The *I*nvestigation of the *M*anagement of *P*ericarditis *in Africa* (*IMPI* Africa) Project: Rationalé, Design, Baseline Characteristics and Mortality in a Multinational Registry of Suspected Tuberculous Pericarditis

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Abstract

Background The incidence of tuberculous pericarditis has increased as a result of the human immunodeficiency virus (HIV) epidemic. However; 1) the impact of HIV co-infection on the clinical features and presentation of patients with tuberculous pericarditis is not well characterised, 2) the current clinical practice with respect to the investigation and diagnosis of the syndrome and the use of adjunctive corticosteroids is unknown; 3) finally, the effect of HIV co-infection on the prognosis in tuberculous pericarditis has only been assessed in small studies.

The aim of the Investigation of the Management of Pericarditis in Africa (IMPI Africa) Registry was to determine clinical presentation, diagnostic evaluation, treatment, and outcome of patients with suspected tuberculous pericarditis in the era of HIV.

Methods Fifteen hospitals in Cameroon, Nigeria, and South Africa collaborated in the IMPI Africa Registry. Consecutive adult patients with suspected tuberculous pericarditis were recruited. Demographic, clinical, diagnostic and therapeutic information at baseline were recorded. The main outcome measures were the stage of pericardial disease, evidence of clinical HIV disease, level of diagnostic certainty of tuberculosis, use of adjunctive corticosteroids and survival at three, six and twelve months.

Results 185 patients were enrolled from 01 March 2004 to 31 October 2004. 147 (79%) had effusive pericarditis, 28 (15%) effusive-constrictive pericarditis, and 10 (5,4%) constrictive pericarditis. Forty percent had clinical features of HIV infection. Patients with clinical HIV disease presented with severe symptoms of heart failure and electrocardiographic features of myopericarditis which may reflect greater myocardial involvement in HIV associated pericardial tuberculosis. Most patients were treated on clinical grounds, with confirmation of diagnosis of pericardial tuberculosis in 8% of patients. Adjunctive corticosteroids were used in 59% of cases; patients with clinical HIV disease were less likely to be treated with

adjunctive corticosteroids. Finally patients with clinical HIV disease had an alarmingly high six-month mortality of 40% while the overall six-month mortality was 26%.

Conclusions In the HIV era, clinical evidence of co-infection with HIV is common. The most frequent clinical presentation of TB pericarditis is with large pericardial effusion. A minority of patients have a definitive diagnosis of TB pericarditis established prior to the commencement of anti-tuberculous drugs. Our data suggest that tuberculous pericarditis has a more severe clinical presentation in patients with clinical HIV disease, and is associated with a high six-month mortality.

Introduction

Pericarditis is a common disorder that has multiple causes (Troughton '04). *Mycobacterium tuberculosis* is considered to be responsible for more than 50% of cases of pericarditis in developing countries where tuberculosis remains a major public health problem (Magula '03). By contrast, it accounts for less than 5% of cases of pericarditis in industrialised countries (Troughton '04). In Africa, the incidence of tuberculous pericarditis is said to be rising as a direct result of the human immunodeficiency virus (HIV) epidemic (Cegielski 90, Taelman 90, Pozniak '94, Longo-Mbenza '97, Maher '97). There is a strong association between HIV infection and tuberculous pericarditis in endemic regions, where 40-75% of patients with large pericardial effusion (suspected to be tuberculosis) are infected with HIV (Magula '03, Cegielski '90).

The effect of HIV infection on the clinical presentation, response to treatment and outcome of patients with tuberculous pericarditis is not well characterised (Trautner '01). HIV infected patients with tuberculous pericarditis have been found to be more likely than HIV negative patients to have disseminated tuberculosis, raising the possibility that dissemination may worsen long-term outcome (Pozniak 94). Preliminary evidence suggests that HIV infection may be associated with higher mortality in tuberculous pericarditis; mortality with anti-tuberculosis chemotherapy ranged from 8% -17% in the pre-HIV era, (Gooi '78, Desai '79 Bhan '90, Strang '88), whereas higher mortality rates of 17-34% have been reported in HIV infected individuals (Hakim '00).

We have conducted the first African multi-centre prospective observational registry of the clinical presentation, diagnostic evaluation, initial treatment, and outcome of patients with suspected tuberculous pericarditis in the HIV era. In this report, the design of the observational study and baseline data including the clinical characteristics, diagnostic work-

up, initial treatment, and mortality at 6 months of the 185 patients who were entered into the registry will be reviewed and discussed.

Methods

The *I*nvestigation of the *M*anagement of *P*ericarditis *i*n Africa (*IMPI* Africa) Registry was a simple, pragmatic international multi-centre prospective observational study of patients admitted to hospital with suspected tuberculous pericarditis, which was designed to assess the clinical presentation, diagnostic evaluation, initial treatment, and outcome of patients with suspected tuberculous pericarditis in Africa in the HIV era. We set out to enrol a minimum of 100 consecutive cases of suspected tuberculous pericarditis presenting to collaborating physicians over 6 months, and follow them prospectively for 6-12 months. The main outcome measures of the study were (1) the clinical presentation with special emphasis on the type of pericardial syndrome, evidence of clinical HIV disease, and the level of diagnostic certainty of tuberculous pericarditis, (2) the therapeutic strategy with a special focus on the use of adjunctive corticosteroids (3) the outcome of patients with suspected tuberculous pericarditis at 3 months, 6 months, and 12 months following commencement of therapy. The specific outcomes of interest at the end of the follow-up period (due on 30 April 2005) were (a) death from all causes, (b) New York Heart Association functional class, (c) development of tamponade requiring intervention, (d) development of constrictive pericarditis requiring pericardiectomy, and e) repeat hospitalisation for any cause. The research ethics committee of the University of Cape Town approved the study, and all participants gave written informed consent.

Twenty-seven hospital-based physicians from eight African countries (Cameroon, 2 physicians; Ghana, 1; Kenya, 1; Lesotho, 1; Nigeria, 1; South Africa, 19; Uganda, 1; Zimbabwe, 1) were invited by electronic mail in January 2004 to participate in the study; these physicians had expressed an interest in the project to one of the investigators (BMM). Fifteen physicians from three countries (Cameroon, 1 physician; Nigeria, 1; and South Africa, 13) contributed patients to the IMPI Africa Registry (56% response rate). Twelve of

the 15 physicians were affiliated to medical schools, and the remainder (all in South Africa) were based in district general hospitals.

Suspected tuberculous pericarditis was defined as a clinical syndrome of pericardial disease, which was suspected to be caused by tuberculosis on the basis of clinical, and/or laboratory findings leading to the commencement of anti-tuberculosis chemotherapy according to the national tuberculosis control programme (WHO/CDS/TB/2003.313). Consecutive incident cases of suspected tuberculous pericarditis were enrolled. Adult patients were eligible for inclusion in the study if the collaborating physician believed that there was sufficient clinical suspicion of tuberculous pericarditis to commence anti-tuberculosis treatment and the patient gave written informed consent. The management of each patient was at the discretion of the collaborating physician in keeping with the observational nature of the study. This included the use of steroids where the choice of steroid, the dose and the route of administration were left to the physician's discretion.

The pericardial disease was classified as acute non-effusive pericarditis, pericardial effusion, effusive-constrictive pericarditis, or constrictive pericarditis on the basis of the collaborating physician's assessment of clinical and imaging information. We classified tuberculous pericarditis as 'definite' or 'probable' depending on the amount of clinical and bacteriological information supporting the diagnosis. A diagnosis of 'definite' tuberculous pericarditis was based on the demonstration of tubercle bacilli in pericardial fluid (smear or culture or both) or on histologic section of the pericardium; 'probable' tuberculous pericarditis on the proof of tuberculosis elsewhere in a patient with otherwise unexplained pericarditis, on the basis of indirect tests (e.g., adenosine deaminase level ≥40IU/l in pericardial fluid) (and/or an appropriate response to a trial of anti-tuberculosis chemotherapy. We chose an adenosine deaminase level of 40 because of the high sensitivity (>90%) and specificity (>90%) in areas with a high prevalence of tuberculosis (Koh '89, Komsouglu '95, Martinez Vasquez' 86,

Mayosi '02) The HIV status of the patients was based on the results of testing for HIV. However, serological testing for HIV is not always available or offered in some medical institutions in Africa. Therefore, the physicians were requested to state whether they suspected HIV infection on clinical grounds and classify all the patients as either having 'clinical HIV disease' or 'no clinical HIV disease' without regard to the HIV serological status of the patient. This assessment was left to the discretion of the collaborating physician, and no criteria were specified. Haemodynamic instability was defined by the presence of at least two of these signs: pulse rate more than 100 beats per minute, systolic blood pressure less than 100 mmHg, and cardiac tamponade requiring pericardiocentesis. The radiological, electrocardiographic, echocardiographic, and laboratory abnormalities were based on the report provided by the collaborating physician without central verification.

Demographic, clinical, diagnostic and therapeutic information was captured by means of a standardized data collection form (available on request) and transmitted (by fax or e-mail) to the IMPI Africa Coordinating Centre at the Cardiac Clinic, Groote Schuur Hospital, Cape Town, South Africa. Enrolment into the registry started on 1 March 2004 in 11 hospitals, and up to two months later in an additional four hospitals, and ended on 31 October 2004. Patients were reviewed for the study outcomes at three, six and 12 months following entry into the registry, with a minimum follow-up period of 6 months for all participants. The follow-up phase of the study ended on 30 April 2005. Patient follow-up was carried out by personal interview, failing which telephonic enquiry and postal services were used. On enrolment, each patient provided a contact person (next of kin or neighbour) who could be contacted if the patient's whereabouts were not known at the time of follow-up. In the event of death or illness the contact person would be able to provide information. In the event of death, every effort was made to obtain a copy of the death certificate. Information on the vital status of patients who did not attend follow-up visits and could not be contacted by phone or post or during home visits was obtained from relatives, neighbors, hospital records, SA

Department of Home Affairs (for South African centers), or a private detective company. All patients were entered in the analysis regardless of the final diagnosis.

Baseline data (clinical profile and clinical presentation) were collected and analysed using the Epi Info statistical software, version 3.3 (CDC, Atlanta, GA, USA). The chi-square test or Fischer's Exact test (as appropriate) was used to compare categorical variables; and analysis of variance or the Kruskal-Wallis test was used to compare continuous variables. Participants were stratified by clinical HIV disease status because the primary reason for conducting this study was to assess on the clinical profile, response to treatment, and outcome of tuberculous pericarditis in Africa in the HIV era.

Statistical analysis for the six-month mortality rate was conducted with the STATA 9.0 package (STATA Corporation, College Station, TX). We used the Kaplan-Meier method to display the mortality rate, and the log-rank test to compare the survival distributions between patients with clinical features of HIV infection (or 'clinical HIV disease') and those without. Cox proportional hazards regression was used to determine which characteristics (i.e., age, gender, clinical HIV disease, serologically confirmed HIV infection, pulmonary tuberculosis, abnormal electrocardiogram, hemodynamic instability, NYHA functional impairment, alternate diagnosis, pericardiocentesis, adjunctive steroid use, geographical region, and antiretroviral drug use) were associated with mortality rate. Clinical HIV disease and serological HIV infection were fitted into separate multivariate regression models. We grouped the 15 participating hospitals into eight geographical regions (4), i.e., Eastern Cape (SA), Gauteng (SA), KwaZulu Natal (SA), Western Cape (SA), Yaoundé (Cameroon), and Ibadan (Nigeria). Geographical region was fitted into the multivariate regression model as an explanatory variable with Eastern Cape (SA) (i.e., the region that contributed the largest number of patients to the registry – 31.3%) as the reference group. Only covariates with a significant effect on mortality rate are reported in the final multivariate model.

The data reported are absolute counts (percentages) for categorical variables, median (range) for continuous variables, and hazard ratios (HR) with 95% confidence intervals (CI). Significance tests were two-tailed and statistical significance was defined at the 5% alpha level.

Results

Clinical profile of patients with suspected tuberculous pericarditis in Africa

The collaborating physicians in 15 hospitals recruited One hundred and eight five consecutive patients with suspected tuberculous pericarditis across three countries over 8 months (1 March 2004 – 31 October 2004) (Table 1). The number of patients recruited per geographic region varied from 17 (9%) in Yaoundé, Cameroon to 58 (31%) in the Eastern Cape, South Africa. The median age was 33 years (range, 14-87 years) and 56% of the participants were male (Table II). The proportion of patients with the various New York Heart Association (NYHA) functional classes were 21% (39/185), 38% (69/185), 25% (46/185), and 16% (30/185) for classes I to IV, respectively. Pericardial effusion was diagnosed in the majority of cases (79%), followed by effusive-constrictive pericarditis (15%), and constrictive pericarditis (2%). Acute dry pericarditis was diagnosed in 4% of patients. Haemodynamic instability was reported in 24% of cases, 84% of who required pericardiocentesis to relieve cardiac tamponade.

Forty percent (74/185) of the patients included in the registry had clinical evidence of HIV disease. There was significant geographic variation in the proportion of patients with clinical HIV disease, with Cameroon having the highest (88%) and Nigeria the lowest (19%) proportion of patients with clinical HIV disease. In South Africa, patients recruited from the Gauteng province had the highest prevalence of clinical HIV disease (52%), and the Western Cape province the lowest (31%). The patients with clinical HIV disease presented with significantly worse NYHA Functional Class than the clinically immunocompetent patients (P=0.004). There was no significant interaction of age, gender, and haemodynamic stability with clinical HIV disease (Table 2).

We evaluated the ability of the collaborating physicians to predict HIV serological status by using clinical criteria of HIV disease in a subset of 91 patients who were tested for HIV.

There was strong agreement between clinical signs of HIV disease and serological HIV status (Table 3). The sensitivity of clinical signs of HIV disease was 75%, specificity 88%, positive predictive value 89%, and negative predictive value 75%, which compares favourably with previous studies in Africa.[15]

Diagnostic evaluation of patients with suspected tuberculous pericarditis in Africa

The chest radiograph and echocardiogram were performed in 97% (179) and 94% (174) of patients, respectively. Electrocardiography (ECG) was carried out in 64% (119), and only 30% (56) of patients were subjected to pericardiocentesis. There was no significant variation in the diagnostic tests used by clinical HIV disease. Forty-eight patients (27%) had radiological signs of active pulmonary tuberculosis (Table 4). Patients with active pulmonary tuberculosis were more likely to be have clinical HIV disease than those without radiological signs of tuberculosis (P=0.003). The most prevalent ECG changes were micro voltage (23%), S-T segment elevation (20%), and P-R segment deviation (17%). Atrial fibrillation and electrical alternans were present in 12 (10%) and 11 (9%) patients with ECGs, respectively. There was no statistically significant relationship between clinical HIV disease and micro voltage (P=0.273), and electrical alternans (P=0.318). However, clinically HIV infected patients were more likely to have S-T segment elevation (P=0.026) and less likely to have atrial fibrillation (P=0.053) than those who were not; there was a trend towards greater prevalence of PR segment deviation, but this was not statistically significant (P=0.09) (Table 5).

Sixty nine patients (37%) had pericardiocentesis for diagnostic (31) or therapeutic (38) purposes (Table 6). Results of chemistry (adenosine deaminase, ADA) and microscopic (Ziehl-Neelsen stain for acid fast bacilli) analyses, and *Mycobacterium tuberculosis* culture were available for 34, 56, and 16 patients, respectively. There were 14 patients in this cohort (8%) who had definite tuberculous pericarditis (on smear or culture or histology), 165 (89%)

with probable tuberculous pericarditis, and six patients (3%) with an alternative diagnosis. There were no significant differences between clinically HIV infected patients and those who were not with regard to having a high ADA level (> 40IU/L) or presence of acid fast bacilli on microscopic analysis (P=0.18 and P=0.39, respectively).

Initial treatment of patients with suspected tuberculous pericarditis in Africa

One hundred and seventy-eight patients (96%) were on four-drug anti-tuberculosis chemotherapy (regimen I) for new tuberculosis cases and the rest were on regimen II for re-treatment tuberculosis cases . Patients on five drugs were more likely to be clinically HIV infected patients (P=0.055). There was marked regional variation in the use of adjunctive corticosteroids, with physicians in Ibadan, Nigeria using corticosteroids in almost all patients (29/31, 94%) whilst no physicians from the Yaoundé, Cameroon or the Gauteng province of South Africa reported adjunctive corticosteroid use in their patients. The route of administration was oral in all cases. The doses used by the physicians were not captured in the data. Overall, fifty-nine percent of the patients received oral adjunctive corticosteroids. Clinically HIV infected patients were less likely to be on an adjunctive corticosteroids (P=0.001). Seven patients (4% of total) were receiving antiretroviral drugs, all of whom were recruited in the non-South African centres.

6 month all cause mortality of patients with suspected tuberculous pericarditis.

Complete survival information was obtained on 173 (94%) of the participants. The all cause mortality at six months was 26%: 40% in patients with clinical HIV and 17% in those without. (p=.001) The Kaplan Meier survival distributions for patients with and without clinical HIV disease show that at any point during follow-up, patients with clinical HIV had a significantly higher mortality rate than those without. (crude long rank $\chi 2 = 10.72$: p=0.001) (Figure 1) The univariate Cox proportional hazards regression analysis identified age (P = 0.019), clinical HIV disease (P = 0.002), pulmonary tuberculosis (P = 0.009), and a proven

non-tuberculosis cause of pericarditis (P = 0.007) to be significantly associated with a higher mortality rate during follow-up. In the multivariate Cox regression model, having a proven non-tuberculosis diagnosis (P = 0.001), residence outside South Africa (P < 0.001), clinical HIV disease (P = 0.002), and age (P = 0.028) were identified as independent predictors of time-to-death. The use of adjunctive corticosteroids and antiretroviral agents, while appearing to be significant in univariate analysis, had no effect on survival in multivariate analyses (Table 7).

Discussion

This prospective study of suspected tuberculous pericarditis reveals for first time that patients with clinical HIV infection have a different clinical presentation and outcome to those without clinical HIV. First, patients with clinical HIV disease and tuberculous pericarditis have a greater proportion of changes of acute pericarditis on the electrocardiogram. Second, clinical HIV is associated with greater symptoms of heart failure, as indicated by a worse New York Heart Association Functional Class. Third, clinical HIV disease is associated with a greater proportion of active pulmonary tuberculosis, suggesting that the tuberculous pericarditis occurs in the context of disseminated tuberculosis. Finally clinical HIV is associated with a significantly higher six-month mortality compared to those without. Overall this suggests that tuberculous pericarditis is more severe in people with advanced HIV and AIDS.

Previous small single centre studies of tuberculous pericarditis in African patients infected with HIV have suggested that tuberculous pericarditis occurs in the early stages of HIV disease. In a Tanzanian study of HIV and tuberculous pericarditis, only 5 of the 28 HIV infected patients had clinical signs of HIV infection, suggesting that pericardial disease was an early manifestation of HIV infection in Tanzania (Cegielski '90). Our finding that nearly half of the patients with suspected tuberculous pericarditis have features of HIV infection may be in keeping with the maturity of the HIV/AIDS epidemic in many parts of Africa relative to , the case 15 years ago when many of the studies were conducted (Cegielski 90, Taelman 90, Pozniak '94, Longo-Mbenza '97, Maher '97.). There was, marked geographic variation in the prevalence of clinical HIV disease in our study. This correlated with the known epidemiological patterns of the HIV epidemic in Africa, with the exception of the Cameroon (http://www.unaids.org/en/geographical+area/by+region/sub-saharan+africa.asp).

There is a strong association between HIV infection and extra-pulmonary tuberculosis; about 67% of patients with extra-pulmonary tuberculosis are HIV infected in Zaire (Quinn '86). In Tanzania, 67% of patients with pericardial disease are seropositive for HIV[3]. Of the 91 patients who were tested for HIV in our study, 50 (55%) were HIV infected, which is similar to estimates obtained in other studies (Smedema '01).

A study of 88 patients from the Western Cape region of South Africa, which included 39 HIV infected patients, suggested that there were no differences in the electrocardiographic findings between HIV infected and HIV negative patients with tuberculous pericarditis (Smedema '01). By contrast, we observed that more patients with clinical HIV disease than those without had ST elevation on ECG (31% vs. 14%), and there was a trend towards greater PR segment deviation, changes which are associated with involvement of the superficial layers of the myocardium in pericarditis (Mayosi 02). In the pre-HIV era, changes of acute pericarditis in tuberculous pericarditis were reported in small minority of patients (i.e., 9-11%) with tuberculous pericarditis (Smedema '01, Rooney '70, Strang '84). Whether the greater prevalence of electrical evidence of acute pericarditis bears relation to greater myocardial involvement in the form of a myopericarditis in immunocompromised patients remains to be established by prospective study (Corallo '88, Reilly '88, Permanyer-Miralda '85). It is possible that the left ventricular dysfunction associated with myopericarditis in patients with tuberculous pericarditis and HIV may account for the greater dyspnoea that was observed in these patients. Alternatively, the increased dyspnoea may have been related to the increased miliary tuberculosis, which may be associated much more with dyspnoea than parenchymal tuberculosis. There were no differences in the incidence of large pericardial effusions causing haemodynamic compromise in the two groups, which is similar to the experience of others (Smedema '01).

The introduction of anti-TB treatment resulted in a dramatic reduction in mortality from TB pericarditis from 80% in the 1950's to 8% just prior to the onset of the HIV epidemic in the early 1980's (Mayosi '02). We have found in this, the largest multi-center prospective study assessing mortality that a quarter of patients with presumed tuberculous pericarditis die within six months despite anti-TB therapy. Our study suggests that clinically evident HIV infection has a major impact on the death rate, more than doubling it from 17% in patients without clinical HIV to 40% in those with them. The extremely high six month all cause mortality is almost equivalent to the ten year all cause mortality reported in patients with pericardial effusion in the only other large survival study of patients with tuberculous pericarditis reported in the pre-HIV Africa (Strang '04). It is also noteworthy that the six month mortality of 40% was much higher than the 12 month mortality of 22-25% noted in HIV sero-positive patients with extra-pulmonary tuberculosis reported from areas where TB is endemic (Badri 02).

Given the controversies and debate around the use of steroids for tuberculous pericarditis (Ntsekhe 03) it is of interest that steroid use in this cohort appeared to have a neutral effect on survival although the study was not designed to assess or answer this particular issue.

There are several factors that may explain the higher mortality observed in centres outside South Africa. Participants from the Cameroon had the highest rate of clinical HIV disease and disseminated tuberculosis and adherence to the WHO approved directly observed treatment-short course strategy is poor in both the Cameroon and Nigeria.

Limitations of the registry

Our study methods can be criticised on several grounds. First, the economic circumstances of medical practice in many African countries result in frequent shortages that, in this study, preclude complete data acquisition in every patient. For example, 6% of patients enrolled in the registry did not have access to echocardiography for confirmation of the diagnosis of pericardial disease. These effects were not linked to this study and are unlikely to introduce bias into the results. Nonetheless, we have refrained from drawing conclusions on data, which are substantially incomplete. Secondly, the lack of bacteriological confirmation of tuberculosis in the vast majority and HIV serology tests in half of the patients results from similar considerations. It should be noted that the most intense investigation may fail to yield clear information as to aetiology in patients presenting with pericardial effusion (Ntsekhe 03).[24] This was a simple, large prospective study in a resource poor environment in which the definition of clinical and laboratory abnormalities were based on self-reports of the collaborating physicians without the verification of the primary data at a central site.

Implications for clinical practice

Patients with suspected tuberculous pericarditis and clinical HIV disease have evidence of a myopericarditis, poorer functional class, and disseminated tuberculosis in Africa. These factors are likely to be associated with a poorer prognosis, and may identify a high risk group that requires more intensive management. 1) Small studies of the use of adjunctive steroids in HIV suggest that they may significantly decrease the morbidity and mortality (Hakim '00), 2) the use of drugs that interfere with the activation of the neuro-humoral cascade such as ace inhibitors and beta blockers may need to be considered where the left ventricular systolic function is significantly impaired. 3) The early use of Highly Active Anti-Retroviral Therapy (HAART) has not been studied in this setting but may have a significant on outcomes.

Implications for research

There are at least three research questions that arise from this work. First, the possibility that tuberculous pericarditis is a myopericarditis in people with advanced HIV disease requires confirmation in prospective studies. Second, the wide variation among clinicians working in Africa with regard to the use of adjunctive corticosteroids in patients with suspected tuberculous pericarditis illustrates the controversy surrounding the effectiveness of these agents in this setting (Ntsekhe '03). A large randomised controlled trial of the effectiveness of adjunctive corticosteroids is required to address this issue, particularly in HIV infected individuals. Finally, only a small minority of patients in the registry had a definitive diagnosis established. In a disease that carries such a high morbidity and mortality, the ability to make a rapid definitive diagnosis and exclude potentially fatal alternative diagnoses would be important and needs to be investigated.

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Appendix 1

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Table 1: Geographic distribution of the hospitals and study population

Country	**Region**	**Hospital**	**Number of patients recruited (%)**
Cameroon	Centre	Centre Hospitalier et Universitaire, Yaoundé	17 (9.2)
Nigeria	South West	University College Hospital, Ibadan	31 (16.8)
South Africa	Eastern Cape	Nelson Mandela Academic, Umtata	42 (22.7)
		Livingstone and Provincial, Port Elizabeth	10 (5.4)
		Cecilia Makiwane, East London	6 (3.2)
	Western Cape	Groote Schuur and GF Jooste, Cape Town	17 (9.2)
		Karl Bremer, Bellville	13 (7.0)
		George , George	3 (1.6)
		Eersterivier, Cape Town	2 (1.1)
	Guateng	Dr George Mukhari, Tshwane	15 (8.1)
		Chris Hani Baragwanath, Johannesburg	6 (3.2)
	KwaZulu Natal	Prince Mshiyeni, Durban	16 (8.6)
		King Edward VIII, Durban	7 (3.8)
Total			185 (100.0)

Table 2: Clinical characteristics of the study population by clinical HIV status

	Clinical HIV disease	No clinical HIV disease	P
Number of patients	74 (40)	111 (60)	
Age (median, range), years	36 (18-87)	32 (15-79)	0.14
Gender			
❖ Men	42 (40.8)	61 (59.2)	
❖ Women	32 (39.0)	50 (61.0)	0.81
Region			
❖ Eastern Cape, SA[+]	20 (34.5)	38 (65.5)	
❖ Western Cape, SA	11 (31.4)	24 (68.6)	
❖ Ibadan, Nigeria	6 (19.4)	25 (80.6)	0.0001
❖ KwaZulu Natal, SA	11 (47.8)	12 (52.2)	
❖ Gauteng, SA	11 (52.4)	10 (47.6)	
❖ Yaoundé, Cameroon	15 (88.2)	2 (11.8)	
Pericardial syndrome			
❖ Acute	1 (14.3)	6 (85.7)	
❖ Effusion	65 (44.2)	82 (55.8)	
❖ Effusive-constrictive	8 (28.6)	20 (71.4)	
❖ Constrictive	0 (0.0)	3 (100.0)	0.09
NYHA[++] Functional Class			
❖ I	8 (20.5)	31 (79.5)	
❖ II	27 (39.1)	42 (60.9)	
❖ III	20 (42.6)	26 (57.4)	
❖ IV	19 (63.3)	11 (36.7)	0.004
Haemodynamic instability**			
❖ Yes	24 (49.0)	25 (51.0)	
❖ No	50 (36.8)	86 (63.2)	0.13
Tamponade requiring centesis	17 (44.7)	21 (55.2)	0.97

Table 3: Ability of collaborating physicians to predict HIV serological status from clinical assessment of HIV disease

	HIV Serological Status		
Clinical HIV Disease	Positive	Negative	
Yes	40	5	**45**
No	13	38	**51**
	53	**43**	**96**

Sensitivity: 40/53 = 75.5%
Specificity: 38/43 = 88.4%
Positive predictive value: 40/45 = 88.9%
Negative predictive value: 38/51 = 74.5%

Table 4: Chest X-ray changes in the study population by clinical HIV status

Feature	**Clinical HIV disease**	**No clinical HIV disease**	**P**
Number of patients	72 (40.2)	107 (59.8)	0.39
Cardiomegaly			
❖ Yes	62 (42.2)	85 (57.8)	0.25
❖ No	10 (31.3)	22 (68.8)	
Pericardial calcification			
❖ Yes	1 (20.0)	4 (80.0)	0.33
❖ No	71 (40.8)	103 (59.2)	
Active PTB**			
❖ Yes	28 (58.3)	20 (41.7)	0.003
❖ No	44 (33.6)	87 (66.4)	

Values are absolute counts (percentages)

Table 5: Electrocardiographic changes in study population by clinical HIV status

Feature	Clinical HIV disease	No clinical HIV disease	P
Number of patients	46 (38.7)	73 (61.3)	0.62
PR segment deviation			
❖ Yes	11 (55.0)	9 (45.0)	0.09
❖ No	35 (35.4)	64 (64.6)	
ST segment elevation			
❖ Yes	14 (58.3)	10 (41.7)	0.03
❖ No	32 (33.7)	63 (66.3)	
Micro voltage			
❖ Yes	8 (29.6)	19 (70.4)	0.27
❖ No	38 (41.3)	54 (58.7)	
Electrical alternans			
❖ Yes	5 (45.5)	6 (54.5)	0.43
❖ No	41 (38)	67 (62)	
Atrial fibrillation			
❖ Yes	2 (16.7)	10 (83.3)	0.09
❖ No	44 (41.1)	63 (58.9)	

Table 6: Results of pericardial fluid analyses by clinical HIV status

Feature	Clinical HIV disease	No clinical HIV disease	P
Pericardiocentesis	31 (44.9)	38 (55.1)	0.29
Indication:			
❖ Diagnostic	14 (45.2)	17 (54.8)	0.97
❖ Therapeutic	17 (44.7)	21 (55.3)	
Pericardial aspirate analyses:			
Adenosine deaminase (n)			
❖ > 40 IU/L	8 (42.1)	11 (57.9)	0.79
❖ < 40 IU/L	7 (46.7)	8 (53.3)	
Ziehl-Neelsen stain for acid-fast bacilli (n)			
❖ Positive	3 (42.9)	4 (57.1)	0.62
❖ Negative	20 (40.8)	29 (59.2)	
TB culture (n)			
❖ Positive	2 (33.3)	4 (66.7)	0.61
❖ Negative	4 (40.0)	6 (60.0)	

Table 7. Cox proportional hazards regression analyses for time to death

Baseline characteristic	Univariate analysis			Univariate analysis, controlling for age			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age	1.02	1.01-1.04	0.019	—	—	—	1.02	1.01-1.05	0.028
Men	1.50	0.81-2.76	0.194	1.50	0.82-2.76	0.192	1.67	0.89-3.13	0.111
Clinical HIV disease	2.61	1.44-4.74	0.002	2.60	1.43-4.73	0.002	3.10	1.52-6.33	0.002
HIV sero-positive	1.35	0.63-2.88	0.437	1.56	0.70-3.46	0.274	—	—	—
Pulmonary tuberculosis	2.22	1.22-4.05	0.009	2.51	1.36-4.65	0.003	—	—	—
Abnormal electrocardiogram	0.76	0.42-1.37	0.361	0.77	0.43-1.38	0.377	—	—	—
Haemodynamic instability*	1.65	0.90-3.01	0.104	1.67	0.92-3.06	0.094	1.75	0.91-3.36	0.095
NYHA classes II to IV**	2.34	0.93-5.95	0.072	2.30	0.91-5.84	0.079	—	—	—
Alternate diagnosis	4.16	1.49-11.63	0.007	4.12	1.47-11.52	0.007	7.33	2.39-22.50	0.001
Pericardiocentesis	1.39	0.77-2.51	0.271	1.35	0.75-2.43	0.322	—	—	—
Adjunctive steroid use	0.61	0.34-1.10	0.098	0.57	0.31-1.02	0.058	—	—	—
Antiretroviral drugs	9.17	2.18-38.64	0.003	8.03	1.82-35.31	0.006	—	—	—
Ibadan***	1.31	0.56-3.06	0.535	0.18	0.07-0.48	0.001	3.22	1.38-7.49	0.007
Yaoundé***	4.63	2.07-10.35	<0.001	0.30	0.13-0.74	0.008	4.89	2.28-10.49	<0.001

HR, Hazard ratio; CI, Confidence interval; P, the probability that the effect of the characteristic on the time to death in this study occurred by chance alone, given that there is truly no relationship between the characteristic and survival; NYHA, New York Heart Association classification of functional status. *Pulse rate more than 100 beats per minute, Systolic blood pressure less than 100 mmHg and or tamponade requiring pericardiocentesis. ***The hazard ratios represent the risk of dying in the respective centers (with Eastern Cape as reference). In the multivariate model, hazard ratios are only indicated for characteristics that were retained in the final model.

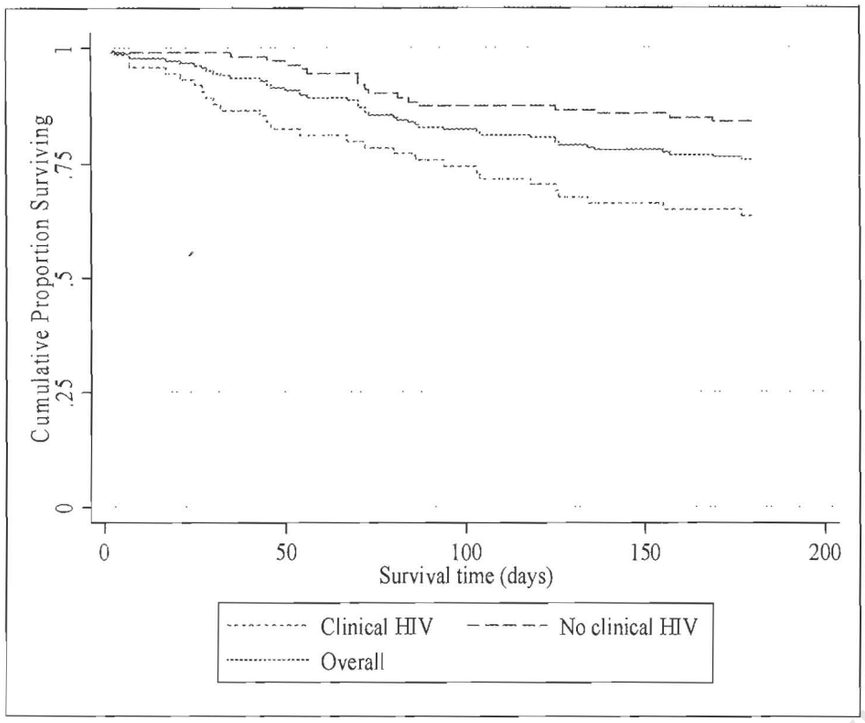

Figure 1: Survival during follow-up in the whole study population and by clinical HIV status (P=0.001 for the difference in survival experiences between groups defined by clinical HIV status).