Tuberculous pericarditis in HIV co-infected compared to those without HIV co-infection

By

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Declaration

I, Dr Justin T Shenje, hereby declare that the dissertation which I am submitting for the degree Master of Science in Clinical Epidemiology at the University of Pretoria is my own work and has not previously been submitted by me for a degree at another university.

_____ 15/08/ 2013

Dr Justin T Shenje Date

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Abstract

Introduction: Tuberculosis (TB) pericarditis is a relatively rare form of tuberculosis which has been on the decline. However, the advent of the human immunodeficiency virus (HIV) pandemic has brought about the resurgence of tuberculosis pericarditis and an even poorer prognosis for patients with HIV co-infection.

Objectives: The aim is to describe the baseline characteristics of tuberculous pericarditis patients and to assess the impact of HIV on the clinical presentation of this disease.

Methods: The study describes baseline data from a randomised clinical trial which explored the use of adjunctive corticosteroids in management of TB pericarditis then went on to compare HIV co-infected patients versus those without HIV co-infection using logistic regression.

Results: There were 1394 patients enrolled into the study, 64% were HIV positive, 19% were HIV negative and 17% had an unknown HIV status. Forty four percent of the participants were female and age had a positively skewed distribution with median 36 years (IQR: of 29-46). HIV co-infected patients were younger with OR 0.97(95% CI: 0.96-0.98), more likely to have previously had TB with OR 2.15(95% CI: 1.25-3.72), had a more acute illness with OR 0.99(95% CI: 0.99-1.00), had lower hemoglobin with OR 0.72(95% CI: 0.67-0.78), lower White Cell Count, (WCC) with OR 0.90(95% CI: 0.86-0.96) and higher globulin with OR 1.07(95% CI: 1.05-1.09).

Conclusion: HIV co-infected participants are younger, more likely to have been previously diagnosed with TB, have a more acute illness, lower haemoglobin, lower WCC and higher globulin.

Key words: *Baseline characteristics, TB pericarditis, HIV co-infection.*

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Abbreviations

AAFBs	Alcohol acid fast bacilli
ADA	Adenine deaminase
CD4	Cluster differential four
CRF	Case report form
ECG	Electrocardiogram
ECHO	Echocardiogram
FBC	Full blood count
HAART	Highly active anti-retroviral therapy
HIV	Human immunodeficiency virus
IMPI	Investigation of Management of TB pericarditis
IQR	Inter quartile range
JVP	Jugular venous pressure
LFTs	Liver function tests
NYHA	New York Heart Association
PCO	Principal coordinating office
TB	Tuberculosis
WHO	World Health Organization
WCC	White cell count

Chapter1: Literature review

1.1 Introduction

Tuberculosis (TB) pericarditis is the most common cause of a large pericardial effusion in the developing world. In a case series in the Western Cape, up to 69.5% of effusions were caused by TB pericarditis whereas only 4% of effusions in the developed world are due to TB pericarditis. TB pericarditis is a form of extra pulmonary TB which accounts for only 1% of all patients with TB but carries with it a high mortality.[1] The high mortality is attributed to pericardial tamponade and constrictive pericarditis.[2] Despite these complications being treatable, in a resource limited environment confirming the diagnosis and providing safe treatment options remains a challenge.

There are three main manifestations of pericardial disease in TB pericarditis. These are pericardial effusion, effusive constrictive and constrictive pericarditis.[2] The most common presentation is of a pericardial effusion, constituting 79.5% of patients with TB pericarditis. An effusion occurs when there is an accumulation of an inflammatory exudate as a result of the presence of mycobacterium in the pericardial space. The mycobacterium is thought to enter the pericardium via either retrograde lymphatic spread from the lungs or haematological spread from the skeletal or genitourinary systems.[1]

The immune response is coordinated by the T helper 1 (TH1) cells, which release cytokines mainly interferon gamma and interleukin 2.[3] These cytokines mobilise macrophages to form granulomas and destroying infected cells, in the process releasing an exudate which in the restricted space may accumulate and compromise maximum diastolic volume ultimately reducing cardiac output. There are three features of tamponade. These are increase pericardial volume, an increase in pericardial fluid which exceeds stretch or absorption rate of pericardial space and reduced pressure gradient for right heart filling.[4]

1.2 Historical background

TB pericarditis has been a recognised as cause of considerable morbidity and mortality in Southern Africa for over 60 years. Schrire et.al. (1959) characterised 160 patients presenting at Groote Schuur Hospital who were diagnosed with TB pericarditis. TB pericarditis was found to be more prevalent in people of poor socio-economic standing, three fold higher incidence in males and a peak incidence between ages 20-50 years old. TB pericarditis had a high morbidity and mortality, about 10% of patients had died after six months and up to 40% of patients went on to develop constrictive pericarditis. Due to the poor clinical outcomes associated with

TB pericarditis Schrire et.al. went on to explore the use of adjunctive corticosteroids in order to improve the management of TB pericarditis.[5]

Strang et.al. (1987) similarly followed up 143 patients with TB pericarditis in the Eastern Cape. An important difference with the study by Schrire et.al. was that the previous diagnosis was based on history, examination, electrocardiography (ECG) and microscopy while echocardiography was now available.[6,7] An echocardiogram (ECHO) has now become the gold standard of diagnosing a pericardial effusion, and has allowed clinicians to be able to detect even smaller pericardial effusions. Coincidentally, 1987 is around the time that HIV pandemic was emerging which would subsequently have a huge impact on the epidemiology of TB.[8]

A team of researchers with the Stellenbosch University in 2006 described the Tygerberg index, a diagnostic algorithm aimed at assisting clinicians in diagnosis of TB pericarditis.[9] An interesting finding was that 55% of TB pericarditis patients were associated with HIV co-infection.[10] This strong association between TB and HIV is consistent for all forms of TB, not surprisingly the World Health Organization (WHO) went on to classify TB as an opportunistic infection.[11] HIV co-infected patients also tended to be younger and had a lower weight and cluster differentiation four (CD4) count.[10] Patients with advanced HIV disease are more likely to have disseminated disease, that is disease involving more than one system. Microscopy results in the HIV co-infected are also less likely to be positive making diagnosis an even greater challenge.[12] With the biomarkers, HIV co-infected patients had a significantly higher serum globulin while for adenine deaminase concentration in pericardial fluid was higher in patients without HIV co-infection.[10]

These results were mirrored in the Investigation of Management of TB Pericarditis (IMPI) registry which laid the foundation for the IMPI trial. The IMPI registry also showed that while there was no difference between baseline blood pressure and pulse, HIV co-infected TB pericarditis patients had a poorer New York Heart Association (NYHA) functional classification (i.e., greater dyspnoea) than their HIV negative counterparts.[13]

However, both these studies were conducted in the early phase of the aggressive role out of highly active anti-retroviral therapy (HAART) and these differences may have been overtaken by time. The HIV pandemic has magnified the problem of TB pericarditis but it remains unknown whether increased access to HAART can mitigate this problem. One would expect that improvement in the care and treatment of people living with HIV would result in the baseline characteristics of HIV co-infected patients becoming more similar to those without HIV co-infection.

Chapter 2: Motivation for study

While previous literature described demographic characteristics of patients with TB pericarditis, these studies were conducted in the pre-HIV and early HIV era. There have been a number of notable developments in the epidemiology of this relatively rare but serious form of extra pulmonary TB. While HIV has significantly increased the incidence of all forms of TB, there has been a greater accessibility to highly active anti-retroviral therapy (HAART) and review of guidelines on initiation of ART. The threshold for initiating HAART, previously set at CD4 count 200 cells/ul and was revised upwards to CD4 count 350 cells/ul. Moreover, the introduction of isoniazid prophylaxis for HIV positive patients is most likely to reduce the incidence of TB amongst people living with HIV. These recent developments have created a need to evaluate whether there are corresponding changes in the baseline characteristics of patients with TB pericarditis. Strategies aimed at preserving the integrity of the immune system and preventing TB in people living with HIV should hopefully reduce the incidence of TB pericarditis and reduce the proportion TB pericarditis HIV co-infection.

Chapter 3: Aims and objectives

The overall aim of the study was to describe the baseline characteristics of TB pericarditis patients. The study descried the demographic characteristics, clinical features based on history and examination, radiological features found on chest x-ray and lastly laboratory investigations performed on both blood and pericardial fluid.

The demographic information included age, sex and weight of the patient. While the clinical features described were the proportion of patients who were HIV positive, who had previously been diagnosed with TB, had an elevated pulsus paradoxus, raised jugular venous pulse, oedema, hepatomegaly and a pericardial knock. The blood pressure, pulse, NYHA functional classification, temperature and duration of symptoms at time of presentation were also characterised. The study described radiological features found on chest x-ray suggestive of TB pericarditis namely cardiomegaly, pulmonary infiltrates, pleural effusion and pericardial calcification. Furthermore, the study described laboratory findings which included haemoglobin, white cell count, serum globulin, serum creatinine, total protein in pericardial fluid, ADA and microscopy and culture results of pericardial fluid.

Once TB pericarditis patients were characterised, patients with HIV co-infection were then compared with those without HIV co-infection. This was done to determine whether there were any variables which were associated with either HIV status.

Chapter 4: Methods

4.1. Study design

Prospective cohort study

4.2. Setting

Patients diagnosed with TB pericarditis after presenting at secondary and tertiary care government hospitals and are part of the investigation of Management of Pericarditis (IMPI) trial in 19 sites distributed in eight countries across Africa from the 1st January 2009 to the 31st August 2013 as shown in the table below.

Table 1 Study sites

Hospital	City	Country
Groote Schuur Hospital	Cape Town	South Africa
Port Elizabeth Provincial Hospital	Port Elizabeth	South Africa
Nelson Mandela Hospital	Mthatha	South Africa
King Edward VIII Hospital	Durban	South Africa
Chris Hani Baragwanath Hospital	Soweto	South Africa
Dr George Mukhari Hospital	Ga Rankuwa	South Africa
Johannesburg Academic Hospital	Johannesburg	South Africa
Maputo Central Hospital	Maputo	Mozambique
Malawi Military Health Service Kamuzu Barracks	Lilongwe	Malawi
University College Hospital	Ibadan	Nigeria
Aminu Kano Teaching Hospital	Kano	Nigeria
Federal Medical Centre	Abeakuta	Nigeria
Abuja Teaching Hospital	Abuja	Nigeria
University Calabar Teaching Hospital	Calabar	Nigeria
University Teaching Hospital Zaria	Zaria	Nigeria
Connaught Hospital	Freetown	Sierra Leone
Parirenyatwa Hospital	Harare	Zimbabwe
Mulago Hospital	Kampala	Uganda
Moi Teaching and Referral Hospital	Eldoret	Kenya

4.3. Patient selection and inclusion criteria

The study reviewed the baseline data of all patients enrolled into the IMPI study. The IMPI study recruited newly diagnosed TB pericarditis patients from the hospitals in table 1. TB pericarditis was diagnosed on basis of a confirmed pericardial effusion on the echocardiogram (ECHO) and either definitive or suggestive evidence TB being the underlying cause of the effusion. A definitive diagnosis of TB was defined by a pericardial effusion with a positive result for mycobacterium tubercle in the pericardial fluid. On the other hand a suggestive diagnosis of TB pericarditis was defined as a pericardial effusion with an elevated adenine deaminase (ADA) accompanied by a lymphocytic infiltrate, a positive mycobacterium tubercle anywhere in the body other than the pericardium or a Tygerberg clinical diagnostic score equal to or greater than six (a clinical diagnostic algorithm see appendix 1).

4.4. Measurements

4.4.1. Measurement tools

The baseline case report form was used to collect the medical history, physical examination findings and the baseline investigation.

4.4.2. Measurement methods

The study definition of TB pericarditis was a patient with a confirmed pericardial effusion and either microbiological evidence of TB, a Tygerberg diagnostic score ≥6 or a biochemical diagnostic criteria based on pericardial fluid with an ADA ≥30 with predominantly lymphocytic infiltrate. Patients who met the criteria and provided written informed consent to participate were enrolled into the study. The participants underwent a consultation by a study doctor and a battery of investigations which included chest X-ray, electrocardiogram (ECG), ECHO, full blood count (FBC), liver function tests (LFTs) and urea and electrolytes. A case report form (CRF) was designed specifically for the study which was used to guide the clinician's history taking, physical examination and choice of clinical investigations (see pages 1-3 of the CRF in appendix 2-4).

Each of the study sites used their respective hospital equipment to measure weight, body temperature and blood pressure. The various clinicians working on the study also made a judgement call based on their understanding of the clinical symptoms and signs listed in the CRF for example pulsus paradoxus, elevated jugular venous pulse (JVP), hepatomegaly and NYHA functional classification. Interpretation of Chest X-ray was also done by the respective physicians. Similarly there was no central laboratory to process the laboratory investigations but each site relied of their own laboratory facilities. Where necessary patients

were offered pericardiocentesis and this decision was left to the discretion of the attending physician. Every attempt was made to confirm the diagnosis of TB by microscopy, culture or GeneXpert.

4.4.3. Variables

a) Demographic data

1. Age in years at date of enrolment into study.
2. Sex.
3. Weight in kilograms.

b) Clinical features

1. HIV status.
2. Previous history of being diagnosed with TB.
3. Duration of symptoms in days.
4. Body temperature in degrees Celsius.
5. Pulsus paradoxus.
6. Elevated JVP.
7. Edema.
8. Hepatomegaly.
9. Pericardial knock.

c) Hemodynamic status

1. Heart rate.
2. Blood pressure.
3. NYHA functional classification.

d) Radiological findings on chest X-ray

1. Cardiomegaly.
2. Pulmonary infiltrates.
3. Pulmonary effusion.
4. Pericardial calcification.

e) Laboratory findings

1. Haemoglobin.
2. WCC.
3. Globulin.
4. Creatinine.
5. Total pericardial fluid protein.
6. ADA.
7. Evidence of alcohol acid fast bacilli (AAFBs) in pericardial fluid.

4.4.4. Data collection and management

Patient data and information were collected on paper based CRF and were kept at each study site in a secure office which was only accessible by authorised study personal. The various sites were then required to send a copy of the CRF via fax or scan to the principal co-ordinating office (PCO) within 48 hours, where a team of data captures entered data into an electronic web based database called idata fax. The idata fax system is password secured web based database and all participant identification information such as name, hospital number and national identification number were replaced by a study number. The idata fax database can easily export the data into a comma separated variable (csv) format which can then be imported into Stata11(Stata LP, Texas, USA) for data analysis.

4.4.5. Statistical analysis

Patient data was exported from idata fax to csv format and the statistical analysis was performed using Stata11(Stata LP, Texas, USA). The aim of the study was to first describe then compare the baseline characteristics of TB pericarditis patients between patients with HIV co-infection versus those without HIV co-infections.

The presence or absence of clinical signs and symptoms for example hepatomegaly and cardiomegaly were binary variables and as a result Fisher's exact test was used to determine if there was a difference in occurrence of these features between HIV positive and HIV negative patients. The study also compared the median age, weight, duration of symptoms at time of presentation, temperature, heart rate, systolic BP, diastolic BP, hemoglobin, white cell count, globulin and creatinine. The Mann Whitney test was used to determine whether there was a difference between the continuous variables since these variables did not conform to normality. The NYHA functional classification is an ordinal categorical data and the Chi-square test was used to compare this variable based on HIV status.

After describing the data a logistic regression univariate analysis was performed for each of the variables with HIV status as the outcome variable. Then starting from a full model which incorporated all variables with a p value less than 0.25 backward logistic regression was performed. Variables with a large p value were dropped from the full model one after the other and the likelihood ratio test was used to determine whether the dropped variable significantly compromised the remaining model.

Missing data presented a challenge during the backward logistic regression process. During some steps of the regression process missing data resulted in a full model and nested model having a different number of observations. The likelihood ratio test cannot be applied to compare models with a different number of observations as a

result multiple imputation was used to predict the missing values. With the imputed data set backward logistic regression was repeated. Nonetheless, multiple imputation uses regression to predict the distribution of the missing variable therefore gives a point estimate and a measure of variability. The comparison of a nested model to the full model the likelihood ratio test still could not be used since it failed to account for variability of the imputed data. The Wald test was then used instead of the likelihood ratio test. The two models derived from the original data and the imputed data were then compared to determine if the results were comparable.

Chapter 5: Results

5.1. Descriptive statistics

Demographic information

One thousand three hundred and ninety four patients presenting with TB pericarditis were enrolled from 19 sites from eight counties across the African continent. Most participants were recruited from South Africa (72%), with the rest of the participants coming from Mozambique, Malawi, Nigeria, Sierra Leone, Zimbabwe, Uganda and Kenya.

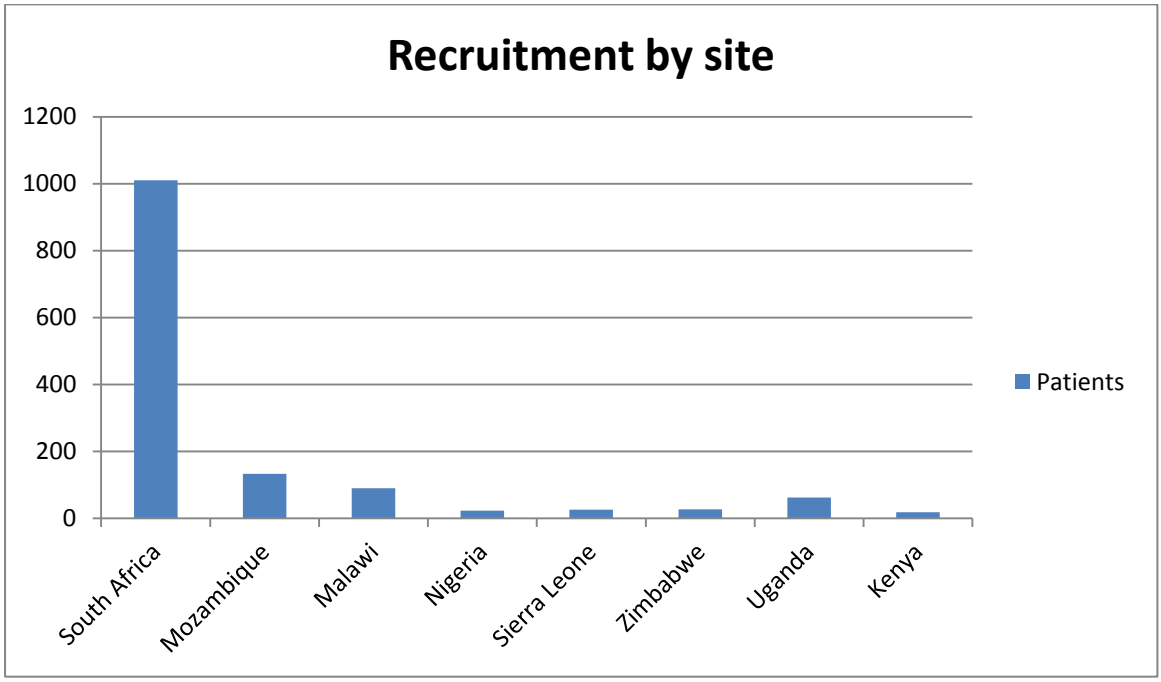

Figure 1: Patient recruitment by site

Of the 1394 participants 17% had an unknown HIV status while 64% were HIV positive and 19% were HIV negative. Seventy nine percent of participants from South Africa, Mozambique, Malawi, Zimbabwe, Uganda and Kenya were co-infected with HIV while only 23% of participants from Nigeria and Sierra Leone also were HIV positive. There were 738 HIV positive patients and 48% of them knew they were HIV positive at the time of diagnosis of TB pericarditis and 28% were already on HAART.

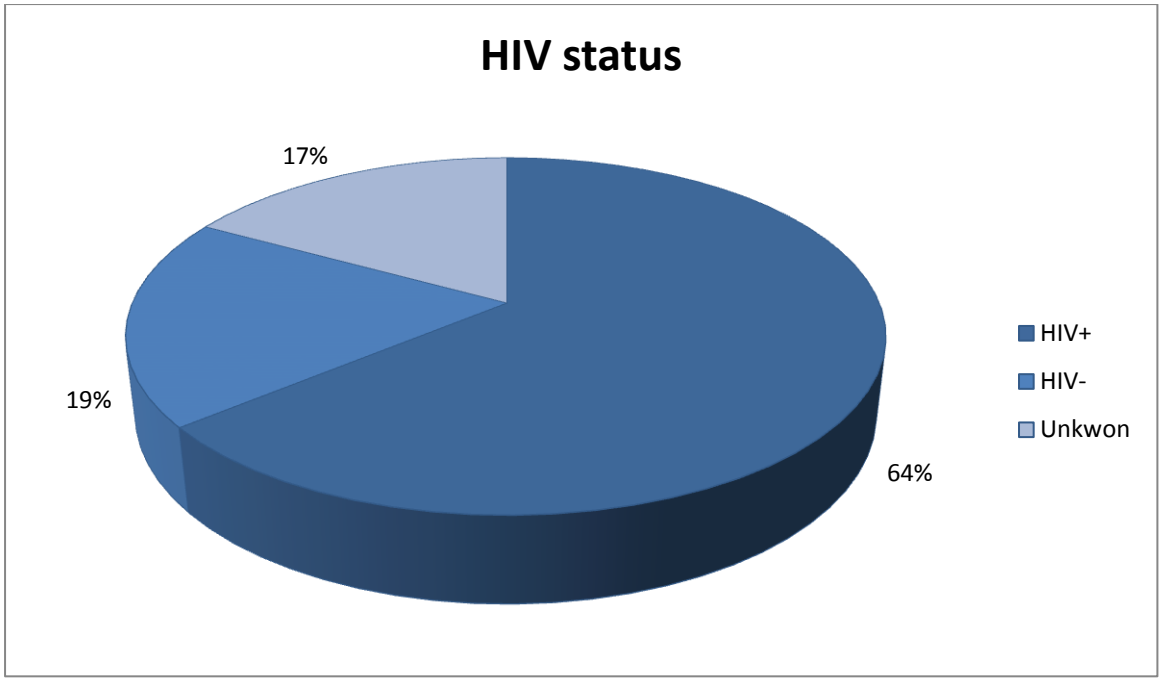

Figure 2: Patient HIV status

Forty four percent of the 1394 participants were female. Both age and weight had a positively skewed distribution with a median age of 36 years (IQR: of 29-46) and a median weight of 58 kg (IQR: 51-67). There was no difference in the ratio of males to females in TB pericarditis patients based on HIV status, with 400 (45%) women in the HIV co-infected group and 112 (41%) in those without HIV co-infection group (p = 0.295).

HIV co-infected participants were younger with a median age 34 years (IQR: 28-40) compared to a median age of 41 years (IQR: 27-56) in participants without HIV co-infection. Furthermore, HIV co-infected patients had a lower weight median 56 kg (IQR: 50-65) versus a median of 60 kg (IQR: 54-68) in patients with HIV co-infection.

Table 2: Patient demographic information

Variable	HIV negative (n=272)	HIV positive(n=890)	P value
Sex (female)	112 (41%)	400 (45%)	0.295
Age (years)	41 (27-56)	34(28-40)	<0.001
Weight (kilograms)	60 (54-68)	56(50-65)	<0.001

Clinical features

There were 11% of patients who had previously been treated for TB. Patients presented with a median duration of symptoms of 30 days (IQR: 14-42). The most frequent clinical sign was elevated JVP which was elevated in 59% followed by hepatomegaly and dependent edema which were present in 46% and 41% respectively.

Table 3: Comparing baseline clinical features

Variable	HIV negative (n=272)	HIV positive (n=890)	P value
Duration of symptoms (days)	30 (15-60)	30 (14-41)	0.008
Temperature (C°)	37.8 (36.8-38.1)	37.5 (36.8-38.2)	0.947
Past history of TB	23 (8%)	129 (14%)	0.010
Pericardiocentesis	148 (54%)	510 (58%)	0.363
Pulsus paradoxus	40 (15%)	170 (19%)	0.106
Elevated JVP	149 (55%)	515 (58%)	0.401
Oedema	101 (37%)	336 (37%)	0.884
Hepatomegaly	110 (40%)	384 (43%)	0.442
Ascites	36 (13%)	78 (9%)	0.036
Pericardial knock	13 (5%)	48 (5%)	0.758

There were no discernible differences in baseline body temperature, proportion with pulsus paradoxus, edema, hepatomegaly, elevated JVP, pericardial knock and rate of pericardiocentesis between HIV co-infected versus those without HIV co-infection. However, HIV co-infected TB pericarditis patients were more likely to present with a more acute illness. While the median duration of symptoms for both groups was 30 days the IQR and Mann-Whitney-Wilcoxon test showed a significant difference further illustrated in the box plot in figure 3. Fourteen percent of HIV co-infected patients had previously been diagnosed with TB as opposed to only 8% of those without HIV co-infection with a p value of 0.01. Ascites seemed to be more commonly associated with patients without HIV co-infection and was present in 13% as compared to 9% in patients with HIV co-infection.

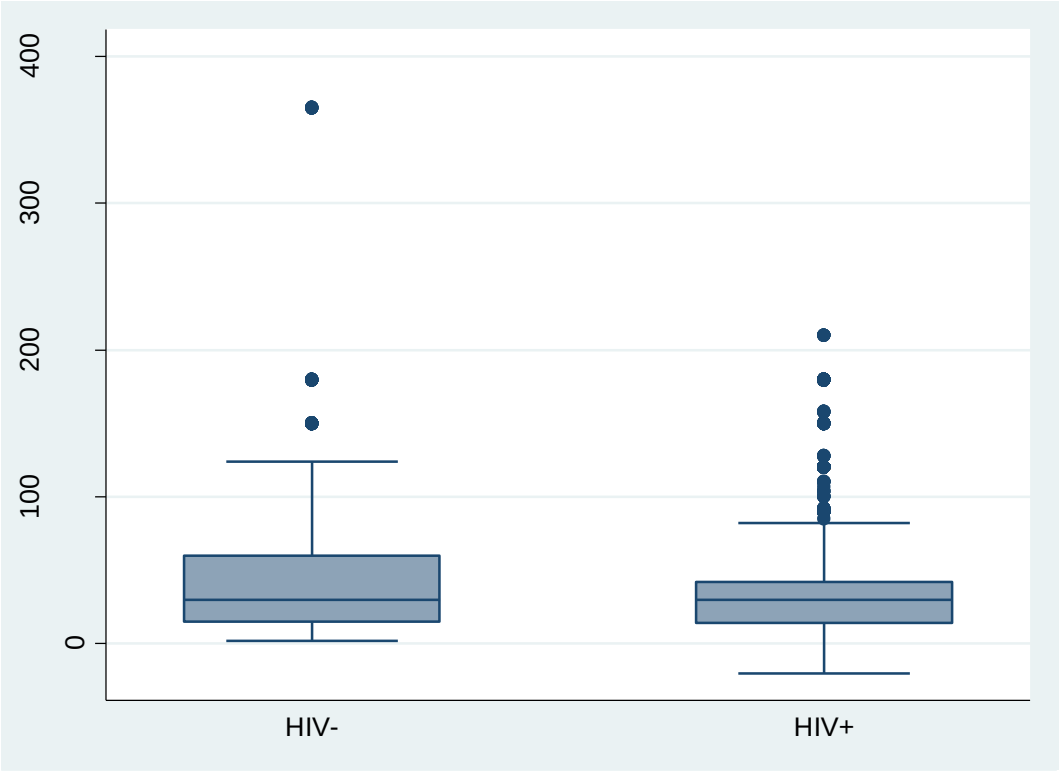

Figure 3: Comparing Duration of symptoms by HIV status (P= 0.008)

Hemodynamic status

There was evidence of hemodynamic compromise in 79% of participants (hemodynamic compromise was defined if either a systolic BP < 100mmHg or heart rate > 90 beats per minute was present). There were 18% of participants with NYHA I, 50% had NYHA II, 24% had NYHA III and 8% had NYHA IV.

Table 4: Comparing hemodynamic parameters by HIV status

Variable	HIV negative (n=272)	HIV positive (n=890)	P value
Pulse rate in beats per min	100 (88-111)	106 (92-120)	<0.001
Systolic BP in mmHg	120 (110-129)	110 (100-120)	<0.001
Diastolic BP in mmHg	77 (70-81)	70 (62-80)	<0.001

TB pericarditis patients with HIV co-infection tended to have a less favorable hemodynamic status. They had a higher pulse rate of 106 beats per minute as compared to 100 beats per minute in those without HIV co-infection, with a p value of zero. HIV co-infected patients were also more likely to have a lower systolic and diastolic BP which was 110mmHg (IQR: 100-120) and 70mmHg (IQR: 62-80) respectively as compared to 120mmHg (IQR: 110-129) and 77mmHg (IQR: 70-81) respectively in those without HIV co-infection, both with p value zero. Similarly the NYHA functional classification was better in patients without HIV co-infection, both NYHA I and II had a higher percentage of patient without HIV co-infection, while

NYHA III and IV had a higher percentage of HIV co-infected patients with a p value of 0.031 on the Chi-square test, shown in the figure 4.

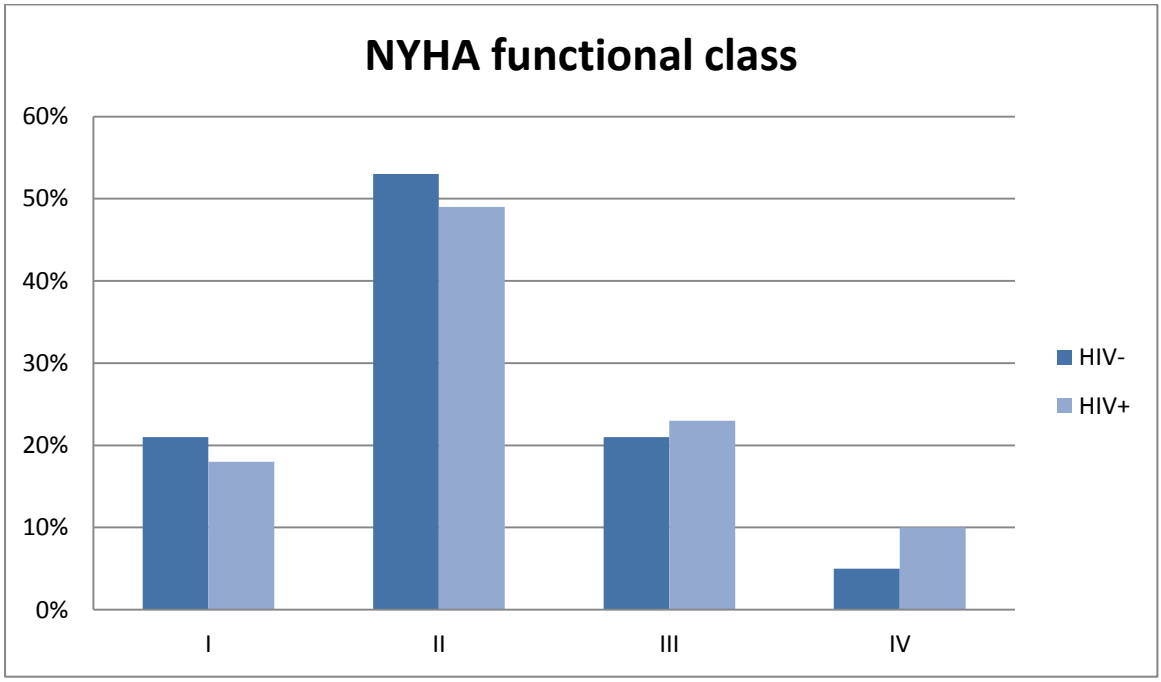

Figure 4: Comparing NYHA functional classification by HIV status (P = 0.031)

Radiological features

A chest x-ray showed cardiomegaly in 85% of patients while radiologic evidence of a pleural effusion and pulmonary infiltrates were found in 28% and 31%of patients respectively. Pericardial calcification was only present in 1% of patients. There were no significant differences on chest x-ray between the two groups except for pericardial calcification. The proportion of patients presenting with pericardial calcification was 4% in the patients without HIV co-infection, and 1% in the patients with HIV co-infection.

Table 5: Comparing radiological features on x-ray by HIV status

Variable	HIV negative	HIV positive	P value
Cardiomegaly	236 (87%)	761 (86%)	0.691
Pulmonary infiltrates	78 (29%)	288 (32%)	0.264
Pleural effusion	79 (29%)	240 (27%)	0.535
Pericardial calcification	11 (4%)	7 (1%)	0.001

Laboratory investigations

Laboratory investigations showed a median hemoglobin of 9.7 g/dl (IQR: 8.3-11.6), WCC of 5.9 /mm^3 (IQR: 4.5-7.7), globulin 49 g/l (IQR: 42-57), creatinine 74 umol/l

(IQR: 60-90), ADA 52 U/l (IQR: 39-70) and pericardial protein 60 g/l (53-68). There were 37% of patients with positive AAFBs on either microscopy or a culture which reported positive for Mycobacterial infection of pericardial fluid specimens and this figure went up to 66% when it was restricted to patients who had pericardiocentesis. Laboratory investigation showed no difference in serum creatinine, ADA and evidence of TB in pericardial fluid. On the other hand the hemoglobin and WCC were lower in patients with HIV co-infection, while globulin was higher in this group, all with a p value of zero on the Mann-Whitney-Wilcoxon test. The hemoglobin median in the HIV co-infected group was 9.2 g/l (IQR: 7.8-10.6) as compared to 11.4 g/l (IQR: 9.8-12.9) in the group with no HIV co-infection. Similarly the WCC was lower in HIV co-infected group with a median of 5.6 /mm^3 (IQR: 4.3-7.4) while in those without HIV co-infection was 6.6 /mm^3 (IQR: 5.1-8.3). Likewise total protein in the pericardial fluid was higher in patients with HIV co-infection with median 62 g/l (IQR: 54-69) compared to 58 g/l (IQR: 52-63) in those without HIV co-infection. Globulin tended to have the opposite relationship with a higher median globulin of 52 g/l (IQR: 45-59) in the HIV co-infected compare to 41 g/l (IQR: 36-47) in those without HIV co-infection.

Table 6: Comparing laboratory investigations by HIV status

Variable	HIV negative	HIV positive	P value
Hemoglobin g/dl	11.4 (9.8-12.9)	9.2 (7.8-10.6)	<0.001
WCC /mm^3	6.6 (5.1-8.3)	5.6 (4.3-7.4)	<0.001
Creatinine umol/l	75 (61-94)	73 (59-90)	0.129
Globulin g/l	41 (36-47)	52 (45-59)	<0.001
Pericardial protein g/l	58 (52-63)	62 (54-69)	0.001
ADA U/l	55 (39-86)	52 (37-66)	0.185
Evidence of TB in the pericardium	105 (39%)	328 (37%)	0.775

5.2. Analysis of data

The variables were then stratified by HIV status to determine whether the clinical presentation of TB pericarditis is affected by HIV status. The 232 patients with an unknown HIV status were excluded and a univariate analysis of each of the variables with the outcome HIV status was performed which showed 14 variables with an association with HIV status.

Table 7: Univariate analysis showing associations with HIV status

	Variable	OR (95% CI)	P value
Demographic variables	Sex	1.17 (0.89-1.54)	0.274
	Age (years)	0.96 (0.95-0.97)	<0.001
	Weight (kilograms)	0.97 (0.92-0.98)	<0.001
Clinical variables	Past history of TB	1.84 (1.15-2.92)	0.011
	Duration of symptoms (days)	0.99 (0.99-1.00)	0.002
	Pericardiocentesis	1.14 (0.87-1.50)	0.347
	Temperature (^{0}C)	1.03 (0.90-1.17)	0.670
	Pulsus paradoxus	1.37 (0.94-1.99)	0.100
	Elevated JVP	1.13 (0.86-1.49)	0.368
	Oedema	1.03 (0.78-1.34)	0.853
	Hepatomegaly	1.12 (0.85-1.47)	0.430
	Ascites	0.63 (0.41-0.96)	0.031
	Pericardial knock	1.34 (0.61-2.13)	0.691
Hemodynamic variables	Pulse rate (beats/min)	1.01 (1.01-1.02)	<0.001
	Systolic BP (mmHg)	0.98 (0.97-0.99)	<0.001
	Diastolic BP (mmHg)	0.97 (0.97-0.98)	<0.001
	NYHA I II III IV	- 1.09 (0.76-1.55) 1.29 (0.85-1.97) 2.37 (1.25-4.48)	- 0.649 0.232 0.008
Radiological features	Cardiomegaly	0.90 (0.60-1.34)	0.603
	Pulmonary infiltrates	1.19 (0.88-1.60)	0.253
	Pleural effusion	0.90 (0.67-1.22)	0.503
	Pericardial calcification	0.19 (0.07-0.49)	0.001
Laboratory investigations	Hemoglobin (g/dl)	0.65 (0.61-0.70)	<0.001
	WCC(mm^3)	0.92 (0.88-0.96)	<0.001
	Creatinine (umol/l)	1.00 (0.99-1.00)	0.078
	Globulin (g/l)	1.08 (1.07-1.10)	<0.001
	Protein	1.02 (1.00-1.04)	0.011
	ADA	0.99 (0.99-1.00)	0.018
	Evidence microbacterial infection in the pericardium	0.95 (0.72-1.26)	0.746

JVP= Jugular Venous Pressure, NYHA= New York Heart Association, WCC=White Cell Count, ADA=Adenosine Deaminase

However, multivariate logistic regression showed only six variables which had a significant association with HIV status, these variables included age, past history of TB, duration of symptoms, hemoglobin, WCC and globulin. The odds ratio for age was 0.97 (95% CI: 0.96-0.98) meaning that for every one year increase in age the

odds of having HIV co-infection decreased by 3%. Patients with a history of previous TB illness had a 2.15 (95% CI: 1.25-3.72) greater odds of having HIV co-infection compared to those without previous history of TB illness. A one day longer duration of symptoms at time of presentation had a decrease in OR of 0.99 (95% CI: 0.99-1.00) of having HIV co-infection. An increase in hemoglobin of one unit decreased the odds of having HIV co-infection by a factor of 0.72 (95% CI: 0.67-0.78). An increase of WCC of one unit decreased the odds of having HIV co-infection by a factor of 0.90 (95% CI: 0.86-0.96). Finally, an increased in globulin increased the odds of having HIV co-infection by a factor of 1.07 (95% CI: 1.05-1.09). All in all HIV co-infected patients tended to be younger, had more acute illness on presentation, had a lower hemoglobin and white blood cell count but were more likely to have been previously diagnosed with TB and had a higher serum globulin.

Table 8: Logistic regression results

Variable	OR (95%CI)	P value
Age	0.97(0.96-0.98)	<0.001
Past TB	2.15(1.25-3.72)	0.006
Duration of symptoms	0.99(0.99-1.00)	0.005
Hemoglobin	0.72(0.67-0.78)	<0.001
WBC	0.90(0.86-0.96)	<0.001
Globulin	1.07(1.05-1.09)	<0.001

. The Hosmer and Lemeshow's goodness of fit statistic had a p value of 0.081 showing that the model fits the data sufficiently. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve was 0.847 suggesting that the model performed well at discriminating between TB pericarditis patients with HIV co-infection and those without HIV co-infection. This was further supported by the confusion matrix table which showed that the model correctly classified 81% of the patients.

While building the logistic regression model it was noted that there was a significant amount of missing data. Out of the 24 variables there were 12 variables with missing data and this presented a challenge. Patients with missing data had to be dropped from the model development process and as a result it was not always possible to compare a full model and nested model when deciding whether to drop a variable. After closely analyzing the missing data it was concluded that there was no evidence to suggest that the missing data was missing for any other reason than by chance. The data was then assumed to be missing by chance, this is an important property when deciding on how best to deal with missing data.[14]

Table 9: Summary of missing data

Variable	Missing data (%)
HIV status	232 (16.6%)
Weight	23 (1.7%)
Duration of symptoms	2 (0.1%)
Temperature	3 (0.2%)
Pulse	3 (0.2%)
Systolic BP	2 (0.1%)
Diastolic BP	2 (0.1%)
NYHA	4 (0.3%)
Hemoglobin	13 (0.9%)
WCC	11 (0.8%)
Creatinine	132 (9.5%)
Globulin	40 (2.9%)

To make efficient use of the available data and to improve the power of the logistic regression model multiple imputation was used to predict the value of the missing data for the independent variables shown in table 8. HIV status was the outcome variable therefore the 232 patients with missing HIV status were not imputed but were dropped from the analysis. The imputation chain equation (ice) method was used, which predicts missing data using regression equations. Five imputations were performed with a random number generator 666. At least five imputations are required for multiple imputation in order to factor in random error and a seed for the random generator was used in order for the imputation process to be reproducible. The logistic regression model derived from the imputed data was similar to the initial model derived from un-imputed data, the six variables remained in the model with similar odds ratios but the imputed model picked an extra variable, pericardial calcification. Presence of pericardial calcification of chest x-ray was less likely associated with HIV co-infection OR 0.17 (95%: 0.04-0.62).

Table 10: Logistic regression with imputed data

Variable	OR (95%CI)	P value
Age	0.97(0.96-0.98)	<0.001
Past TB	2.41(1.39-4.16)	0.002
Duration of symptoms	0.99(0.99-1.00)	0.003
Pericardial calcification	0.17(0.04-0.62)	0.007
Hemoglobin	0.72(0.67-0.78)	<0.001
WBC	0.90(0.86-0.96)	0.001
Globulin	1.07(1.05-1.08)	<0.001

Chapter 6: Discussion

There are still significant differences in the baseline characteristics of TB pericarditis patients between HIV co-infected versus those without HIV co-infection. Firstly, HIV co-infected patients were younger than those without HIV co-infection and this relationship is consistent the work done by both Mayosi et.al. (2006) and Reuter et.al. (2005). About a third of the world's population has latent TB infection which usually does not cause illness but when the immune system starts to fail may develop into a full blown TB infection. On the other hand HIV in the developing world mainly affects young sexually active adults between the ages of 25 to 44years. The probability of developing TB disease in a patient with LTBI increases from 10% in a life time in a HIV negative patient to 5-8% per annum in a HIV positive patient.[3,15] This means that patients are more likely to get TB at a younger age and more likely to present with recurrent TB.[3,15]

Secondly, HIV co-infected patients had a more acute illness at presentation. While there is no literature specifically on acuteness of illness at presentation in TB pericarditis in relationship to HIV status this is well characterised in tuberculosis in general. Tuberculosis has a more acute progression in HIV co-infected patients as opposed to HIV negative patients. There is no reason for this relationship that is well established for tuberculosis in general to be any different in TB pericarditis.[12] The HIV virus targets the CD4 cells, these cells are responsible for coordinating the response of the adaptive immune system. A disruption of the function of the CD4 cells compromises the body's ability to recognize cells that harbor the intracellular mycobacterium bacilli and allows the infection to spread unabated leading to faster spread of disease with a higher risk of disseminated disease.[3]

Both HIV and TB are associated with anemia and leucopenia, it is therefore not surprising that patients with TB pericarditis and HIV co-infection are more likely to have a lower hemoglobin and WCC than those with TB pericarditis alone. The mechanism by which HIV and TB cause anemia remains unclear but some of the proposed theories include direct infection of erythroid progenitor cells, HIV virus thought to produces proteins that suppress erythropoiesis, malnutrition and vitamin deficiencies could be the cause of anemia.[16]

The anemia associated with HIV and TB resemble anemia of chronic illness. Similarly, both HIV and TB are associated with leucopenia and have been shown to cause a reduction in granulocyte progenitor cells like the colony forming unit granulocyte-monocyte (CFU-GM).[17,18]

Globulin can be simply defined as total plasma protein minus albumin. These however are a heterogeneous group of proteins that include antibodies, carrier proteins and enzymes produced by both the liver and cells of the immune system.[3]

An elevated globulin suggests the presence of an underlying chronic inflammatory process and has been shown to be of importance in diagnosing TB as evidenced by the Tygerberg diagnostic score (see appendix 1 eligibility form).[9] HIV co-infected patients had a higher globulin than those without HIV co-infection. HIV infection causes dis-regulation of the immune system and an elevation of acute phase proteins.

There were four times as many patients with pericardial calcification in patients without HIV co-infection as compared to those with HIV co-infection but pericardial calcification was a rare feature and was not of predictive value in differentiating TB pericarditis patients by HIV status in the un-imputed data. However, when multiple imputation was adopted pericardial calcification became more significant. Pericardial calcification suggests pericardial thickening and constriction which has been shown to be more common in patients without HIV co-infection.[19,20]

Study limitations

Firstly, the study only focused on baseline characteristics of patients with TB pericarditis and did not compare these finding to morbidity and mortality. This study deliberately chose to focus on describing the presenting features of TB pericarditis in order to better improve our ability to diagnose TB and understand the impact of HIV on the presentation of TB pericarditis. The effective management of any condition heavily relies on the ability of clinicians to make a prompt and accurate diagnosis especial in a condition like TB pericarditis which is notoriously difficult to diagnose.

Another limitation of the study was the study was conducted over eight countries and 19 different sites. There is concern that the inter-observer variability could have been high, physicians from different sites may have different thresholds when determining the presence of absence of certain variables for example hepatomegaly and cardiomegaly. To overcome this challenge the definition of a positive diagnosis was very specific and at the time of recruitment a patient the eligibility of the patient was cross checked by an independent researcher. One may argue that having several different independent clinicians working in the study adds credibility to the study and allows the study results to be generalized to a broader population.

Conclusion

HIV co-infected TB pericarditis patients have a slightly different clinical picture compared to those without HIV co-infection. HIV co-infected patients are younger, have a lower white cell count and more likely to have been previously treated for TB, these differences are consistent with previous literature. Other differences included HIV co-infected patients also had more acute illness, lower hemoglobin but had a more elevated globulin. AAFB microscopy and culture of pericardial fluid have a high yield in diagnosis of TB pericarditis and a patient's HIV status did not affect the accuracy of these investigations. Lastly cardiomegaly on chest x-ray is a useful screening tool for patients with a suspected pericardial effusion.

Chapter 7: References

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Appendix1: Patient eligibility and screening log

IMPI Trial Facing Page PATIENT ELIGIBILITY SCREENING LOG Page 1 of 1

The screening log should be completed after each patient is screened.

Complete the centre number by adding the 4 digit site number (e.g. 0108) in the boxes provided.

The Site Investigators name should be printed on the line provided..

Report numbers should be completed starting from 001 with the numbers continuing consecutively - e.g. 002, 003, 004, etc.

Write the screen number, screen date, date of birth and participant initials (Pt initials) in the relevant boxes. Note that a four-digit year of birth is required.

If participant is not eligible according to responses to the criteria below, please indicate which particular criteria they failed in by checking the appropriate box.

Research Coordinator (R.C.) should initial the last column.

Form should be faxed to the project office after details of each participant screened is completed. As more participants are screened, their details can be added and the form refaxed.

NON-ELIGIBILITY CRITERIA:

A.

1. Participant <18 years old.
2. Use of corticosteroids within the previous month.
3. Hypersensitivity or allergy to *Mycobacterium w* vaccine.
4. Presence of an alternative cause of pericardial disease e.g malignancy or penetrating chest trauma in previous 12 months.

B.

1. Participant did not have **confirmed** pericardial effusion on echocardiogram
2. Participant did not have evidence of definite/probable TB pericarditis:
   a. No Tubercle bacilli found in stained smear or culture of pericardial fluid or
   b. No Tubercle bacilli found in caseating granulomata found on histological examination of pericardium or
   c. No Tubercle bacilli found in stain smear or culture of sputum, gastric or lymph node aspirate or other site or
   d. No Lymphocytic pericardial exudates with elevated ADA activity or Tygerberg Index Score ≤6*
3. Participant had been on TB treatment for ≥1 week.
4. Participant was not willing to participate for duration of the trial & did not give written consent.

C. Female Participants:

1.Pregnancy test positive

*Tygerberg Index Score	Score
A history of weight loss	1
A history of night sweats	1
Documented temperature of >37.8'C	1
White cell count <10x10^9	3
Serum globulin >40g (total serum protein-serum albumin)	3

Appendix 2: Page 1 of data collection form

IMPI Trial **Baseline Data Form** **Page 1 of 3** **CRF 2**

DataFax # 128 Plate # 003 Visit # 001

PARTICIPANT ID# ☐☐☐☐ (Center number) ☐☐☐☐ (Medication Kit number) Participant Initials ☐☐☐ (F M L)

1. Participant information

a. Sex ☐ Male ☐ Female

b. Date of birth ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)

c. Weight ☐☐☐.☐ kg

2. Past Medical History

a. TB ☐ No ☐ Yes

b. HIV ☐ No ☐ Yes → Any opportunistic infections? Specify below:

Herpes Zoster	☐ No	☐ Yes	Oesophageal candidiasis	☐ No	☐ Yes	Other (specify):		
Genital Herpes	☐ No	☐ Yes	Cryptococcal meningitis	☐ No	☐ Yes			
Oral thrush	☐ No	☐ Yes	Disseminated Tuberculosis	☐ No	☐ Yes			

c. Malignancies ☐ No ☐ Yes → Specify: → Kaposi's Sarcoma ☐ No ☐ Yes; Lymphoma ☐ No ☐ Yes; Other: _____ (specify)

d. Heart Failure ☐ No ☐ Yes

e. Any other known medical conditions? ☐ No ☐ Yes → Please list _____

3. Current Medication _____

a. On what date was TB treatment commenced ☐☐☐☐☐☐ (year month day)

Please indicate drugs below:

☐ Isoniazid (INH) ☐ Pyrazinamide ☐ Streptomycin ☐ Other: _____ (specify)

☐ Rifampicin ☐ Ethambutol ☐ Thiacetazone

b. Is participant HIV positive? ☐ No → Go to question 3c ☐ Yes → Is participant on ARV's? ☐ No ☐ Yes → For longer than 6 months? ☐ No ☐ Yes

Please indicate drugs below:

☐ Stavudine (d4t) ☐ Nevirapine ☐ Zidovudine (AZT) ☐ Kaletra/Aluvia

☐ Lamivudine (3tc) ☐ Efavirenz ☐ Didanosine (DDI) ☐ Other: _____ (specify)

c. Is participant on treatment for heart failure? ☐ No ☐ Yes

d. Is participant on any other medication? ☐ No ☐ Yes → Specify _____

4. Baseline Clinical Assessment

a. Duration of symptoms related to heart failure, pericardial disease or TB before admission: ☐☐☐ days

b. Body temp ☐☐.☐ °C

c. Pulse rate ☐☐☐ bpm

d. Blood pressure ☐☐☐ / ☐☐☐ mmHg

e. NYHA class ☐ I ☐ II ☐ III ☐ IV

f. Palpable paradoxus ☐ No ☐ Yes

g. Pulsus paradoxus ☐☐ mmHg

Investigation of the Management of Tuberculous Pericarditis Version 4.8 dated 2010APR15

Appendix 3: Page 2 of data collection form

IMPI Trial **Baseline Data Form** **Page 2 of 3** **CRF 2**

DataFax # 128 Plate # 004 Visit # 001

PARTICIPANT ID# ☐☐☐☐ (Center number) ☐☐☐☐ (Medication Kit number) Participant Initials ☐☐☐ (F M L)

4. Baseline Clinical Assessment (continued)

h. Jugular vein distension ☐ No ☐ Yes
i. Peripheral oedema ☐ No ☐ Yes
j. Hepatomegaly ☐ No ☐ Yes
k. Ascites ☐ No ☐ Yes
l. Pericardial knock ☐ No ☐ Yes
m. Chest: Pleural effusions ☐ No ☐ Yes
n. Chest: Other Diagnosis/findings ☐ No ☐ Yes → _____
o. Neuro: Other diagnosis/findings ☐ No ☐ Yes → _____
p. Abdomen: Other diagnosis/findings ☐ No ☐ Yes → _____
q. Skin: Other Diagnosis/findings ☐ No ☐ Yes → _____
r. Genitourinary: Other diagnosis/findings ☐ No ☐ Yes → _____

5. Was a Baseline echocardiogram performed?

a. ☐ No ☐ Yes → ☐☐ (year) ☐☐ (month) ☐☐ (day) ECHO Shuttle Report # ☐☐☐

6. Was a Baseline ECG performed?

a. ☐ No ☐ Yes → ☐☐ (year) ☐☐ (month) ☐☐ (day) ECG Shuttle Report # ☐☐☐

7. Was Baseline chest x-ray done? ☐ No ☐ Yes → ☐☐ (year) ☐☐ (month) ☐☐ (day)

a. Cardiomegaly ☐ No ☐ Yes
b. Pulmonary infiltrates ☐ No ☐ Yes
c. Pleural effusion ☐ No ☐ Yes
d. Pericardial calcification ☐ No ☐ Yes

8. Which Baseline laboratory investigations were done? **Lab shuttle report numbers**

a. HIV Serology ☐ No ☐ Yes → ☐ +ve ☐ -ve ☐☐☐
i. If HIV positive, results of CD4 count → ☐☐☐☐ /ul ☐☐☐
results of HIV RNA → ☐☐☐☐☐☐☐ copies/ml ☐☐☐

b. Haemoglobin ☐ No ☐ Yes → ☐☐.☐ g/dl ☐☐☐
c. Total WBC ☐ No ☐ Yes → ☐☐.☐ /mm^3 ☐☐☐
d. Creatinine ☐ No ☐ Yes → ☐☐☐☐ umol/l ☐☐☐
e. Globulin ☐ No ☐ Yes → ☐☐☐ g/l ☐☐☐
(i.e., total protein minus albumin)

Please fax all Randomization forms (CRFs 1-2) to the Project Coordinating Office within 48 hours of randomization. All source documents (i.e., echo report, ECG, and laboratory reports) should be stored with original CRFs.

Investigation of the Management of Tuberculous Pericarditis Version 4.8 dated 2010APR15

Appendix 4: Page 3 of data collection form

IMPI Trial **Baseline Data Form** **Page 3 of 3** **CRF 2**

DataFax # 128 Plate # 005 Visit # 001

PARTICIPANT ID# [ ][ ][ ][ ] [ ][ ][ ][ ] Participant Initials [ ][ ][ ]
Center number Medication Kit number F M L

9. Was pericardiocentesis performed?

☐ No ☐ Yes → Which of the following analyses were requested? Lab shuttle form #

a. Total protein ☐ No ☐ Yes → [ ][ ][ ] g/l [ ][ ][ ]

b. Lymphocyte count ☐ No ☐ Yes → Fluid lymphocyte predominant? ☐ No ☐ Yes [ ][ ][ ]

c. Adenosine deaminase (ADA) level ☐ No ☐ Yes → [ ][ ][ ] U/l [ ][ ][ ]

d. Microscopy for AFBs ☐ No ☐ Yes → ☐ +(pos) ☐ -(neg) [ ][ ][ ]

e. Culture for AFBs ☐ No ☐ Yes → ☐ +(pos) ☐ -(neg) [ ][ ][ ]

10. Were any of the following non-pericardial samples sent for TB investigations? Lab shuttle report #

a. Sputum ☐ No ☐ Yes → ☐ +(pos) ☐ -(neg) [ ][ ][ ]

b. Lymph node aspirate ☐ No ☐ Yes → ☐ +(pos) ☐ -(neg) [ ][ ][ ]

c. Pleural Fluid ☐ No ☐ Yes → ☐ +(pos) ☐ -(neg) [ ][ ][ ]

d. Other: ☐ No ☐ Yes → ☐ +(pos) ☐ -(neg) [ ][ ][ ]

_____
(specify)

11. Medication dispensed: Date [ ][ ] [ ][ ] [ ][ ]
year month day

For week 1 dispensed ☐ Yes ☐ No → Reason? _____

For week 2 dispensed ☐ Yes ☐ No → Reason? _____

Mycobacterium w administered ☐ Yes ☐ No → Reason? _____

↓ Week 0 Vial No. [ ][ ]

12. Schedule date of next (2 weeks ± 4 days) [ ][ ] [ ][ ] [ ][ ]
year month day

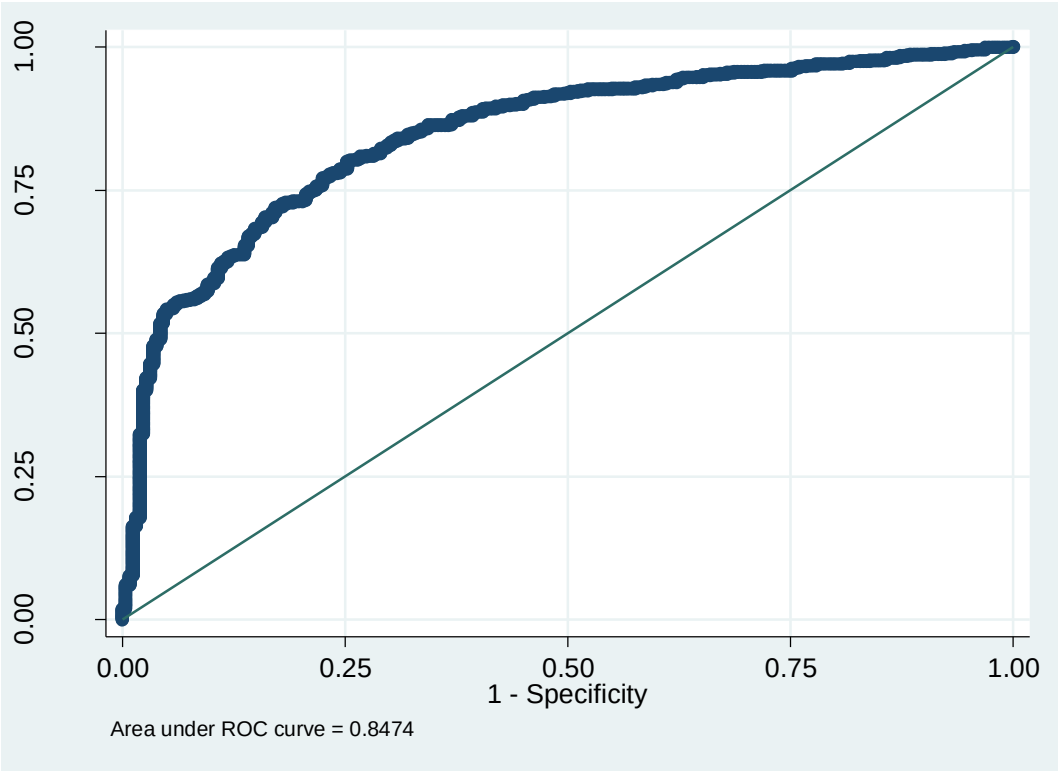
Surname of clinician completing form: _____ Signature: _____

Date completed: [ ][ ] [ ][ ] [ ][ ]
year month day

Please fax all Randomization forms (CRFs 1-2) to the Project Coordinating Office within 48 hours of randomization. All source documents (i.e., echo report, ECG, and laboratory reports) should be stored with original CRFs.

Appendix 5: Logistic regression

```
. logistic fhiv age pasttb durasymp hb wbc globulin

Logistic regression                             Number of obs   =       1121
                                                LR chi2(6)      =     312.90
                                                Prob > chi2     =     0.0000
Log likelihood = -453.07348                     Pseudo R2       =     0.2567

------------------------------------------------------------------------------
        fhiv | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   .9718919   .0063069    -4.39   0.000     .9596088    .9843322
      pasttb |   2.152936   .5993823     2.75   0.006     1.247541    3.715417
   durasymp |   .9935303   .0023182    -2.78   0.005      .988997    .9980844
          hb |   .7197769   .0283918    -8.34   0.000     .6662267    .7776314
         wbc |   .9049547   .0256743    -3.52   0.000     .8560075    .9567008
    globulin |    1.07018   .0083713     8.67   0.000     1.053898    1.086714
------------------------------------------------------------------------------

. lroc

Logistic model for fhiv

number of observations =      1121
area under ROC curve   =    0.8474
```



Appendix 6: Logistic regression diagnostic test (confusion matrix)

```
. estat class

Logistic model for fhiv

                 ———— True ————
Classified |         D          ~D |      Total
———————————+———————————————————————+———————————
         + |       802         155 |        957
         - |        57         107 |        164
———————————+———————————————————————+———————————
     Total |       859         262 |       1121

Classified + if predicted Pr(D) >= .5
True D defined as fhiv != 0
——————————————————————————————————————————————————
Sensitivity                     Pr( +| D)   93.36%
Specificity                     Pr( -|~D)   40.84%
Positive predictive value       Pr( D| +)   83.80%
Negative predictive value       Pr(~D| -)   65.24%
——————————————————————————————————————————————————
False + rate for true ~D        Pr( +|~D)   59.16%
False - rate for true D         Pr( -| D)    6.64%
False + rate for classified +   Pr(~D| +)   16.20%
False - rate for classified -   Pr( D| -)   34.76%
——————————————————————————————————————————————————
Correctly classified                        81.09%
——————————————————————————————————————————————————
```