A ten-year retrospective review of patients presenting to Inkosi Albert Luthuli Central Hospital with infective endocarditis with special reference to HIV positive patients

by

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Dedication

To my parents

Overview of the thesis

Current research has demonstrated a change in the epidemiological profile of infective endocarditis (IE) in the Western world. However, there remains a paucity of data on the clinical profile and outcomes of patients with IE in Southern Africa. This is surprising considering that rheumatic heart disease (RHD) is endemic in Southern Africa, which has a large burden of human immunodeficiency virus (HIV) infection. The incidence of IE in South Africa (S.A) is unknown, and furthermore, research regarding the clinical presentation and treatment outcomes of IE in HIV infected patients is limited. Research conducted on the clinical profile and outcomes of patients with HIV and IE is therefore essential in improving the time to diagnosis, management and outcomes associated with this disease.

The objectives of this study were:

- To describe the clinical, echocardiographic, and microbiological profile of infective endocarditis in our developing country.
- To describe and compare the clinical profile and treatment outcomes of infective endocarditis in HIV positive versus HIV negative patients.
- To describe the patterns of infective endocarditis amongst different subgroups with respect to age at presentation, clinical manifestations, aetiological organism, and outcomes.

The knowledge obtained from this study may assist with the earlier identification of patients with IE, and therefore facilitate the timeous institution of therapy. Ultimately, this will have an impact on morbidity and mortality associated with this disease.

This study is a single centre, retrospective analysis performed on all patients with suspected IE, who were reviewed by the Department of Cardiology at Inkosi Albert Luthuli Central Hospital (IALCH), the tertiary referral centre in the province of KwaZulu-Natal. The study period was from June 2006-June 2016. The modified Duke criteria was used to differentiate cases of definite IE from possible, and refuted cases of IE. Patients' records were identified and accessed via the hospitals data bases, Speedminor and Meditech software programs. The demographic data, clinical presentation, laboratory, microbiological, histological, echocardiographic, and surgical data as well as the patient outcomes were recorded and analysed.

Of 161 patients screened for IE, 97 (mean age 29.7± 15.6 years, M: F 1.4:1) met the study criteria for definite IE. An underlying valve lesion (rheumatic heart disease) was present in 84.5% of the study population. There were 2 cases of IE associated with intravenous drug use, 9 cases of paediatric IE, 10 cases of prosthetic valve endocarditis and 12 subjects who were HIV-positive. There were 11(12.9%) cases of poor dentition in the HIV negative group and 2(16.7%) cases in the HIV positive group. There were 5(5.9%) cases of prolonged venous catheter use in the HIV negative group and none in the HIV positive group.

The clinical presentation was characterised by pallor (80.4%), high grade dyspnoea (NYHA grade III and IV) in 67% of cases and clubbing (40.2%). Significant morbidity included heart failure (61.9%), renal impairment (47.4%) and embolic events (right or left) in 42.3% of cases. Right sided embolic events resulted in pulmonary emboli and lung abscess and left sided embolic events resulted in CVA, cerebral abscess, threatened limbs and ischaemic digits.

Blood cultures revealed *S. aureus* infection as the main pathogen in the HIV negative (20%), Acute IE (17.9%), Right-sided IE (50%) and Prosthetic valve (50%) subgroups. Organisms not typically associated with IE were present in 7 (58.3%) of the HIV-positive subjects of which Bacillus cereus was present in 2 (16.7%) cases. There was a high overall culture negative rate (35.1%) attributed to prior antibiotic therapy at the base hospital. At echocardiography, vegetations were present in 85 (87.6%) cases. Fifty-three of the eighty-five patients with vegetations were blood culture positive and thirty-two patients were blood culture negative. Left sided infection predominated (mitral (40.2%), aortic (19.6%), mitral and aortic (27.8%)). Chordal rupture was the most frequent finding in both the HIV positive and HIV negative subjects, occurring in eight cases (66.7%) and thirty-three (33.8%) respectively.Chordal rupture was unlikely due to degenerative disease, except for two patients who were over 65 years of age. Of the eighty-two patients with RHD seventeen of these patients were blood culture negative and chordal rupture was present. Abscess cavities were noted in eleven patients. This included an aortic root abscess in nine HIV negative patients (10.6%) and one HIV positive case (8.3%) who had a CD4 count of 87 x 10^6/L. There was no significant difference in the EF between the HIV positive and HIV negative subgroups (57.8% vs 55.6%, p= 0.479).

Seventy three subjects underwent surgery of which forty-four were blood culture positive and twenty-nine were culture-negative. At operation, IE was confirmed in 60 cases: vegetations were present in 41

subjects and leaflet perforation/chordal rupture observed in 36 cases (HIV positive n=5, HIV negative n=31).IE was confirmed in seven (87.5%) of eight HIV positive subjects who underwent surgical intervention. Six out of the ten patients with prosthetic valve endocarditis underwent surgery. Of the ten cases, three demised prior to surgery and two demised post-surgery (50%).

IE could not be confirmed in the 3 cases where the surgical records were not found. In total there were 23 deaths yielding an overall mortality rate of 23,7%. Correcting for the ten cases in whom IE was excluded at surgery yielded an adjusted overall mortality of 26.4% and surgical mortality of 9.5%. The mortality rate was high across all the subgroups, ranging from 22.2% in the paediatric cohort to 50% in patients with prosthetic valve IE. Regression analyses were performed to identify predictors of mortality in left-sided IE. Rheumatic heart disease, fever, haematuria, low haemoglobin, and medical management alone were predictive of death in the univariate analysis. Multivariate analysis identified acute onset IE (odds ratio (OR)10.54, 95% CI 1.05-106.29, p=0.046) and medical management only (OR.156.66, 95% CI 11.73-2092.23 p=0.000) to be associated with increased in-hospital mortality rates.

Conclusion

IE affects mainly young people with underlying RHD and is strongly associated with a high morbi-mortality which is attributed to valve destruction resulting in haemodynamic failure. *S. aureus* has become the predominant pathogen identified in cases of IE. The clinical presentation and outcomes in this study were found to be similar in the HIV positive and HIV negative groups, however the HIV positive group was too small for statistical comparisons to be made.

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List of Abbreviations and Acronyms

AIDS - Acquired immunodeficiency syndrome

A.R abscess - Aortic root abscess

BREC - Biomedical Research Ethics Committee

CAIE - Community acquired infective endocarditis

CD4 - Cluster of differentiation 4

CHD - Congenital heart disease

CI - Confidence intervals

CRP - C reactive protein

C - section - Caesarean section

CT- Computer Tomography

DRC- Democratic Republic of Congo

EF - Ejection fraction

EIA - Echo in Africa

ESC - European society of cardiology

ESR - Erythrocyte sedimentation rate

FDG - PET - Fluoro de oxy glucose positron emission tomography

HACEK - Haemophilus spp, Actinobacillus, Cardiobacterium, Eikenella corrodens, Kingella kingae

HAIE - Hospital acquired infective endocarditis

HB - Haemoglobin

HCIE - Health care associated infective endocarditis

HIV - Human immunodeficiency virus

IBM - International Business Machine

IALCH - Inkosi Albert Luthuli Central Hospital

ICD - International classification of disease

IE - Infective endocarditis

IVDU - Intravenous drug use

KZN - KwaZulu - Natal

LSIE - Left sided infective endocarditis

MRI - Magnetic resonance imaging

MRSA - Methicillin resistant staphylococcus aureus

NVE - Native valve endocarditis

NYHA - New York Heart Association

OR - Odds ratio

PE - Pericardial effusion

PVE - Prosthetic valve endocarditis

RHD - Rheumatic heart disease

RSIE - Right sided infective endocarditis

S.A - South Africa

S. aureus - Staphylococcus Aureus

SD - Standard deviation

SPSS - Statistical package for the social sciences

Staph. epidermidis - Staphylococcus epidermidis

Staph. haemolyticus - Staphylococcus haemolyticus

Staph. species - Staphylococcus species

Strept. nutritional variant - Streptococcus nutritional variant

Strept. pneumonia - Streptococcus pneumonia

Strept. species - Streptococcus species

Strept.viridans - Streptococcus Viridans

TOE - Transoesophageal echocardiography

TOF - Tetralogy of Fallot

TTE - Transthoracic echocardiography

USA - United States of America

WCC - White cell count

Chapter 1: Review of the Literature

Introduction

Infective endocarditis (IE) was first diagnosed by William Osler in 1885.[1] It is an endovascular infection of the cardiovascular structures.[2] This infection which results in the inflammation of the inner layer of the heart can affect both native and prosthetic heart valves.[3] Other structures within the heart such as the chordae tendineae, interventricular septum, sinuses of Valsalva and intracardiac foreign bodies such as pacemaker leads, and surgical conduits may also be infected.[2,3] The pathognomonic lesion of infective endocarditis is the vegetation, which is a mass consisting of fibrin, platelets, microcolonies of bacteria and inflammatory cells.[3]

Despite being first described in the 19th century, IE remains a challenging condition.[1,4] Over the past few decades there has been no decrease in the incidence or mortality rate associated with IE.[4] According to Baddour *et al* (2015), IE is the fourth most common life-threatening infection syndrome.[5] The three other life-threatening infection syndromes that are more common than IE are: Sepsis, pneumonia, and intra-abdominal abscess.[5] Furthermore, these authors report that, "Globally, in 2010, IE was associated with 1.58 million disability-adjusted life-years or years of healthy life lost as a result of death and nonfatal illness or impairment." [5]

Hill *et al* (2006) report an in-hospital mortality rate for community acquired IE to be 16-20%, increasing to 24-50% for hospital acquired IE.[6] Furthermore, Prendergast (2004) and Bedeir *et al* (2014) note a high rate of infective endocarditis one-year mortality of 40%.[1,7] These mortality rates are high despite recent advancements in the ability to diagnose and treat IE.[8] According to Chu *et al* (2004), the early identification of patients who are at high risk of complications from IE will assist in reducing the high morbidity-mortality associated with IE.[8] Wang (2012) also pointed out that intensifying efforts towards reducing the high morbidity and mortality rates are imperative in decreasing the negative outcome associated with this disease.[9]

Classification of infective endocarditis

Researchers have used many classifications to categorise infective endocarditis. The following classifications are pertinent to this study. In their review done 16 years ago, Moreillon and Que (2004)

classified IE into four categories: native-valve IE (NVE), prosthetic-valve IE (PVE), IE in intravenous drug users and IE related to nosocomial infection.[10] These authors found that native valve endocarditis is typically associated with congenital heart disease (CHD) and chronic rheumatic heart disease (RHD).[10] They also established that patients with regurgitant lesions are more at risk of developing IE.[10]

Moreillon and Que (2004) documented that prosthetic valve endocarditis accounted for 1 to 5% of patients with IE.[10] Furthermore, these researchers classified PVE as either due to early or late infection.[10] Early infection was diagnosed when IE was present within 60 days of surgical intervention.[6,10] This classification of PVE used by Moreillon and Que (2004), differs from the classification used by Lomas *et al* (2010) who classified early PVE as infection occurring within 12 months of valve implantation and late PVE as infection occurring after 12 months of valve implantation.[11] It is important to note that the type of prosthetic valve material used did not seem to influence the development of IE.[12,13] A similar risk was observed for the development of IE with mechanical or bioprosthetic valves.[12,13]

McDonald (2009) states that, "acute IE is increasing in frequency relative to subacute and chronic IE."[13] This author also noted that left-sided disease affecting the mitral and/or aortic valve predominated over right-sided infection affecting the tricuspid and/or pulmonary valves.[13] In a recent review Hubers *et al* (2020) classified IE according to the onset of the patient's symptoms as follows: acute IE (symptoms occurring within days and up to 6weeks), subacute IE (symptoms occurring between 6 weeks and 3 months), and chronic IE (symptoms of >3 months).[14]

Epidemiology of infective endocarditis

The clinical and epidemiological profile of IE has changed significantly since it was first described by William Osler.[15,18] Most of the literature from current Western series report that the annual incidence of IE is between 2-10 cases per 100 000 people, occurring predominantly in males and in the elderly population.[13]

In recent years there has been a noticeable change in the age and aetiology of patients presenting with IE.[4-6] The epidemiology of IE has shifted from being a disease of younger adults with underlying Rheumatic heart disease, to a disease affecting older people.[4-6] Delahaye *et al* (2017) reported that the mean age for IE during the years 1980-1984 in Olmsted county Minnesota was 46.5 years; this has increased significantly to 70.5 years between the years 2001 to 2006.[16] Similarly, in 1991 in France the mean age for IE was 57.9 years. This figure rose to 59.8 years in 1999 and 61.6 years in 2008.[16] With this

increase in age there is now a higher incidence of IE reported in patients with degenerative valve disease, previous valve surgery, intracardiac devices, end stage renal disease undergoing dialysis and indwelling venous catheters.[17,18] Another factor that has altered the disease profile of IE, is the rise in intravenous drug use, especially in the developed countries.[17]

This changing risk factor profile is also evident in a Spanish population-based study done by Olmos *et al* (2017).[18] These authors observed an increase in IE in patients with diabetes mellitus, implantable devices, and cardiac prosthesis which they attributed to the aging population.[18] The changes in the risk factor profile, patient demographic characteristics, and the microbiology of IE in modern times is further illustrated by Cahill *et al* (2017), who state that the average patient with IE is, "older and frailer, with increasing comorbidities."[19]

Although there is an abundance of data regarding the epidemiology of IE in developed countries, there is currently limited data regarding the epidemiological profile of IE in South Africa (S.A).[20] Koegelenberg *et al* (2003) from Stellenbosch (S.A), attributed a change in the profile of IE to several factors.[20] These factors include the following: an aging population, a decline in the incidence of rheumatic fever, greater prevalence of degenerative heart disease, an increased prevalence of intravenous drug use, an increasing number of patients with prosthetic valves and the longer survival of patients with congenital heart disease.[20] The new risk factors for IE as well as the non-specific clinical presentation may explain the continuing high rate of morbidity and mortality associated with IE.[21]

Rheumatic heart disease (RHD), however, is still endemic in South Africa and in underprivileged socioeconomic demographic groups.[14] The younger patient population is more susceptible to IE.[14] This explains the strong association between chronic RHD and IE in young to middle aged subjects in South Africa.[22]

Predisposing factors for IE

- **Rheumatic heart disease**

Cahill *et al* (2017) report a significant decline in the incidence of rheumatic heart disease (RHD) in the developed world.[19] These authors attribute the decline to better living conditions and the accessibility to antibiotics in the developed world.[19] However, in sub-Saharan Africa RHD remains the main predisposing factor for the development of IE with an estimated prevalence of 5.7 per 1000 cases.[23]

Sub-Saharan Africa has the highest number of children with RHD between the ages of 5-14 years, with just over a million cases (1,008,207), compared to about 33000 cases in the developed countries.[24] In Cape Town (SA), the Echo-in Africa (EIA) project screened over 6000 secondary school pupils in the Tygerberg Hospital referral network.[22] The findings of this project noted a prevalence of 20 out of 1000 pupils to have borderline or definite RHD, placing a high percentage of the population at risk for the development of IE.[22]

In their prospective observational study, Koegelenberg *et al* (2003) examined the risk factors for IE and found that 76.6 % of their sample population had RHD (20). Furthermore, all the cases of prosthetic valve endocarditis occurred in patients who have had previous RHD.[20] In a more recent study from the Western Cape, South Africa (2018), focus was on the long-term outcome and Euro Score II validation in native valve surgery for active infective endocarditis.[25] In this study RHD was the most common underlying cardiac condition, accounting for 84% of the study population. Congenital heart disease was observed in only 2% of the patient population.[25]

- **Congenital Heart Disease and Grown Up Congenital Heart disease (GUCH)**

Infective endocarditis in children is rare and the clinical spectrum of IE differs from that in adults.[26] With the eradication of rheumatic fever in the developed world, congenital heart disease is becoming the most common predisposing factor for IE in the young.[27] Baltimore *et al* (2015) have observed that the spectrum of IE has changed due to the early surgical correction of the congenital lesions that were once risk factors for IE.[27] These authors have identified that children who have undergone previous corrective or palliative surgery requiring implanted vascular grafts, patches or prosthetic cardiac valves are now at high risk for the development of IE.[27]Due to advancements in medical technology patients with CHD are now surviving longer than they did in the past.[4] Over the past few decades early corrective surgical intervention has led to an increase in the population of young adults with congenital heart disease.[4] Baumgartner *et al* (2011) highlight this point by reporting that there are currently over 12 million adults with CHD living in Europe.[4]

The incidence of IE varies for the different congenital defects.[4] Lesions such as secundum atrial septal defects and pulmonary valve stenosis carry a low risk, in comparison with ventricular septal defects, which are considered a higher risk.[4] IE that is associated with CHD offers a more favourable prognosis when compared to community acquired IE.[4] However, this condition is still associated with a

significant mortality rate which ranges between 4-10%.[4] IE can also be present in approximately 8-10% of paediatric cases without structural heart disease.[27] In these subjects indwelling venous lines can be a predisposing factor and the infection usually involves the aortic or mitral valve with *S. aureus* bacteraemia.[27]

In developing countries, the main predisposing factors for IE are CHD and RHD.[28] There are only a few South African studies that have described the profile of IE in the paediatric age group. Moethilalh and Coovadia (1982) documented thirteen cases of infective endocarditis in children between the years 1974-1981.[29] In this study RHD was present in majority of the study population (69.2%) and CHD was documented in only 1 child.[29] The remaining three children (23.1%) had no underlying structural heart disease. *S. aureus* was the most common organism isolated in 5 children.[29] The mortality rate was high with 8 deaths (88.9%) and neurological complications were found in 44.4% of the cases.[29] Subsequently, in 1989 Hugo-Hamman *et al* (1989) reported the clinical and laboratory findings in 29 children with infective endocarditis over a ten-year period.[30] Similar to Western series,[4,27] these authors found that CHD (70%) and to a lesser extent RHD (16%), were the main predisposing factors for IE. The most common organisms cultured in this study were *S. aureus, S. epidermidis* and *Strept. viridans.*[30]

More recently, in a 5-year retrospective analysis, Willoughby *et al* (2019) described IE in 49 children.[26] They established that CHD was the most frequent predisposing factor for IE in their study (59.2%).[26] RHD was present in only 5 cases (10.2%). Similar to the studies of Moethilalh and Coovadia, (1982) and Hugo Hamman *et al,* (1989) *S. aureus* was the most common organism cultured (16 cases), followed by *Strept. viridans* (5 cases).[26,29,30]

Only a few South African studies, have reviewed the clinical profile of patients with CHD and IE.[26,30,31] In an early study from 1978, Rose described the findings of an autopsy study on 728 patients with CHD during the period 1927-1974.[31] Infective endocarditis was documented in 34 of these patients (4,7%), whose age ranged from 2-69 years.[31] In these patients with IE the most common congenital lesions identified were Tetralogy of Fallot (TOF) in ten cases and ventricular septal defects (VSD) in seven cases.[31] Of the ten cases which were culture positive, *Strept. viridans* was. the most frequent pathogen isolated (6 cases).[31] In more recent reports of IE in South Africa, CHD as the predisposing factor for IE was identified in cases ranging from 3.3% (Koegelenberg *et al* 2003*)*[20] to 10.5% (de Villiers *et al* 2019).[32]

- **Health care-associated / Hospital acquired infective endocarditis**

Health care-associated infective endocarditis (HCIE) is one of the most serious complications that can occur in a hospitalised patient.[33] This condition is described in patients who develop infective endocarditis more than 48 hours after admission to hospital, or IE associated with a significant invasive procedure performed in the 6 months prior to diagnosis.[11] This infection carries a higher morbidity and mortality rate than community acquired IE.[33]

In more recent years, there has been an increase in HCIE, accounting for 10-34% of all cases of IE.[33] Lomas *et al* (2010) attribute the rise of health care-associated IE to: the increase in invasive diagnostic and therapeutic procedures, modification of the definition of nosocomial infection to include non-hospitalized patients with recent healthcare contact, and prolonged incubation periods to promote the culture of fastidious causative organisms.[11] In their study, Lomas *et al* (2010) reported 793 cases of IE, of which 127 (16%) cases were health care-associated IE. This study emphasises that HCIE is associated with an older population (mean age 60 years), patients with comorbidities are at higher risk for HCIE and *S. aureus* is the most frequent pathogen isolated in HCIE.[11] Vascular manipulation was the main cause of bacteraemia in this study, accounting for 63% of cases. The findings in this study are consistent with current literature on HCIE from the developed world.[11]

In another study set in Brazil, a developing country, an observational prospective case series by Francischetto *et al* (2014) reported HCIE in 53 (35.1%) out of 151 cases of IE.[33] The male to female ratio was almost equal at 49% for males and 51% for females.[33] These researchers report that a significant proportion of patients with HCIE have prosthetic valve involvement (43%).[33] *Enterococcus faecalis* was the most common organism isolated at 19%. This finding is consistent with current reports from the West documenting enterococci infection in 17.3-47% of all cases of HCIE.[33]

In a more recent study by Camou *et al* (2019), which reviewed 493 patients with IE, 231 (46.9%) patients were diagnosed with HCIE.[34] This study further highlights that: HCIE is more common in the elderly (median age of 70.9 years), prosthetic valve endocarditis is a common feature in HCIE (55%), and comorbidities increase the risk for the development of HCIE.[34] Similar to the study by Lomas *et al* (2010) *S. aureus* was the most frequent pathogen isolated in health care-associated IE (45%).[11,34] From this study it can be inferred that in a developed world where there is better health care, the life expectancy of a patient is longer, providing an explanation for the change in the disease pattern of IE.

- **Intravenous drug users**

In the developed world there is a high rate of intravenous drug use and the prevalence of IE reported in these studies is 30-70%.[35] According to Miro *et al* (2002) intravenous drug-associated IE, commonly affects the right sided valves and *S. aureus* is the most common pathogen isolated.[35] There is an increased predisposition to HIV infection with recurrent intravenous drug use. Ntsekhe and Hakim (2005) identified markers of poor prognosis in patients with intravenous drug-associated IE who were also HIV-positive. These markers include involvement of the left sided valves, decreased CD4 counts of less than 200 x 10^6 /L and infection caused by gram negative organisms or fungi.[36]

In the developed world Ribera *et al* (1998*)* studied 283 cases of intravenous drug-associated IE, of whom 216 were HIV infected. In the HIV-positive patients right-sided infection with *S. aureus* predominated versus left sided infection with *Strept. viridans* in the HIV negative cases.[37] Although the clinical presentation differed in the HIV positive and HIV negative groups with intravenous drug associated IE, the overall mortality rates between the HIV positive and HIV negative patients were similar. However, among the HIV positive patients the mortality rate was significantly higher in severely immunosuppressed patients and in those who had concomitant left-sided valve involvement.[37]

In sub-Saharan Africa, however, RHD and CHD remain the most common predisposing factors to IE. This point is further emphasized by Koegelenberg *et al* (2003).[20] None of the 92 patients in their cohort, studied in the Western Cape were intravenous drug users.[20] However, in a more recent study in the Western Cape (S.A), de Villiers *et al* (2019) noted an increase in the number of cases of IE secondary to intravenous drug use.[32] These authors documented intravenous drug-associated IE in 14.2% of their study population.[32]

In Gauteng (S.A), Meel *et al* (2014) described three cases of IE in intravenous drug users (IVDU).[38] All of these patients were HIV-positive and presented with infection on the tricuspid valve.[37] These authors have identified an emergence of intravenous-drug associated IE.[39] In their subsequent study in 2018, IE was described in 68 patients who were IVDU.[39] The increased predisposition to HIV with recurrent IV drug use was underscored in this study with a HIV prevalence of 76.1%.[39] The most common clinical presentations were progressive dyspnoea and fever.[39]

The studies by Meel *et al* (2018*) and* de Villiers *et al* (2019) have highlighted the rise of IV drug use in Southern Africa and the complication of infective endocarditis.[32,39] Therefore, the awareness of

Intravenous drug use and the predisposition to IE in such cases is crucial in early diagnosis and management of these patients.[39]

Infective endocarditis and HIV

- **IE and HIV in the developed world**

There is currently insufficient data on the impact of HIV infection on the morbidity and mortality of patients presenting with IE.[40] In Western series infective endocarditis in HIV positive patients occurs almost exclusively in intravenous drug users with *S. aureus* being the main causative organism.[37,40] Bouza *et al* (2001) observed that HIV infection was present in 33% of their study population and similarly a high proportion (35.7%) were intravenous drug users.[41] These researchers also noted that the clinical and microbiological characteristics of IE in HIV infected patients did not defer from those previously described in HIV-negative intravenous drug users.[41] The findings by of Ribera *et al* (1998) evidently differs from that of Bouza *et al* (2001), in that the clinical and microbiological characteristics were different in the HIV positive and HIV negative group with intravenous drug associated IE.[40-41]

The study by *Barbaro et al* (2002) observed that the presentation and survival from infective endocarditis was similar in HIV-positive and HIV-negative patients.[42] Similar to Ribera *et al* (1998), the research by Barbaro *et al* (2002) provided evidence that the subjects with IE and advanced HIV disease conferred a worse prognosis than patients who were not severely immunosuppressed.[40,42] These authors reported that in the patients with advanced HIV infection the mortality rate was as high as 30%.[42] It is therefore postulated that if HIV positive patients are taking HAART and are immune competent, this group will be less prone to a high mortality rate.

- **IE and HIV in Southern Africa**

HIV infection continues to pose a serious health concern in Southern Africa. In 2017 it was reported that the prevalence of HIV infection in South Africa was 14% of the global total with 7.9 million people infected with HIV.[43]KwaZulu-Natal was the province with the highest prevalence of HIV infected cases in the country (18.1%).[43] In spite of the increased risk for bacterial infection due to HIV-related immunosuppression, it is worth noting that infective endocarditis is rarely considered a complication of HIV.[44] In the study by Koegelenberg *et al* (2003) only 1 of the cohort of 92 patients was HIV seropositive. [20] In another study in the Democratic Republic of Congo only 1% of the 83 patients with infective endocarditis was HIV-positive.[36]

In a prospective cohort study conducted at Inkosi Albert Luthuli Hospital (IALCH) over a 3 year-period, Nel *et al* (2014) described the echocardiographic features of 77 patients with IE.[45] They identified 17 (22.1%) with definite infective endocarditis to be HIV positive. Furthermore, these authors suggested that the pattern of infective endocarditis in HIV subjects may differ.[45] In their study perivalvular complications and aortic root abscesses were more common in the HIV-infected patients with decreased immunity.[45] However, their HIV study sample was small, and the role of immune suppression in the development of complications, such as root abscesses was not clearly established.[45]

In more recent studies from the Western Cape (S.A), Koshy *et al* (2018) and de Villers *et al* (2019) reported HIV infection in 8% and 23% of their study populations, respectively.[25,32] The findings of these South African researchers demonstrate that further studies are required to establish the impact of HIV infection on patients with infective endocarditis.

Microbiological profile of IE

The microbiological profile of IE has changed over the past few decades.[15] According to Cresti *et al* (2016), in the mid-1990s infection was mainly due to streptococcal infection.[15] They also point out that since the late 1990s *S. aureus* has replaced *Strept. viridans* as the most frequent pathogen isolated.[9,15] Wang, (2012) also reports that *S. aureus* is now the most common organism found in both native and prosthetic valve endocarditis.[9] Furthermore, Millar *et al* (2016) reported that *S. aureus* as the primary causative pathogen in IE has been found in up to 31% of cases, followed *by Strept. viridans* in up to 17% of cases.[46]

It has been observed that a patient's risk factors and exposures have an impact on the microbiological profile of infective endocarditis.[9,46] The change in risk factors leading to the development of IE such as intravenous drug abuse, health case associated IE, and increased incidence of invasive procedures are possible explanations for the higher incidence of *S. aureus* infection.[9,46] Koshy *et al* (2018), also emphasize this point, they state that coagulase negative Staphylococci and *S. aureus* endocarditis have been shown to be associated with hospital acquired infection, and streptococcal endocarditis is more likely to be found with community acquired infections.[25]

The failure to reduce the morbidity and mortality rates in IE may be related to the causative organism. This is evident in the study by Chu *et al* (2004), where *S. aureus* was the most common organism cultured

(44%) and was associated with both a higher rate of complications and likelihood of in-hospital death.[8] These authors have concluded that earlier intervention before the development of complications may offer greater benefit for these patients.[8]

The finding of positive blood cultures is an important criterion in the diagnosis of infective endocarditis. [10] However, negative blood cultures do occur in 2.5 to 31% of all cases of IE.[1] In South African studies a high rate of culture negative IE has been reported. In the study by Koegelenberg et al (2003) the incidence of culture negative IE was high at 55%.[20] Similarly, Nel *et al* (2014) reported 54.5% of their cases to have negative blood cultures.[45] In a more recent study by de Villiers *et al* (2019) 40.7% of left sided IE cases were culture negative.[32]

According to Prendergast *et al* (2004) negative blood cultures may lead to a delay in the diagnosis of IE and the commencement of antibiotic therapy, which results in negative clinical outcomes.[1,19] Some of the factors that could explain the negative blood cultures are: prior antibiotic administration, infection by fastidious organisms which require longer incubation periods to be identified, and organisms requiring specialised tests for diagnosis.[1,10,19,46] Such pathogens include *Coxiella, Legionella*, the HACEK group, *Chlamydia, Bartonella* and fungal organisms.[1,19]

Levison and Abrutyn (1999) note that the HACEK group of fastidious gram-negative bacilli account for 5% of cases of infective endocarditis.[47] These authors also linked fungal endocarditis to patients who are intravenous drug users, patients with prosthetic valves, catheter-related sepsis and to immunocompromised patients.[47] Furthermore, they identified Candida albicans as the most common fungal pathogen isolated in IE.[47]

Diagnosis of Infective endocarditis

In suspected cases of IE, the rapid and accurate diagnoses of IE is crucial to instituting early therapy, thereby reducing the high mortality rate associated with this disease.[19] Delayed diagnosis leads to adverse clinical outcomes, and if untreated, the mortality rate associated with IE approaches 100%.[2] Cahill *et al* suggest that a possible reason for the delay in diagnosis of IE, is that patients present with a diverse clinical spectrum.[19] These authors point out that this presentation can range from, acute sepsis to an indolent low-grade febrile illness, heart failure or stroke syndrome.[19] Todd *et al* (2006) concur with the view that the diagnosis of IE is challenging.[21] They attribute this to the non-specific clinical features of IE that patients

present with, and the variable medical and surgical settings in which IE can occur.[21]

There have been several diagnostic guidelines and criteria that have been proposed over the past few decades for the diagnosis of IE.[46] This includes the Von Reyn criteria (1981), the Duke criteria (1994) and the Modified Duke criteria (2000).[1,10,46] The original von Reyn diagnostic criteria was found to be inadequate as it was based solely upon clinical and microbiological features.[1] Recently the European Society of Cardiology 2015 modified criteria has also been used, which includes the newer imaging modalities of cardiac CT and FDG PET/CT in its criteria.[46] However, the modified Duke criteria is currently the most widely used diagnostic criteria worldwide.[19,46] According to Cahill *et al* (2017) the modified Duke criteria, which is endorsed by the American Heart Association (AHA) and the European Society of Cardiology (ESC), for the evaluation of patients with suspected infective endocarditis, was originally designed for research purposes.[19] Millar *et al* (2016), recognise the benefit of the Modified Duke criteria for the diagnosis of IE, as this guideline is based on the clinical and microbiological features, and emphasizes the role of echocardiography for both the diagnosis and assessment of prognosis of patients with IE.[46]

Cahill *et al* (2017), however, point out that although the modified Duke criteria is being used world-wide, it has certain limitations.[19] Among these limitations are, a lower sensitivity for patients with prosthetic valve endocarditis and cardiac device infection and up to 30% of patients with subsequently proven IE have been labelled as "possible IE." Cases of "possible IE" are due to equivocal or negative findings on echocardiography or blood cultures.[19] These authors believe that definitive cardiac imaging and microbiology are therefore crucial in diagnosing IE. This in turn directs management, identifies complications, and assists with monitoring therapy.[19]

- **Imaging in IE**

Imaging plays a pivotal role in assisting with the diagnosis of IE.[22] In a recent review on IE in South Africa, Pecoraro *et al* (2020) identified four imaging modalities that are currently available for the diagnosis of IE: Transthoracic echocardiography (TTE), Transoesophageal echocardiography (TOE), Cardiac computer tomography (CT) and FDG-PET/CT or leucocyte labelled SPECT.[22] According to Millar *et al* (2016), TTE and TOE are the initial imaging modalities used for the diagnosis and assessment of severity of IE.[46] Cahill *et al* (2017) concur with this view.[19] They report that TTE is recommended as the initial modality of choice for both native and prosthetic valve endocarditis.[19]

Horstkotte *et al* (2004) list the following as characteristic findings of IE on echocardiography: a vegetation which is the pathognomonic lesion of IE, evidence of destruction of the valve, ulceration, and abscess formation.[48] Pecoraro *et al* (2020) identified that the echocardiographic features of peri-annular extension of infection, particularly abscess or fistula formation were more commonly associated with the aortic valve in NVE.[22]In patients with suspected native valve endocarditis (NVE) transthoracic echocardiography (TTE) has a sensitivity of 50% to 90%.[19,22] This decreases to 40% to 70% in patients with PVE.[19,22] According to Cahill *et al* 2017) and Pecoraro *et al* (2020) the value of echocardiography is the ability to assess ventricular size and function, gauge the haemodynamic severity of valve lesions and aid in the diagnosis of anterior prosthetic aortic valve abscesses.[19,22] These researchers also note that TOE is indicated when TTE is non-diagnostic, when complications are suspected or when intracardiac device leads are present.[19]

For suspected NVE, Pecoraro *et al* (2020), also report that the TOE has sensitivity of 90% to 100% and is superior to TTE for detection of complications such as perforations, abscesses, and fistulae.[22] Furthermore, Millar *et al* (2016) have proposed that the newer imaging modalities for the diagnosis of IE, such as CT, FDG PET and magnetic resonance imaging (MRI), maybe more effective in assisting with the detection of embolic and metastatic complications.[46] McDonald (2009), however, identified the following limitations with cardiac CT and MRI: difficulties in evaluating the valve motion, spatial resolution, and the time required to acquire images.[13]

Management and outcomes in IE

Researchers have documented that there is a high rate of morbidity and mortality associated with IE, if this condition is not identified and treated timeously.[10,19,33] Moreillon *et al* (2004) emphasize this when they state that, "Infective endocarditis is lethal if not aggressively treated with antibiotics and, where indicated, with surgical intervention."[10] Similarly, Francischetto *et al* (2014) identify the critical need for infective endocarditis to be appropriately treated as it is a severe disease that, "is potentially lethal if not treated with antimicrobials or with surgical therapy**."**[33] Olmos *et al* (*2017)* reported an in-hospital mortality rate of 20.4% in their study,[18] which is consistent with data from Western series (16%-20%).[6] This is in contrast to the mortality rates reported in South African studies, with rates varying from 35.6% (Koegelenberg *et al* 2003), to 23.4% (Nel *et al* 2014), and 16.2% (de Villiers *et al* 2019).[20,32,45] Furthermore, the study by Nel *et al* (2014) showed high mortality rates in both the HIV positive (23.5%) and HIV-negative (23.3%) subgroups.[45]

Appropriate treatment of infective endocarditis requires a structured management plan. Bedeir *et al*. (2014) highlight important points in the principles of management of IE.[7] These researchers point out that the eradication of sepsis, and the restoration of cardiac structure and function, are the main goals in the management of patients with infective endocarditis.[7] They also state that this can be done medically and/or surgically, in order to prevent spread of infection, maintaining haemodynamic stability, and preventing immunological or embolic complications.[7] McDonald (2009) states that intravenous antibiotics are preferred over oral regimens and longer durations of therapy are required in order to eradicate infective endocarditis.[13] This author also advocates that the duration of therapy should be counted from the first negative blood culture.[13]

According to some researchers apart from the medical management, approximately 50% of patients presenting with IE, will also require surgical intervention.[7,19,22] These authors are therefore making a strong case for a definitive role of surgery in the management of IE.[19,22] This finding is consistent with local studies conducted on IE, with Nel *et al* (2014) reporting 51.9% and de Villiers *et al* (2019) noting 42.3% of their study populations requiring surgical intervention.[32,45] Heart failure was the most common indication for surgery (66.7%) in the study by de Villiers *et al* (2019).[32] Another significant finding in this study, was that surgery was associated with a reduced risk of death further emphasising the benefits of surgical intervention.[32]

Sandre *et al* (1996) also emphasised the benefits of surgery in the treatment of patients with IE.[49] In their review of 135 cases over 9 years, the medical versus surgical management of patients with IE were compared.[49] There was a significantly lower mortality rate (9%) among the surgically treated patients, when compared with those receiving antibiotics alone (24%) in the entire cohort.[49]

In a later study done by Kang *et al* (2012), the expanding role of early surgery in the treatment of infective endocarditis is reinforced.[50] In this randomised controlled trial set in Korea, patients with left sided infective endocarditis with severe valve disease and large vegetations were subjected to early surgery (within 48 hours after randomisation) or conventional treatment.[50] The authors in this trial reported a reduction in the composite primary end point of death (23% to 3%) from any cause or embolic events.[50] The risk of systemic embolism was reduced by surgery.[50] The patient profile in this study was young, with a mean age of 47, with little comorbidity.[50] The timing and indications for surgery to prevent systemic embolization, however, remain controversial.[6]

Hill *et al* (2006) for example report that, "the major dilemma is whether to operate early to prevent embolization, or to delay surgical intervention until resolution of infection, in order to reduce the risk of surgery, and secondary prosthetic valve endocarditis."[6] Pierce *et al* (2012), also give emphasis to the importance of surgery in the treatment of IE.[51]They point out that infection with IE, affects the structure and function of the cardiac valves. If left untreated this would lead to severe valvular regurgitation or even flow obstruction in the valves with large vegetations necessitating surgery."[51]

More studies are required to provide information on whether there is any benefit to early surgery and reduction in mortality rates related to IE. Cahill *et al* (2017) have also identified the need for further data in order to make evidence-based decisions regarding the timing of surgery in the management of patients with IE. They state that, "resolving the controversy of early surgery requires robust evidence to move the field forward. RCT-level data is required to drive practice change." [19]

Rationale

It is evident that there is insufficient data on the epidemiological and clinical profile of IE in sub-Saharan Africa. The relationship between HIV infection and the development of infective endocarditis has not been clearly established. Also, the impact of HIV infection in subjects with valvular heart disease is poorly understood. There is a high prevalence of both HIV infection and rheumatic valvular heart disease in Africa. Therefore, there is an increased probability of infective endocarditis occurring in HIV-infected subjects with valvular heart disease in the future. There is also currently a lack of data regarding the diagnosis, management, and outcomes in patients with IE and concomitant HIV infection who are not intravenous drug users. Furthermore, there is insufficient research on the outcome of surgery in HIV positive and HIV negative patients with IE in sub-Saharan Africa. An informed understanding of the clinical profile and treatment outcomes of IE in sub-Saharan Africa, as well as the impact that HIV infection has on patients with IE, will enable clinicians to address the diagnostic issues and optimally manage these patients.

This study will evaluate the clinical profiles and the spectrum of infective endocarditis at Inkosi Albert Luthuli Central Hospital, a tertiary hospital setting, and determine the influence of subgroups including HIV infection on the disease patterns and clinical outcomes.

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A ten year retrospective review of patients presenting to Inkosi Albert Luthuli Central Hospital with infective endocarditis with special reference to HIV positive patients

Abstract

Objective: To examine the clinical profile and treatment outcomes of infective endocarditis (IE) at a tertiary referral centre in KwaZulu-Natal.

Methods: A ten year retrospective analysis was conducted on cases of definite IE (modified Duke criteria).

Results: Ninety-seven subjects (HIV positive, n=12) satisfied the study criteria (mean age 29.7 ± 15.6 years, M: F 1.4:1). There was a female predominance in the HIV positive group with a F:M ratio of 3:1. Underlying rheumatic heart disease was present in 84.5% of the study population and present in all of the HIV infected cases. Severe dyspnoea was present in 67.0 % and Heart failure in 61.9% of all patients. *S. aureus* was the commonest pathogen isolated (18.6%). Echocardiography revealed vegetations in 87.6% (HIV (+) n=11, HIV (-) n=74) subjects resulting in 41(42.3%) embolic events. Surgery was performed in 73 subjects (HIV (+), n=8) with a surgical mortality of 9.5% and a total mortality of 26.4%. A multivariate analysis identified acute onset IE (odds ratio (OR) 10.54, 95% CI 1.05-106.29, p=0.046) and medical management alone (OR.156.66, 95% CI 11.73-2092.23 p=0.000) as predictors for increased in-hospital mortality.

Conclusion

IE affects young people with underlying RHD and is associated with high morbidity and mortality attributable to advanced disease at presentation and to haemodynamic failure resulting from valve destruction due to acute onset of aggressive infection. The clinical presentation and outcomes in this study were found to be similar in the HIV positive and HIV negative groups, however the HIV positive group was too small for statistical comparisons to be made.

Key words: Infective endocarditis, HIV positive, rheumatic heart disease, vegetations, surgery.

Introduction

Infective endocarditis (IE) is an infection that poses a serious health concern for subjects in both the developing and the developed world.[1] Despite significant advances in the diagnosis and management, this condition remains a serious challenge.[2] Of concern is that neither the incidence, nor the mortality rate of IE has decreased over the last few decades.[2] In a retrospective population based study set in Spain, Olmos *et al,* reported an in-hospital mortality rate for IE of 20.4%.[3] This figure is in keeping with current literature from the developed world demonstrating a 16-20% in-hospital mortality rate for community acquired IE(CAIE), increasing to 24-50% for hospital acquired IE(HAIE) and a high one-year mortality rate of 40%.[4]

It has been postulated that the current high mortality rates associated with IE in the developed world, are due to changes in the risk factor profile of patients presenting with IE.[5] The age-related incidence of infective endocarditis has changed from a younger to a more elderly patient population.[6] There is also a higher incidence of IE in intravenous drug users and subjects with degenerative valve disease, previous valve surgery, intracardiac devices and in-dwelling catheters.[6] This change in the risk factor profile for IE is considered to be one of the main reasons for the change in the pathogen profile of IE.[7] S. aureus has emerged as the most common organism isolated in both native and prosthetic valve endocarditis.[7] The findings noted above emphasise that the clinical pattern of infective endocarditis has changed dramatically since it was first described by William Osler in the 19th Century.[5]

According to Millar *et al* (2016) several factors have contributed to an increasing incidence of IE.[8] These include the longer survival of patients with degenerative heart disease, an increase in the incidence of prosthetic heart valve disease, advances in medical and surgical treatments, increase in the number of intravenous drug users and a higher detection rate due to improved diagnostic methods for IE.[8]

Despite these changing trends in the developed world, infective endocarditis in Southern Africa remains a disease that is predominantly seen in a younger patient population with rheumatic heart disease (RHD) remaining the main predisposing factor.[9] The relationship between chronic rheumatic heart disease and IE and the emergence of HIV infection is highlighted in two South African studies. The first was a three-year prospective study of IE in Stellenbosch (S.A) by Koegelenberg *et al* (2003) who found underlying RHD in 76.6 % of their study population.[10] None of their study population were intravenous drug users and only 1 subject with definite IE was HIV positive.[10] In the second study also from the Western Cape (S.A), Koshy *et al* (2018) reported underlying RHD in 84% and 8% of their study population to be HIV infected.[11]

The impact of HIV infection and the related degree of immunosuppression in subjects with IE has not been clearly defined.[12] In series documented in the developed world infective endocarditis in HIV positive patients, have been almost exclusively associated with intravenous drug users.[12] In a 15-year review of 54 infectious disease centres in Italy, Cicalini *et al* (2001) observed that drug abuse was the most important risk factor for the development of IE in HIV-infected patients.[12] With the increased susceptibility to bacterial infection caused by HIV-related immunosuppression, it is worth noting that infective endocarditis is rarely considered a complication of the acquired immunodeficiency syndrome (AIDS).[13] HIV infection continues to pose a serious health concern in Third World settings with an estimated 7.9 million people infected with HIV in S.A.[14] Currently there is insufficient of data on the clinical profile of IE in KwaZulu-Natal(KZN) which had the highest prevalence of HIV infection (18.1%) recorded in the country for 2017.[14] There are limited studies on HIV and IE in developing countries.[15] Little is known about the clinical profile of IE and causative organisms in the setting of HIV infection.[12] This study describes the clinical profile and outcomes of IE at a tertiary hospital in a Third World setting with special reference to HIV positive patients.

Aims

The present study aims to review the clinical profile, microbiological and echocardiographic findings as well as the early treatment outcomes of patients with infective endocarditis in a referred tertiary setting in Kwazulu-Natal (S.A).

Methods

A retrospective analysis was conducted on patients with a suspected diagnosis of infective endocarditis over a ten-year period (June 2006-June 2016), at Inkosi Albert Luthuli Central Hospital (IALCH). IALCH is an 846-bed tertiary referral centre serving patients from KZN, as well as a portion of the Eastern cape. Case records of suspected infective endocarditis (ICD 10 coding I33.0) were identified via the hospital's database which used the Speedminer software programme (Speedminer, Selangor, Malaysia), and the patient information was accessed via the Meditech software programme (Meditech, Massachusetts, USA). The modified Duke criteria was used to differentiate cases of definite infective endocarditis from cases of possible and rejected diagnoses of IE.[16] Only cases that met the modified Duke criteria for definite infective endocarditis were included in the current study. Briefly, these included clinical criteria based on

microbiological, echocardiographic, and clinical features (2 major criteria, or 1 major and 3 minor criteria, or 5 minor criteria) and pathological criteria (demonstration of microorganisms in tissue, or vegetation/intracardiac abscess).[16] (Appendix VII - VIII) Acute onset IE was defined as symptoms of IE occurring within and up to 6 weeks prior to presentation to hospital.[17] Paediatric IE was classified as patients with definite IE who were 12 years or younger. Late prosthetic valve endocarditis was defined as infection occurring twelve months after valve implantation.[18] Transthoracic echocardiography (TTE) was performed to determine the echocardiographic data. The demographic data, clinical presentation, laboratory, microbiological, histological, and echocardiographic data as well as the clinical and surgical outcomes were captured in Microsoft EXCEL.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS version 23), (International Business Machine (IBM), Los Angeles) was utilized in the analysis of data for the current study. Descriptive statistics were used to summarise the demographic, clinical and microbiological variables. The categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as means (SD). The Student's t-test was used to compare continuous variables and the Chi square tests were used to compare categorical variables. A p value of < 0.05 suggested statistical significance for the variables being evaluated. A univariate and multivariate logistic regression model was performed to ascertain the association of mortality and relevant clinical characteristics. This was done using the Fisher's exact test (for cell counts below 5) and the Pearson's chi-square test. The univariate analysis included the variables for demographic data, onset of IE, valve type, HIV status, NYHA class, fever, clubbing haematuria, heart failure, embolic events, haemoglobin, white cell count, organism cultured, ejection fraction, presence of vegetations and management type. Variables from the univariate analysis were retained in the multivariate model if the p-value was <0.25. Unadjusted and adjusted odds ratios (ORs) were presented with their corresponding 95% confidence intervals. (CIs)

Ethics approval

The current study was approved by the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu Natal (BREC No.BE571/16) (Appendix II), as well as the IALCH hospital board (Appendix III) and by the KwaZulu Natal Department of Health (Appendix IV). A copy of the study protocol is attached (Appendix 1).

Informed consent for HIV testing was obtained during the patient's admission to the cardiology unit at IALCH.

Results

Diagnostic stratification

One hundred and sixty-one patients with a suspected diagnosis of infective endocarditis were screened over a ten year period. Ninety-seven cases were classified as definite IE, fifty-four cases as possible IE and ten cases were rejected. The ninety-seven patients with definite IE fulfilled clinical criteria in eighty cases and pathological criteria in the other seventeen cases. They comprised the study group and were further classified according to their HIV status (HIV positive, n=12, HIV negative, n=85).

Demographic Data

The mean age of the study population was 29.7 ± 15.6 years. The majority were of Black African descent (79.4%) and were under the age of thirty years (n=59, 60,8%) (**Table 1**). Amongst the HIV negative subjects there was a male predominance with a M:F ratio of 1.7:1 whereas nine of the twelve HIV positive subjects were female. All twenty-three subjects (23.7%) under 18 years of age were HIV negative (**Figure 1**).

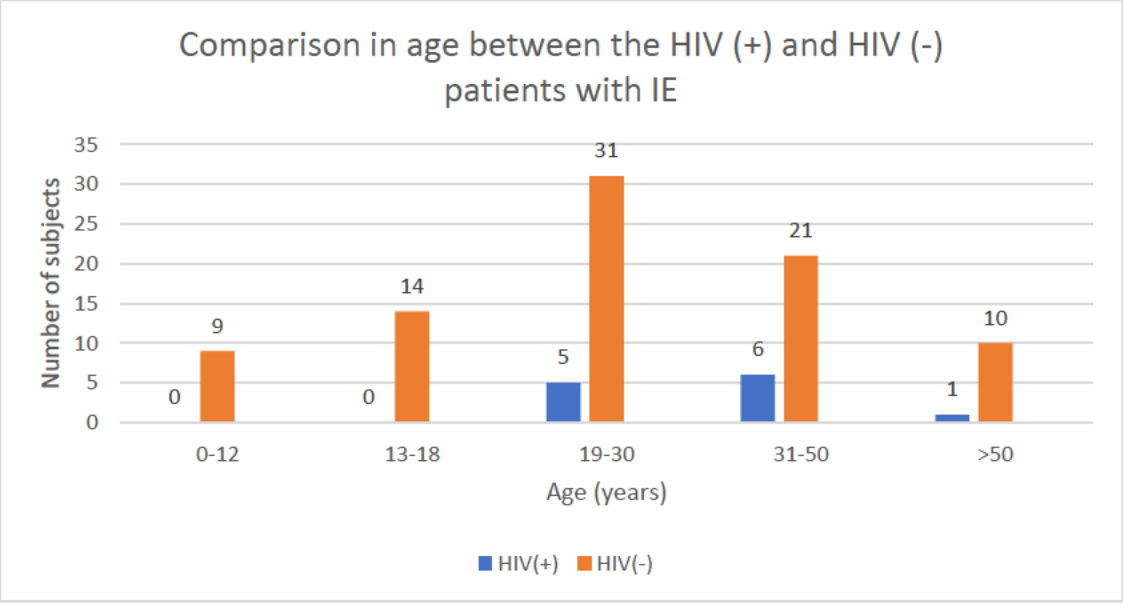

Figure 1. Concomitant HIV infection was present in subjects 19 years and older.

1.Clinical profile

1.1 Predisposing factors

The most frequent predisposing factor to IE in this study population was underlying RHD which was present in eighty-two cases (84.5%). Of these, all twelve of the HIV positive subjects also had RHD. Infective endocarditis secondary to congenital heart disease was present in six (6.2%) cases. (**Table 1**).

Causative aetiology

Poor dentition was found in 11(12.9%) subjects in the HIV negative and two (16.7%) subjects in the HIV positive group. There were five (5.9%) cases of prolonged venous catheter use in the HIV negative and none in the HIV positive group. There were two(2.1%) cases of intravenous drug use related IE which was present in the same patient. This patient initially presented with native valve endocarditis. He underwent successful tricuspid valve replacement but continued to abuse heroine and presented with early prosthetic valve endocarditis. There was one(1.0%) case of septic arthritis resulting in infective endocarditis.

1.2 Clinical Presentation

In twenty-eight cases (28.9%), the onset of infective endocarditis was acute. There was no significant difference in the mode of onset between the HIV positive and HIV negative subgroups (25.0% vs. 29.4%, p=0.752). Left-sided disease predominated in both groups (HIV positive n=12(100%), HIV negative n=73 (85.9%)). Ten cases (10.3%) of prosthetic valve endocarditis were observed, none of whom were HIV positive. Non-valvular IE (related to pacemaker sepsis) was identified in one HIV negative subject (**Table 1**). There were four cases of recurrent IE in the HIV negative group.

The clinical presentation was characterised by pallor (80.4%) and high-grade dyspnoea (NYHA III and IV) in 67% of the subjects. Clubbing (40.2%), fever (38.0%) and haematuria (33.0%) were the other common clinical findings identified. Clubbing (75.0% vs 35.3%, p=0.009), haematuria (58.3% vs 29.4%, p=0.046) and splenomegaly (33.3% vs 9.4%, p=0.018) were more common in the HIV positive group **(Table 2**).

Heart failure, renal impairment and embolic episodes were the most common complications of IE. There was no difference in the prevalence of heart failure (66.7% vs 61.2%, p=0.714), renal impairment (58.3% vs 43.5%, p=0.464) or embolic events (33.3% vs 45.5% p=0.503) between the HIV positive and HIV negative subgroups respectively **(Table 2).**

2.Investigations

2.1 Laboratory findings

There was no difference in the mean haemoglobin levels (9.7g/dL vs 9.9 g/dL, p=0.079), CRP values (61.7mg/L vs 93.8mg/L, p=0.188) white cell count (8.2 x 10^9/L vs 11.9 x 10^9/L, p= 0.060) and ESR levels (67.6 mm/h vs 54.6mm/h, p=0.296) between the HIV positive and HIV negative groups, respectively. The mean serum albumin levels were low in both groups (30.6g/L (HIV+) vs 32.6 g/L (HIV-), p=0.337). The mean CD4 count was 386.5 ± 262.3 x 10^6 /L in the HIV positive group. Three subjects had an AIDS defining CD4 count of less than 200 x 10^6 /L.

2.2 Causative organisms

Of the ninety-seven subjects, positive blood cultures were observed in sixty-three cases (64.9%). Fifty-four of these cases were from the HIV negative subgroup and the remaining nine cases from the HIV positive group. The most common pathogens isolated in the HIV negative population were *S. aureus* (n =17, 20.0%) and *Strept. viridans* (n=12, 14.1%). *S. aureus* was also the most frequent pathogen isolated in cases of acute IE (n=5, 17.9%), right-sided IE (n=6, 50.0%) and prosthetic valve endocarditis (n=5, 50.0%). In contrast, organisms not typically associated with infective endocarditis were cultured in seven (58.3%) HIV positive subjects, with Bacillus cereus the most common organism isolated (n=2, 16.7%) in this group **(Table 3).** *Brucella abortus w*as cultured in one subject with prosthetic valve endocarditis who was HIV negative. Negative blood cultures were observed in 34 cases (35.1%), thirty-one cases in the HIV negative and three cases in the HIV positive subgroup. Acute IE was diagnosed in eleven of these 34 cases (32.4%). Twenty-nine patients underwent surgery and the overall mortality rate in the culture negative IE subgroup was 17.6% (n=6).

2.3 Echocardiographic findings

At echocardiography, the mean ejection fraction (EF) was 55.9 ± 6.6%. There was no significant difference in the EF between the HIV positive and HIV negative subgroups (57.8% vs 55.6%, p= 0.479). The mitral valve was the most common site of infection (HIV positive 41.7% vs 40.0% HIV negative, p=0.589). Right-sided involvement (Tricuspid valve n=8, Pulmonary valve n=3 and pacemaker lead) was present in twelve cases (12.4%) **(Table 4).**

A vegetation was present in eighty-five (87.6%) cases. There was no significant difference in the presence of vegetations in the HIV positive and HIV negative subgroups (91.7%, vs 87.1%, p=0.654). The vegetation size was documented in thirty-six cases (HIV positive n=5, HIV negative n=31), with the size varying from 4mm-24mm in the HIV positive subjects, vs 4mm-34mm in the HIV negative subjects. A vegetation size of greater than 10mm was observed in three out of the four patients with embolic events in the paediatric population and twenty-seven patients of the total study population. In the HIV positive subjects, vegetations were present on echocardiogram in eleven out of the twelve cases (91.7%) and was >10mm in size in four cases.

Chordal rupture was the most frequent finding in both the HIV positive and HIV negative subjects, occurring in eight (66.7%) cases and thirty-three (33.8%) respectively. Chordal rupture was present in thirty-nine cases of left sided disease and two cases of right sided disease. Abscess cavities were noted in eleven patients. This included an aortic root abscess in nine HIV negative patients (10.6%) and one HIV positive case (8.3%) who had a CD4 count of 87 x 10^6/L. There was one case of mitral annular abscess and four cases of prosthetic valve dehiscence.

Three cases of mycotic cardiac aneurysms were observed. The first case, a 52 year old HIV positive female who presented with acute native LSIE. Her CD4 count was 90 x 10^6/L, and she was clinically in heart failure. Bacillus cereus was isolated on blood cultures. Echocardiogram revealed a linear mobile structure attached to the distal tip of the non-coronary cusp aortic valve cusps prolapse into the LVOT. There was aneurysmal dilatation of the right sinus of Valsalva with failure of coaption of the aortic valve cusps. Surgery revealed a perforated aortic valve with a subaortic 20mmx20mm septal aneurysm containing a vegetation at the bottom of the aneurysm.

The second case, a 2-year old HIV negative female presented with moderate mitral regurgitation and an embolic stroke. Echocardiogram revealed a large vegetation (10mmx20mm) attached to an aneurysm of the posterior mitral leaflet. *S. aureus* was isolated on blood cultures. Surgery confirmed the large vegetation on posterior leaflet as well vegetations that had eroded through the posterior mitral leaflet and into the mitral annulus and the posterior ventricular muscle.

The third case was 12 years old lad who presented acutely in heart failure with renal impairment and first degree heart block. Blood and intraoperative cultures were negative. Echocardiogram showed large vegetations (19mmx17mm) on the aortic valve as well as a sinus of Valsalva aneurysm and aortic root

abscess formation. Surgery revealed vegetations that completely eroded the non-coronary cusp and the aortic had ruptured showing fistulisation into the left atrium. This patient demised intra-operatively.

2.4 Subgroup characteristics

2.4.1 Acute onset infective endocarditis

Twenty-eight subjects were classified as having acute onset IE, of whom three cases were HIV positive and a further three were pregnant women. The mean age of the patients were 28.3 ± 12.8 years and the male: female ratio of 1.5:1. The majority had left-sided infection (n=25, 89.3%) and five (17.9%) had PVE. Blood cultures revealed a high culture negative rate (n=11, 39.3%); the commonest organisms cultured were *S. aureus* (n=5,17.9%), and *Strept. viridans* in 10.7% of cases (n=3). Echocardiography revealed vegetations in twenty-four (85.7%) cases, with an embolic event observed in twelve (42.9%) subjects. Twenty-two (78.6%) patients underwent surgery, the main indication being heart failure secondary to severe valvular regurgitation in ten cases (45.6%) cases. Both the surgical mortality rate (n=4, 18.2%) and the overall (surgical + medical) mortality (n=10, 35.7%) were high.

Among the three pregnant women one had prosthetic valve dehiscence with an aortic root abscess and underwent surgery successfully. The second subject had tricuspid valve endocarditis due to intravenous catheter sepsis. She was treated medically and underwent a caesarean section at term. The third had severe aortic and mitral regurgitation with heart failure and renal impairment and underwent successful double valve replacement.

2.4.2 Right-sided infective endocarditis

Right-sided infective endocarditis (RSIE) was documented in twelve subjects, all of whom were HIV negative. The mean age in this subgroup was 24.3 ± 17.5 years, four of whom were <12 years old. The male: female ratio was 3:1. Congenital heart disease was the underlying lesion in four (33.3%) cases followed by extension of infection from the left side (RHD) in three (25.0%) cases. Intravenous drug use (n=2), septic arthritis (n=1), indwelling venous catheter (n=1) and pacemaker sepsis (n=1) made up the remainder of the cases. The most common site of infection was the tricuspid valve (n=8, 66.7%) followed by the pulmonary valve (n=3, 25.0%) and an infected pacemaker lead (n=1, 8.3%). The commonest pathogens were *S. aureus* (n=6, 50.0%) followed by *Strept. viridans* (n=3, 25%). Vegetations were observed at echocardiography in all twelve cases: seven cases (58.3%) had a vegetation size>10mm and four (33.3%)

were>20mm.The main contributors to morbidity were right heart failure (n=5, 41.7%) and pulmonary emboli (n=4, 33.3%). Eight (66.7%) subjects underwent surgery and one died. In total there were three deaths (overall mortality 25.0%).

The first case was a 21-year old male patient who presented in right heart failure and had a large vegetation measuring 16mmx14mm on the tricuspid valve. Blood cultures were negative. He underwent tricuspid valve replacement and demised nine days later from septic shock and with multi-organ failure.

The second case was a 30 year-old male, an intravenous drug user who had a previous tricuspid valve replacement for infective endocarditis. He presented nine months later in right heart failure with renal impairment, pulmonary emboli and disseminated intravascular coagulopathy, and demised within 24 hours of admission. Methicillin resistant *S. aureus* was cultured from the blood and large mobile vegetations measuring 34mmx22mm were attached to the prosthetic valve.

The final case was a 50 year old male patient with rheumatic heart disease. There was extension of infection from the left side. The mitral valve leaflets were noted to be thickened on echocardiogram. He was in right heart failure with a large vegetation on the tricuspid valve measuring 32x29mm. *S. aureus* was cultured on blood. The patient demised while awaiting surgery.

2.4.3 Prosthetic valve endocarditis

All ten cases of the prosthetic valve endocarditis (PVE) subgroup were HIV negative. The mean age in this group was 35.5 ± 22.0 years. The male: female ratio was 1.5:1. Acute IE was observed in five (50.0%) cases. Six (60.0%) cases were classified as late onset prosthetic valve endocarditis. Nine (90.0%) subjects had left-sided PVE, and the remaining subject was an intravenous drug user who had RSIE affecting the tricuspid valve prosthesis. High grade dyspnoea (Grade III or Grade IV) was noted in six (60.0%) subjects. *S. aureus* was the most frequent offending organism isolated (n=5, 50.0%). Two of these cases were due to methicillin resistant *S. aureus.* The other organisms cultured in this subgroup were: Enterococcus faecium (n=1), Group C streptococcus (n=1), Brucella abortus (n=1), Proteus mirabilis (n=1), and S. haemolyticus (n=1). Echocardiography revealed vegetations in four cases, an aortic root abscess in four cases and prosthetic valve dehiscence (mitral 1 and aortic 3) in four cases. Six (60.0%) subjects underwent surgery and two of them died (surgical mortality rate 33.3%). The overall mortality rate was 50% (n=5 cases).

2.4.4 Paediatric infective endocarditis

There were nine cases of IE in the paediatric age group with a mean age of 7.3 ± 3.5 years and the male: female ratio was 3.5:1. The onset was acute in three cases (33.3%) and right-sided in four (44.4%). Five subjects had underlying RHD (55.6%), three had congenital heart disease and septic arthritis was present in the remaining child. *S. aureus* (n=2), *S. epidermidis* (n=1), *Strept. viridans* (n=1) *and Stenotrophomonas* (n=1) were cultured in five cases and the remaining four (44.4%) were culture negative. At echocardiography, vegetations were observed in all nine cases, with a vegetation size >10mm being present in five (55.6%) subjects and giving rise to embolic events in three cases (33.3%). Seven (77.8%) subjects underwent surgery. There were two deaths in subjects with severe aortic regurgitation: one was the 12 year old lad (described above) with a ruptured aortic root abscess who died at surgery and the second was a six-years old child with an aorto-pulmonary window, who was admitted *in extremis* in heart failure and cardiogenic shock with renal failure and died shortly after admission.

2.4.5 HIV and infective endocarditis

The mean age of the twelve HIV positive patients was 33.8 ± 9.0 years with no significant difference noted when compared to the HIV negative subgroup (29.2 ± 16.3 years, p-value 0.211). There was a female: male ratio of 3:1. All twelve patients in this group had left-sided native valve endocarditis with underlying RHD as the predisposing factor for IE. Three cases presented with acute onset IE. High grade dyspnoea was present in seven (58.3%) cases. As mentioned earlier, clubbing (n=9, 75.0%), haematuria (n=7, 58.3%), splenomegaly (n=4, 33.3%) and organisms not typically associated with IE were more common in this group.

Vegetations were present on echocardiogram in eleven of the twelve cases (91.7%) and was >10mm in size in four cases. One subject with a CD4 count of $87x10^6$/L had an aortic root abscess and another with a CD4 count of 90 $x10^6$/L had a subaortic 2x2cm septal aneurysm. Eight (66.7%) patients underwent surgical intervention and there was one peri-operative death. Infective endocarditis was confirmed in seven (87.5%) of the eight subjects who underwent surgery. Four HIV positive patients demised of whom one had an AIDS defining CD4 count of $87x10^6$/L. This patient who was mentioned above, with an aortic root abscess presented with high grade dyspnoea associated with complications of heart failure and renal impairment that did not appear to be related to HIV myocardial involvement since the EF was 53%.

3.Outcomes of Management

3.1 Medical management

All ninety-seven subjects with suspected infective endocarditis were treated with antibiotic therapy as per the European Society of Cardiology (ESC) infective endocarditis guidelines.[19] Twenty-four patients received medical management only. Seventeen of these patients demised and seven survived. Of the seventeen patients who demised preoperatively, eight patients demised shortly after admission and seven patients demised whilst awaiting surgery. One patient was elderly with multiple comorbidities and poor premorbid condition precluding surgery and in one patient surgical intervention was declined.

Of the twenty-four patients, there was one patient who was lost to follow up and presumed dead. This subject was a 24 year old male who was admitted in 2007 with advanced HIV infection (CD4 count 82 x 10^6/L) and was ARV naive. On clinical examination pyrexia, pallor, clubbing, splinter haemorrhages, splenomegaly and features of severe mitral and aortic incompetence were present. Echocardiography revealed multiple vegetations on the mitral and the aortic valve. He received empirical antibiotic therapy and was to commence anti-retroviral therapy but did not return for surgery. The remaining seventy-three subjects received antibiotic therapy and underwent surgery (HIV positive n=8, HIV negative n=65).

3.2 Surgery

The main indications for surgery were intractable heart failure (n=35, 47.9%), large vegetations with increased risk for embolization (n=21, 28.8%) and ongoing sepsis despite appropriate antibiotic therapy (n=11, 15.1%). Surgery was also performed for complications such as valve dehiscence, valve perforation, root abscess/aneurysm rupture or fistula, and /or a large perivalvular abscess.

During surgery IE was confirmed in sixty of the seventy-three subjects (HIV positive n=8, HIV negative n=65). In ten subjects features of chronic rheumatic heart disease were observed with no findings in keeping with infective endocarditis and in the remaining three the operative notes were not found. In the sixty subjects with confirmed IE, vegetations were observed in 41 cases (HIV positive n=6, HIV negative

n=35) and chordal rupture/leaflet perforation was present in thirty-six cases (HIV positive n=5, HIV negative n=31). Of the thirty-six cases of chordal rupture/leaflet perforation nineteen cases were blood culture positive and seventeen cases were blood culture negative. Aortic root abscess was confirmed in seven cases **(Table 5).**

Acute kidney injury (n=3), prolonged ventilation (n=3), neurological complications (n=3, seizures, cerebrovascular accident with left frontal haematoma, and subdural haematoma) and cardiac-related complications (n=3: heart failure, third degree heart block, and recurrent tamponade) contributed to

Postoperative morbidity. Left-sided infective endocarditis was noted in five out of the six cases that demised peri-operatively (intra-operative n= 1 and post-operative n=5). The intra-operative death was the twelve-year old patient with a ruptured aortic root abscess who could not be weaned off cardiopulmonary bypass because of septic emboli to the coronary vessels. The remaining five deaths were due to septic shock with multiorgan failure (n=4) and cardiogenic shock with renal failure (n=1).

3.3 Mortality

The total number of deaths (17 preoperative and 6 post-operative) yielded an overall mortality rate of 23,7%. Correcting for the ten cases in whom IE was excluded at surgery yielded an adjusted overall mortality of 26.4% and surgical mortality of 9.5%. Seven patients demised whilst awaiting surgery (n=7, 7.2%). The mean age of the 23 patients who demised was 33.8 ± 17.0 years. The majority (n=20) had left sided infection and ten (43.5%) cases were classified as acute in presentation. The mean haemoglobin (8.9 ± 3.3 g/dL), serum albumin (29.5 ± 6.3 g/L) were low and the mean white cell count (13.5 ± 8.2x 10^9/l) and c-reactive protein (107.6 ± 85.9 mg/L) were elevated in subjects who died. The mortality rate in our patients with heart failure was 25.0% and it was 24.4% in patients with an embolic event. *S. aureus* (n=4, 17.4%) and *Strept. viridans* (n=3,13.0%) were the most frequent pathogens and six (26.1%) had negative blood cultures. The mean EF was 55 ± 7.5%. The vegetation size was more than 10mm in nine cases. The three patients with RSIE that demised, had large vegetations (34mmx22mm,16mmx14mm and 32mmx29mm) and a mean EF of 56.9 ± 6.4%.

The mortality was highest (50.0%) in the prosthetic valve endocarditis subgroup with five out of ten deaths. The mean EF of these five patients were 56.2 ± 14.9%. The second highest mortality rate was

observed in those with acute onset IE (10/28, 35.7%), followed by those who were HIV positive (4/12, 33.3%). All four of the HIV positive patients had LSIE and relatively preserved ventricular function. The underlying valve pathology was severe mitral regurgitation only in two cases, severe aortic regurgitation in one case and severe mitral and aortic regurgitation in the remaining case. Regression analyses were performed to identify predictors of mortality in the LSIE group. Univariate analysis showed that rheumatic heart disease, fever, haematuria, low haemoglobin, and medical management alone were predictive of death in patients with LSIE. On multivariate analysis, only acute onset (odds ratio (OR)10.54, 95% CI 1.05-106.29, p=0.046) and medical management alone (odds ratio 156.66 (OR), 95% CI 11.73-2092.23 p=0.000) were associated with increased in hospital mortality rates **(Table 6).**

Discussion

This study shows that IE is a disease that affects young subjects and is associated with a high mortality in our setting. Over two thirds of our subjects were under the age of 30, reflecting the predisposing valve lesion which was underlying RHD in 85% of cases. These findings are identical to previous studies undertaken in the Western Cape (S.A) where RHD was observed in 76.6%-84% of the study population.[10,11]In our study congenital heart disease, indwelling catheters and intravenous drug use featured in less than 15% of cases. Our findings are quite different from the findings in the developed world, which report a higher incidence of IE in intravenous drug users, and in subjects with degenerative valve disease, congenital heart disease, previous valve surgery, and intravenous procedures.[4,6] In a more recent update from the Western Cape, de Villiers *et al* (2019) documented a rise in the cases of intravenous drug use (14.2%) and congenital heart disease (10.5%) with underlying RHD present in only 34.3% of their study population.[1] Meel *et al* (2018) also recently reported sixty-eight cases of IE in IV drug users over a two-year period (Dec 2014-Feb 2017) in Gauteng (S.A).[20] Most of Meel *et al's* subjects were male (97%) and HIV-positive (76.1%)**,** not unlike Western series which report HIV infection and IE almost exclusively in IV drug users.[20]

This changing profile of IE characterised by an increase in intravenous drug use, corrective surgery, and device related sepsis probably explains why *S. aureus* infection has replaced *Strept. viridians* as the most frequent pathogen isolated in recent studies.[21]

These factors, however, do not explain the emergence of staphylococcal infection as the predominant pathogen in our cases. We found *S. aureus* infection as the main pathogen in the HIV negative, Acute

onset IE, RSIE and PVE subgroups **(Table 3)**, followed by *Strept. viridans* in the HIV negative, Acute onset IE and RSIE subgroups. The pattern of *S. aureus* as the dominant pathogen followed by *Strept. viridans* is documented in other local studies.[1,22-24]

Among our twelve HIV positive subjects, infection with *S. aureus* and *Strept. viridans was* noted in only one case each. Numerous other organisms not typically associated with IE were present in the remaining seven HIV positive cases including Bacillus cereus which is rarely cultured in native valve endocarditis.[25] Just over a third of subjects had negative blood cultures which we attributed in part to prior antibiotic therapy administered at the referring hospital. Another explanation for culture negativity was the less than ideal specificity of the modified Duke criteria since the surgeon found no evidence of IE in ten of the seventy-three subjects who underwent surgery, five of whom were culture negative.

The 26.4% adjusted mortality rate in our study is high, compared to in-hospital mortality rates of 16-20% for community acquired IE in western series,[4] but consistent with local studies that reported mortality rates of 23.4%-35.6% [10,15] and other studies from developing countries that reported rates of 19-46%.[1] De Villiers *et al* (2019) attributed the low mortality rate of 16.2% in their most recent report to the liberal use of cardiac surgery for patients according to international guideline-based indications for surgery.[1] In our study the main indications for surgery were intractable heart failure, large vegetations with increased risk for embolization and ongoing sepsis despite appropriate antibiotic therapy as well as complications such valve dehiscence, aneurysm rupture or fistula, and /or a large perivalvular abscess. Although our indications for cardiac surgery followed established guidelines,[19] several factors contributed to the high mortality in our study. Firstly, our preoperative mortality was high because eight patients presented late in a critically ill state precluding surgery. Delay due to difficulties in access to care as well as late diagnosis and appropriate treatment at the referring hospital led to many cases presenting with complications and in advanced heart failure resulting in most deaths occurring prior to surgery, even in patients with RSIE which is known to be associated with a lower mortality.[26] As a result, the mortality rate was high across all the subgroups, ranging from 22.2% in the paediatric cohort to 50.0% in patients with prosthetic valve IE. A very sobering finding was that seven patients demised whilst awaiting surgery which may have been preventable had surgery been expedited in these cases. In this respect the recent paper by de Villiers *et al* (2019) bears relevance since these authors were able to show a much lower mortality with early surgical intervention.[1]

Known predictors of mortality in IE include congestive cardiac failure, systemic embolisation and the presence of large mobile vegetations.[27] The mortality rate in our patients with heart failure was 25% and it was 24.4% in patients with an embolic event. Furthermore, large vegetations (>10mm) were present in nine of the twenty-three patients who demised in our study.

Myocardial dysfunction was therefore not the main contributing factor to mortality since the mean EF was 55% in those who demised. The mortality rate with HIV infection was high but the few cases in this group did not allow an analysis of the role of immune suppression in the development of complications/death related to coexisting HIV infection. Regression analysis showed that only the acute onset of IE and medical management without surgical intervention were associated with increased mortality. This indicates that aggressive disease led to valve destruction and haemodynamic failure which could only be addressed with corrective surgery if executed timeously.

Limitations and strengths

Our study has several limitations pertaining to its retrospective design. This included lack of complete datasets and our post hoc classification using the modified Dukes criteria to identify definite cases of IE. Furthermore, prior antibiotic therapy at the base hospital probably contributed to the high rate of culture negativity rate and limiting the inferences relating to the causative organisms in our sample. Furthermore, most subjects perceived to be stable and less symptomatic would have been managed at the base hospitals which have limited echocardiographic facilities and therefore would not been referred early for evaluation. Our study is therefore skewed towards referrals for cases of advanced disease and more seriously ill subjects requiring intervention. Despite these caveats there are a few strengths to our study: most subjects underwent surgery so that we were able to confirm/ refute the clinical findings. This enabled us to withdraw ten cases which showed no evidence of IE at operation and obtain a more accurate mortality rate. Also, our follow up rate was almost complete with only one patient who was lost to follow up.

Conclusion

This study demonstrates that IE in a developing country environment is associated with significant morbidity and mortality despite majority of the study subjects being young with first time infection. As a

preventative strategy, patients at risk for the development of IE should be offered prophylactic antibiotics as per current guidelines. A sobering finding was the high number of subjects in whom life-saving surgery could not be performed. The high preoperative mortality was related in part to staphylococcal infection as well as to advanced disease at presentation resulting in valve destruction with haemodynamic failure. The clinical presentation and outcomes in this study were found to be similar in the HIV positive and HIV negative groups, however the HIV positive group was too small for statistical comparisons to be made.This study emphasizes the importance of early evaluation of all cases of IE at a tertiary referral centre so that guideline-based surgical intervention may be planned and timeously implemented.

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Table 1. Baseline characteristics of IE stratified by HIV status

Parameter		**HIV (+) n=12 (%)**	**HIV (-) n=85 (%)**	**Total n=97 (%)**	**p-value**
Age (mean) years	(SD)	33.8 ± 9.0	29.2 ± 16.3	29.7 ± 15.6	0.211
Gender	Male	3 (25.0)	54 (63.5)	57 (58.8)	0.011
	Female	9 (75.0)	31 (36.5)	40 (41.2)	
Race	African	12 (100.0)	65 (76.5)	77 (79.4)	0.313
	Indian	0 (0.0)	13 (15.3)	13 (13.4)	
	Coloured	0 (0.0)	1 (1.2)	1 (1.0)	
	White	0 (0.0)	6 (7.0)	6 (6.2)	
Onset	Acute	3 (25.0)	25 (29.4)	28 (28.9)	0.752
	Non-acute	9 (75.0)	60 (70.6)	69 (71.1)	
Site	Left side	12 (100.0)	73 (85.9)	85 (87.6)	0.164
	Right side	0 (0.0)	12 (14.1)	12 (12.4)	
Valve type	Native	12 (100.0)	74 (87.0)	86 (88.7)	0.417
	Prosthetic	0 (0.0)	10 (11.8)	10 (10.3)	
	Non-valvular**	0 (0.0)	1 (1.2)	1 (1.0)	
Predisposing factors					
Poor dentition		2 (16.7)	11 (12.9)	13 (13.4)	0.723
Pregnancy		0 (0.0)	3 (3.5)	3 (3.1)	0.509
Underlying valve* lesion		12 100.0)	70 (82.4)	82 (84.5)	0.129
Septic arthritis		0 (0.0)	1 (1.2)	1 (1.0)	0.706
Congenital heart disease		0 (0.0)	6 (7.1)	6 (6.2)	0.342
Pacemaker lead sepsis		0 (0.0)	1 (1.2)	1 (1.0)	0.706
Venous catheter sepsis		0 (0.0)	5 (5.9)	5 (5.2)	0.388

***Underlying valve lesion = Rheumatic heart disease; **Pacemaker lead sepsis**

Table 2. Clinical presentation of IE stratified by HIV status

Parameter	HIV (+) n=12 (%)	HIV (-) n=85 (%)	Total n=97 (%)	p-value
Dyspnoea class				
NYHA class 1	0 (0.0)	8 (9.4)	8 (8.3)	0.242
NYHA class 2	5 (41.7)	19 (22.4)	24 (24.7)	
NYHA class 3	6 (50.0)	31 (36.5)	37 (38.1)	
NYHA class 4	1 (8.3)	27 (31.7)	28 (28.9)	
Clinical examination				
Fever	6 (50.0)	31 (36.5)	37 (38.1)	0.366
Osler nodes	0 (0.0)	0 (0.0)	0 (0.0)	
Clubbing	9 (75.0)	30 (35.3)	39 (40.2)	0.009
Pallor	10 (83.3)	68 (80.0)	78 (80.4)	0.785
Janeway lesions	0 (0.0)	0 (0.0)	0 (0.0)	
Roth spots	0 (0.0)	0 (0.0)	0 (0.0)	
Cutaneous vasculitis	1 (8.3)	7 (8.2)	8 (8.2)	0.991
Splenomegaly	4 (33.3)	8 (9.4)	12 (12.4)	0.018
Haematuria	7 (58.3)	25 (29.4)	32 (33.0)	0.046
Clinical complications				
Heart failure	8 (66.7)	52 (61.2)	60 (61.9)	0.714
Renal Impairment	7 (58.3)	39 (45.9)	46 (47.4)	0.340
Embolic events	4 (33.3)	37 (45.5)	41 (42.3)	0.503
Neurological deficit*	1 (8.3)	15 (17.7)	16 (16.5)	0.416
Cerebral haemorrhage	0 (0.0)	1 (1.2)	1 (1.0)	0.706
Mycotic cerebral aneurysm	0 (0.0)	2 (2.4)	2 (2.1)	0.591
Limb arterial occlusion	0 (0.0)	6 (7.1)	6 (6.2)	0.342
Pulmonary emboli	0 (0.0)	4 (4.7)	4 (4.1)	0.443
Conduction abnormalities	0 (0.0)	4 (4.7)	4 (4.1)	0.443
Persistent fever	1 (8.3)	8 (9.4)	9 (9.3)	0.904
Reinfection	0 (0.0)	4 (4.7)	4 (4.1)	0.443
Mortality	**4 (33.3)**	**19 (22.4)**	**23 (23.7)**	0.402
Demised (Medical)	3 (25.0)	14 (16.5)	17 (17.5)	
Demised (Surgical)	1 (8.3)	5 (5.9)	6 (6.2)	

***Neurological deficit= embolic CVA**

Table 3. Causative organism in the different IE subgroups

PARAMETERS	HIV (+) IE n=12 (%)	HIV (-) IE n=85 (%)	ACUTE IE n=28 (%)	RSIE n=12 (%)	PVE n=10 (%)	TOTAL IE N=97 (%)
Causative organism						
*S. aureus**	1 (8.3)	17 (20.0)	5 (17.9)	6 (50.0)	5 (50.0)	18 (18.6)
Strept. Viridans	1 (8.3)	12 (14.1)	3 (10.7)	3 (25.0)	0 (0.0)	13 (13.4)
Enterococcus	0 (0.0)	4 (4.7)	0 (0.0)	0 (0.0)	1 (10.0)	4 (4.1)
HACEK group**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Culture negative***	3 (25.0)	31 (36.5)	11 (39.3)	2 (16.7)	0 (0.0)	34 (35.1)
Other organisms	**7 (58.3)**	**21 (24.7)**	**9 (32.1)**	1 (8.3)	4 (40.0)	**28 (28.9)**
Staph. species	1 (8.3)	2 (2.4)	2 (7.1)	0 (0.0)	0 (0.0)	3 (3.1)
Staph. haemolyticus	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	1 (10.0)	2 (2.1)
Staph. epidermidis	1 (8.3)	3 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (4.1)
Strept. pneumonia	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Group A. streptococcus	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Group C. streptococcus	0 (0.0)	1 (1.2)	1 (3.6)	0 (0.0)	1 (10.0)	1 (1.0)
Strept. nutritional variant	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)
Strept. Species	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Micrococcus	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Klebsiella pneumonia	1 (8.3)	1 (1.2)	2 (7.1)	0 (0.0)	0 (0.0)	2 (2.1)
Corynebacterium	0 (0.0)	2 (2.4)	1 (3.6)	0 (0.0)	0 (0.0)	2 (2.1)
Stenotrophomonas	0 (0.0)	2 (2.4)	0 (0.0)	1 (8.3)	0 (0.0)	2 (2.1)
Proteus. Mirabilis	0 (0.0)	2 (2.4)	1 (3.6)	0 (0.0)	1 (10.0)	2 (2.1)
Brucella abortus	0 (0.0)	1 (1.2)	1 (3.6)	0 (0.0)	1 (10.0)	1 (1.0)
Bacillus cereus	2 (16.7)	1 (1.2)	1 (3.6)	0 (0.0)	0 (0.0)	3 (3.1)

***S. aureus*, dominant pathogen in the HIV (-), Acute IE, RSIE and PVE subgroups; **HACEK = Haemophilus spp, Actinobacillus, Cardiobacterium, Eikenella corrodens and Kingella kingae; ***High culture negative rate in Acute IE, HIV(-),HIV(+) and total IE groups.**

Table 4. Echocardiographic findings stratified by HIV status

Parameter	HIV (+) n=12(%)	HIV (-) n= 85(%)	Total n=97(%)
EF% mean (SD)	57.8 ± 6.7	55.6 ± 6.4	55.9 ± 6.6
Infection site			
Mitral	5 (41.7)	34 (40.0)	39 (40.2)
Aortic	4 (33.3)	15 (17.7)	19 (19.6)
Mitral & Aortic	3 (25.0)	24 (28.2)	27 (27.8)
Tricuspid valve	0 (0.0)	8 (9.4)	8 (8.3)
Pulmonary	0 (0.0)	3 (3.5)	3 (3.1)
Other *	0 (0.0)	1 (1.2)	1 (1.0)
Vegetations			
Present **	11 (91.7)	74 (87.1)	85 (87.6)
Size in mm (range)	4 - 24 mm	4 - 34 mm	4 - 34 mm
Complications			
Chordal Rupture**	8 (66.7)	33 (38.8)	41 (42.3)
Pericardial Effusion (PE)	6 (50.0)	33 (38.8)	39 (40.2)
Aortic Root Abscess	1 (8.3)	9 (10.6)	10 (10.3)
Dehiscence of prosthetic valve (DOPV)	0 (0.0)	4 (4.7)	4 (4.1)
Annular abscess	0 (0.0)	1 (1.2)	1 (1.0)
Aneurysm ***	1 (8.3)	2 (2.4)	3 (3.1)

***Pacemaker lead sepsis; ***Aneurysm = Septal n= 1, Sinus of Valsalva n=1 and Posterior mitral valve leaflet n=1. ** There was no difference in the prevalence of vegetations (p=0.654) and chordal rupture (p=0.536) between the HIV positive and negative groups.**

Table 5. Surgical findings in IE stratified by HIV status

Parameter	HIV (-) n=65 (%)	HIV (+) n=8 (%)	Total n=73 (%)
Vegetations *	**35 (53.8)**	**6 (75.0)**	**41 (56.2)**
Vegetations only	11 (16.9)	2 (25.0)	13 (17.8)
Vegetation+Leaflet perforation/Chordal rupture	22 (33.8)	3 (37.5)	25 (34.2)
Vegetation + A.R. Abscess	2 (3.1)	0 (0.0)	2 (2.7)
Vegetation + Aneurysm	0 (0.0)	1 (12.5)	1 (1.4)
Valve destruction	**15 (23.1)**	**1 (12.5)**	**16(21.9)**
Leaflet perforation/ Chordal rupture only	10 (15.4)	1 (12.5) **	11 (15.1)
Root Abscess/Fistula	5 (7.7)	0 (0.0)	5 (6.8)
Prosthetic valve dehiscence	2 (3.1)	0 (0.0)	2 (2.7)
Pacemaker sepsis	1 (1.5)	0 (0.0)	1 (1.4)
Not in keeping with IE	9 (13.8)	1 (12.5)	10 (13.7)
Surgical records not found	3 (4.6)	0 (0.0)	3 (4.1)

*** There was no difference in the prevalence of vegetations between the HIV positive and negative groups (p=0.932). **Tear in the non - coronary cusp**

Table 6. Univariate and multivariate logistic regression analyses of Mortality in left-sided IE

Clinical variable	Unadjusted Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value
Acute onset IE*	2.51 (0.88-7.13)	0.085	10.54 (1.05-106.29)	0.046
Prosthetic valve IE**	0.33 (0.08-1.39)	0.131	0.11 (0.00-2.60)	0.171
Rheumatic heart disease***	0.05 (0.01-0.43)	0.007	1.00 (omitted)	
Fever	4.50 (1.55-13.02)	0.006	2.33 (0.39 -13.95)	0.353
Clubbing**	0.47 (0.16-1.37)	0.168	1.10 (0.18-6.63)	0.916
Pallor**	4.75 (0.58-38.81)	0.146	0.79 (0.05-11.61)	0.866
Haematuria	3.63 (1.28-10.30)	0.015	1.50 (0.26-8.73)	0.655
Renal impairment**	1.98 (0.71-5.50)	0.189	3.39 (0.52-22.03)	0.202
HB < 10	1.32 (1.02-1.70)	0.033	1.13 (0.48-2.65)	0.782
Medical management only*	45.00 (10.75-188.30)	0.000	156.66 (11.73-2092.23)	0.000

***Acute onset IE and medical management only were identified as significant predictors for mortality in the multivariate analysis.**Variables were included in the multivariate analysis if the p value <0.25 in the univariate analysis. ***Rheumatic heart disease variable was omitted from the multivariate analysis in order to ensure the accuracy of the current model.**

Chapter 3: Appendices

APPENDIX I: Study protocol

Research Topic

A ten year retrospective review of patients presenting to Inkosi Albert Luthuli Central Hospital with infective endocarditis with special reference to HIV positive patients.

Motivation for the study

Despite important developments over the past two decades with regards to the diagnosis and management of infective endocarditis, there still remains a high rate of morbidity and mortality associated with the disease. During my time as a medical officer working in the department of cardiology at Inkosi Albert Luthuli Central Hospital (IALCH) I have encountered a number of patients with infective endocarditis, many of whom were HIV positive. It is surprising considering the large HIV burden in South Africa, that there is a paucity of data on the clinical profile of infective endocarditis in HIV infected patients. The relationship between HIV and the development of infective endocarditis has not been adequately documented. Not much is known about the presentation and management of patients with infective endocarditis, and still less about the morbidity and mortality associated with the disease. There is a need for data that will provide more information and a better understanding of the patient profile and influence of HIV infection on the clinical outcomes of patients with infective endocarditis.

Research Questions

1. What is the current clinical profile of the patients presenting with infective endocarditis?
2. Has there been a change in the pattern of infective endocarditis over the past decade?
3. Are there differences in the profile of the subgroups of the patients presenting with infective endocarditis?
4. Does the pattern of infective endocarditis in HIV positive patients differ as compared to HIV negative patients?

Aim

To review the patient profile and clinical outcomes in patients with Infective endocarditis.

Objectives

1. To describe the clinical, echocardiographic, and microbiological profile of infective endocarditis in our third world setting.
2. To describe the clinical profile of infective endocarditis in HIV positive versus HIV negative patients.
3. To describe the patterns of infective endocarditis amongst different subgroups with respect to age at presentation, clinical manifestations, aetiological organism and outcomes.

Literature Review

Infective endocarditis is an endovascular infection of the cardiovascular structures. Left untreated, the mortality approaches 100% (1). Despite advances in the ability to diagnose and treat infective endocarditis, there still remains a high rate of morbidity and mortality (2).

In the developed world with regards to the age and aetiology, there has been a shift in the profile of patients presenting with infective endocarditis. The age related incidence of infective endocarditis has changed from a younger patient population to more elderly patients and there is now a higher incidence of infective endocarditis in patients with degenerative valve disease, previous valve surgery and in intravenous drug users (2). In Southern Africa infective endocarditis still remains a disease that is predominantly seen in a younger patient population. Rheumatic valvular heart disease remains the main predisposing factor with an estimated prevalence of 5.7 per 1000 cases (3).

In addition, HIV-infection continues to pose a serious health concern in Southern Africa. In 2014 it was reported that the incidence of HIV infection was 12.2%, the highest in the world with a prevalence of 6.4million people (4). In 2012 the prevalence of HIV in Kwa Zulu Natal was 16.9%, the largest percentage in the country (5). Despite the increased susceptibility to bacterial infection caused by HIV related immunosuppression, it is surprising that infective endocarditis is not usually considered a complication of the human immunodeficiency syndrome (6).

The relationship between HIV infection and the development of infective endocarditis is not clear and the implications of infection with HIV have not been completely defined in relation to infective endocarditis (6). Despite their predisposition to opportunistic infection, there is little data on the nature of the infecting organism in HIV positive patients with infective endocarditis.

Western series have documented that infective endocarditis in HIV positive patients occurs almost exclusively in intravenous drug users (7), with staphylococci being the main causative organism. In contrast there has only been one South African study describing three cases of infective endocarditis in intravenous drug users, all of whom were HIV infected. (8)

Furthermore, there has also been little data on the impact of HIV on the clinical outcomes of patients with Infective endocarditis. Koegelenberg *et al* conducted a prospective observational study in Stellenbosch, South Africa, that examined the risk factors for infective endocarditis. Only 1 of the cohort of 92 patients was HIV seropositive. The main risk factor for the development of infective endocarditis was rheumatic valvular heart disease which was present in 76% of the patients (9). In another study done in the Democratic Republic of Congo (DRC) only 1% of the 83 patients with infective endocarditis was HIV positive (10). At our center a prospective cohort study conducted at Inkosi Albert Luthuli Hospital over a 3 year period, Nel *et al* described the echocardiographic features of patients with infective endocarditis and showed that 22% of the 59 patients with infective endocarditis were HIV positive.(11) Furthermore Nel suggested that the pattern of infective endocarditis in HIV subjects may differ, in her study perivalvular complications and aortic root abscesses were more common in HIV infected patients with decreased immunity. The numbers in this study were small and the role of immune suppression in the development of complications such as root abscesses was not clearly established (11).

This pattern is in contrast to western regions of the world where the use of intravenous (IV) drugs is high and the prevalence of infective endocarditis is 30-70% in HIV positive cohorts (12). In intravenous drug addict's infective endocarditis has a predilection for the right side and S. aureus is the most common organism (12), followed by other organisms such as Gram negative bacteria and fungi (13). Markers of poor prognosis in HIV positive patients include involvement of the left sided valves, decreased CD4 counts of less than 200, and infection caused by gram negative organisms or fungi (10).

The high prevalence of both HIV infection and rheumatic valvular heart disease in Africa increases the likelihood of infective endocarditis occurring in HIV infected subjects with valvular heart disease in future. A better understanding of the clinical profile of these patients will enable us to the diagnostic issues and optimally manage these patients. This study aims to evaluate the clinical profile of the spectrum of infective endocarditis at Inkosi Albert Luthuli Central Hospital over the last decade and determine the influence of subgroups including HIV on the disease patterns and clinical outcomes.

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Research Design

This is a retrospective descriptive chart review of infective endocarditis. Patients will be selected for this study by using the ICD 10 coding system to identify all patients diagnosed with infective endocarditis at IALCH from June 2006-June 2016.

Inclusion Criteria

- All patients with infective endocarditis based on modified Dukes Criteria will be included in this study.

Exclusion Criteria

- All patients whose HIV status was unknown will be excluded from this study.
- Patients who do not meet the modified Dukes criteria for infective endocarditis will be excluded from this study.

Sampling strategy

Purposive

Study population

All patients referred to Inkosi Albert Luthuli Central Hospital with a presumed diagnosis of infective endocarditis will be screened for selection into this study. The modified Dukes criteria will be used to further classify patients as having definite or probable infective endocarditis.

Sample Size

The sample will include all patients who met the criteria for inclusion for the period from June 2006 to June 2016. The estimated sample size will be approximately 150 patients over a 10 year period, since on average 15 patients per year are admitted to the cardiology department at Inkosi Albert Luthuli Central Hospital with a diagnosis of infective endocarditis.

Data Collection

Data will be collected using the Inkosi Albert Luthuli Central Hospital electronic database (Speedminer) to gain access to patient records. Patients diagnosed with infective endocarditis will be identified using the

ICD 10 coding system. Hospital records including the demographic data, clinician notes and results of all the investigations performed for the patients in this study will be accessed from the hospital database. The information will then be captured on a data collection tool and entered onto a software program such as Microsoft excel.

Statistical Analysis

Descriptive statistics will be used to describe baseline characteristics, demographics, and any underlying risk factors. Morbidity parameters will be documented to attain their relative frequency in the definite and possible Infective endocarditis cases. Comparisons between the HIV-infected and HIV negative patients for categorical outcomes will be evaluated by chi-square tests or Fishers exact tests, where applicable. Where the outcomes are numerical, Mann Whitney tests will be used to compare mean ranks in the HIV positive and HIV negative groups. The significance level will be taken at $p<0.05$. Data will then be analysed in Stata version 14.

Study Location

Inkosi Albert Luthuli Central Hospital is an 842 bed tertiary referral centre. The study source is the entire area that refers patients to the cardiology unit at IALCH. This includes Kwa-Zulu Natal and part of the Eastern Cape.

Limitations of the Study

1. This study is limited to only patients that have been referred to IALCH most of whom subsequently underwent surgery. This study therefore does not include patients that received medical treatment at the peripheral hospitals and where not referred to IALCH.

2.Follow up of patients is challenging as some patients come from a rural setting.

3.Lack of a complete data set due to the retrospective design of the study.

4.Patients receiving medical therapy prior to presentation at IALCH would affect the data set in terms of successful identification of the organism causing the infective endocarditis.

Ethical Considerations

Ethics permission to conduct this study will be sought from BREC.

With regards to confidentiality this is a retrospective chart review, therefore there is no patient contact. The patients will be identified by using their IALCH numbers only. At no point during the data collection will the patients' names be used.

With regards to informed consent, in view of the fact that this is a retrospective review, the patients were informed by their consulting doctors during their hospital stay of the procedures and investigations that were performed and written informed consent was obtained prior to the investigations being performed as per protocol at IALCH.

There is no conflict of interest related to this study.

APPENDIX II: Ethics approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

24 February 2017

Dr NS Naidoo (203501441)
Discipline of Internal Medicine
School of Clinical Medicine
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Title: A ten-year retrospective review of patients presenting to Inkosi Albert Luthuli Central Hospital with infective endocarditis with special reference to HIV positive patients.
Degree: MMed
BREC REF NO: BE571/16

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 07 October 2016.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 21 February 2017 to BREC letter dated 11 January 2017 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval** and may begin as from 24 February 2017.

This approval is valid for one year from **24 February 2017**. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be RATIFIED by a full Committee at its next meeting taking place on **14 March 2017**.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor [redacted] Gwegweni
Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee
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APPENDIX III A: Hospital Approval

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Tel: 0312401059 Fax: 0312401050 Email: ursulanun@ ialch.co.za
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Office of [redacted]
IALCH

Reference: BE571/16
Enquiries: Medical Management

23 January 2017

Dr N S Naidoo
Discipline of Internal Medicine
IALCH

Dear Dr Naidoo

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **A ten-year retrospective review of patients presenting to Inkosi Albert Luthuli Central Hospital with infective endocarditis with special reference to HIV positive patients.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

[redacted]

Dr L P Mtshali
Medical Manager

APPENDIX III B: Hospital Approval

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:
Office of The Medical Manager
IALCH

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X08, Mayville, 4058
Tel: 0312401059 Fax: 0312401050 Email: [redacted]
www.kznhealth.gov.za

24 January 2017

Dr N S Naidoo
Discipline of Internal Medicine
School of Clinical Medicine

Dear Dr Naidoo

Re: Approved Research: Ref No: BE571/16: A ten-year retrospective review of patients presenting to Inkosi Albert Luthuli Central Hospital with infective endocarditis with special reference to HIV positive patients.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langaliballe Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg, 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

[redacted]

Dr L P Mtshali
Medical Manager

APPENDIX III C: Hospital approval

PERMISSION TO CONDUCT A RESEARCH STUDY/TRIAL

This must be completed and submitted to the Medical Superintendent/s / Hospital Manager/s for signature.

For **King Edward VIII Hospital (KEH) and Inkosi Albert Luthuli Central Hospital (IALCH)** studies please submit the document together with the following:

1. Research proposal and protocol.
2. Letter giving provisional ethical approval.
3. Details of other research presently being performed by yourself if in the employ of KEH, (individually or as a collaborator).
4. Details of any financial or human resource implications to KEH, including all laboratory tests, EEGs, X-rays, use of nurses, etc. (See Addendum 1)
5. Declaration of all funding applications / grants, please supply substantiating documentation.
6. Complete the attached KEH Form - *"Research Details"*

Once the document has been signed it should be returned to **Mrs Patricia Ngwenya:** at the Biomedical Research Ethics Administration, Room N40, Govan Mbeki Building, Westville Campus, University of KwaZulu-Natal.

To: Chief Medical Superintendent / Hospital Manager

Permission is requested to conduct the above research study at the hospital/s indicated below:

Site 1 address:
IALCH

Investigator/s:
Principal: DR N.S. Naidoo
Co-investigator: Prof D.P. Naidoo
Co-Investigator: _____

Signature of Chief Medical Superintendent/Hospital Manager:
[redacted]

Date: 28/01/2017

Site 2 address:

Investigator/s
Principal: _____
Co-investigator: _____
Co-Investigator: _____

Signature of Chief Medical Superintendent / Hospital Manager:

Date: _____

NB: Medical Superintendent/s / Hospital Manager/s to send a copy of this document to Natalia

APPENDIX IV: Department of Health Approval

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email: [redacted]
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

HRKM Ref: 68/17
NHRD Ref: KZ_2016RP58_569

Date: 20 February 2017
Dear Dr NS Naidoo

Approval of research

1. The research proposal titled **'A ten year retrospective review of patients presenting to Inkosi Albert Luthuli Central Hospital with infective endocarditis with special reference to HIV positive patients'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

[redacted]
Dr E Lutge
Chairperson, Health Research Committee
Date: 20/02/17

APPENDIX V: Certificate of completion by Good Clinical Practice

TRREE

Zertifikat

Certificat

Certificado

Certificate

Promouvoir les plus hauts standards éthiques dans la protection des participants à la recherche biomédicale
Promoting the highest ethical standards in the protection of biomedical research participants

Clinical Trials Centre
The University of Hong Kong

Certificat de formation - Training Certificate

Ce document atteste que - this document certifies that

nerissa naidoo

a complété avec succès - has successfully completed

Good Clinical Practice (GCP)

du programme de formation TRREE en évaluation éthique de la recherche
of the TRREE training programme in research ethics evaluation

[redacted]

August 16th, 2015
CID : doSeSprMQ

Professeur Dominique Sprumont
Coordinateur TRREE Coordinator

FMH Continuing Education Program Programme de Formation continue

Foederatio Pharmaceutica Helvetiae FPH Programmes de formation continue Continuing Education Programs Programmes de formation continue

GCP training program for investigator recognized by Swissmedic
Programme de formation GCP pour investigateur reconnu par Swissmedic

Ce programme est soutenu par - This program is supported by :

European and Developing Countries Clinical Trials Partnership (EDCTP) (www.edctp.org) - Swiss National Science Foundation (www.snf.ch) - Canadian Institutes of Health Research (http://www.cihr-irsc.gc.ca/e/2891.html) - Swiss Academy of Medical Science (SAMS/ASSM/SAMW) (www.samw.ch) - Commission for Research Partnerships with Developing Countries (www.kfpe.ch) - Université de Neuchâtel (www.unine.ch)

[REV : 20140328]

APPENDIX VI: Data collection tool

DATA COLLECTION SHEET

DATA NUMBER: FILE NUMBER:

A] DEMOGRAPHIC DATA

AGE:				
GENDER:	MALE	FEMALE		
RACE:	AFRICAN	INDIAN	COLOURED	WHITE
HIV STATUS	REACTIVE	NON- REACTIVE		
IF REACTIVE (WHO)	STAGE 1	STAGE 2	STAGE 3	STAGE 4

B] TYPE OF INFECTION

ONSET	Acute	Non acute
SITE	RIGHT SIDED IE	LEFT SIDED IE
NATIVE VALVE	YES	NO
PROSTHETIC VALVE	YES	NO

C] ASSOCIATIONS

POOR DENTITIAN	YES	NO
SKIN LESIONS	YES	NO
BONE LESIONS	YES	NO
PREGNANCY	YES	NO
UNDERLYING VALVE LESION	YES	NO
CONGENITAL HEART DISEASE	YES	NO
PACEMAKER	YES	NO
VENOUS CATHETER	YES	NO
ILLICIT DRUG USE	YES	NO

D] CLINICAL MANIFESTATIONS

NYHA	GRADE 1	GRADE 2	GRADE 3	GRADE 4
FEVER	YES	NO		
OSLER NODES	YES	NO		
CLUBBING	YES	NO		
PALLOR	YES	NO		
JANEWAY LESIONS	YES	NO		
ROTH SPOTS	YES	NO		
NEW MURMUR	YES	NO		
CUTANEOUS VASCULITIS	YES	NO		
SPLENOMEGALY	YES	NO		
HAEMATURIA	YES	NO		

E] BLOOD INVESTIGATIONS

HAEMOGLOBIN
WHITE CELL COUNT
PLATELETS
ERYTHROCYTE SEDIMENTATION RATE
C REACTIVE PROTEIN
CD4
VIRAL LOAD
RHEUMATOID FACTOR
COMPLEMENT
ALT
ALBUMIN
BILIRUBIN
UREA
CREATININE

F] MICROBIOLOGY

BLOOD CULTURES POSITIVE	YES	NO
IF POSITIVE ORGANISM CULTURED		

G] ECHOCARDGRAM

INFECTION SITE	TRICUSPID	PULMONARY	MITRAL	AORTIC	OTHER
VEGETATIONS			YES	NO	
SITE OF VEGETATION		VALVE	ENDOCARDIUM	CHORD	PAPILLIARY MUSCLE
SIZE OF VEGETATIONS					
COMPLICATIONS OF I/E ON ECHO					
VALVULAR PERFORATION			YES	NO	
ROOT ABCESS			YES	NO	
ANNULAR ABCESS			YES	NO	
CHORDAL RUPTURE /LEAFLET PROLAPSE			YES	NO	
PERICARDIAL EFFUSION			YES	NO	
DEHISCENCE OF THE PROSTHETIC VALVE			YES	NO	
EJECTION FRACTION					
END DIASTOLIC DIMENSION					
END SYSTOLIC DIMENSION					
RIGHT VENTRICLE DIAMETER					
PULMONARY ARTERY PRESSURES					
TAPSE VALUE					

H] COMPLICATIONS

HEART FAILURE	YES	NO
ACUTE KIDNEY INJURY	YES	NO
EMBOLIC EVENTS	YES	NO
CEREBRAL HAEMORHAGE	YES	NO
MYCOTIC ANEURSYM	YES	NO
PERSISTENT FEVER	YES	NO
CONDUCTION ABNORMALITY	YES	NO
LIMB ARTERIAL OCCLUSION	YES	NO
NEUROLOGICAL DEFICIT	YES	NO
PULMONARY EMBOLI	YES	NO
REINFECTION	YES	NO
DEATH	YES	NO

I]MANAGEMENT

MEDICAL MANAGEMENT	YES	NO
SURGICAL MANAGEMENT	YES	NO
IF SURGICAL MANAGEMENT:		
SURGICAL FINDINGS		
HISTOLOGICAL FINDINGS		
OPERATIVE SPECIMAN CULTURE		
PERIOPERATIVE COURSE		
PERIOPERATIVE COMPLICATIONS: DEATH, ORGAN FAILURE, LOW OUTPUT		

IE =INFECTIVE ENDOCARDITIS

APPENDIX VII: The Modified Duke Criteria, Definitions of Definite, Possible or Rejected IE

Definite IE • Pathologic criteria 1.Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolised, or an intracardiac abscess specimen; or 2.Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis.
• Clinical criteria 1.Two major criteria 2.One major criterion and three minor criteria 3.Five minor criteria
Possible IE 1.One major criterion and one minor criterion 2.Three minor criteria
Rejected Cases 1.Firm alternate diagnosis explaining evidence of IE 2.Resolution of infection endocarditis syndrome with antibiotic therapy for less than or equal to 4 days 3.No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for less than or equal to 4 days 4.Does not meet criteria for possible IE, as described previously

Modified from Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Jr., Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30(4):633-8.

APPENDIX VIII: Modified Dukes Clinical Criteria

Major Criteria

- Blood culture positive for IE
  - Typical microorganisms consistent with IE from two separate blood cultures
    - Viridans streptococci; Streptococcus bovis, HACEK group, Staphylococcus aureus; or community-acquired enterococci, in the absence of a primary focus
  - Microorganisms consistent with IE from persistently positive cultures, defined as follows:
    - At least two positive blood cultures of blood samples drawn >12 h apart; or
    - All of three or a majority of 4 or more separate cultures of blood (with first and last sample drawn at least 1 hr apart)
  - Single positive blood culture for Coxiella burnetii or antiphase 1 IgG antibody titre > 1:800
- Evidence of endocardial involvement
- Echocardiogram positive for IE
  - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or
  - Abscess; or
  - New partial dehiscence of prosthetic valve
- New valvular regurgitation (worsening or changing or pre-existing murmur is not sufficient)

Minor Criteria

- Predisposition, predisposing heart condition or injection drug use
- Fever, temperature > 38 degrees Celsius
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages and Janeway lesions
- Immunologic phenomena: Glomerulonephritis, Osler nodes, Roth's spots, and rheumatoid factor
- Microbiological evidence: Positive blood culture but does not meet a major criterion as noted previously (excluding single positive cultures for coagulase -negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organisms consistent with IE.
- Echocardiographic minor criterion eliminated.

Modified from Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Jr., Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30(4):633-8.

APPENDIX IX: Guidelines for authorship for the Cardiovascular Journal of Africa

INFORMATION FOR AUTHORS

The Cardiovascular Journal of Africa is pleased to consider original articles, reviews, discussions on topical issues, case studies, meeting reports and other contributions relevant to the understanding, treatment, and care of vascular disease.

Original articles and reviews are sent for independent peer-review. Material is accepted for publication on the understanding that it has not been published elsewhere. Authors will be asked to confirm this in writing and transfer copyright to the Journal.

Authors submitting papers to CVJA should also register as a reviewer as a quid pro quo for authors for reviewers reviewing your submission. If authors do not register as reviewers it may be taken in consideration when deciding on acceptance and rejection, and the time of publication. We do try not to call on a reviewer more than once a year but in rare circumstances it may be twice.

Important Notice to all Authors:
Manuscript Submission Fee & Article Processing Charge (effective 13 December 2016)

It has become necessary for the Cardiovascular Journal of Africa to charge a manuscripts submission fees for all articles submitted for publication. On acceptance of a manuscript an additional Article Processing Fee will apply before publishing.

- **Manuscript Submission Fee:** South African and International Authors: ZAR 1000.
  Paid on Submission of Manuscript.

- **Article Processing/Publishing Fee:** South African and International Authors: ZAR 6000.
  Paid on Article Acceptance for Publication in the CVJA.

This is normal for most, if not all, journals. We so far have been able to survive without charging authors for submissions and processing but can no longer do so. We regret that we have to implement this as from the 13 of December 2016. Payment will need to be made online and once payment has been received, the manuscript will be further processed for possible publication.

The payment of the manuscript submission fee and does not guarantee publication of the article. The manuscript submission fee is not refundable in the event of rejection as processing cost will have been incurred. **(Payment can be made online with a valid credit card)**

Guidelines for Authors and Readers of the CVJA
The Cardiovascular Journal of Africa (CVJA), which incorporates the Cardiovascular Journal of South Africa, is particularly concerned with publication of scientific articles related to Cardiac and Vascular conditions and situations, concerning adults and children, in Sub Saharan Africa. But will accept articles from all parts of the world.

Basic Science publications related to clinical aspects either for elucidation, in-depth understanding or therapeutic approaches are accommodated. The Journal functions as official medium for other related societies which do not as yet have own Journals such as, Hypertension, Stroke, Nuclear Medicine and Magnetic Resonance in Cardiology, Paediatrics, Molecular and Cellular Cardiology, and Vascular disease in Diabetes and Obesity.

Index Medicus / PubMed Central / Medline and Sabinet lists the Journal for indexing and electronic citation. A printed version and an electronic version for citation and publication of abstracts are produced. The abstracts of articles published appear on PubMed with a link out to Sabinet to give access to full text retrieval of published material. **In order to improve visibility for our authors, the CVJ Africa is now also able to index articles for PubMed Central.**

ARTICLE SUBMISSION

All categories of manuscripts for the Cardiovascular Journal of Africa must be submitted on-line to Editorial Manager. You will be assigned your own password and username. This will allow complete interaction between the editor and authors. Internally, reviewers will be approached to review material in their field of expertise and assigned with similar interaction. All information will be entirely protected and confidential.

All submissions should be written in a clear and succinct manner, following the style of the Journal. Title page should include a descriptive title, authors' surname and forename, address of each author and full address, telephone, fax, and e-mail contacts for the corresponding author. In text: tables and figures are either inserted as part of sentence, for example Table 1, or in parentheses, for example (Fig. 1). Each table should carry a descriptive heading.

Editorial Manager will clearly indicate which aspects of the submission must be supplied off-line (**download off-line document**). This must be provided to the Journal by mail (PO Box 1013, Durbanville, South Africa, 7551) or e-mail to **info@clinicscardive.com**

All images MUST be at or above intended display size, with the following image resolutions: Line Art 800 dpi, Combination (Line Art + Halftone) 600 dpi, Halftone 300 dpi Image files also must be cropped as close to the actual image as possible.

Preferred Image Format

Image Format	.tiff
Image Width	Greater than or equal to intended display size
Color space	RGB
DPI	500+
Alpha Channels	None
Layers	Flattened

Alternative Image Format

Image Format	.jpg
Image Width	Greater than or equal to intended display size
Color space	RGB
DPI	500+
Compression Quality	Maximum

References numbered in the order of appearance in the text, according to Vancouver style. For articles: Author AB, Author C, Author M. The title of the article. Abbreviated journal title 1999; 14: 172–183. For book chapters: Author AB, Author CD. The title of the chapter. In: Editor A, Editor BC, ed. Title of the book, 2nd edn. Location: Publisher, 1999: 133 –139. DOI Numbers / PMID (PubMed ID / PMC ID) must be added to all references to facilitate tagging for PubMed Central.

Original articles: Title page as above. Abstract (150 words) a short inclusive statement suitable for direct electronic abstracting, identifying the purpose of the study, key methods, the main results, and the main conclusion. Keywords: maximum of six keywords for indexing. Introduction: concise description of background, sufficient for the non-specialist to appreciate the context of the work. Clear statement of the purpose of the study. Methods: a brief description of study design, procedures, analytical techniques, and statistical evaluation. Results: a clear account of the study findings using quantitative language where possible and cross-referenced to tables and figures. Discussion: an interpretation of the study placed within the context of current knowledge, leading to specific conclusions where possible. Acknowledgements. References, figures, and tables as above.

Reviews

Title page as above. Abstract (150 words) setting out the scope, key messages, and conclusions of the review. Body of text liberally partitioned with headings and subheadings leading to a synopsis with conclusions at the end. Key messages in a separate box itemising two to five short principal statements. Acknowledgements, references, tables, and figures as above.

Other articles should adopt a concise style consistent with similar articles previously published in the journal. Manuscripts should include a title page, and appropriate subheadings for text. Style of tables, figures, and references as above. Figures be sent to us in a high-resolution JPEG format, but they MUST be sent separately from the Word document. If not in high resolution JPEG, then PowerPoint will do.

Editorial Manager will clearly indicate which aspects of the submission must be supplied off-line (**download off-line document**). This must be provided to the Journal by mail (PO Box 1013, Durbanville, South Africa, 7551) or e-mail to **info@clinicscardive.com**

The status of progression of the peer-review system will be directly accessible by authors. The Editorial Manager

system is particularly useful to authors and reviewers as there is a direct link to PubMed for viewing all related articles on the subject matter.

Submitted manuscripts must be supplied with a covering letter with any additional information that may be helpful to the editor, such as the type or format of article that the manuscript represents. If the manuscript has been submitted previously to another journal, it is helpful to include the previous editor's and reviewers' comments with the submitted manuscript, along with the authors' responses to those comments. Copies of any permission to reproduce published material, to use illustrations or report information about identifiable people, or to name people for their contributions must accompany the manuscript.

Editorial Policy

Statements and opinions expressed in articles and communications in CVJA are those of the authors and not those of the Editor or publisher. The Editor and publisher disclaims any responsibility or liability for such views. Neither the Editor nor the publisher guarantees, warrants, or endorses any product or service advertised in this publication; neither do they guarantee any claim made by the manufactures of such product or service.

Material submitted for publication in the Cardiovascular Journal of Africa is accepted on condition that it has not been published elsewhere. The management reserves the copyright of the articles published. Aspects of cardiovascular medicine related to Sub-Saharan Africa will be encouraged.
Authors submitting papers to CVJA should also register as a reviewer as a quid pro quo for authors for reviewers reviewing your submission. If authors do not register as reviewers it may be taken in consideration when deciding on acceptance and rejection, and the time of publication. We do try not to call on a reviewer more than once a year but in rare circumstances it may be twice.

ONLINE FIRST: ADVANCED ONLINE PUBLICATION AHEAD OF PRINT

The Cardiovascular Journal of Africa is launching an **online First Advance Online Publication (ePublication ahead of print)** with full text availability via PubMed and this website which is accessible via Google and other search engines.

This facility is also known internationally as E-publication, ahead of print and offers authors the opportunity to publish their research articles sooner for an international audience.

Articles published online with CVJA will be published with unique DOI numbers, which ensures that the article can be cited using the date of the manuscript's first online posting and its DOI number. DOI's provide a persistent, permanent way to identify manuscripts in an electronic environment and are generated via our Editorial Management system and in accordance with the policy of the **DOI foundation**.

An example, of how articles are cited first online and then in print version is provided below:
Webster I et al. AMP Kinase activation and glut4 translocation in isolated cardiomyocytes. Cardiovasc J Afr. Prepublished month, day, year. DOI: 10.5830/CVJA-2011-042

The initial PubMed citation will be updated after the print version appears.

Cost of First Advance Online Publication (Payment can be made online with a valid credit card)
ZAR 4000 for Authors outside of Africa
ZAR 1500 for African Authors (including South Africa)

Please note that the Online First option is only available once your article has been accepted for publication. Also note there will be no refunds, any payment made before an article is accepted / rejected will be forfeited.