

THE UNIVERSITY OF THE WITWATERSRAND

**DEGREE OF MASTER OF MEDICINE IN
INTERNAL MEDICINE**

**INTERACTION BETWEEN HIV/AIDS AND
INFECTIVE ENDOCARDITIS IN AFRICA: A
RETROSPECTIVE CASE REPORT AND
LITERATURE REVIEW**

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the Degree of Master of Medicine in Internal Medicine.

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DECLARATION

I, Dr Robert S Mvungi, declare that this research report is my own work. It is submitted for the degree of Master of Medicine in Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted previously for any degree or examination at this or any other University.

Signed:

Robert Sostenes Mvungi

Date:

DEDICATION

To my parents, for their guidance, support and encouragement; to my teachers, for their dedicative knowledge, clinical skills and experience; to my patients for their enthusiasm and hope for cure; to my wife, Liti, for her love and constant encouragement; and to my sons, Asseri, Muna and my daughter Esther for the joy and inspiration they have brought to our life.

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ABSTRACT

Background

In Africa, infective endocarditis (IE) is still a disease of young adults with underlying rheumatic heart disease (RHD). As of 2006, almost two-thirds of all persons infected with human immunodeficiency virus (HIV) are living in sub-Saharan Africa. Southern Africa thus remains the epicentre of the global HIV epidemic. The HIV sero-prevalence data reported in Southern Africa are as high as 20% - 30% of the adult population aged between 15 and 49 years. In South Africa, the prevalence of HIV among adults aged 15 - 49 is 18.8%. Based on a simple extrapolation, there is a higher possibility of encountering a significant number of patients infected with HIV and underlying RHD with IE in Southern Africa than in any other part of the world. In Africa because both HIV and valvular heart disease are relatively common, the co-existence of the two conditions in individual patients is not rare.

Despite the major advances in diagnosis and management of this classical disease, the overall mortality rates for both native-valve and prosthetic-valve endocarditis remain as high as 20 to 25 percent after 1 year and at 50% after 10 years. However, the mortality rate varies, depending on a number of factors, such as:

- the causative microorganism
- the presence of complications
- the development of perivalvular extension or a myocardial abscess
- neurological events
- the existence of conditions such as congestive heart failure
- renal failure
- severe immunosuppression due to HIV infection in intravenous drug abusers
- the use of combined medical therapy and surgical therapy in appropriate patients.

The clinical outcome of infective endocarditis in HIV patients is poor, severe immunodeficiency in IVDAs with IE has been reported to be associated with poor outcome. However, such an association has never been documented in non-IVDAs, particularly in Africa, where the expected majority patients with HIV and IE are non-IVDAs.

The clinical profile including bacteriology of infective endocarditis in HIV patients is different from HIV uninfected patients. The clinical impact of the HIV epidemic on infective endocarditis in Africa has not been elucidated in the world literature and there is, moreover, a paucity of literature describing this clinical entity of HIV and IE in Africa.

Objective

The objective of this study was to highlight the co-existence of infective endocarditis in HIV positive, non-intravenous drug abuse in South Africa and Africa by: reporting three cases admitted at the researcher's institution within a period of two months; and undertaking a literature review.

Methods

This was a retrospective case report and literature review study of IE in HIV infected patients. Three HIV positive patients with IE and with or without underlying chronic rheumatic heart disease were reported. The patients were admitted at the researcher's institution within a period of two months. All three patients did not report intravenous drug abuse. However, all patients died within a short period of admission to the hospital.

The systematic review of cases published in the literature was delivered from **MEDLINE SEARCH** from January 1985 to December 2006. The following key words were used: **Human Immunodeficiency Virus, Acquired Immunodeficiency Syndrome, Rheumatic Heart Disease, Infective Endocarditis, and Intravenous Drug Abusers and Non-Intravenous Drug Abusers**. Most of the articles were identified in English; where articles were identified in Spanish and French, only abstracts were used.

Literature emanating from Africa was emphasized. In addition, the references quoted in this study were reviewed for relevance on the topic.

Results

Three patients with definitive IE and infected with HIV were reported: one patient was without underlying chronic rheumatic valvular heart disease and two showed underlying chronic rheumatic valvular heart disease. There are few reported studies of IE not related to intravenous drug abuse in HIV infected patients in the literature, which is probably attributable to the reported low prevalence of IE in this sub-group of patients. Most of these published studies are limited to a series of case reports and very little data or reports originate from Africa.

Conclusion

The clinical pattern of IE in HIV positive patients who are not IVDAs is not well described in literature. However, in this anecdotal case report, the three patients studied retrospectively had a poor outcome. Based on this anecdotal report of three cases described, if an extrapolation was done from these numbers and a prospective analysis performed, we would observed a substantial number of non-IVDU cases with infective endocarditis and HIV/AIDS in Africa. The literature review in its current form may shed some light on HIV and IE in non-IVDU patients, but doesn't specifically address the issue of the potential co-existence of HIV and IE in Africa. Given the high prevalence both HIV/AIDS and rheumatic valvular heart disease in Africa, in future, we are more likely to see a significant proportion of patients with IE and underlying rheumatic valvular heart disease who are coincidentally HIV infected. There is a useful need for prospective studies describing the prevalence and outcome and for subsequently defining the management of this condition in Africa.

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LIST OF ABBREVIATIONS

HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Disease Syndrome
ARF	Acute Rheumatic Fever
CHF	Congestive Heart Failure
RHD	Rheumatic Valvular Heart Disease
IE	Infective Endocarditis
IVDAs/IVDUs	Intravenous Drug Abusers/Users
Non-IVDAs/IVDUs	None Intravenous Drug Abusers/Users
HAART	Highly Active Antiretroviral Therapy
ELISA	Enzyme Linked Immunoabsorbant Assay
ECG	Electrocardiography
TTE	Transthoracic Echocardiography
TEE	Transoesophageal Echocardiography
DIC	Disseminated Intravascular Coagulopathy
RNA	Ribonucleic Acid

NORMAL REFERENCE LABORATORY VALUES

White cell count (Wcc) $4.0 - 10 \times 10^9/l$

Direct bilirubin $0 - 6\mu\text{mol/l}$

Haemoglobin (Hb) $14.3 - 18.3 \text{ g/dl}$

Total protein $60 - 85 \text{ g/l}$

Mean corpuscular volume (MCV) $79.1 - 98.9 \text{ fl}$

Albumin $35 - 52 \text{ g/l}$

Platelets $137 - 373 \times 10^9/l$

Alkaline phosphatase (ALP) $47 - 119 \text{ U/l}$

Erythrocyte sedimentation rate (ESR) $0 - 31 \text{ mm in } 1^{\text{st}} \text{ hour}$

Gamma glutamyltransferase (GGT) $0 - 35 \text{ U/l}$

C-reactive protein (CRP) $0 - 10\text{mg/l}$

Alanine aminotransferase (ALT) $5 - 40\text{U/l}$

Potassium $3.3 - 5.3 \text{ mmol/l}$

Aspartate aminotransferase (AST) $5 - 40$

Sodium $135 - 147 \text{ mmol/l}$

Lactate dehydrogenase (LDH) $210 - 430 \text{ U/l}$

Chloride $99 - 113 \text{ mmol/l}$

Serum Iron $10 - 30 \mu\text{mol/l}$

Carbon dioxide $18 - 29 \text{ mmol/l}$

Transferrin $2.0 - 3.6\text{g/l}$

Urea $2.6 - 7.0 \text{ mmol/l}$

Percentage Iron saturation $25 - 35\%$

Creatinine $60 - 100\mu\text{l}$

Ferritin $15 - 150 \text{ ng/l}$

Total bilirubin $0 - 21 \mu\text{mol/l}$

Compliment C3 $0.5 - 1.53\text{g/l}$

Compliment C4 $0.2 - 1.0 \text{ g/}$

CHAPTER ONE

1.1 BACKGROUND

In the last half century we have seen major changes in the epidemiology, bacteriology and clinical presentation of infective endocarditis in developed countries, where the incidence and prevalence of acute rheumatic fever and its subsequent long term complication, rheumatic heart disease, has significantly declined. These changes observed in the patient profiles and clinical presentations of infective endocarditis in the developed world have been highlighted extensively in the literature.^{1 - 7, 15, 16, 18, 19} In Africa and other developing countries, where acute rheumatic fever still is prevalent, infective endocarditis is still a disease of young adults with underlying rheumatic heart disease.^{1 - 14, 17}

1.1.1 Rheumatic Heart Disease and Infective Endocarditis in Africa (sub-Saharan Africa) and South Africa

According to WHO (2004), at least 15.6 million people worldwide had RHD. The prevalence of RHD is highest in sub-Saharan Africa and is estimated to be 5.7 per 1000 in children aged 5 – 14 years.^{6, 7} This prevalence has been estimated mainly from surveys of school-going children and varies from 2.7/1000 in Kenya (Nairobi)⁸, Zambia (Lusaka) 12.5/1000⁹, Ethiopia (Addis Ababa) 6.4/1000¹⁰, Republic of Guinea (Conakry) 3.9/1000¹¹ to 14.3/1000 in Democratic Republic of Congo (Kinshasa).¹² In a survey of 12,050 black school children in Soweto, South Africa, in 1975, McLaren et al. found a prevalence of 6.9/1000, with a maximum of 20/1000 in seventh and eighth-grade children.^{6, 13} The prevalence of RHD increases with age, peaking in adults aged 25 – 34 years.^{6, 7}

In Africa and other developing countries, infective endocarditis remains a disease of young adults with underlying rheumatic heart disease; unlike in the developed world, where the prevalence has shifted towards older patients with degenerative heart disease and other co-morbid risk factors.^{1 - 19}

Keogelenberg et al.¹ (2003) reported that in the Western Cape, in South Africa, as in other developing countries, infective endocarditis is a disease of younger adults, with rheumatic heart disease being the major predisposing factor and that degenerative heart disease and intravenous drug abuse are not important risk factors.

Despite improvements in diagnostic accuracy, medical therapy and surgical techniques, the mortality remains high. The overall mortality rates for both native-valve and prosthetic-valve endocarditis remain as high as 20% to 25% after 1 year and at 50% after 10 years. However, the mortality rate varies depending on the number of factors associated with patients, including: the causative micro-organism, the presence of complications, the development of perivalvular extension or a myocardial abscess, neurological events or the existence of conditions such as congestive heart failure, renal failure, severe immunosuppression due to HIV infection in intravenous drug abusers, and the use of combined medical therapy and surgical therapy.^{2, 4, 5, 19, 20, 21} Although severe immunodeficiency in IVDAs with IE has been reported to be associated with poor outcome,^{27, 29, 31 - 37} such a relationship has not been documented in non-IVDAs, particularly in Africa, where the expected majority of patients with HIV and IE are non-IVDAs.

1.1.2 HIV/AIDS in Africa (sub-Saharan Africa) and South Africa

In 2006, almost two thirds (63%) of all persons infected with HIV were living in sub-Saharan Africa. The number was estimated to be 24.7million; [21.8 million – 27.7 million]. An estimated 2.8 million [2.4 million – 3.2 million] sub-Saharan adults and children became infected with HIV in 2006, more than in all other regions of the world combined.²³ Southern Africa remains the epicentre of the global HIV epidemic: 32% of people with HIV globally live in this sub-region and 34% of AIDS deaths globally occurred here.^{23, 24} The sero prevalence data reported in Southern Africa is as high as 20% - 30% of the adult population aged between 15-49.^{23, 24}

South Africa is the country with the largest number of HIV infections in the world, estimated at a total 5.7 – 6.7 million, comprising 3.07 – 3.6 million females and 2.6 – 3.1 million men. The epidemic varies considerably between provinces, from 15% in the Western Cape to 39% in the province of KwaZulu-Natal, with a national prevalence rate of about 29%.^{23, 24}

1.1.3 Infective Endocarditis in HIV positive, non-IVDAs in South Africa and Sub-Saharan Africa

There is limited published data available for infective endocarditis in HIV positive individuals in South Africa and other sub-Saharan Africa countries, despite the high prevalence of HIV/AIDS and rheumatic heart disease being a major predisposing risk factor for IE in this region. Koegelenberg et al.¹ (2003) established in Cape Town that HIV infection is not an independent risk factor for IE: the authors assert that given the high prevalence of both HIV and rheumatic valvular heart disease, future prospective studies may find that a significant proportion of patients with infective endocarditis and underlying rheumatic valvular disease are coincidentally HIV infected. In Africa because both HIV and valvular heart disease are relatively common, the co-existence of the two conditions in individual patients is not rare.

Based on this hypothesis, the author postulated a relationship between HIV and IE in Sub-Saharan Africa, as shown in Figure 1 below.

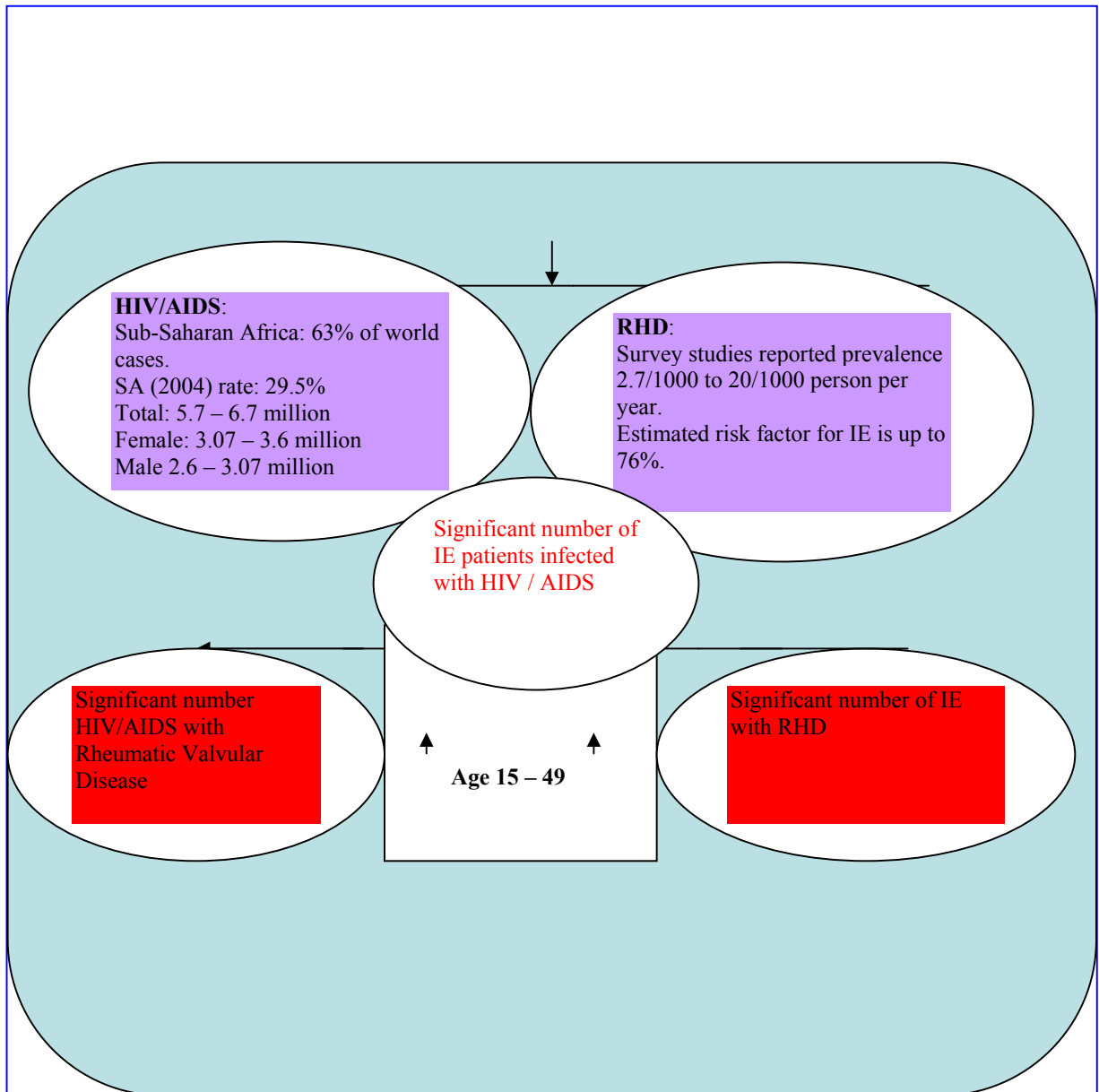


Figure 1: The postulated epidemiological and demographic similarities between HIV/AIDS and infective endocarditis in Africa

1.1.4 Clinical Profile of infective endocarditis in HIV positive, non-IVDAs

The clinical profile including bacteriology of infective endocarditis in HIV is different from HIV uninfected patients. The clinical impact of the HIV epidemic on infective endocarditis in Africa has not been elucidated in the world literature. There is a paucity of literature addressing this reported, rare, clinical entity of HIV and IE in Africa.²²

The relationship between HIV/AIDS and infective endocarditis and its implications in non-intravenous drug abusers has not been clearly and completely defined.^{1, 22, 25}

Reported studies worldwide do not support the notion that in intravenous drug abuse HIV alone is an independent risk factor for infective endocarditis. This seems to suggest that concomitant intravenous recreational drug abuse,^{2, 27} in Western countries, is confounding the apparent association with HIV.

In Cape Town, in 2003, Koegelenberg et al.¹ observed that in non-intravenous drug abuse only one (2.9%) of the 34 patients with definite IE who were tested actually had positive serology for HIV; this supports the view that HIV is not an independent risk factor for developing IE. However, in IVDAs, it has been suggested that HIV infection related to immunodeficiency may independently increase the risk of infective endocarditis among injecting drug users.^{2, 26, 27} The degree of HIV induced immunosuppression in IVDAs has shown to modify the IE clinical characteristics and the outcome.^{27, 28} The overall mortality for HIV-infected or non-HIV infected IVDA with IE is similar. However, among HIV-infected IVDA, mortality is significantly higher in those who are most severely immunosuppressed, with CD4+ cell counts below 200cells/ μ L or with AIDS criteria and left-sided endocarditis.^{27, 29, 31 - 37} Moreover, it has been reported that infective endocarditis in IVDA and HIV infected patients is not exclusively associated with intravenous drug abuse behaviour, as left-sided and mixed endocarditis has been reported.^{29 - 34}

The clinical patterns of IE in HIV positive patients with non-IVDAs are not well established and defined due to the reported low prevalence of IE in this sub-group in the literature.^{1, 25} There are very few studies that have looked at the clinical pattern and prognosis of infective endocarditis in non-IVDA HIV infected patients in Africa. ^{1, 38, 39, 40, 41}

A series of case reports on non-IVDA and HIV infected patients have been published outside Africa, which support the notion that infective endocarditis, is rare in HIV infected patients in the absence of intravenous drug abuse.^{25, 42 - 55, 59}

In Africa, and particularly in Sub-Saharan Africa, where HIV is pandemic and where rheumatic valvular heart disease is the main risk factor for developing infective endocarditis, in this setting (and affecting similar demographic groups of patients), there is significant potential to observe a significant number of patients with infective endocarditis and with underlying rheumatic valvular disease who are coincidentally infected with HIV.

1.2 OBJECTIVE

The objectives of this study are:

1. To highlight the co-existing diagnosis of HIV and IE in non-intravenous drug abusers; in the same patient is not rare in Africa
2. To describe three cases diagnosed with HIV and infective endocarditis at an institution (Chris Hani Baragwanath Hospital) within a period of two months.
3. To perform literature search on HIV/AIDS and infective endocarditis in non - intravenous drug abusers using the MEDLINE search engine covering the period January 1985 to December 2006.

CHAPTER TWO

2.1 MATERIALS AND METHODS

2.1.1 Study design

This is a retrospective case report and literature review study of infective endocarditis in HIV infected patients who are non-intravenous drug abusers.

2.1.2 Source of patients: Case reports

Three adult patients diagnosed with infective endocarditis and concomitant HIV disease at the department of cardiology, Chris Hani Baragwanath Hospital, between 1 April and 31 May 2006 were included in this study. All patients gave written consent to the HIV test. Ethical approval was obtained from the University of the Witwatersrand, Human Research Ethics Committee (Medical) - see the copy at Appendix 1.

The clinical data were obtained from patient record files, hospital charts and video cassette tapes from the Department of Cardiology after being granted permission from the hospital administration. The study was performed between April and May 2006.

Inclusion criteria

Patients described in this study fulfilled the following criteria:

1. IE: The diagnosis of IE was made according to the 1994 Dukes criteria.⁵⁶
2. HIV infection: HIV infection was confirmed by two positive ELISA tests or a positive ELISA test plus a positive Western blot test.
3. Neither active nor previous IVDA.

2.1.3 Review of the Literature

The systematic review of cases published in literature between January 1985 and December 2006 and delivered by **MEDLINE SEARCH**. The following key words were used: **Human Immunodeficiency Virus, Acquired Immunodeficiency Syndrome, Rheumatic Heart Disease, Infective Endocarditis, and Intravenous Drug Abusers and Non-Intravenous Drug Abusers**. The references quoted in this study were reviewed for their relevance. Cases were accepted if they fulfilled the inclusion criteria described above and if they were well described. Only papers in English, Spanish and French were considered. Where articles in Spanish and French were identified, only abstracts were used.

2.1.4 Ethics

Ethical approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, clearance certificate protocol number M060714. See the copy provided at Appendix 1.

CHAPTER THREE

3.1 RESULTS - CASE REPORT

Three adult patients admitted at Chris Hani Baragwanath Hospital between 1 April and 31 May 2006 fulfilled the inclusion criteria and the diagnosis of infective endocarditis, according to modified Duke Criteria^{56, 57} as summarized below in Table 1, and were confirmed as having HIV infection. Their clinical profiles and the outcome of each individual case are described below in Table 1 below.

3.1.1 Case 1

3.1.1.1 Clinical presentation

A 23 year old female patient was admitted to the medical ward on 30 May 2006, presenting with acute onset of shortness of breath on mild exertion, associated with a persistent fever, anorexia, fatigue, malaise and oligoarthralgias for the duration of four days. She denied the use of antibiotics prior to admission; she had never been diagnosed with rheumatic heart disease or thrombotic illness nor documented miscarriage previously.

On admission, she was febrile, with a temperature of 39° degree Celsius, and tachypnoeic, with a respiratory rate of 36 breaths per minute. She had a tachycardia of 156 beats per minute, differential arterial pulse volume and weak right radial and dorsalis pedis pulse compared with the respective left side. Her blood pressure was 134/68 mmHg. She had pedal oedema, raised jugular venous pressure, pallor and generalized short lymphadenopathy, but with no significant features of HIV stigmata. Her glucose on haemoglucotest was 4.5mmol/l. A urine dipstick test showed haematuria and proteinuria of less than 1g. The heart was clinically enlarged with the apex beat displaced in the sixth intercostals space lateral to the mid-clavicular line.

Table 1: Definitive diagnosis of infective endocarditis fulfilling modified Duke Criteria for the three cases selected

Duke Criteria	Case 1	Case 2	Case 3
Major Criteria	***Vegetation on Mitral valve.	**Vegetation on Aortic valve.	*Vegetation on Aortic valve.
Minor Criteria	Predisposing rheumatic heart disease.	Predisposing rheumatic heart disease.	Predisposing rheumatic heart disease.
	Fever: 39.0 degree Celsius.	Fever: 38.5 degree Celsius	Fever: 38.9 degree Celsius
	Vascular phenomena; arterial thrombus	Vascular phenomena; subconjunctival haemorrhage, Splenomegaly and clubbing	Vascular phenomena; arterial thrombus
	Elevated C-reactive protein and erythrocyte sedimentation rate	Elevated C-reactive protein and erythrocyte sedimentation rate	Elevated C-reactive protein and erythrocyte sedimentation rate

***Vegetation confirmed on both Transthoracic and Transoesophageal Echocardiogram; **only on Transthoracic Echocardiogram, and; *Transoesophageal Echocardiogram

Auscultation revealed a left-sided third heart sound - a feature of left-heart failure with a 3/6 pansystolic murmur, most audible at the apex and radiating to the axilla, which signified mitral incompetence. A chest examination revealed bilateral basal crackles. The liver was palpable three centimeters below the right costal margin, tender and having a smooth surface and sharp margin. No spleen was felt on abdominal examination. She had a tender right shoulder, left elbow, right elbow and right knee without features of arthritis. Fundoscopy examination was normal. No hemorrhage or Roth's spots were reported.

3.1.1.2 Investigations

3.1.1.2.1 Imaging tests

3.1.1.2.1.1 Chest X-ray

The Chest X-ray showed an increased cardiothoracic ratio of more than 60% and features of pulmonary oedema, without other parenchymal lung features suggestive of an infective process.

3.1.1.2.1.2 Electrocardiography

The electrocardiography revealed sinus tachycardia with a rate of 120 beats per minute, a PR- interval of 0.16 seconds, normal p-waves configuration and voltage. The QRS complex axis was normal at + 60°. See Figure 2 below.

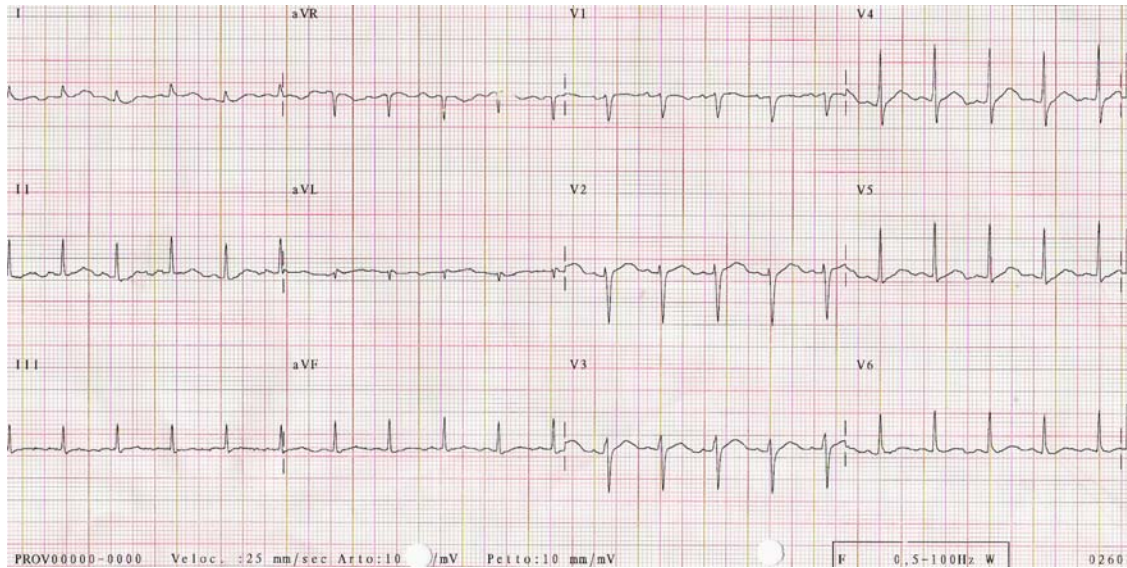


Figure 2: ECG of a 23 year old patient (Case 1) on admission

3.1.1.2.1.3 Transthoracic echocardiography

Transthoracic echocardiography showed large mobile vegetation (2.2cm) on the anterior mitral valve leaflet flopping into the left atrium. The mitral valve was thickened, with calcification on both leaflets and with moderate to severe mitral regurgitation. The left ventricle had a normal end-diastolic diameter of 4.9cm and a normal end-systolic diameter of 2.8cm, resulting in a fractional shortening of 42% and ejection fraction of 73%. She had mild aortic regurgitation and moderate tricuspid regurgitation with a right ventricular systolic pressure of 30mmHg. See Figure 3 below.



Figure 3: Transthoracic echocardiography of a 23 year old patient (Case 1) showing a large vegetation on the mitral valve both on anterior and posterior leaflet

3.1.1.2.1.4 Transoesophageal echocardiography

Transoesophageal echocardiography was performed to exclude vegetation on the aortic valve. This revealed the large vegetation on the anterior and posterior mitral leaflets. The aortic valve was normal, except for mild calcification. No vegetation was seen on the aortic valve. See Figure 4 and Figure 5 below.



Figure 4: Transoesophageal echocardiography of a 23 year old patient (Case 1) showing large vegetations on the tips of both anterior and posterior mitral valve leaflets



Figure 5: Transoesophageal echocardiography of a 23 year old (Case 1) revealing the aortic valve without vegetation, but confirming the vegetation on the mitral valve

3.1.1.2.2. Laboratory blood results and culture

On admission, her full blood count revealed: leucocytosis with a white cell count of $14.7 \times 10^9/l$; anaemia of a chronic disorder with haemoglobin of 6.5g/dL; and thrombocytopenia with a platelets count of $48 \times 10^9/l$. The inflammatory markers were raised (Table 2). The prothrombin time was prolonged (Table 2). Her HIV ELISA tests were positive twice with CD4+ count of 203cells/ μl and viral load less than 25 RNA copies/ μl . The antinuclear antibody test was negative. The sets of all blood cultures taken before antibiotics were initiated on admission were negative. Table 2 below demonstrates detailed blood results on admission.

3.1.1.3 Diagnosis

Based on the findings above, the definitive diagnosis of negative blood culture infective endocarditis with vegetation on the mitral valve was established (Table1). Disseminated intravascular coagulopathy (DIC) was also diagnosed as secondary to sepsis in view of the fact that her prothrombin time was prolonged and she was thrombocytopenic.

Table 2: Laboratory results on admission of a 23 old patient (Case 1).

FBC→	Wcc 14.7 x 10 ⁹ /l	Hb. 6.3 g/dl	Hct 0.180	MCV 84.9 fl	Platelets 48 x 10 ⁹ /l	Neutr. 72.5 %	Mono. 11.2 %	Lymph 16.2%	Eos. 0.1 %	Baso. 0.1 %
Urea and Electrolytes →		Potassium 3.2 mmol/l	Sodium 134 mmol/l	Chloride 92 mmol/l	Carbon dioxide 20 mmol/l	Urea 6 mmol/l	Creatinine 85 µmol/l	Blood Culture All six sets taken were negative		
Total liver function tests →		Total bilirubin 23 µmol/l	Direct bilirubin 13 µmol/l	Total protein 68 g/l	Albumin 22 g/l	Alkaline phosphate 71 U/l	GGT 21 U/l	ALT 16 U/l	AST 54 U/l	
Inflammatory markers→		CRP 134 mg/l	ESR 50 mm1 st hour	Iron Studies →		S- Iron 28 µmol/l	Transferrin 3 g/l	%Saturation 29%	Ferritin 108 ng/ml	
HIV Positive ELISA test →		CD4+ 203 cells/µl	Viral load 25 copies/µl	Coagulation Test →		PTTp 48.3	PTTc 24.2	INR 1.81		

Wcc; White cell count, Hb; Haemoglobin, Hct; Haematocrit, MCV; Mean Corpuscular Volume, Neutr; Neutrophils, Mono; Monocytes, Baso; Basophils, Eos; Eosinophils, Lymph; Lymphocytes, CRP; C-reactive protein, ESR; Erythrocyte sedimentation Rate, GGT; Gamma glutamyltransferase, ALT; Alanine aminotransferase, AST; Aspartate aminotransferase, LDH; Lactate dehydrogenase, PTTp; Partial prothrombin time patient, PTTc; Partial prothrombin time control, INR; International normalization ratio, S-Iron; Serum Iron level.

3.1.1.4 Treatment and clinical outcome

After admission to the medical ward, establishment of the diagnosis and three blood culture sets being taken, the patient was started on intravenous antibiotics: penicillin G 4 million units 4-hourly, cloxacillin 2g 6-hourly, gentamicin 80 mg 8-hourly. She was transfused one unit of packed red cells - her haemoglobin was 6.3 g/dl. Within 24 hours she deteriorated clinically: her blood pressure dropped, she became hypotensive and her heart failure worsened. She was transferred to the Coronary Care Unit (CCU) where her haemodynamics, blood pressure, pulse rate, oxygen saturation, fluid intake and output were closely monitored. She was started on: inotrope dobutamine infusion to augment the cardiac contractility, so as to raise the blood pressure and improve cardiac output; and diuretics furosemide (lasix) intravenously, for pre-load reduction as an anti-failure treatment, with a potassium supplement to replenish the loss of potassium caused by the diuretic (lasix) administration.

The patient showed significant clinical improvement within 72 hours in CCU. Her thrombocytopenia improved and the prothrombin time normalized in response to intravenous antibiotics therapy.

On the sixth day in the coronary care unit, she had a single episode generalized seizure - on examination she was found to be afebrile and normoglycaemic. On clinical examination, she showed no features of meningism. The brain CT scan was done to exclude space occupying lesions and revealed normal findings. A lumbar puncture performed was also normal. On the tenth day she developed right lower lobe pneumonia and was subsequently started on tazocin (piperacillin / tazobactam) 4.5g 6-hourly, intravenously. She developed what was suspected to be septic shock with multiple organ dysfunctions. She was subsequently intubated and ventilated on the mechanical ventilator. The transthoracic echocardiography then revealed increased pulmonary arterial pressure of 76mmHg, a slightly dilated right-side and tricuspid regurgitation, with good preserved left ventricular function at an ejection fraction of 70%. A pulmonary embolus was suspected and a full anticoagulation heparin infusion was initiated. Unfortunately,

the patient died before the diagnosis was confirmed on the eleventh day. No autopsy study was performed.

3.1.2 Case 2

3.1.2.1 Clinical presentation

A 46 year male patient presented at the cardiac clinic on 30 April 2006, with: a one-week history of night sweats, fever, productive cough with mild to moderate haemoptysis, dyspnoea grade four, orthopnea, paroxysmal nocturnal dyspnoea and bilateral painless leg swelling. Previously, he had been diagnosed with rheumatic valvular heart disease, mitral and aortic regurgitation and been admitted at the same institution on 23 March 2006 with biventricular heart failure. His left ventricular function on that particular admission was preserved, with an ejection fraction of 60%.

On admission he was febrile, with a temperature of 38.5 degree Celsius, and tachypnoeic, with a respiratory rate of 40 breaths per minute. He had a tachycardia with a pulse rate of 116 beats per minute, a collapsing pulse and both the Corrigan's sign and Durosoy's sign were positive. His blood pressure was normal, at 102/51 mmHg, with a wide pulse pressure. He had raised jugular venous pressure, pedal oedema, digital clubbing, clinical pallor, wasting and sub-conjunctival hemorrhage with generalized short lymphadenopathy. The cardiac examination showed an enlarged heart - the apex beat displaced in the 6th intercostals space lateral to the mid-clavicular line. He had apical systolic thrill, left parasternal heave and a palpable P₂ component of the second heart sound. Auscultation revealed a loud P₂, left-sided third heart sound, the mitral incompetence murmur 3/6 apical pansystolic murmur radiating to the axilla and the aortic incompetence murmur, with early diastolic murmur 3/6 louder at the left sternal edge. Chest examination demonstrated bilateral scattered crackles with wheezing and he had no bronchial breathing sound pointing to severe pulmonary oedema. The liver was palpable 6cm below the right costal margin, tender and smooth. He had a splenomegaly of 3cm

below the left intercostals space mid-clavicular line with ascites. Urine dipsticks showed haematuria and proteinuria of less than 1g.

3.1.2.2 Investigations

3.1.2.2.1 Imaging tests

3.1.2.2.1.1 Chest X-ray

Chest X-ray showed an increased cardiothoracic ratio of more than 80%, in keeping with an enlarged left ventricle due to increased left ventricular volume from severe aortic regurgitation. The parenchymal lung fields demonstrated diffuse severe pulmonary oedema.

3.1.2.2.1.2 Electrocardiography

Electrocardiography showed sinus normal rhythm, a rate of 96 beats per minute, left axis deviation and left ventricular hypertrophy with left ventricular strain secondary to volume overload from severe aortic regurgitation. See Figure 6 below.

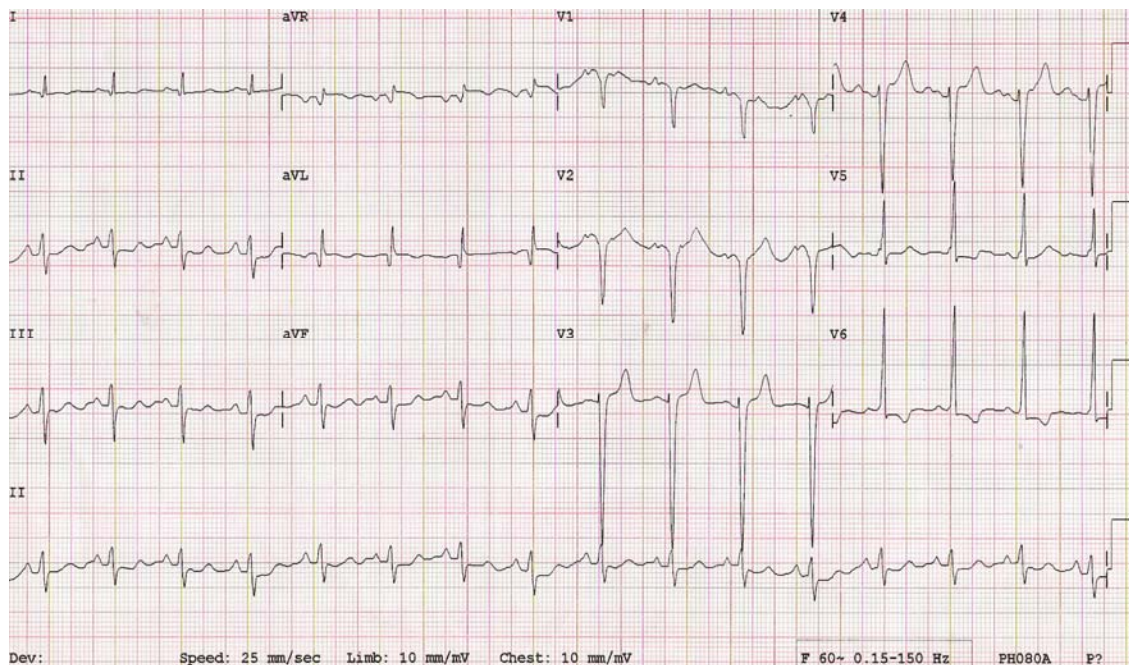


Figure 6: ECG of a 46 year old patient (Case 2)

3.1.2.2.1.3 Transthoracic echocardiography

Transthoracic echocardiography showed a rheumatic mitral valve, both anterior and posterior leaflets moderately thickened with moderate to severe mitral regurgitation. The left ventricle was dilated with an end-diastolic diameter of 7.2cm and an end-systolic diameter of 5.4cm, producing a fraction shortening of 25% and an ejection fraction of 45%, thereby demonstrating left ventricular systolic dysfunction. The aortic valve cusps (non-coronary, right and left coronary) were all thickened and calcified with vegetation less than 10mm thick and showed severe aortic regurgitation. The patient had tricuspid regurgitation with an elevated pulmonary arterial pressure of 40mmHg. See Figure 7 below.



Figure 7: Transthoracic echocardiography of a 46 year old patient (Case 2) showing vegetation on aortic valve with calcified cusps

3.1.2.2.2 Laboratory blood results and culture

On admission the patient's full blood count revealed: a normal white cell count of $8.7 \times 10^9/l$, a normal platelets count of $236 \times 10^9/l$, anaemia of chronic disorder with haemoglobin 7.8g/dL and low mean corpuscular volume of 78fl with iron deficiency picture, low serum iron level, low percentage iron saturation with normal transferrin and ferritin levels. The inflammatory markers were slightly raised. He had two ELISA HIV tests, which were both positive, with a CD4+ count of 556 cells/ μ/l and a viral load of 68,880 RNA copies/ μL .

He had mild renal dysfunction, with a slightly elevated urea of 10.7mmol/l and creatinine 128 μ mol/l. He had mild cholestatic hepatitis, with the gamma glutamyltransferase elevated fourfold and slight elevated alkaline phosphatase, with normal synthetic liver function. The sets of all blood cultures taken before antibiotics were given were negative. Table 3 below shows detailed results of all tests on admission.

3.1.2.3 Diagnosis

Based on the findings above, the definitive diagnosis of negative blood culture infective endocarditis with vegetation on aortic valve was established (Table 1).

Table 3: Laboratory results on admission of a 46 old patient (Case 2)

FBC →	Wcc 8.7 x 10 ⁹ /l	Hb. 7.8 g/dl	Hct 0.232	MCV 78 fl	Platelets 236x10 ⁹ /l	Neutr. 60 %	Mono. 6 %	Lymp 32.7 %	Eos. 0.1 %	Baso. 0.2 %
Urea and Electrolytes →		Potassium 4.3 mmol/l	Sodium 146 mmol/l	Chloride 104 mmol/l	Carbon dioxide. 19mmol/l	Urea 10.7 mmol/l	Creatinine 128 µmol/l	Blood Culture All six sets were negative		
Total liver function tests →		Total bilirubin 18 µmol/l	Direct bilirubin 11 µmol/l	Total protein 89 g/l	Albumin 31 g/l	Alkaline phosphate 139 U/l	GGT 163 U/l	ALT 23 U/l	AST 35 U/l	LDH 35 U/l
Inflammatory markers →		CRP 36 mg/l	ESR 45 mm1 st hour	Iron Studies →		S- Iron 4.1 µmol/l	Transferrin 3.3 g/l	%Satura tion 5%	Ferritin 51 ng/ml	
HIV Positive ELISA test →		CD4+ 556 cell/µl (*433)	Viral load 68,880 copies/µl	Coagulation Test →		PTTp 26.5	PTTc 27.8	INR 1.56	C3 1.090	C4 0.139

Wcc - White cell count; Hb - Haemoglobin; Hct - Haematocrit; MCV - Mean Corpuscular Volume; CRP - C-reactive protein; ESR - Erythrocyte sedimentation Rate; Complement C3 - Complement C4; GGT - Gamma glutamyltransferase; ALT - Alanine aminotransferase; AST - Aspartate aminotransferase; LDH - Lactate dehydrogenase; PTTp - Partial prothrombin time patient; PTTc - Partial prothrombin time control; INR - International normalization ratio; S-Fe - Serum Iron level; Trans - Transferrin; % Sat - Percentage saturation; Ferri - Ferritin; CD4+ (*433) repeated after six week of antibiotics.

3.1.2.4 Treatment and clinical outcome

After establishment of a definitive diagnosis, the patient was started on intravenous antibiotics in the medical ward: penicillin G 4 million units' 4-hourly, cloxacillin 2g 6-hourly, gentamicin 80mg 8-hourly. Other therapies given were: Adalat (nifedipine long acting) XL 30mg (daily) orally for aortic regurgitation; diuretics for pre-load reduction to relieve the congestion and raise the cardiac output; furosemide (lasix) 80mg mane and 80mg nocte intravenously and aldactone 50mg (daily) orally. Perindopril (coversyl) 2mg (daily) orally was given as a vasodilator to reduce systemic peripheral resistance and support cardiac output. He was given prophylactic anticoagulation unfractionated heparin 5000u 12-hourly subcutaneously, to prevent systemic venous coagulation, and ferrous sulphate 200mg 8-hourly supplementation due to a low level of serum iron.

He was transferred to Coronary Care Unit (CCU) on the eighth day, due to refractory heart failure, persistent fever, haemodynamic instability and worsened renal dysfunction. In CCU, the medical therapy was optimized. He was started on: inotrope dobutamine infusion, to improve the cardiac contractility and raise the blood pressure; and a vasodilator nitroglycerine infusion, to reduce systemic peripheral vascular resistance and improve the cardiac output. Strict fluid management was instituted, balancing input and output, gentamicin level was monitored and he was transfused with two units of packed red cells as his haemoglobin dropped from 7.8g/dl to 5.9g/dl.

The cardiothoracic surgeons were consulted and accepted the patient for emergency aortic and mitral valve replacement with tricuspid annuloplasty at Johannesburg Hospital. Unfortunately, surgery was not performed due to unavailability of a bed in the Intensive Care Unit at Johannesburg Hospital. The surgeons were constantly informed of the progress of the patient, who improved significantly on medical therapy and it was decided to take him to surgery after completion of his full intravenous antibiotics therapy for infective endocarditis.

He completed four weeks of intravenous antibiotics, with significant clinical improvement in CCU. His left ventricular systolic function improved from a 45%

ejection fraction, on admission, to 58%. The aortic vegetation resolved and disappeared on transthoracic echocardiography. The transoesophageal echocardiography was not performed to confirm the findings, due to the patient declining consent. He was transferred from CCU to a medical ward, where he completed eight weeks of intravenous antibiotics and was discharged in a stable condition and awaiting elective surgical therapy.

The patient was re-admitted on 23 June 2006 in a decompensated state and worsened biventricular heart failure. He had a raised jugular venous pressure, mild pedal oedema, ascites, a tender congested liver and gallop rhythm. Generally, the patient was afebrile with a temperature of 37 degree Celsius, a blood pressure of 161/74mmHg and a pulse rate of 108 beats per minute. Chest examination revealed features of left lower lobe pneumonia, complicated to small para-pneumonic exudative pleural effusion, which were confirmed by chest ray.

The transthoracic echocardiography was unchanged from the previous admission. It demonstrated the same severity of aortic and mitral incompetence as on the first admission. However, aortic vegetation and root abscess was suspected, but could not be confirmed on transoesophageal echocardiography as, once again, the patient declined consent. Magnetic Resonance Imaging (MRI) was performed, which did not confirm the aortic root abscess.

On this re-admission he had: mild anaemia with haemoglobin of 10.4g/dl, a normal white cell count of $9.68 \times 10^9/l$, and a normal platelets count of $208 \times 10^9/l$. The inflammatory markers were significantly elevated. The renal function was worse when compared to the first admission: urea was 22.6mmol/l and creatinine was 139 μ mol/l. His CD 4+ count dropped from 556cells/ μ l to 433cells/ μ l. The blood culture; of a single set of three sets taken, cultured coagulase negative Staphylococci bacteria sensitive to cloxacillin and vancomycin within 24 hours. The subsequent cultures failed to yield the same organism. Although the blood culture evidence was not strong enough to support the diagnosis of infective endocarditis, he was treated with caution due to atypical presentation of

endocarditis in an HIV patient. Table 4 below shows the results of all tests done on re-admission.

He was started on intravenous antibiotics: ceftriaxone 2g daily, cloxacillin 2g 6-hourly and vancomycin 750mg 12-hourly, with close monitoring of renal function and vancomycin serum level. He was also started on an intravenous inotrope, dobutamine and a vasodilator (glyceryl trinitrate) infusion. The cardiothoracic surgeons were re-consulted and in principal accepted him for surgical therapy. Unfortunately, he died before he was transferred to Johannesburg Hospital for surgery on 17 July 2006.

3.1.3 Case 3

3.1.3.1 Clinical presentation

A 37 year old male patient was admitted on 22 May 2006 and presented at the medical admission ward with: a three-week history of fever, night sweats, a productive cough with mild haemoptysis, bilateral painless lower limb swelling, dyspnoea grade four, orthopnea, and paroxysmal nocturnal dyspnoea. He has no previous documented history of rheumatic valvular heart disease.

On admission, he was febrile, with a temperature of 38.9 degree Celsius, and tachypnoeic, with a respiratory rate of 30 breaths per minute. He was tachycardiac, had a heart rate of 114 beats per minute and a differential pulse volume that was absent on the right dorsalis pedis associated with acrocynosis on the first, second and third toe. He was hypotensive, with blood pressure of 92/65 mmHg. His internal jugular venous pressure was raised. He had clinical pallor, generalized short lymphadenopathy, temporal wasting oral thrush and was jaundiced.

Table 4: Laboratory results of a 46 year old patient (Case 2) on re-admission

FBC→	Wcc 9.68 x 10 ⁹ /l	Hb. 10.4 g/dl	Hct 0.322	MCV 82.5 fl	Platelets 208 x 10 ⁹ /l	Neutr. 60%	Mono. 7%	Lymp 29%	Eos. 6%	Baso. 3%
Urea and Electrolytes →		Potassium 5.4 mmol/l	Sodium 136 mmol/l	Chloride 101 mmol/l	Carbon dioxide 19 mmol/l	Urea. 22.6 mmol/l	Creatinine 139 µmol/l	Blood Culture Single set Coagulase negative staphylococci		
Total liver function tests →		Total bilirubin 11 µmol/l	Direct bilirubin 6 µ mol/l	Total protein 99 g/l	Albumin 39 g/l	Alkaline phosphate 215 U/l	GGT 187 U/l	ALT 50 U/l	AST 46 U/l	
Inflammatory markers→		CRP 105 mg/l	ESR 220 mm in 1 st hour	HIV Positive ELISA test →		CD4+ 433 cells/µl	Coagulation Test →	PTTp 27.3	PTTc 28.7	INR 1.28

Wcc - White cell count; Hb - Haemoglobin; Hct - Haematocrit; MCV- Mean Corpuscular Volume; CRP - C-reactive protein; ESR - Erythrocyte sedimentation Rate; GGT - Gamma glutamyltransferase; ALT - Alanine aminotransferase; AST - Aspartate aminotransferase; LDH - Lactate dehydrogenase; PTTp - Partial prothrombin time patient; PTTc - Partial prothrombin time control; INR - International normalization ratio; S-Fe - Serum Iron level; Trans - Transferrin ; % Sat - Percentage saturation; Ferri - Ferritin.

The heart examination demonstrated an enlarged heart; the apex beat was displaced in the 6th intercostals space lateral to the mid-clavicular line. He had left parasternal heave, palpable P2 - a component of second heart sound. Auscultation revealed loud P2, left-sided third heart sound - a feature of left ventricular failure - 3/6 pansystolic murmur maximally audible at the apex and radiating to the axilla - in keeping with mitral regurgitation and apical mid-diastolic murmur 2/4 pointing to mitral stenosis, describing features of mixed mitral valve disease. Moreover, the auscultatory findings demonstrated aortic regurgitation murmur, an early diastolic murmur 2/4 louder at the left sternal edge on expiration and in a forward leaning position. The chest examination showed bilateral scattered crackles, demonstrating pulmonary oedema - a feature of left ventricular failure. The abdomen examination demonstrated an enlarged, tender liver with smooth and sharp edges. The urine dipsticks indicated haematuria and proteinuria of 1g/dl.

3.1.3.2 Investigations

3.1.3.2.1 Imaging tests

3.1.3.2.1.1 Chest X-ray

The chest X-ray demonstrated a cardiothoracic ratio of more than 80%, supporting clinical findings of enlarged left ventricle, enlarged left atrium, prominent pulmonary vessels and features of pulmonary oedema with small bilateral pleural effusion.

3.3.2.1.1.2 Electrocardiography

Electrocardiography showed tachycardia, with a rate of 115 beats per minute and occasional premature atrial ectopics, and left ventricular enlargement on voltage criteria. The QRS complex axis was +90°, as seen in Figure 8 below.

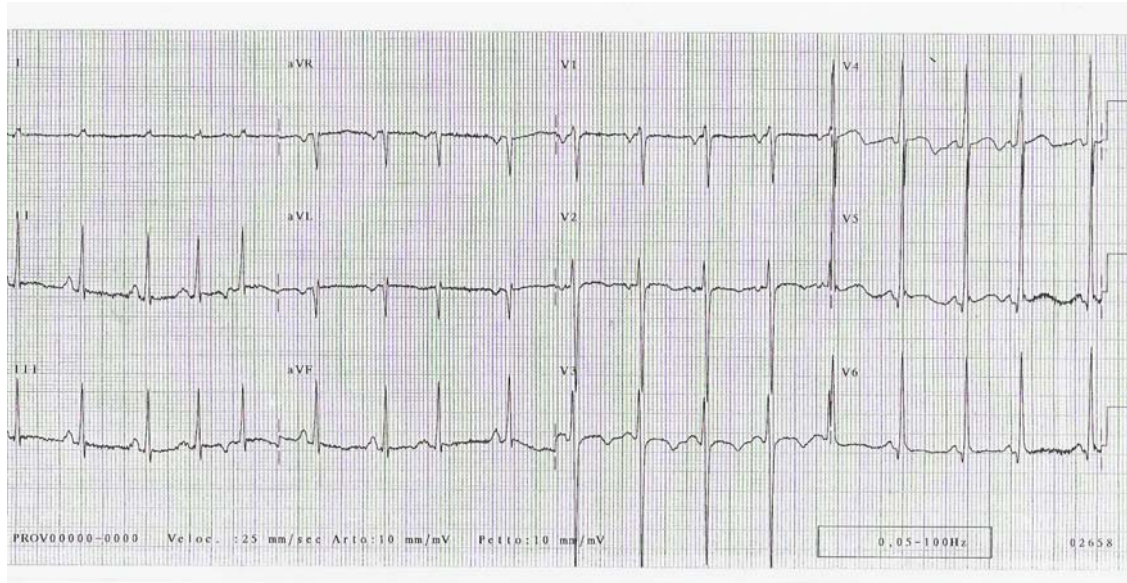


Figure 8: ECG of a 37 year old patient (Case 3) on admission

3.1.3.2.1.1.3 Transthoracic echocardiography

Transthoracic echocardiography demonstrated a rheumatic mitral valve, with thickened, retracted and calcified posterior leaflet. It revealed severe mitral stenosis, as the mitral valve area on planimetry measured 0.6cm^2 and had a doppler pressure half-time of 0.8cm^2 . The maximum pressure gradient was 42mmHg ; the mean pressure gradient was 18mmHg with moderate mitral regurgitation. In terms of the aortic valve: all cusps were thickened, retracted and calcified, with suspected vegetation on the tip of the cusps and with severe aortic incompetence. The left ventricle was dilated, with an end-diastolic diameter of 6.1cm and end-systolic diameter of 4.9cm , giving a fraction shortening of 22% and an impaired left ventricle function ejection fraction of 42% . The patient had tricuspid regurgitation, with right ventricular systolic pressure of 88mmHg and small pericardial effusion.

3.1.3.2.1.1.4 Transoesophageal echocardiography

Transoesophageal echocardiography confirmed the suspected vegetation on the transthoracic echocardiography - the vegetation of 10mm in size, seen on the tips of the

aortic cusps - and revealed a large left atrial appendage mural thrombus (Figure 9 and Figure 10).

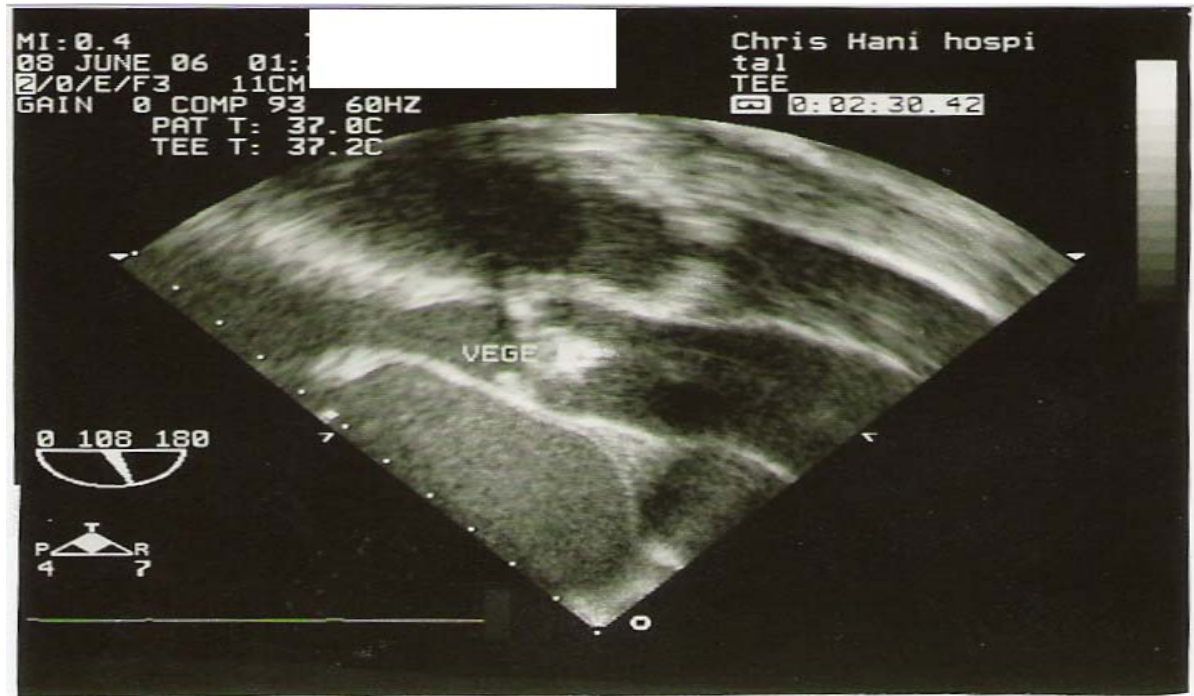


Figure 9: Transoesophageal echocardiography showing the vegetation on aortic valve in a 37 year old patient (Case 3)



Figure 10: Transoesophageal echocardiography showing mural thrombus in left atrial appendage in a 37 year old patient (Case 3)

3.1.3.2.2. Laboratory blood results and culture

On admission, the patient's full blood count demonstrated leucocytosis and a white cell count of $13.4 \times 10^9/l$ with relative neutrophilia on the background of lymphopenia. He had anaemia of a chronic disorder, with haemoglobin 12g/dl and a normal platelets count. The inflammatory markers were significantly elevated. The ELISA HIV tests were positive twice, his CD4+ count was 67cells/ μl and viral load was at 65,000copies/ μl . A blood culture, a single set of the three sets taken on admission before starting antibiotics, yielded coagulase negative Staphylococci with suspicion of contamination. He had renal dysfunction, with elevated urea and creatinine associated with mild hyperkalaemia, and liver dysfunction suggestive of severe sepsis from endocarditis with multiple organ dysfunctions. Table 5 below summarizes the detailed blood results on admission of this patient.

3.1.2.3 Diagnosis

Based on the findings above, the definitive diagnosis of negative blood culture infective endocarditis with vegetation on the aortic valve was established (Table1). This diagnosis was complicated due to septic shock and multiple organ dysfunctions.

3.1.3.3 Treatment and clinical outcome

The patient was transferred to the Coronary Care Unit within 24 hours and started on intravenous antibiotics after the blood cultures were taken. He was given: intravenous ceftriaxone 2g daily; gentamicin 80mg 8-hourly; cloxacillin 2g 6-hourly; with supportive therapy including dobutamine and adrenaline. He received additional therapy with a vasodilator infusion, diuretic infusion, oral fluconazole and enoxaparin (Clexane) subcutaneously. His renal and hepatic dysfunction improved significantly on antibiotics during the first week of therapy. He was transfused two units of packed red cells blood, as his haemoglobin dropped from 12g/dl to 6.8g/dl.

In the second week, the patient developed pneumonia. Tazocin (piperacillin / tazobactam) 4.5g 6-hourly intravenously was initiated immediately. Unfortunately, the patient died on the 12 June 2006.

The clinical profile and outcome of the three cases described in Chapter 2 are summarized below in Table 6.

Table 5: Laboratory results on admission of Case 3

FBC→	Wcc 13.4 x 10 ⁹ /l	Hb. 12 g/dl	Hct 0.38	MCV 80.2 fl	Platelets 241 x 10 ⁹ /	Neutr. 92.7%	Mono. 4.3%	Lymp 2.9%
Urea and Electrolytes →	Potassium 6 mmol/l	Sodium 130 mmol/l	Chloride 96 mmol/l	Carbon dioxide. 20 mmol/l	Urea 20.3 mmol/	Creatinine 130 µmol/l	Blood Culture Single Set of three sets Cultured Coagulase negative Staphylococci	
Total liver function tests →	Total bilirubin 100 µmol/l	Direct bilirubin 41 µmol/l	Total protein 59 g/l	Albumin 22 g/l	Alkaline phosphate 123 U/l	GGT 44 U/l	ALT 542 U/l	AST 125 U/l
Inflammatory markers→	CRP 213 mg/l	ESR 110 mm1 st hour	Iron Studies →		S-Iron 4.1 µmol/l	Transferrin 1.4 g/l	% Saturation 12%	Ferritin 301 ng/ml
HIV Positive ELISA test →	CD4+ 67 cells/µl	Viral load 65,000 copies/µl	Coagulation Test →		PTT 27.5	PTTc 29.6	INR 1.0	
			Hepatitis studies		B Negative	C Negative	A Negative	

Wcc - White cell count; Hb - Haemoglobin; Hct - Haematocrit; MCV - Mean Corpuscular Volume; CRP - C-reactive protein; ESR - Erythrocyte sedimentation Rate ; GGT - Gamma glutamyltransferase ; ALT - Alanine aminotransferase ; AST - Aspartate aminotransferase ; LDH - Lactate dehydrogenase; PTTp - Partial prothrombin time patient, Hepatitis B and C negative; PTTc - Partial prothrombin time control; INR - International normalization ratio; S-Fe - Serum Iron level.

Table 6: Summary of clinical profile and outcome for the three cases described in Chapter 2

	Case 1	Case 2	Case 3
Age (years)	23	46	37
Gender	Female	Male	Male
HIV CD4+ Count	203 cells/ μ L (423)	556 cells/ μ L (433)	67 cells/ μ L
Viral load	< 25 copies/ μ L	68,880 copies/ μ L	65,000 copies/ μ L
Aetiology - Blood Culture	Negative	Negative	Negative
Underlying rheumatic valvulopathy	None	Aortic and Mitral valve	Mitral and Aortic Valve
Echocardiographic Vegetation site	Mitral Valve	Aortic valve	Aortic Valve
Co-morbid and Complications	DIC, Suspected Pulmonary Embolus	Renal dysfunction	Renal dysfunction LAA thrombus
Therapy	Intravenous antibiotics	Intravenous antibiotics	Intravenous antibiotics
Outcome	Death	Death	Death

DIC - Disseminated Intravascular Coagulopathy; LAA - left Atrial Appendage.

3.2 RESULT OF LITERATURE REVIEW

The researcher performed a **Medline search** of literatures using the following key words: **human immunodeficiency virus, acquired immunodeficiency syndrome, rheumatic heart disease, infective endocarditis, intravenous drug abusers and non-intravenous drug abusers. The search time-frame** was January 1985 to December 2006. Most articles used were identified in English; where other language articles (French and Spanish) were identified, only abstracts were used.

The researcher found forty-four (44) cases of infective endocarditis with HIV not related to intravenous drug abuse in literature published between January 1985 and December 2006. Among these cases, 24 reported the gender of the patient (22 male and 2 female). In 21 cases, the age was reported, which ranged from 29 - 64 years. In 23 cases, no age was reported.

The mean CD4⁺ count was 161cells/ μ l, ranging from 4 - 922 cells/ μ l among 36 known CD4⁺ cases; in 9 cases the CD4⁺ count was not reported. The causative microorganisms were reported in 36 of 44 cases (80%): 32 had bacterial endocarditis; 4 were fungal endocarditis. Among bacterial endocarditis, the common organism isolated was probably Staphylococcus aureau. However, there was one definitive case reported and one was Methicillin Resistance Staphylococcus aureus (MRSA). Nel et al., ³⁸ in their prospective observational study, described 13 cases - among them the common isolated organism was Staphylococcus aureau. Other isolates were:

- Enterococcus fecalis ; 4
- Salmonella enteritidis ; 4
- Streptococci viridians ; 2
- Streptococcus pneumoniae ; 2
- Listeria monocytogenes ; 1
- Salmonella typhimurium ; 1

- Streptococcus agalactiae ; 1
- Coagulase negative - staphylococci ; 1
- Coxiella burnettii ; 1
- Bartonella quintana ; 1
- Fungal endocarditis - Candida albicans ; 1
- Candida zeylanoides ; 1
- Aspergillums fumigates ; 2
- Pseudallescheria boydii ; 1

The majority of cases (89% - 40 cases) were native valve endocarditis; prosthetic valve endocarditis totalled only 5%. Among the case, the following additional information was provided:

- 26% : aortic valve endocarditis
- 24% : mitral valve endocarditis
- 10% : mixed mitral and aortic valve endocarditis
- 2% (one case) : tricuspid bioprosthesis valve endocarditis

In 38% of cases the site of endocarditis was not reported.

The reported pre-existing valvulopathy was in 16% of cases (7 cases: mitral valve – 2; aortic valve – 2; mixed aortic and mitral valve – 1; metallic prosthesis valve1 and bioprosthesis valve - 1). There was no underlying valvulopathy in 29% of cases (13 cases); in 55% of cases (25 cases) the underlying valvulopathy was not reported.

In terms of management among 46 cases reported in literature:

- 15 cases (33%) underwent medical therapy
- 11 cases had surgery (25%)
- in 19 patients (42%) the mode of treatment was not reported and no data were available.

Among those who underwent medical therapy, 10 cases survived and 5 cases died. Among those who had surgery 7 cases survived and 4 cases died. In 13 cases, the outcome data were not available.

The findings showed that there are few reported studies of infective endocarditis not related to intravenous drug abuse in HIV infected patients in the literature, due to a relatively low prevalence of infective endocarditis. Most of these published studies are limited to a series of case reports, most of them originating outside Africa.^{25, 42 - 55, 59}

There was no case report from Africa published in the literature and all the cases published were from prospective observational cohort-studies^{1, 38 - 41}

The detailed results of the literature search of cases with IE infected with HIV, non-IVDAs are summarized below in Table 7. The variables described in the table may be inadequate, but briefly demonstrate the clinical profiles of these cases.

Table 7: IE in non-IVDA HIV infected patients described in the literature

Case	Ref.	Date	Age	Gender	HIV Stage CD4	Aetiological Agent	Type of Valve	Pre-existing Valvulopathy	Valve involved	Echo- Vegetation	Surgery	Outcome
1	42	1990	No data	M	No data	<i>Streptococci viridians</i>	Native	No data	Mitral	No data	No data	No data
2	43	1993	No data	M	No data	<i>Enterococcus fecalis</i>	No	Mitral	No data	No data	No data	No data
3	44	1991	54	M	25	<i>Streptococcus pneumoniae</i>	Native	Aortic	Aortic	Yes	No	Survival
4	45	1994	35	M	6	<i>Streptococcus pneumoniae</i>	Native	No	Aortic	Yes	No	Survival
5	46	1988	55	M	No data	<i>Listeria monocytogenes</i>	Native	No	Aortic & Mitral	Yes	Yes	Survival
6	47	1989	51	F	No data	<i>Salmonella typhimurium</i>	Native	No	Aortic & Mitral	Yes	No	Survival
7	48	1983	24	M	15	<i>Salmonella enteritidi</i>	Native	No data	No data	No data	No data	No data
8	49	1996	59	M	No data	<i>Salmonella enteritidi</i>	Prosthetic	Prosthesis	Mitral	No	No	Death
9	49	1996	64	M	242	<i>Salmonella enteritidis</i>	Native	No	Mitral	No	Yes	Survival
10	50	1993	50	M	200	<i>Bartonella quintana</i>	Native	No	Aortic & Mitral	Yes	No	Survival
11	51	1993	40	M	922	<i>Candida albicans</i>	Prosthetic	Bio	Tricuspid	Yes	Yes	Survival
12	52	1996	44	M	< 50	<i>Candida zeylanoides</i>	Native	No	Mitral	Yes	No	Death
13	53	1990	31	M	12	<i>Aspergillums fumigates</i>	Native	No	Mitral	Yes	No	Death

Ref - Reference; M - Male; F - Female; **Echo-Vega-** Echocardiographic Vegetation; Bio - Bioprothesis.

Table 7 (Continued)

Case.	Ref.	Date	Age	Gender	HIV Stage CD4	Aetiological Agent	Type of Valve	Pre-existing Valvulopathy	Valve involved	Echo- Vegetation	Surgery	Outcome
14	54	1992	53	M	No data	<i>Pseudallescheria boydii</i>	Native	No	Mitral	Yes	No	Death
15	25	1991	29	M	199	<i>Enterococcus faecalis</i>	Native	No	Aortic	Yes	No	Survival
16	25	1991	48	M	274	<i>Salmonella enteritis</i>	Native	MS	Mitral	Yes	No	Survival
17	25	1993	51	M	8	<i>Enterococcus faecalis</i>	Native	No	Aortic	Yes	No	Survival
18	25	1995	64	M	5	CN- <i>staphylococci</i>	Native	No	Mitral	Yes	No	Survival
19	25	1995	43	M	5	<i>Viridians grp streptococci</i>	Native	AS & AR	Aortic	Yes	No	Survival
20	25	1997	29	M	6	<i>Enterococcus faecalis</i>	Native	No	Aortic	Yes	Yes	Survival
21	25	1999	42	M	118	<i>Coxiella burnettii</i>	Native	BC Aortic V	Aortic & Mitral	Yes	Yes	Survival
22	25	1994	44	M	4	MRSA	Native	No data	No data	Not performed	No	Death
23	55	2001	45	M	248	<i>Streptococcus agalactiae</i>	Native	No	Aortic & Mitral	Yes	No	Survival
24	1	2003	No data	F	413	No data	Native	No data	No data	No data	No data	No data
25*	38	2006	No data	No data	Mean 138	Most common <i>Staphylococcus aureus</i>	Native	No data	Mitral 2 Aortic 4 *Others 7	6 cases Yes	No data Yes	No data
37*	"	"	"	"	"	"	"	"	"	"	"	"

Ref - Reference; M - Male ; F - Female; **Echo-Vega** - Echocardiographic Vegetation; MS - Mitral Stenosis; CN-Staphylococci - Coagulase negative staphylococci; grp - group; AS & AR - Aortic Stenosis & Regurgitation; BC Aortic V - Bicuspid aortic valve; MRSA - Methicillin Resistance *Staphylococcus aureus*.

*Not well defined. * Individual characteristic of each case not described in the study.

Table 7 (Continued)

Case	Ref.	Date	Age	Gender	HIV Stage CD4	Aetiological Agent	Type of Valve	Pre-existing Valvulopathy	Valve involved	Echo- Vegetation	Surgery	Outcome
38	39	2005	62	F	79	<i>Aspergillus fumigatus</i>	Native	No data	Mitral	Yes	No	Death
38	39	2006	No data	No data	37	No data	Native	No data	Aortic	No data	Yes	Death
39	39	2006	No data	No data	204	No data	Native	No data	Aortic	No data	Yes	Death
40	39	2006	No data	No data	81	No data	Native	No data	Mitral	No data	Yes	Death
41	39	2006	No data	No data	868	No data	Native	No data	No data	No data	Yes	Death
42	39	2006	No data	No data	No data	No data	No data	No data	No data	No data	Yes	Survival
43	39	2006	No data	No data	438	No data	No data	No data	No data	No data	Yes	Survival
44	40	1995	No data	No data	No data	No data	Native	No data	No data	No data	No data	No data
45	41	1997	No data	No data	No data	<i>Salmonella enteritidis</i>	Native	No data	No data	No data	No data	No data

Ref - Reference; M - Male; F - Female; **Echo-Vega** - Echocardiographic Vegetation

CHAPTER FOUR

4.1 DISCUSSION AND LITERATURE

This study described the clinical profile and outcome of three patients with definitive native infective endocarditis, who were infected with HIV and non-intravenous drug abusers and who were admitted within a period of two months at the researcher's institution in South Africa.

The literature review in its current form as described in the section 3.2 results of literature review and this chapter below; does shed some light on HIV and IE in non-IVDU patients, but doesn't specifically address the issue of the potential co-existence of HIV and IE in Africa. In literature, the experience of infective endocarditis in HIV/AIDS, non-intravenous drug abuse appears limited to case reports (attributed to a reported relative low prevalence of infective endocarditis in this sub-group of patients), with most of these published series of case reports originating outside Africa.^{25, 42 - 55}. Surprisingly, no case reports published from Africa were found. Instead, all the cases published were from prospective observational cohort-studies.^{1, 38 - 41}

In a South African prospective observational study (2003), which examined the risk factors for infective endocarditis, only 1 (1%) of the cohort of 92 patients was HIV seropositive. The main risk factors included: rheumatic valve disease (76%); congenital heart disease; the presence of prosthetic valves; A history of infective endocarditis and HIV infection was not associated with an increased risk of infective endocarditis.¹ In the DRC, Longo-Mbenza et al.^{40, 41} (1995) reported that: of 83 consecutive HIV-infected patients with cardiac disease, only 1.2% had infective endocarditis⁴⁰; and in 1997 reported that of 166 HIV-infected patients with heart disease 0.6% developed Salmonella enteritidis infectious endocarditis.⁴¹

In South Africa, Nel et al.³⁸ (2006, in Durban) reported that of 59 patients with IE, 22% (n= 13) were HIV positive in a prospective cohort study.

Blyth et al.³⁹ (2006), in a prospective cohort study of HIV infected patients undergoing cardiac surgery, with or without cardiopulmonary bypass, reported that of 49 patients, 4 patients (8.2%) had HIV and infective endocarditis.

Given the high prevalence of both HIV and rheumatic valvular heart disease in Africa, a cross examining data trend from the above mentioned studies reported from Africa and, future prevalence studies may find that a significant proportion of patients with infective endocarditis and underlying rheumatic valvular disease are coincidentally HIV infected.

In this anecdotal report of three cases described, one could extrapolate from these numbers to arrive at approximately 10 cases/6 months. If a prospective analysis was attempted, with regard to such a retrospective analysis as performed here, there would be a substantial number of cases to highlight the clinical importance of the co-existence of infective endocarditis and HIV/AIDS in Africa.

The clinical profile, management and outcome observed in these three reported cases are discussed below in comparison with similar cases reported in the literature.

4.1.1 Clinical Profile

The demographic relationship of IE and HIV infection in Africa was depicted from the three cases reported: all were young and aged between 23 and 46 years. Similarly, in the literature, in the majority of other reported cases outside Africa, the patients were relatively young.

It has been described that IE in HIV infected patients can cause a wide variety of symptoms, particularly in the earlier stages of infection. Clinical characteristics do not differ significantly by HIV serostatus. The disease begins acutely and patients may experience such general symptoms as fever, chills, fatigue, weight loss, muscle aches and sweating. Fever is the most important and frequent symptom. The mean duration of fever

before hospitalization is, in some series, longer in HIV+ patients than in HIV– ones. Mean platelets, leukocyte, neutrophil and CD4+ cells counts are significantly higher in patients with HIV without AIDS and also in subjects without HIV when compared to HIV+ individuals.^{60, 61} The clinical manifestations depend mainly on the affected valve and are different when this varies between either the right or left location.

The clinical course of IE in all three reported cases was acute (<1month). Losa et al.²⁵ in Barcelona, Spain, reported a similar observation. The cases presented with acute illness, fever in all cases and symptoms of heart failure, which were prominent in Case 2 and Case 3, where: there were underlying rheumatic mitral and aortic valvulopathy; both had vegetations on the aortic valve. This in comparison with Case 1; who had vegetation on the mitral valve and no underlying rheumatic mitral valvulopathy.

The clinical difference in term of morbidity and mortality on either involvement of aortic or mitral valve in this sub-group of patients is not well known. However, involvement of the aortic valve is a predictor of increased morbidity and mortality in HIV infected patients in intravenous drug users with infective endocarditis.³⁵ Valencia Ortega et al.³² (1999) generally reported that left-sided endocarditis in HIV infected patients, intravenous drug users had increased morbidity and mortality. In HIV-infected patients with IE not related to intravenous drug abuse, the mitral and aortic valves are those most frequently affected. Losa et al.²⁵ (2003) observed that most cases occur in native valves and that the overall mortality rate was not higher than in HIV– patients with IE.

Thromboembolic events were present in all three reported cases, i.e:

- Case 1 had peripheral arterial embolus and developed pulmonary embolus
- Case 2 had peripheral arterial embolus
- Case 3 had peripheral arterial embolus with left atrial appendage thrombus.

The development of pulmonary embolus in first case was unusual for left-sided IE, since the high rate of pulmonary embolus is common in right-side IE, especially in IVDAs.

In the literature, there was no study found that reported the relationship between thrombotic events in HIV infected patient with infective endocarditis. However, in non-HIV patients, thromboembolic events are a relatively common complication of IE: the incidence is high, ranging from 13% - 49% and is a strong predictor of mortality.^{62, 63, 64}

The following variables have been accepted as characterizing patients who may have increased risk for embolic events:

- a) Morphologic feature of the vegetation: risk for embolic events is closely correlated with demonstration of vegetation large enough to be detected by echocardiography and the vegetation size as a predictor for embolic complication is controversial.^{62, 65} However, there is a significant correlation between large vegetation and thromboembolic events: patients with embolic events have significantly larger vegetations than those without embolic events.^{65, 66, 67} Moreover, when vegetation size is greater than or equal to 10mm, particularly if the native valve is involved, mobility and low density vegetations at initial echocardiography have been suggested to have a prognostic implication.^{68, 69, 70}
- b) Site of infection: a high incidence of embolic complications has been observed in native mitral when compared to aortic valve endocarditis.⁶²
- c) Causative organism: there is no consensus. However, most published series report 2 - 3 times higher frequency of embolic complication in IE due to Enterococci, Abiotrophic spp, fastidious gram negative bacteria - HACEK and fungi, when compared to streptococci.^{62, 71}

d) Duration since onset of the infection: It has established that the hazard for embolic events peaks at the beginning of IE, often before hospital admission ends or before or within the first two weeks of initiation of antimicrobial therapy.^{62, 71} It has been established that it is not only the vegetation size and morphologic characteristics, the site of infection, the causative organism and the relative duration onset of IE and initiation antimicrobial therapy that predicts thromboembolic events. Inflammation-induced procoagulant changes and alterations in platelet activity appear to play an important role in thromboembolic complications of infective endocarditis.^{63, 64, 66, 67, 72, 73}

The IE patients with thrombotic events have increased systemic coagulation activation, enhanced platelet activity / damage and impaired fibrinolysis - as evidenced by increased plasma levels of prothrombin fragment 1 and 2, thrombin–antithrombin III complex, plasminogen activator inhibitor-1, β -thromboglobulin and platelet factor 4 - than do those without embolic event.^{66, 67}

Infection-associated elevated antiphospholipid antibodies levels in patients with infective endocarditis may contribute to the increased risk for major embolic events in these patients.⁷² On the other hand, thrombotic events in patients infected with HIV, when compared to the general population, is relatively high.^{74, 75, 76,77}

Studies have shown that:

- HIV irritates endothelial cells and disrupts storage and excretion of the Von Willebrand factor and tumour necrotic factor- α .^{74, 75, 76,77}
- Pro-inflammatory cytokines increases the expression of plasminogen activator inhibitor-1 in endothelial cells.^{74, 75, 76,77}

- The presence of a persistent or transient autoantibody to phospholipids, including lupus anticoagulant and anticardiolipin, diminishes the levels of anticoagulant proteins, protein C, protein S and antithrombin III. ^{74, 75, 76,77}
- Elevated levels of factor VIII and homocysteine may contribute to increased thrombotic events in HIV patients. ^{75, 76}

It is unknown whether the HIV infection has an additive contribution to thromboembolic complications to already pre-existing pro-thrombotic milieu in patients with infective endocarditis. Future prospective studies may describe and characterize the thromboembolic events in HIV patients with IE.

4.1.2 Pathogens of infective endocarditis in HIV patients, non-intravenous drug abuse

Identification of the causative agent is a very important piece of information in the management of IE and has a positive implication on the morbidity and mortality. Blood cultures with negative endocarditis often delay diagnosis and the start of treatment - with a profound impact on the clinical outcome. ^{18, 62}

In this study, in all three cases, no causative organism was isolated. It was established that at least three blood samples were taken from each case, but it was not established whether the samples were labelled suspected / query IE or prolonged incubation period of more than six days or special culture conditions were performed to try to isolate those organisms requiring special culture. Spach et al., ⁵⁰ in their case report, illustrated the value of prolonged incubation of blood cultures in an attempt to isolate fastidious organisms. Moreover, they emphasized the need for communication between clinicians and microbiologists to ensure that the necessary steps are taken in order to isolate fastidious organisms such as *Rochalimaea quintana* (*Bartonella quintana*).

Koegelenberg et al.¹ (2003, in Cape Town) reported a high frequency of culture negative endocarditis 20.5% (8/39 cases). Valencia Ortega et al.³² (1999) reported culture negative endocarditis in 62% of 34 cases of left-sided endocarditis – most of whom were IVDAs and notably severe immunosuppressed.

In this latter study, among 46 reported cases of IE in HIV, non-IVDA culture positive endocarditis was reported in 37 cases (80%). A wide etiologic range was reported, as shown in Table 7 above (see Chapter 3).^{25, 38, 41 - 54, 59}. The bacterial endocarditis included:

- *Staphylococcus aureus*
- *Staphylococcus epidermiditis*
- *Salmonella species*
- *Streptococcus pneumoniae*
- *Streptococcus agalactiae* *Streptococcus viridians*
- *Haemophilus influenzae*
- *Enterococcus faecalis*
- *Viridians group streptococci*
- *Streptococcus agalactiae*
- *Listeria monocytogenes*
- *Bartonella quintana*
- *Coxiella burnettii*
- Coagulase negative *staphylococci*.

The fungi endocarditis the pathogens reported included:

- *Candida albicans*
- *Candida zeylanoides*
- *Cryptococcus neoformans*
- *Aspergillus fumigatus*
- *Pseudallescheria boydii*.

In addition, polymicrobial pathogens were described in the case reports. This reflects different clinical and environmental conditions in which these studies – the compiled series of case reports - were undertaken. However *Staphylococcus aureus* was the most common etiologic agent reported in these case reports.

The frequency of negative blood culture endocarditis in HIV, non-IVDAs in Africa is not well characterized, nor described in literature. The reported frequency of culture negative in non-HIV IE ranges from 5% to 14% and is commonly attributed by previous administration of antibiotics. It may also be associated with fastidious pathogens, including:

- *Legionella*
- *Coxiella*, *Bartonella* species
- the HACEK group (*Haemophilus* species, *Actinobacillus actinomycetecomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kiengella kingae*)
- fungi such as *Candida*, *Histoplasma*
- *Aspergillus* species, which are difficult to culture.^{18, 78, 79}

Beynon et al.¹⁸ suggested serological testing can be particularly useful for investigating the possibility of *Coxiella burnetti* (Q fever) and *Bartonella* infection, and that this should be done in all patients who are initially culture negative. The advent of molecular techniques, notably polymerase chain reaction, definitely has a place in the detection of fastidious and non-culturable agents in this sub-group of patients.⁸⁰

Although obtaining a good microbiological result is difficult in IE, the compilation of other case reports clearly show that causative agents can be identified in many cases; there is no specific reason why that should not be possible in our setting, if one could follow the framework of the laboratory diagnosis of common organisms associated with culture negative endocarditis. See Table 8 below, which is well described.

Table 8: Laboratory Diagnosis of Common Causes of Culture Negative Endocarditis

Organism	Approach
Abiotrophia species (previously classified as nutritionally Variant streptococci)	Grow in thioglycolate medium of blood culture and as satellite colonies around <i>Staphylococcus aureus</i> on blood agar or on medium supplemented with pyridoxal Hydrochloride or L – cysteine.
Bartonella species (usually <i>Bartonella henselae</i> or <i>B. quintana</i>)	Serologic tests. Lysis-centrifugation system for blood cultures. PCR of valve or embolized vegetations ^{81, 82, 83} ; special culture techniques available, but organisms are slow growing and may require a month or more for isolation.
<i>Coxiella burnetii</i> (Q fever)	Serologic tests. PCR, Giemsa stain, or immunohistologic techniques on operative specimens.
HACEK organisms	Blood cultures positive by day 7; occasionally require prolonged incubation and sub-culturing.
Chlamydia species (usually <i>Chlamydia psittaci</i>)	Culture from blood has been described. Serologic tests. Direct staining of tissue with use of fluorescent monoclonal antibody.
<i>Tropheryma whipplei</i>	Histologic examination (silver and PAS stains) of excised heart valve; PCR26 or culture of vegetation. □ □
Legionella species	Sub-culture from blood cultures, lysis-centrifugation pellet from blood cultures, or operative specimens on BCYE agar; direct detection on heart valves with fluorescent antibody. Serologic test.
Brucella species (usually <i>Brucella melitensis</i> or <i>B. abortus</i>)	Serologic tests. Prolonged incubation of standard or lysis-centrifugation blood cultures.
Fungi	Regular blood cultures often positive for candida species; lysis-centrifugation system with specific fungal medium can increase yield; testing urine for <i>Histoplasma capsulatum</i> antigen or serum for <i>Cryptococcus neoformans</i> polysaccharide capsular antigen can be helpful. Accessible lesions (such as emboli) should be cultured and examined histologically

for fungi

*PCR denotes polymerase chain reaction; HACEK organisms - haemophilus species (*Haemophilus parainfluenzae*, *H. aphrophilus*, and *H. paraphrophilus*), *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*; PAS - periodic acid-Schiff; BCYE - buffered charcoal yeast extract.

4.1.3 Antimicrobial treatments standard for IE in HIV

The standard antimicrobial treatment of IE in HIV, non-IVDAs is not well established in literature. Likewise the antimicrobial therapy of IE in IVDAs HIV positive patients is not fully established.⁶² However, the most important advance in antibiotic therapy is that non-complicated *S. aureus* right-sided endocarditis can be successfully treated with an intravenous 2-week course of nafcillin or cloxacillin plus an aminoglycoside, although the aminoglycoside administration could probably be stopped after the first 3 to 5 days once a two-week course has been suggested.^{21, 61} Fowler et al.⁸⁴ (2006) have shown that daptomycin is not inferior therapy to standard therapy for the treatment of *S. aureus* bacteremia and right-sided endocarditis caused by MSSA or MRSA. Daptomycin may be considered an alternative to vancomycin where clinical failure or resistance to vancomycin is reported. However the number of HIV positive patients in this study was relatively small.

The choice and length of treatment are dictated by the pathogen isolated from cultures and require the close collaboration of a microbiologist and physician. However, in clinical practice, the initiation of antimicrobial treatment doesn't wait for culture results. Therefore, the empiric treatment: should be started as soon, as appropriate; it should always cover the most common isolated organisms in the locality, depending on the suspected microorganisms, site in the heart and specific clinical characteristics of the patient. Some authors^{62, 78, 85, 86} suggest empiric treatment should consist of vancomycin and gentamicin or penicillinase-resistant penicillin or/and vancomycin, gentamicin and cloxacillin. Vancomycin is less preferred as empiric therapy due to potential nephrotoxicity, especially when combined with gentamicin and a growing concern of increasing resistance to vancomycin. When culture and sensitivity results are obtained, appropriate antimicrobial treatment should be instituted. Delaying appropriate therapeutic measures whilst waiting for culture is unacceptable and is associated with increased mortality.^{2, 62}

In all three cases reported in this study, empiric therapy was initiated consisting of penicillin, cloxacillin and gentamicin for first and second case. On re-admission, the second case was treated with ceftriaxone, cloxacillin and vancomycin, after isolating coagulase negative staphylococcus sensitive to cloxacillin and vancomycin in single set of culture. In the third case, the treatment included ceftriaxone, gentamicin and cloxacillin. The empiric therapy combination given was intended to cover the most common isolates in the setting (*Staphylococcus aureus* and *Streptococcal viridians*).

In non-HIV, the most common causes of infective endocarditis and their treatments are summarized in Table 9 below. Prolonged parenteral administration of a bactericidal antimicrobial agent or combination of agents is currently recommended.^{78, 85, 86}

4.1.4. Surgical management of IE in HIV. Does IE influence surgery results?

Surgery during active IE in non-HIV patients has significantly contributed to prognostic improvement during the last decade.⁶² The combined medical and surgical therapy for infective endocarditis can decrease mortality among patients who have congestive heart failure, perivalvular invasive disease, or uncontrolled infection despite maximal antimicrobial therapy. Congestive heart failure is the strongest indication for surgery in infective endocarditis. For example, medically treated patients with moderate-to-severe congestive heart failure due to endocarditis-related valvular dysfunction have a mortality rate of 56 to 86 percent, compared with 11 to 35 percent among patients treated with combined medical and surgical therapy.²

Table 9: Usual antimicrobial therapies for common causes of infective endocarditis

PATHOGEN	NATIVE-VALVE ENDOCARDITIS		PROSTHETIC-VALVE ENDOCARDITIS	
	ANTIMICROBIAL THERAPY	COMMENTS	ANTIMICROBIAL THERAPY	COMMENTS
1. Penicillin-susceptible <i>viridans streptococci</i> , <i>Streptococcus bovis streptococci</i> with MIC of penicillin 0.1 µg/ml	Penicillin G or ceftriaxone for 4 wk †	A 2-wk regimen of penicillin G (or ceftriaxone) and gentamicin can be used some cases, ^{87 88} but not recommended for patients with myocardial extra cardiac foci of infection or prosthetic valve endocarditis	Penicillin G for 6 wk and gentamicin for 2 wk	Shorter duration of treatment with an aminoglycoside (2 wk) is usually appropriate for prosthetic valve endocarditis due to penicillin susceptible <i>viridans streptococci</i> , <i>S bovis</i> , or other <i>Streptococci</i> with MIC of penicillin ≤0.1 µg
2. Relatively penicillin-resistant <i>streptococci</i> (MIC of penicillin >0.1 to 0.5 µg/ml)	Penicillin G for 4 wk and gentamicin for 2 wk†		Penicillin G for 6 wk and gentamicin for 4 wk†	
3. <i>Streptococcus</i> species with MIC of penicillin >0.5 µg/ml, <i>enterococcus species</i> , or <i>abiotrophia species</i>	Penicillin G (or ampicillin) and gentamicin or 4–6 wk†	6 wk of therapy is recommended for patients with symptoms lasting longer than 3 mo, myocardial abscess, or selected other complications	Penicillin G (or ampicillin) and gentamicin for 6 wk†	
4. Methicillin-susceptible <i>Staphylococci</i>	Nafcillin or oxacillin for 4–6 wk, with or without addition of Gentamicin for the first 3-5 days of therapy‡	In the few patients infected with a penicillin susceptible <i>staphylococcus</i> , penicillin G may be used instead of nafcillin or oxacillin.	Nafcillin or oxacillin with rifampin for 6 wk and gentamicin for 2 wk‡	It may be prudent to delay initiation of rifampin for 1 or 2 days, until therapy with two other effective antistaphylococcal drugs has been initiated.
5. Methicillin-resistant <i>Staphylococci</i>	Vancomycin, with or without addition of gentamicin, for the first 3–5 days of therapy		Vancomycin with rifampin for 6 wk and gentamicin for 2 wk	If the <i>staphylococcus</i> is resistant to gentamicin, an alternative third agent should be chosen on the basis of in vitro susceptibility
6. Right-sided <i>staphylococcal</i> native-valve endocarditis in selected patients	Nafcillin or oxacillin with gentamicin for 2 wk	This 2-wk regimen has been studied for infections due to aminoglycoside- susceptible isolate. Exclusions to short course therapy include any cardiac or extracardiac complications associated with infective endocarditis, persistence of fever for 7 days or more, and infection with HIV. Patients with vegetations greater than 1–2 cm according to echocardiography should probably be excluded from short course therapy. ⁷⁵⁻⁷⁷		
7. HACEK organisms	Ceftriaxone for 4 wk	Ampicillin and gentamicin for 4 wk is an alternative regimen, but some isolates may produce beta-lactamase, thereby reducing the efficacy of this regimen.	Ceftriaxone for 6 wk	Ampicillin and gentamicin for 6 wk is an alternative regimen, but some isolates may produce beta-lactamase, thereby reducing the efficacy of this regimen.

*Data are from Bayer et al.,⁷⁸ Working Party of the British Society for Antimicrobial Chemotherapy,⁸⁵ and Wilson et al.⁸⁶ MIC denotes minimal inhibitory concentration; HACEK organisms - haemophilus species (*Haemophilus parainfluenzae*, *H. aphrophilus*, and *H. paraphrophilus*), *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*; HIV - human immunodeficiency virus. †Vancomycin therapy is indicated for patients with confirmed immediate hypersensitivity reactions to beta-lactam antibiotics. ‡For patients who have infective endocarditis due to methicillin-susceptible staphylococci and who are allergic to penicillins, a first-generation cephalosporin or vancomycin can be substituted for nafcillin or oxacillin. Cephalosporins should be avoided in patients with confirmed immediate-type hypersensitivity reactions to beta-lactam antibiotics.

Surgery is also indicated in active native IE patients with:

- acute aortic or mitral regurgitation, especially when associated with congestive heart failure
- evidence of peri and para-valvular extension (locally uncontrolled infection)
- persistent infection after 7 - 10days of adequate antibiotic therapy, pointing to a failure of therapy of conservative management
- infection due to microorganisms with poor response to antibiotics therapy (fungi, *Brucella species*, *Coxiella species*, *Staphylococcus lugdunensis*, *Enterococcus species*) with a high level of resistance to gentamicin and gram negative organisms
- mobile large vegetation (> 10mm – 15mm in size) before or after the first week of antibiotic therapy, especially when there is an increase in size despite antibiotic therapy and which represents mitral kissing vegetation
- recurrent emboli, despite appropriate antibiotics therapy
- obstructive vegetation.⁶²

The beneficial effect of surgery versus medical treatment has been demonstrated, despite a higher perioperative mortality associated with surgery for PVE than NVE. Surgery for active PVE should be considered in:

- early PVE,^{89, 91}
- late PVE complicated by prosthetic valve dysfunction, including perivalvular leaks, persistent blood culture, abscess formation, conduction abnormalities, or large vegetation, particularly when left-sided valves are involved and Staphylococci are the infecting agent.^{90 - 93}

HIV-infected patients with active IE who needed surgery, as indicated above, and who underwent surgery, have shown to achieve good results, at least in the short term.^{29, 38, 39,}

^{46, 50, 52} Good outcome has been reported with the use of mechanical heart valves,

bioprosthetic valves and homografts⁵ in patients who have endocarditis in this sub-group of patients.⁹⁴ Cardiac surgery in HIV-infected patients with IE does not worsen the prognosis.^{29, 35, 95} Nor does the cardiopulmonary by-pass (CPB) seem to accelerate immunodeficiency or to produce adverse effects on patients with HIV- infection.^{39, 96, 97} However, high mortality has been reported in patients with severe immunosuppression (CD⁺ cell count less than 200cells/ μ l) or with AIDS and left-sided IE in IVDAs.^{94, 95, 98} Miro et al.⁹⁵ indicated that in IVDAs with right-sided IE, the overall mortality with surgery is less than 2%. In contrast, the prognosis of left-sided IE is less favourable with surgery in IVDAs - it is 15% to 25%. No data on surgical management for HIV infected patients with non-IVDAs was found in the literature.

In this study, the compiled series of case reports demonstrated that 11 cases underwent surgery, seven had a good outcome, but 4 died. In the cases reported here:

- Case1 and Case 2 had absolute indications for surgical management. Case1 had a large mobile vegetation ~22cm on the anterior mitral valve leaflet flopping into the left atrium, with acute mitral regurgitation and features of heart failure. Moreover, Case 1 developed haemodynamic instability within 24 hours of intravenous antibiotics.
- Case 2 had biventricular heart failure and chronic underlying rheumatic mitral and aortic valvulopathy associated with moderate to severe mitral regurgitation and severe aortic regurgitation on admission. Despite being on antibiotics for eight days, Case 2 had persistent infection (persistent fever) associated with refractory heart failure, haemodynamic instability and worsened renal dysfunction.

Both Case 1 and Case 2 had CD 4⁺ more than 200/ μ l.

Blyth et al.³⁹ (2006, in South Africa) reported an early higher mortality rate in a series of a small group than in uninfected patients. Out of six emergency valve replacements, carried out according to the major indicators of haemodynamic and infective compromise, four died within three months - two of these with CD4⁺ counts of 37 and 204/ μ l, respectively - from apparent ongoing or recurrent infections. A third, with a CD4⁺ count of 81/ μ l, died at three months after complaining of dyspnoea. The fourth, with a CD4⁺ count of 868/ μ l, died on day 13, possibly with tamponade. Two survived: one with an unknown CD4⁺ cell count, lost to follow up; the other (with a count of 438/ μ l) was well more than five years later. In this small series, it would be difficult to discount the degree of immune compromise in the outcome of the patients with low CD4⁺ cell counts of 37 and 204/ μ l. It would have been expected that the surgical therapy could have changed the outcome of these two cases.

4.1.4 Relationship between immune status and clinical course of patients with IE and HIV

Healthy adults have CD4⁺ cell counts ranging from 500 to 1450 cells/ μ l. In HIV individuals with counts more than 500, their immune system is less unaffected, but when this is less than 500cells/ μ l, it means that the immune system is damaged. If the CD4⁺ count is below 200cells/ μ l, it means that HIV has progressed to AIDS. It has been confirmed that there is a strong relation between HIV-RNA levels and disease stage or CD4⁺ levels.

It is not clearly defined whether HIV infection is responsible for the worst evolution of IE in HIV infected patients. However, in IVDAs, the clinical outcome of these patients depends on the affected valve and the cultured organisms, rather than on the HIV serostatus. HIV

infection has shown to not affect the clinical manifestations or evolution of IE. The presence of AIDS or CD4⁺ lymphocytes below 200cells/ μ l predicts the worst prognosis ⁶¹

In HIV non-IVDAs, data available are only limited to series of case reports. In this compiled series of case reports:

- the mean CD4⁺ count was 161cells/ μ l ranging from 4-922cells/ μ l among 36 known CD4⁺ cases
- in 9 cases, the CD4⁺ counts were not reported
- two cases had CD4⁺ more than 500cells/ μ l, one (with counts of 868cells/ μ l) died and the other case (with counts of 922 cells/ μ l) survived
- in the majority, the CD4⁺ was less than 500cells/ μ l and where the clinical outcome was reported, four out of five (with a count less than 500cells/ μ l but more 200 cells/ μ l) survived and eight out of thirteen (with a count less than 200cells/ μ l) survived.

4.1.5 Complication of IE in HIV patients

The complications of IE in HIV positive, non-intravenous drug user patients are not well described nor well defined.^{25, 38} Nel et al.²⁵ (2006, in Durban) observed, in a small series of cases, a higher prevalence of perivalvular complication - aortic root abscess - in HIV positive IE than in HIV negative; this was related to the compromised immune status. The role of immunosuppression on root abscess formation is not yet established. However, it is well known that bacterial invasion at the periannular level causes tissue weakening, necrosis and subsequent formation of periannular complications. Once established, periannular abscesses place the patient at increased risk for adverse outcomes, including heart failure, requirement for surgery, and death.

In the cases reported in this study, Case 2 was suspected to have aortic root abscess on transthoracic echocardiography examination, but this was not confirmed on

transoesophageal echocardiography, which has high sensitivity and specificity (80 - 90%).⁹⁹ The MRI that was performed revealed no aortic root abscess. However, the sensitivity and specificity of MRI on aortic root abscess is not well defined.^{100, 101}

Disseminated intravascular coagulopathy was observed in the first case, on admission, based on thrombocytopenia and prolonged prothrombin time, which improved during the course of treatment. However, thrombocytopenia could have been associated with HIV status⁷⁴. It is less likely that prolonged prothrombin time could have been triggered by an auto-anticoagulation phenomenon in the presence of arterial thrombus, due to the background of normal liver functions. A further complication described in the first case was pulmonary embolus (which is unusual for left-sided endocarditis), based on echocardiographic findings that revealed increased pulmonary arterial pressure of 76mmHg. Unfortunately, the pulmonary embolus was not confirmed as the patient died soon after.

Case 3 also had thrombotic complications, presenting with arterial and left atrial appendage thrombus. It is unknown whether the HIV infection has an additive contribution to thromboembolic complications, on already pre existing pro-thrombotic milieu, in patients with infective endocarditis.

Renal dysfunction was observed in Case 2 and Case 3, the causation of which may have been multifactorial, e.g. reduced renal perfusion complicated by haemodynamic instability, immunological complication of IE glomeronephritis, nephrotoxic agent antibiotics administered (gentamicin and vancomycin) and/or HIV related nephropathy.

Systemic complications are more frequent in left-sided endocarditis and the need for surgical treatment is more than ten times that observed in right-sided endocarditis^{102,103} In IVDAs with HIV infection, complications are quite different if patients have right-sided or left-sided IE. The most important complications are:

- congestive heart failure (30%)
- renal failure (35%)
- major systemic emboli that often involve a major arterial bed, including coronary arteries, the spleen, the central nervous system, the bowel and extremities.

Congestive heart failure (CHF) has the greatest impact on prognosis and occurs more frequently in aortic valve infections (30%) than with mitral (20%) or tricuspid disease (8%).⁶² CHF most likely to complicate left-sided IE may develop acutely from the perforation of a valve leaflet, rupture of infected chordae or valve obstruction from bulky vegetations. It may also develop more insidiously, despite antibiotics, as a result of a progressive worsening of valvular insufficiency and ventricular dysfunction. In IVDAs Ribera et al.²⁷ found a statistical significance between HIV+ and HIV– patients in regard to CHF (15.7 vs. 32.8%), renal failure (19.9 vs. 37.3%) and surgical treatment (7.4 vs. 23.9%).

4.1.6 Clinical outcome of HIV positive patients with IE

It is well known that, if untreated, IE is a fatal disease, even in HIV negative patients. Major diagnostic advances and therapeutic progress has contributed to some prognostic improvements during the last few decades. Differences in morbidity and mortality recently reported point to the importance of an early and proper diagnosis and adequate treatment.

Successful management requires a multidisciplinary approach involving microbiologists, cardiologists and cardiothoracic surgeons.^{2, 16, 17, 18, 62, 104} The morbidity and mortality of infective endocarditis in HIV positive non-intravenous drug abuse patients is not well characterized or defined. Studies reported in the literature are limited to a series of case reports.^{25, 42 – 55, 59}

It is unfortunate that the outcome of all three cases in the study reported here were disappointing. The high mortality in this study could have been contributed to by an inadequate therapeutic approach. Urgent cardiac surgery could have changed the outcome of Case 2 and Case 3, who both had absolute indications for surgical intervention. Case 1 had large mobile vegetation ~22cm on the anterior mitral valve leaflet flopping into the left atrium, with acute mitral regurgitation and features of heart failure, as well as developed haemodynamic instability within 24 hours of intravenous antibiotics. Case 2 had: biventricular heart failure on a background of chronic underlying rheumatic mitral and aortic valvulopathy, associated with moderate to severe mitral regurgitation and severe aortic regurgitation on admission; persistent infection, despite being on antibiotics for eight days (persistent fever), haemodynamic instability and worsened renal dysfunction. Both cases had CD4⁺ more than 200/μl. Surgical intervention would have been appropriate. Case 3 had no absolute indication for surgical treatment, but was severely immunocompromised with a CD4⁺ count of 67cells/μl.

In IVDAs, the prognosis is good, with a mortality rate between 5 and 10%, when the tricuspid valve is involved and caused by *S. aureus*. When the left side is affected, the diagnosis is more difficult and mortality increases to more than 15 to 18%. Although, in general, HIV infection does not affect the clinical manifestations or evolution of IE, the presence of AIDS or CD4⁺ lymphocytes below 200cells/μl predicts a worse prognosis. Cardiac surgery is not usually necessary, except in complicated left-sided IE; fungal disease does not worsen the prognosis.^{2, 16, 35, 95, 105}

Nahass et al.³⁶ found that the mortality was higher in patients with symptomatic HIV disease. Valencia et al.¹⁰⁶ found a similar rate of mortality in patients with and without HIV infection. Pulvirenti et al.³⁷ reported that IE in IVDAs with HIV infection had a differing outcome, depending on the degree of immunosuppression, and that higher mortality rates correlated with lower CD4⁺ cell counts. Ribera et al.²⁷ in a prospective

study in 1998 observed that outcome was similar relative to HIV serostatus, but mortality was higher in severely immunosuppressed patients and in those with mixed or left-sided involvement. Cicalini ET al.³¹ reviewed 108 episodes of IE in 105 patients with HIV infection and also observed that severe immunosuppression and left-sided valvular involvement are associated with a greater risk of mortality.

4.2 CONCLUSION AND PERSPECTIVE

The clinical pattern of IE in HIV positive patients who are not IVDAs is not well described in literature. However, in this anecdotal case report, the three retrospectively studied patients had a poor outcome. Given the high prevalence of both HIV/AIDS and rheumatic valvular heart disease in Africa, in future, we are more likely to see a significant proportion of patients with IE and underlying rheumatic valvular heart disease who are coincidentally HIV infected.

Based on this anecdotal report of three cases described, if an extrapolation was done from these numbers, the result provided would be approximately 10 cases/6 months. If a prospective analysis could be attempted with regard to such a retrospective analysis of this anecdotal case report as performed here, there would be a substantial number of cases to highlight the clinical importance of the co-existence of infective endocarditis and HIV/AIDS in Africa. The literature review in its current form may shed some light on HIV and IE in non-IVDU patients, but doesn't specifically address the issue of the potential co-existence of HIV and IE in Africa. There is a useful need for prospective studies describing the prevalence and outcome and for subsequently defining management of this condition in Africa.

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Appendix 1

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

R14/49 Mvungi

CLEARANCE CERTIFICATE

PROTOCOL NUMBER M060714

PROJECT

Interaction between HIV/AIDS and
Endocarditis in Africa: A Retrospective
Case report and Literature Review

INVESTIGATORS

Dr RS Mvungi

DEPARTMENT

Dept of Internal Medicine

DATE CONSIDERED

06.07.28

DECISION OF THE COMMITTEE*

APPROVED UNCONDITIONALLY

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 06.11.23

CHAIRPERSON


(Professors PE Cleaton-Jones, A Dhali, M Vorster,
C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof K Sliwa

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

