive, and were shown to have brain infarcts, both of whom had strokes. None of the patients in our study had evidence of mycotic aneurysms, which has been reported more frequently when presentation is delayed, especially in developing countries.[22]

5.3.2 Pericardial Effusion

Pericardial effusion (PE) was a common finding in both groups in this study and was attributed largely to heart failure. A higher rate of pericardial effusions was seen in the HIV negative patients, twenty-six HIV negative (43.3%) patients compared to six HIV positive patients (35.3%). Twenty-two patients in the HIV negative group had advanced valvular insufficiency, with associated heart failure seen in twelve cases, versus two of the six HIV positive patients with PE. Pericardial effusions are considered to be a common form of cardiovascular involvement in HIV infected individuals, the cause of which includes *S. aureus*, as a result of endocarditis.[39] Recent reports show that pericardial effusion is associated with a low CD4 cell count, and is a marker of end-stage HIV infection. In our study pericardial effusions were seen in six out of the seventeen HIV positive patients, and the average CD4 count in these patients was 166/mm^3. Two of the four AIDS patients had PE, one associated with heart failure and one had a tuberculous aetiology.

5.3.3 Complications in IE:

We looked carefully for evidence of complications, defined as the presence of congestive heart failure, new valvular regurgitation, refractory infection, systemic embolization, or valvular vegetations.[47,] 42.9% (n=33) of our patients had heart failure, and nine (11.7%) had strokes, three of whom were HIV positive. Large vegetations (>10mm) were seen overall in seventeen patients (22.1%), (four were HIV positive)

Furthermore, early diastolic closure of the mitral valve is an indication of an unstable haemodynamic status.[48] One of the patients in our study were shown to have early closure of the mitral valve on the echocardiogram, in the presence of acute aortic regurgitation, an indication of severe haemodynamic sequelae, which according to Evangelista[48], et al. is likely to precipitate heart failure. In this patient there was premature closure of the mitral valve in the presence of severe aortic regurgitation. The patient had an aortic root abscess, a 1.4cm vegetation, with a sinus of valsalva fistula.

Perivalvular complications leading to leaflet perforation and flail leaflets, was seen in three patients. Perivalvular extension of the infection with abscess formation and the development of fistula has a poor prognosis.[48] Six aortic root abscesses were found in our study, all in native valves (three HIV positive, and three HIV negative patients). These abscesses were larger in size in the HIV positive patients (0.73cm depth x 1.2cm width vs. 0.3cm depth x 0.45cm width). We also found total of five aneurysms at TTE in the study. Two of these were cuspal aneurysms of the aortic valve, both of whom were in the HIV positive group. The remaining three aneurysms were located on the mitral valve, two of which were in the HIV positive patients. One leaflet aneurysm was found along the annulus of a mitral prosthesis in an HIV negative patient, confirmed at TEE. The leaflet aneurysms, like the aortic root abscesses were larger in the HIV positive patients, (0.86cm depth x 0.85cm width vs. 0.21cm depth x 0.3cm width).

Expansion of the abscess cavity with pseudoaneurysm formation resulted in perforation and fistulous connection to the right atrium in an HIV negative patient. In aortic

endocarditis the regurgitant jet is directed onto the mitral-aortic intervalvular fibrosa, leading to spread of the infection along the anterior mitral leaflet.[48] Infection of the mitral valve secondary to aortic valve infection in this way was found in eleven (14.3%) patients in our study. Maintaining the morphological and functional integrity of the mitral valve apparatus requires early detection of the spread of infection so that timely surgical intervention may enhance preservation of the valve.[49] Here the echocardiographer has an has an important role in defining the extent of infection and identifies the risk of extension to the mitral valve.

5.3.4 Diagnostic criteria in Infective Endocarditis:

In 1994, D.T. Durack proposed a set of diagnostic criteria for the diagnosis of IE, which became known as the Duke criteria.[50] Prior to the Duke criteria, the Beth Israel criteria were the only recognised diagnostic criteria for IE.[34] Although the Duke criteria have incorporated echocardiographic findings, major diagnostic weight was given to three typical findings, which are: mobile echodense mass/masses seen attached to valvular leaflets; periannular abscesses; and new dehiscence of prosthetic valves.[24] The Duke criteria recognise the high sensitivity and specificity of echocardiography in detecting vegetations, and therefore included this tool as a major criterion.[4] Classification criteria, prior to the Duke criteria, did not include echocardiography, and proved to be of limited value when blood cultures were negative.[19] Although the sensitivity and specificity for the Duke criteria has been validated, several shortcomings of this schema remain.[50]

Limitations of the Duke criteria lie in the misclassification of 'possible' endocarditis, thereby yielding a sensitivity of only 76%.[16] Modifications to the Duke criteria have included *S. aureus* bacteremia as a major criterion, with the addition of minor criteria such as splenomegaly, splinter hemorrhages, petechia, newly diagnosed clubbing, elevated ESR, elevated CRP levels, the presence of central non-feeding lines, peripheral lines, and microscopic haematuria.[50] Li et al have proposed that vascular phenomena should remain a minor criterion as numerous febrile patients with stroke, vasculitis, or rickettsial disease could be erroneously classified as 'possible IE'.[50]

In our study the modified Duke's classification was used. When compared to surgery the positive predictive value of the modified Dukes is only 72%, highlighting the difficulties in using this classification in the absence of positive blood cultures. Incorporation of the inflammatory markers into the criteria decreases the 'possible' cases from twenty-three in the original Dukes to nine with the modified Dukes criteria and increases the 'definite' cases from sixty-three in the original Dukes to seventy-seven with the modified criteria (table 1), without any change in the 'rejected' cases. A deficiency in the modified criteria becomes apparent when diagnosing IE in the HIV population, as these patients often have elevated ESR and CRP levels which is likely due to non-cardiac infection. Therefore, using these additional minor criteria could result in a higher rate of false-positive diagnoses of IE, particularly in the absence of positive blood cultures. Adding additional minor criteria upgrades the classification of IE from 'possible' to 'definite', and with a resultant increase in false positive diagnoses and a change in specificity, although, those rejected by original Duke criteria, remained

rejected.[34]

5.3.5 Healed endocarditis

A principle limitation of echocardiography is that it is unable to reliably differentiate between active and healed endocarditis.[9] Healed vegetations have been characterized on echocardiography as an indentation of the free margin of a cusp. (identifiable on TEE), possible perforation of the body of the cusp with thickened edges, cuspal aneurysms, ruptured chordae tendineae, and healed fistulae.[9] In the majority of patients in our study we could detect no appreciable differences in the appearance of vegetations at the echocardiography after one month of treatment. Calcified healed vegetations were seen in three HIV negative patients. One HIV negative patient showed a reduction in the vegetation size after one month of treatment with antibiotics. In another case (HIV positive) repeat echocardiogram showed complete disappearance of a vegetation confirmed on TEE, after five weeks of antibiotics. No clinical evidence of embolisation was documented. The natural history of vegetations could not be determined in this study because of the fact that most patients discharged did not return for follow-up. A sobering finding in this evaluation was the over-diagnosis of vegetations at echocardiography, even with the use of TEE.

5.3.6 Surgery in IE:

Surgical intervention is warranted in severe valvular insufficiency associated with heart failure unresponsive to medical therapy, and valve related complication.[24] In the group as a whole, congestive heart failure (CHF) was the most common indication for surgery

(n=10), progressive worsening of valvular insufficiency (n=33), and ventricular dysfunction (n=1), the mortality of which is dramatically reduced by surgery, especially in the presence of aortic regurgitation.[24] Overall, thirty-three patients in the study had CHF, three had echocardiographic evidence of ventricular dysfunction, and more than two-thirds (n=71) had severe valvular insufficiency at the echocardiogram. CHF may develop from native valve perforation, chordal rupture, and valvular obstruction by the presence of large vegetations, sudden intracardiac shunts due to fistulous tracts or prosthetic dehiscence.[24] In the patients who had have positive blood cultures, the mitral valve (n=19) was more frequently involved compared to the aortic valve (n=14). Further analysis showed the mitral to be the most frequently affected valve in the patients with CHF, in both the HIV positive (four of nine patients with CHF) and the HIV negative (nine of twenty-one with CHF). None of the patients had acute aortic regurgitation with acute heart failure; this was evident in the average size of the ventricular dimensions. [24]

Echocardiographic features that suggested the need for surgical intervention included a persistent vegetation after systemic embolization, especially those of the anterior mitral leaflet with a size of >10mm, and an increase in the size of a vegetation despite antimicrobial treatment, also paravalvular extension of the infection, and valvular dysfunction.[24] These features were seen in approximately 90% of the patients in our study, although there was an overlap of lesions in twenty-one patients (seven of whom were HIV positive).

We defined a poor surgical outcome by the development of stroke, prosthetic valve leaks or a reduced ejection fraction, which was seen in fifteen of the thirty-nine patients who had surgery. Although Baddour[24] et al noted a poor surgical outcome in patients with CHF, renal insufficiency and advanced patient age, this was not a finding in our study. Ten patients were seen to have impaired ventricular function post operatively, of which, four had leaks across the prosthetic valves (three were mild leaks, two were paravalvular leaks, and the third was a central leak; the fourth was a mild to moderate leak), and one had a stroke. Twelve of the thirty-nine patents referred for surgery (one HIV positive and eleven HIV negative) had features of heart failure prior to surgery. One patient was also shown to have an impaired ventricular function of 35%.

Surgery revealed evidence of IE in thirty of the thirty-nine patients who had definite endocarditis. The underlying pathology was chronic rheumatic valvulitis (with features of endocarditis) in thirteen patients and interestingly seven had acute valvulitis.

5.3.7 Surgery in HIV:

Although valve replacement surgery may be life saving for some patients with active endocarditis, the difficulty lies with deciding which patients should undergo surgery.[47] This has become more difficult in HIV positive patients as reflected in the fact that only five of seventeen patients who tested positive were submitted to surgery. Despite the fact that 90% of patients had features suggesting the need for surgery only 39 underwent valve replacement. Of the thirty-nine patients in the study who received surgical intervention only five were HIV positive. According to Blyth[51], et al, surgery in patients with active IE, who are HIV positive, is associated with a significant

mortality rate. CD4 counts >200/ul are acceptable for surgery, however, counts of 400/ul and above are more likely to be associated with a better outcome.[51] Blyth suggests that surgery in HIV positive patients with an acceptable CD4 count is likely to have a similar early outcome when compared with the HIV negative patients.[51]

Successful treatment of IE relies on the ability of antibiotics to kill bacteria in situ, rather than on host defences, which probably explains why IE is not more frequent in immunocompromised patients.[1] Identifying patients who are at high risk is important because these patients require close monitoring.[40] Surgical intervention in these patients is aimed at eradication of the infection, and correction of any haemodynamic abnormalities.[24] Understanding how and when to intervene surgically is central to the outcome of operation with reduction in mortality.[8] Here again the skill and experience of the echocardiographer is important in defining the complications warranting early surgical intervention. One of three HIV positive patients who had reduced ventricular function demised after surgery compared to three deaths among the fifteen HIV negative patients with reduced ventricular function. Like Barbaro[33] we feel that HIV infection is not a contraindication to cardiac surgery, and is not clearly associated with an increase in the postoperative complication rate or increased mortality. However, the overall impression is that the hospital morbidity and mortality rate in this group of patients is higher than most groups.[52]

5.4 Outcome

According to Katz[39], et al, past studies have shown no difference in the presentation of IE, or the survival of patients with IE who are HIV positive. The difference however, is presumably seen in the late stage of HIV infection, where the mortality among HIV infected patients is supposed to be markedly increased.[39] According to Monseuz[53], et al, non-survival of patients depends on two factors: clinically overt cardiac disease, and having AIDS rather than AIDS–related complex, and it is assumed that cardiac symptoms are less likely to be present in patients with AIDS–related complex. We found a similar rate of morbidity and mortality in the HIV positive and HIV negative patients. There were four known deaths amongst the HIV positive patients (23.6%), and fourteen deaths amongst the HIV negative patients (23.3%). Four of these patients demised after surgery. The remaining patients demised either during admission at our hospital, or at their respective referring centre. Of the known HIV positive patients from our study who demised, none had CD4 counts <100/mm^3, in keeping with the data from Fowler, et al, who found that overall morbidity and mortality related to cardiac disease in AIDS is low.[54]

5.5 Study limitations:

The small sample size of the study was a limiting factor. This could be due to the poor referral system from the base hospital to our hospital, or in fact, that IE is not as common in HIV positive patients as we had presumed. Also not all patients diagnosed with IE at TTE received a TEE. This was due to various reasons such as a patients' inability to tolerate the TEE probe and elevated international normalized ratio (INR)

levels at the time of examination. A further limitation in the study was the high rate of negative blood cultures. This was most likely the result of administration of antibiotics to the patient prior to referral to our institution, or in the case of the HIV positive patient the possibility of NBTE.

Of the 91 patients initially screened, 77 were accepted as having had a 'definite' diagnosis of IE according to the modified Duke criteria. The remaining 14 were deemed not having IE and excluded from analysis. Whether any patients in this group had IE or not (true negative and false negative) could not be determined with certainty since they were not subjected to surgery. We believe the modified Dukes criteria were responsible for the higher false positive rates since it permits diagnosis of IE based on the echocardiographic criteria in the absence of positive blood cultures. While this reflected a potential flaw in the study, since the diagnosis of infective endocarditis was based on the finding of vegetations in the absence of positive blood cultures, (yielding a sensitivity of 100% and a specificity of 0% for the detection of vegetations), this study highlights the difficulty in diagnosis when the blood cultures are negative, placing more reliance on the detection of vegetations. We have done a further analysis on Table 13 (page 42) showing that echocardiography had overdiagnosis of vegetations and underdiagnosis for the detection of the other structural abnormalities related to infective endocarditis.

Unless supported by clinical features and bacteriologic evidence, vegetations alone are not diagnostic of IE because they may represent healed infection.[48] It is known that

vegetations may persist long after bacteriologic cure.[55] The diagnosis of IE postoperatively, is rendered more difficult by the now common practice of leaving the chordal mechanisms intact. Five of the thirty-three patients clinically diagnosed as 'definite' IE, and one 'possible' IE, had no evidence of infection at operation, supporting the need for bacteriological confirmation of infection.

Not all patients however were referred for surgery. The low CD4 counts in the HIV positive patients meant an even smaller group of these patients were accepted for operation, as the acceptable CD4 level for surgery at our institution is >200/mm^3

In this study attempts were made to define the valve pathology on echocardiography more accurately. According to Taams, et al, there are five distinct pathological features of IE that may be seen clearly on TEE and these are (1) mitral stenosis with vegetations; (2) myxomatous degeneration of leaflets with vegetations; (3) chordal rupture with vegetations; (4) chordal rupture without vegetations; and (5) mycotic aneurysms with fistulous connections.[38] It is often difficult to decide on the underlying pathology with this degree of accuracy with transthoracic imaging (TTE). In our study harmonic imaging (HI) was employed to improve the diagnostic value of TTE by improving the image quality, as documented by Chirillo[35], et al. Harmonic imaging works on the principle of limiting near field artefacts, and because the harmonic energy increases with the distance the ultrasound wave propagates most harmonics will result from the central ultrasound beam rather than the weaker side lobe artefacts.[35] This modality is used primarily to enhance left ventricular endocardial borders. Its use did not really

increase the resolution in visualizing vegetations. Therefore, we used TEE to differentiate and define chordal rupture in association with vegetations, leaflet prolapse and flail leaflets. Our surgical findings reveal that even within TEE there were limitations, which were resolved at surgery when the subtlety of the findings could not be dissected.

CHAPTER 6

CONCLUSION:

Over a three year period we analyzed ninety-one patients with IE, of whom seventy-seven were diagnosed as having definite IE at a tertiary referral centre in KZN. There was a high morbidity and mortality in the group as a whole because of the late presentation of these patients. The study calls for a careful evaluation of patients with suspected IE, since the final diagnosis at surgery could only be confirmed in 72% of cases using the modified Dukes criteria. Although literature states that modern echocardiography has an increased specificity for detecting vegetations, this study clearly indicates the limitations of relying on echocardiography alone to make a diagnosis of IE and draws attention to the importance of blood cultures in diagnosis.

Overall, the study showed no significant increase in the complication rate as seen echocardiographically, in the HIV positive patients. Certain lesions, such as leaflet aneurysms and root abscesses did appear to be more frequent, and were of a larger size when compared to the HIV negative patients, but were not related to the stage of HIV infection. Vegetations were also a larger size in the HIV positive patients with CD4 counts $<100/mm^3$.

In the West IE is a severe illness seen in intravenous drug users with or without HIV infection. Patients with HIV infection are at increased risk of bacterial infection, and it

is thought that the more advanced stages of immunodeficiency modifies the clinical course and increase the severity of bacterial infection. In fact Koegelenberg found that *S. viridans* was still the commonest organism in his series. Many of the findings in our study were similar to the study by Koegelenberg[52], but our pathogen profile was different and we had a high culture negativity rate.

The commonest infecting organism in our series was *S. aureus*, followed closely by *S. viridans*. The high rate of culture negative endocarditis was a serious limitation to the study, and was most likely the result of prior antibiotic therapy. The presence of NBTE in culture-negative cases could not be determined with certainty. However with the increased levels of serum CRP and the underlying valvular stenosis found in four HIV positive patients, there is a possibility that they could have had NBTE.

There have been few studies that have prospectively examined IE in HIV subjects, except for subgroup analysis of smaller numbers of subjects with IE. In this series IE was not as common as expected. It is estimated that at least 4% of these will develop cardiac complications.[29] In our study the overall rate of complications was 50.6%, of whom 17% were HIV positive. In contrast to the Western series we did not identify intravenous drug abuse as a risk factor but rheumatic heart disease remains as an important predisposing factor for developing endocarditis. With the increasing drug abuse, the prevalence of endocarditis in HIV will likely increase, posing problems in detection and management. Improved culture techniques are important to detect the causative organism, since this remains a major criterion in the diagnosis of IE in

developing countries where rheumatic heart disease is endemic and repeated infection common. Considerable skill is needed in differentiating vegetations from damage due to previous infection disease or to rheumatic carditis, and in differentiating vegetations from damaged chordal apparatus which is frequent in patients with valvular disease. Further more patients with HIV infection already have elevated ESR and CRP and concurrent anaemia from antecedent infection rendering these criteria non-specific in evaluating IE.

CHAPTER 7

APPENDICES:

APPENDIX 1a:

PATIENT INFORMATION LEAFLET AND INFORMED CONSENT

(Each patient must receive, read and understand this document before the start of the study)

Subject initials:

Subject study number:

Study Title:

Echocardiographic features of the complications of Infective Endocarditis with special reference to patients with HIV.

Introduction:

You are invited to volunteer to participate in a research study. This information leaflet is to help you decide if you would like to participate. Before you agree to take part in this study, you should fully understand what it entails. If you have any questions that are not fully explained in this leaflet, do not hesitate to ask. You should not agree to take part unless you are completely happy about all the procedures involved.

What is the purpose of this study?

1. To investigate the complications of Infective Endocarditis.

2. To assess how common the complications of Infective Endocarditis is in patients with HIV.

You have been diagnosed with Infective Endocarditis, and therefore, we would like you to consider taking part in this study.

What is Infective Endocarditis?

Infective Endocarditis is inflammation of the inner lining of the heart.

What is the duration of this study?

A minimum of 60 subjects will be in the research, the duration of the study per subject will depend on the duration of their treatment, followed-up to their period of recovery (+/- 6 weeks). The entire study will be completed in 2 years.

What does involvement in the study entail?

1. If you agree to participate in the study, you will be seen by doctors in the ward / clinic / CCU.
2. Once diagnosis of Infective Endocarditis has been done, you will have a few blood tests. This will include a test for HIV. Counseling, by appropriately qualified personnel at IALCH, will be offered to you before and after the HIV test, provided you have not been already tested and counselled at your base hospital.
3. You will then have an echocardiogram. This involves coming to the Echo Lab, lying on a couch, a small amount of gel placed on your chest, and an ultrasound probe placed over the gel. This is done in order to perform a study of your heart valves.

It may be necessary to make further assessment of your valves in detail using a transesophageal probe. This involves passing an ultrasound probe / a tube (this is twice the size of a pen) through your throat, and you will be required to do is swallow the probe.

Has the study received ethical approval?

The study protocol was submitted to the Nelson R Mandela Research Ethics Committee, and approval has been granted by that committee. The study has been structured in accordance with the Declaration of Helsinski (2000), which deals with research involving human subjects.

What are my rights as a participant in this study?

Your participation in this study is voluntary, and you may refuse to participate, or stop at any time, without stating your reasons for doing so. Refusing to participate in the study, or withdrawing, will not affect the medical care you receive at this institution; you may also be withdrawn from the study, if it thought to be in your best interests.

What are the risks involved in this study?

There is a minimal risk in experienced hands, in patients with an intact mucosa, and a normal esophageal wall, with no infections. However, there is an increased risk in a small percentage of patients who have mucosal insults, or perhaps weakened esophageal walls which could perforate, gastric ulcers, esophageal varices, and strictures, but, every effort is made to exclude these before the procedure is carried out. Further risks include trauma to the teeth and gums, trauma to the oropharynx, and any risks associated with the agents used for sedation of the patient. Rare complications such as esophageal tears may possibly cause perforation of the esophagus, or stricture formation. Minor trauma, e.g trauma to gums, will be managed with observation, and the patient will be kept nil per mouth for 24 hours. Major trauma, e.g esophageal tears, will be managed with investigative x-rays, such as contrast swallows, enlisting the help of ENT, and the surgeons to determine whether surgery is an option. However, transesophageal echocardiography is considered to be a low-risk procedure for infective endocarditis.

Source of additional Information

For the duration of this study, you will be under the care of the Cardiology Unit at IALCH. The telephone number is 204 1746 / 1736, through which you can reach Dr M.Mbizeni, Sister W. Tobias, or Miss S.Nel. The Research Ethics Committee Administrator, Mrs C. Borresen can be contacted at the following telephone number should you have any queries regarding the ethical aspects of this study, (031) 260 4416.

Confidentiality

All the information obtained during the course of this study is strictly confidential. Reported data will not be including information that identifies you as a patient in the study. You will be informed of any finding of importance to your health, and the information only disclosed to the above mentioned persons.

INFORMED CONSENT

1. I hereby confirm that I have received and understood the Patient Information leaflet
2. I am aware that all information will be kept strictly confidential, and the persons who will be informed about my HIV status are the doctor, ultrasonographer and attending professional nurse
3. I may at any stage withdraw my participation from this study, without any prejudice
4. I am prepared to participate in this study

Patient sign: Date:

Patients guardian (if applicable)

Sign: Date:

Person explaining informed consent

Sign: Date:

Witness

Sign: Date:

APPENDIX 1b:

IPHESHANA LOLWAZI KANYE NEMVUME YESIGULI:
(Isiguli ngasinye kumele samukeliswe ipheshana, bese silifunda siqonde okuqukethwe ngaphambi kokuba kuqale ucwaningo)

Izinhlamvu zokuqala zamagama akhe(initials):

Inombolo yobamba iqhaza:

ISIHLOKO SOCWANINGO:

Izimpawu zezinkinga ze Infective Endocarditis ezibonwa kwi Echocardiogram, ikakhulukazi esigulini esinesandulela ngculazi.

ISINGENISO:

Uyacelwa ukuba ubambe iqhaza ocwaningeni ngokuzikhethela. Inhloso yaleli pheshana elinolwazi wukuthi likusize ukuthatha isinqumo uma uthanda ukubamba iqhaza. Ngaphambi kokuba uvume ukuzimbandakanya kulolu cwaningo, kumele uqonde kahle ukuthi liquketheni. Uma unemibuzo engaphendulekanga ngokugcwele kuleli pheshana, ungangabazi ukubuza. Ungalokothi uvume ukubamba iqhaza uma ungakhululekile ngokuphelele ngemigomo ezolandelwa kulolu cwaningo.

YINI INHLOSO YALOLU CWANINGO

1.Ukucwaninga ngezinkinga ezibangwa wukuhlaseleka kontwentwesi olungaphakathi lwenhliziyo okubizwa ngokuthi yi-Infective Endocarditis

2.Ukuhlola ukuthi zivame kangakanani izinkinga ezidalwa yi-Infective Endocarditis ezigulini ezinesandulela ngculazi.

Utholwe une-Infective Endocarditis, ngakho-ke singathanda ukuba ucabange ngokubamba iqhaza kulolu cwaningo.

YINI I - INFECTIVE ENDOCARDITIS

I-Infective Endocaditis- ukuvuvukala kontwentwesi olungaphakathi lwenhliziyo.

LUZOTHATHA ISKHATHI ESINGAKANANI LOLU CWANINGO

Lolu cwaningo luyodinga abantu abangamashumi ayisithupha. Isikhathi sokuphela kocwaningo kuyoncika esikhathi sokwelashwa kwabo, okuyolandeleka esikhathini abasinda ngaso (okungaba ngaphezulu noma ngaphansi kwamasonto ayisithupha). Selulonke ucwaningo luyoqedwa esikhathini esingangeminyaka emibili.

NGAKUBE UKUZIBANDAKANYA KULOLU CWANINGO KUQUKETHENI?

1.Uma uvuma ukubamba iqhaza kulolu cwaningo uyobe uhlolwa ngodokotela egunjini leziguli noma emtholampilo noma e-CCU

2.Uma ukuhlolwa kwe-Infective Endocarditis sekuphelile, uyobe usuhlolwa igazi izikhathi ezimbalwa. Lokhu kubandakanya nokuhlolelwa isandulela ngculazi. Uyonikwa izeluleko ngabeluleki abasezingeni eliphezulu base-IALCH, ngaphambi nangemuva kokuhlolelwa isandulela ngculazi, ngaphandle uma ungazange uhlolwe futhi unikezwe iziyalo esibhedlela sangakini.

3.Uyobe usuwenziwa i-echocardiogram okusho ukuhlolwa kwezinhliziyo ngemishini ehlola ingaphakathi lomzimba ("emafutheni"). Lokhu kubandakanya ukuza kwakho elebhu, ulalilwe ohlakeni, kufakwe imbijanyana yejeli esifubeni sakho, bese kuthathwa umshini ubekwe phezu kwayo. Lokhu kwenzelwa ukuthi kuhlolwe izivimbo zegazi enhliziyweni yakho. Kungenzeka kube nesidingo sokuba kuphindwe kuhlolisiswe izivimbo zenhliziyo yakho ngokujulile ngomshini obizwa ngokuthi yi-transesophageal ECHO lokhu kubandakanya ukufaka emphinjeni ithumbu lokuhlola ngaphakathi (elinobukhulu obuphindwe kabili kobepeni), wena okufanele ukwenze ukuba uligwinye leli thumbu.

NGABE LOLU CWANINGO LUGUNYAZIWE YINI NJENGOLUFANELEKILE NA?

Imigomo elawula lolu cwaningo yethulwa phambi kwekomiti i-Nelson R. Mandela Research Ethics Committee, layamukela. Lolu cwaningo luhlelwe lwahambisana ne-Declaration of Helsinski (2000), okuyiyo ebhekele ucwaningo okusetshenziswa abantu kulo.

YIMAPHI AMALUNGELO ENGINAWO NJENGOBAMBA IQHAZA KULOLU CWANINGO?

Ukungenela kwakho lolu cwaningo kungokuzikhethela, futhi uma uthanda unganqaba ukulungenela, noma uhoxe noma ngasiphi isikhathi ngaphandle ngokuthi uze ubeke izinkinga zokwenze njalo. Ukunqaba okanye uhoxa kulolu cwaningo ngeke kuze kuthikameze ukwelashwa kwakho okuthola kulesi sikhungo. Usengahoxiswa futhi kulolu cwaningo uma kukhona isidingo.

YIBUPHI UBUNGOZI OBUKHONA KULOLU CWANINGO

Buncane ubungozi obungaba khona kulabo asebejwayele, ezigulini ezine-intact mucosa futhi ezingenayo inkinga emphinjeni yazo. Nokho-ke kunokwenyuka kancane kwezinga lobungozi ezigulini ezinenkinga yontwentwesi noma ukukhathala kontwentwesi lomphimbo okungadala izilonda nenkinga yokugwinya nokuvaleka kwamapayipi wokugwinya (oesophageal strictures), nokho-ke iyenziwa imizabo yokukhipha bonke laba ngaphambi kokuthi kuqalwe. Obunye ubungozi bubandakanya iminjunju emazinyweni nasezinsinini kanye nasemankankeni, nanoma yibuphi ubungozi obunobudlelwane bokusetshenziswa kwezidakamizwa ezisetshenziswa esigulini. Enye inkinga engajwayelekile enjengobuhlungu obuvuthayo emphinjeni obubanga kube nzima ukuphefumula, kubange nokuphalaza okukhalisa izinyembezi. Ukuhlukumezeka okuncane, isibonelo, ubuhlungu bezinsini kungabhekisiswa, kanti futhi nesiguli singaqashelwa amahora angu-24. ukuhlukumezeka okukhulu, isibonelo, ubuhlungu obushisayo esifubeni obuholela ekuphalazeni obukhalisa izinyembezi kona kuyohlolwa ngemishini yase-X-ray ukubheka ushintsho ekugwinyeni, ukusiza nge-ETN, nokuthi odokotela babone ukuthi ngakube isejari iyona yini engaba yisixazululo. Nokho-ke indlela yokuhlolwa kokushaya kwenhliziyo ebizwa ngokuthi yi-transesophageal echocardiagraphy kuthathwa njengobungenabo ubungozi bokuhlola ukuhlukumezeka kwenhliziyo.

LAPHO OKUNGATHOLAKALA KHONA OLUNYE ULWAZI

Uma usengaphansi kwalolu cwaningo uzobe unakekelwe ngabakwa-Cardiology Unit e-IALCH. Inombolo yocingo u-204 1746/1736, lapho ungathola khona u-Dkt. M. Mbizeni, Sister W. Tobias, noma uNksz. S. Nel umphathi weKomiti lezokucwaninga Research Ethics Committee (031) 260 4416, uNkk C. Borresen angatholakala kule nombolo uma unemibuzo mayelana nokwemukeleka kwalolu cwaningo.

UBUMFIHLO

Lonke ulwazi olutholakale ngalolu phenyo luyimfihlo. Umbiko ngalolu phenyo ngeke ulufake ulwazi olukuvezayo njengesiguli.Uyokwaziswa ngakho konke okubalulekile okutholakele mayelana nempilo yakho, lolo lwazi luyodalulwa kuphela kulabo ababalwe ngenhla.

IMVUME EKHULULEKILE

1.Ngiyavuma ukuthi ngilitholile ipheshana lesiguli elinolwazi futhi ngakuqonda konke okumayelana nesiguli.

2.Ngiyazi ukuthi lonke ulwazi luyogcinwa luyimfihlo, nokuth abantu abayokwaziswa ngesimo sami negciwane lengculazi kuyoba ngudokotela, yilowo ohlola ingaphakathi lomzimba okuthiwa yi-ultrasonographer kanye nabahlengikazi abafikayo abasezingeni eliphezulu.

3.Ngingayeka ukuzibandakanya noma nini kulolu cwaningo ngaphandle kokusatshiswa.

4.Ngizimisele ukuba mdibi munye kulolu cwaningo.

Isishicilelo sesiguli

Sayina: .... Usuku.....

Umuntu okunike incazelo ngalesi sivumelwano

Sayina: ..... Usuku.....

Umuntu okunike incazelo ngalesi sivumelwano

Sayina:..... Usuku.....

Ufakazi

Sayina: ..... Usuku.....

APPENDIX 2:

Duke Criteria: Major

1. Positive blood cultures for IE	**2.** Evidence of endocardial involvement
(a) Microorganisms typically associated with IE from 2 separate blood cultures, these are *viridans streptococci*, *streptococcus bovis*; HACEK group (*Haemophilus species*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium homonis*, *Eikenella species*, *and Kingella kingae*); or community acquired *staphylococcus aureas* or *entrococci*. (b) Microorganisms that are consistent with IE from persistently positive blood cultures, which are defined as ≥ 2 positive cultures of blood drawn > 12 hours apart or ≥ 4 separate cultures with the first and last samples drawn ≥ 1 hour apart[58].	(a) an oscillating intracardiac mass, located at a site where vegetations typically occur, e.g. valves, chordae, atrial septal defects, ventricular septal defects, and along the path of a turbulent jet. (b) intracardiac abscesses (c) dehiscence of a prosthetic valve (d) detection of a new regurgitant murmur

Ref: Predergast, B.D. Heart. 2004: 90: 611 – 613.

Duke Criteria: Minor

1. Predisposition to heart disease	
2. Fever > 38 degrees	absence of which can be considered negative predictive value.
3. Vascular phenomena	arterial emboli; septic pulmonary infarcts; mycotic aneurysms; intracranial hemorrhage; conjunctival hemorrhages; and Janeway lesions.
4. Immunological phenomena	glomerulonephritis; Osler's nodes; Roth spots; and an elevated rheumatoid factor.
5. Microbiological	when a bacterium is neither typical nor persistent, it can still provide some supporting evidence for the diagnosis of IE.
6. An echocardiogram consistent with endocarditis, which does not meet with major criteria (omitted from modified criteria)	non-oscillating targets; new valvular fenestrations; and nodular valvular thickening [8, 17].

Ref: Bayer, A., et al, Circulation. 1998; 98: 2936 – 2948.; El-Ahdab, F., et al, Am J Med. 2005; 118: 225 – 229.

Modified Duke Criteria

Additional major criteria

- Positive serology for *Coxiella burnetti*
- Bacteremia due to *staphylococcus aureas*
- Positive molecular assay for specific gene targets and universal loci for bacteria and fungi
- Positive serology for *Chlamydia psittaci*
- Positive serology for *Bartonella* species[48]

Additional minor criteria

- Newly diagnosed splenomegaly
- Newly diagnosed clubbing
- Splinter heamorrhages
- Petechiae and purpura
- High ESR, defined as more than one and one-half times the upper limits of normal (>30 mm/h in patients < 60 years, >59mm/h in patients >60 years)
- High CRP levels, >100mg/L
- Microscopic heamaturia
- Central nonfeeding venous lines and peripheral venous lines
- Organisms from metatstatic lesions[40]

Ref: Lamas, C.C., and Eykyn, S.J. Clin Infect Dis. 1997; 25: 713 – 719.; McDonald, et al, Clin Infect Dis. 1994; 18:648 – 649.

Appendix 3: Referring Hospitals

HOSPITALS	HIV(+) n=17	HIV(-) n=60	TOTAL
KEH	7	11	18
ADDINGTON	0	3	3
RKK	4	3	7
PMH	0	8	8
MGH	3	11	14
GREYS	0	5	5
IALCH	0	3	3
ST. MARY	0	1	1
NGWELEZANE	0	3	3
WENTWORTH	0	2	2
VRYHEID	0	1	1
GJ CROOKS	1	1	2
NELSON MANDELA	0	1	1
KOKSTAD	0	1	1
MURCHISON	1	1	2
PARKLANDS	0	1	1
CITY	0	1	1
UMTATA	0	1	1
PORT SHEP	0	1	1
ST AUGUSTINE	0	1	1
OSINDISWENI	0	1	1

APPENDIX 4a:

Diagnosis according to Duke Criteria

Patient	Major		Minor											
Neg	**B/cul+**	**Echo**	**Fever**	**Club**	**Splint**	**Va**	**Splen**	**ESR**	**CRP**	**Haem**	**RF**	**Maj**	**Min**	**Diag**
1	•	•		•								2	1	Def
2	•	•								•		2	1	Def
3	•	•						•				2	1	Def
4	•	•		•				•	•		•	2	4	Def
5		•						•				1	1	Pos
6		•		•				•			•	1	3	Def
7		•				•		•	•			1	3	Def
8	•						•	•	•		•	1	4	Def
9		•		•				•	•		•	1	4	Def
10		•							•		•	1	2	Pos
11		•		•				•	•		•	1	4	Def
12		•			•			•	•			1	3	Def
13	•	•		•				•	•		•	2	4	Def
14		•						•	•			1	2	Pos
15		•						•	•			1	2	Pos

Neg	B/cul+	Echo	Fever	Club	Splint	Va	Splen	ESR	CRP	Haem	RF	Maj	Min	Diag
16		•						•	•			1	2	Pos
17	•	•						•				2	1	Def
18	•	•						•	•		•	2	3	Def
19	•	•						•	•		•	2	3	Def
20								•	•			0	2	Rej
21		•				•		•	•			1	3	Def
22	•	•		•				•				2	2	Def
23		•									•	1	1	Pos
24		•						•	•			1	2	Pos
25		•				•		•	•		•	1	4	Def
26									•			0	1	Rej
27	•	•	•					•	•		•	2	4	Def
28		•						•				1	1	Pos
29		•		•				•	•		•	1	4	Def
30		•					•	•				1	2	Pos
31	•	•		•			•	•	•		•	2	5	Def
32	•	•						•	•		•	2	3	Def
33		•		•	•			•	•		•	1	5	Def

Neg	B/cul+	Echo	Fever	Club	Splint	Va	Splen	ESR	CRP	Haem	RF	Maj	Min	Diag
34		•						•	•			1	2	Pos
35	•	•						•	•	•		2	3	Def
36		•		•				•	•		•	1	4	Def
37	•	•						•			•	2	2	Def
38	•	•		•				•	•	•	•	2	5	Def
39		•		•				•	•			1	3	Def
40		•							•			1	1	Pos
41		•		•				•	•		•	1	4	Def
42	•	•		•				•	•			2	3	Def
43		•										1	0	Rej
44		•						•				1	1	Pos
45	•	•						•	•			2	2	Def
46	•	•		•		•		•	•			2	4	Def
47		•		•		•		•	•		•	1	5	Def
48	•	•	•	•				•	•		•	2	5	Def
49		•		•					•		•	1	3	Def
50	•	•		•		•	•	•	•		•	2	6	Def
51		•		•				•			•	1	3	Def

Neg	B/cul+	Echo	Fever	Club	Splint	Va	Splen	ESR	CRP	Haem	RF	Maj	Min	Diag
52		•		•				•	•			1	3	Def
53		•						•	•			1	2	Pos
54				•				•	•		•		4	Pos
55		•						•	•			1	2	Pos
56	•	•		•				•	•		•	2	4	Def
57		•		•				•	•			1	3	Def
58	•	•	•					•	•			2	3	Def
59		•		•				•				1	2	Pos
60								•				0	1	Rej
61		•		•								1	1	Pos
62								•	•		•	0	3	Pos
63		•		•				•	•		•	1	4	Def
64		•		•				•				1	2	Pos
65		•						•	•			1	2	Pos
66		•						•	•			1	2	Pos
67		•		•				•	•			1	3	Def
68	•	•						•	•		•	2	3	Def
69	•	•		•							•	2	2	Def

Neg	B/cul+	Echo	Fever	Club	Splint	Va	Splen	ESR	CRP	Haem	RF	Maj	Min	Diag
70		•										1	0	Rej
71	•	•		•			•	•	•		•	2	5	Def
72	•	•			•			•	•		•	2	4	Def
73		•		•				•	•			1	3	Def
Pos														
74		•		•			•	•	•			1	4	Def
75		•		•				•	•		•	1	4	Def
76	•	•		•				•	•			2	3	Def
77	•	•						•	•			2	2	Def
78		•		•			•	•		•		1	4	Def
79		•				•	•	•				1	3	Def
80	•	•		•				•	•		•	2	4	Def
81	•	•	•	•	•		•	•	•		•	2	7	Def
82		•		•	•			•				1	3	Def
83	•	•					•	•	•			2	3	Def
84		•						•				1	1	Pos
85		•						•	•		•	1	3	Def
86		•		•				•	•			1	3	Def

Pos	B/cul+	Echo	Fever	Club	Splint	Va	Splen	ESR	CRP	Haem	RF	Maj	Min	Diag
87		•	•					•	•			1	3	Def
88	•		•	•				•	•			1	4	Def
89		•		•			•	•	•			1	4	Def
90		•	•	•		•		•	•			1	5	Def
91		•						•	•			1	2	Pos

KEY

Neg	negative
B/cul+	positive blood culture
Echo	echocardiographic features of IE
Club	clubbing
Splint	splinter heamorrhages
Va	Vascular phenomena / stroke
Splen	splenomegaly
ESR	erythrocyte sedimentation rate
CRP	c-reactive protein
Haem	haematuria
RF	rheumatoid factor
Maj	number of major
Min	Number of minor criteria
Diag	diagnosis
Def	definite diagnosis
Pos	possible diagnosis
Rej	Rejected diagnosis

APPENDIX 4b:

Diagnosis according to modified Duke Criteria

Patient	Major		Minor											
Neg	**B/cul+**	**Echo**	**Fever**	**Club**	**Splint**	**Va**	**Splen**	**ESR**	**CRP**	**Haem**	**RF**	**Maj**	**Min**	**Diag**
1	•	•		•								2	1	Def
2	•	•								•		2	1	Def
3	•	•						•				2	1	Def
4	•	•		•				•	•		•	2	4	Def
5		•						•				1	1	Pos
6		•		•				•			•	1	3	Def
7		•				•		•	•			1	3	Def
8	•						•	•	•		•	1	4	Def
9		•		•				•	•		•	1	4	Def
10		•							•		•	1	2	Def
11		•		•				•	•		•	1	4	Def
12		•			•			•	•			1	3	Def
13	•	•		•				•	•		•	2	4	Def
14		•						•	•			1	2	Def
15		•						•	•			1	2	Def

Neg	B/cul+	Echo	Fever	Club	Splint	Va	Splen	ESR	CRP	Haem	RF	Maj	Min	Diag
16		•						•	•			1	2	Def
17	•	•						•				2	1	Def
18	•	•						•	•		•	2	3	Def
19	•	•						•	•		•	2	3	Def
20								•	•			0	2	Rej
21		•				•		•	•			1	3	Def
22	•	•		•				•				2	2	Def
23		•									•	1	1	Pos
24		•						•	•			1	2	Def
25		•				•		•	•		•	1	4	Def
26									•			0	1	Rej
27	•	•	•					•	•		•	2	4	Def
28		•						•				1	1	Pos
29		•		•				•	•		•	1	4	Def
30		•					•	•				1	2	Def
31	•	•		•			•	•	•		•	2	5	Def
32	•	•						•	•		•	2	3	Def
33		•		•	•			•	•		•	1	5	Def

Neg	B/cul+	Echo	Fever	Club	Splint	Va	Splen	ESR	CRP	Haem	RF	Maj	Min	Diag
34		•						•	•			1	2	Def
35	•	•						•	•	•		2	3	Def
36		•		•				•	•		•	1	4	Def
37	•	•						•			•	2	2	Def
38	•	•		•				•	•	•	•	2	5	Def
39		•		•				•	•			1	3	Def
40		•							•			1	1	Pos
41		•		•				•	•		•	1	4	Def
42	•	•		•				•	•			2	3	Def
43		•										1	0	Rej
44		•						•				1	1	Pos
45	•	•						•	•			2	2	Def
46	•	•		•		•		•	•			2	4	Def
47		•		•		•		•	•		•	1	5	Def
48	•	•	•	•				•	•		•	2	5	Def
49		•		•					•		•	1	3	Def
50	•	•		•		•	•	•	•		•	2	6	Def
51		•		•				•			•	1	3	Def

Neg	B/cul+	Echo	Fever	Club	Splint	Va	Splen	ESR	CRP	Haem	RF	Maj	Min	Diag
52		•		•				•	•			1	3	Def
53		•						•	•			1	2	Def
54				•				•	•		•		4	Pos
55		•						•	•			1	2	Def
56	•	•		•				•	•		•	2	4	Def
57		•		•				•	•			1	3	Def
58	•	•	•					•	•			2	3	Def
59		•		•				•				1	2	Def
60								•				0	1	Rej
61		•		•								1	1	Pos
62								•	•		•	0	3	Pos
63		•		•				•	•		•	1	4	Def
64		•		•				•				1	2	Def
65		•						•	•			1	2	Def
66		•						•	•			1	2	Def
67		•		•				•	•			1	3	Def
68	•	•						•	•		•	2	3	Def
69	•	•		•							•	2	2	Def

Neg	B/cul+	Echo	Fever	Club	Splint	Va	Splen	ESR	CRP	Heam	RF	Maj	Min	Diag
70		•										1	0	Rej
71	•	•		•			•	•	•		•	2	5	Def
72	•	•			•			•	•		•	2	4	Def
73		•		•				•	•			1	3	Def
Pos														
74		•		•			•	•	•			1	4	Def
75		•		•				•	•		•	1	4	Def
76	•	•		•				•	•			2	3	Def
77	•	•						•	•			2	2	Def
78		•		•			•	•		•		1	4	Def
79		•				•	•	•				1	3	Def
80	•	•		•				•	•		•	2	4	Def
81	•	•	•	•	•		•	•	•		•	2	7	Def
82		•		•	•			•				1	3	Def
83	•	•					•	•	•	•		2	4	Def
84		•						•				1	1	Pos
85		•						•	•	•	•	1	4	Def
86		•		•				•	•			1	3	Def

Pos	B/cul+	Echo	Fever	Club	Splint	Va	Splen	ESR	CRP	Haem	RF	Maj	Min	Diag
87		•	•					•	•			1	3	Def
88	•		•	•				•	•			1	4	Def
89		•		•			•	•	•			1	4	Def
90		•	•	•		•		•	•			1	5	Def
91		•						•	•			1	2	Def

KEY

Neg	negative
B/cul+	positive blood culture
Echo	echocardiographic features of IE
Club	clubbing
Splint	splinter heamorrhages
Va	Vascular phenomena / stroke
Splen	splenomegaly
ESR	erythrocyte sedimentation rate
CRP	c-reactive protein
Haem	haematuria
RF	rheumatoid factor
Maj	number of major
Min	Number of minor criteria
Diag	diagnosis
Def	definite diagnosis
Pos	possible diagnosis
Rej	Rejected diagnosis

APPENDIX 5: SURGICAL FINDINGS

	Echo findings	B/culture	Surgical		Surgical findings	Tissue culture	Histology	Underlying: RHD/ Normal/ other
			IE	Rh/ other				
HIV positive								
1.	AO abscess , aneurysm	-	+		Aneurysm NCC, Subaortic aneurysm	-	Chronic inflammation	Rheumatic
2.	AO NCC vegetation	*S. aureus*	+		Perforated NCC	-	Acute rheumatic valvulitis	Rheumatic
3.	AO vegetation	-	+		NCC vegetation	-	Chronic valvulitis/ fibrin vegetation	Rheumatic
4.	Disrupted RCC	*S. aureus*	+		Disrupted RCC	*S .aureas*	Fibrotic valve	Normal
5	AO vegetation	-	-		AO FOC	-	Fibrosis	Rheumatic
HIV negative								
1.	NCC, RCC Vegetation	*S. epidermis*	+		Calcific IE	-	-	Rheumatic
2.	MV, TV vegetation	*Corynebacterium*	+		Perforated PML, vegetation on chord + anterior TV, chord rupture	-	Calcified vegetation	Normal
3.	AO vegetation	-	+		IE	-	Cal vegetation, fibrin vegetation	Rheumatic
4.	MV vegetation	-	-		No vegetation	-	Thick fibrotic valve	Rheumatic
5.	MV vegetation	-	+		IE with leaflet perforation		Fibrosis	Rheumatic
6.	MV vegetation	*S. aureus*	+		Multiple vegetations	-	IE	Rheumatic
7.	AO NCC vegetation	*S. aureus*	+		LCC perforation, destroyed NCC, RCC vegetation	-	-	Rheumatic
8.	MV AML vegetation	*S. viridans*	-	+	Thick MV		Chronic calcific RHD	Rheumatic
9.	AO RCC, NCC vegetation	*S. viridans*	-	+	Thick MV, AO		Chronic RHD	Rheumatic
10	AO flail NCC ? vegetation	-	+		AO abscess, detached NCC	-	*Gram+ cocci*, acute RHD	Rheumatic
11	AO, RCC vegetation	-				-		
12	AO NCC vegetation	-	+		Perforated LCC, NCC	-	IE with vegetation, acute RHD	Rheumatic
13	MV AML vegetation	*S. aureus*	+		AML vegetation	*Serratia*	Valvulitis, RHD	Rheumatic
14	AO NCC vegetation	*S. aureus*	+		Vegetation LCC, NCC, AO abscess	-	*Gram pos cocci*, abscess	Rheumatic
15	AO NCC, RCC vegetation	-	-	+	No vegetations, RHD	-	No IE, chronic valvulitis	Rheumatic
16	AO NCC vegetation	*S. epidermis*	+	+	NCC vegetation, disrupted NCC, thick leaflets	-	Chronic valvulitis, no IE	Rheumatic

17	AO vegetation	-	+		Bicuspid AO, destroyed NCC, IE	-	Fibrosis, RHD, No IE	Rheumatic
18	MV AML vegetation	*S. viridans*	+		Chordal rupture, calcific MV+ vegetation, IE	-	Fibrosis, chronic valvulitis, no IE	Rheumatic
19	Multiple MV AML vegetations	-	+	+	AML vegetation, thick MV, IE	-	Chronic valvulitis, RHD, No IE	Rheumatic
20	MV AML vegetation	-	+	+	PML vegetation, Pap muscle vegetation, thick AO	-	Chronic RHD, IE	Rheumatic
21	MV+AO vegetation	*S. aureus*	+		AML vegetation, AO vegetation	-	IE, RHD	Rheumatic
22	MV PML vegetation, NCC RCC vegetation + aneurysm	-	+	+	Destroyed AO, AO vegetation, thick MV	-	Chronic RHD, fibrosis	Rheumatic
23	MV AML vegetation	-	-	+	No vegetation, shrunken MV	-	RHD, no IE	Rheumatic
24	AO + MV vegetation	-	+	+	NCC + AML vegetation, chordal rupture, perforation	-	Chronic valvulitis, no IE	Rheumatic
25	AO RCC vegetation	-	+		IE noted	-	Acute RHD, valvulitis, *gram pos cocci*, IE	Rheumatic
26	MV AML vegetation	-	?	+	Thick shrunken leaflets, ?AML vegetation	*Staph species*	Chronic RHD, No IE	Rheumatic
27	MVR vegetation	*Pseudomonas aeruginosa*	+		IE, AO aneurysm	-		
28	AO NCC vegetation, AML chordal rupture	-	+	+	NCC vegetation, shrunken thick MV	-	Acute RHD, sterile vegetation	Rheumatic
29	AO abscess, SOV fistula	-	+		Fistula, AO abscess, RCC vegetation	-	IE/, acute valvulitis	Rheumatic
30	MV AML vegetation	*S. aureus*	+	+	RHD, NCC perforation, AML vegetation	-	RHD, no IE	Rheumatic
31	MV AML vegetation	-	-	+	Bicuspid AO	-	Fibrosis, no IE	Rheumatic
32	MV AML vegetation	-	+	+	MV vegetation	-	Fibrosis, no IE	Rheumatic
33	AO vegetation, MV chord rupture	-	-	+	Calcific AO		Fibrosis	Rheumatic
34	MV AML vegetation, prolapse	-	-	+	Thick shrunken leaflets, FOC	-	Chronic valvulitis, no IE	Rheumatic

KEY

B/culture	blood cultures	MV	mitral valve
IE	infective endocarditis	PML	posterior mitral leaflet
Rh	rheumatic findings at surgery	AML	anterior mitral leaflet
RHD	rheumatic heart disease	TV	tricuspid valve
AO	aortic	FOC	failure of coaption
NCC	non coronary cusp	SOV	sinus of valsalva
RCC	right coronary cusp	Cal	calcified
LCC	left coronary cusp	pos	positive
+	IE found at surgery	-	negative

CHAPTER 8

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