ASSOCIATION OF SEVERE ANAEMIA WITH TUBERCULOSIS MYCOBACTERAEMIA IN HIV POSITIVE PATIENTS ADMITTED WITH SEVERE SEPSIS TO THE UNIVERSITY TEACHING HOSPITAL, LUSAKA, ZAMBIA.

By

Levy Muchemwa

November 2015

DEDICATION

I would like to dedicate this work to my children Mercy, Kukenga and Able and my nephew Nathan for remaining strong during a very difficult period in 2013 when the family passed through one sickness after another. The strength they exhibited during that time gave me a reason to go on.

DECLARATION

I Levy Muchemwa do hereby declare that this dissertation here in presented for the degree of Master of Medicine in Internal Medicine has not been previously submitted wholly or in part for any other degree at this or any other university nor is it being submitted for any other degree.

SIGNED _____

DR. LEVY MUCHEMWA

APPROVED _____

DR. S. LAKHI

STATEMENT

I hereby state that this dissertation is entirely the result of my own personal effort. The various sources to which i am indebted have been clearly indicated in the acknowledgement and reference list.

SIGN _____

DR. LEVY MUCHEMWA

APPROVAL

The dissertation for Dr. Levy Muchemwa is approved as fulfilling part of the requirement for the award of Master of Medicine in Internal Medicine.

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ABSTRACT

INTRODUCTION: *Tuberculosis is recognised as one the leading causes of severe sepsis among HIV positive patients. Most patients with tuberculosis mycobacteraemia have advanced HIV disease with CD4 counts less than 100cells/ul and many do not present with the classical signs of tuberculosis. Unusual presentation of tuberculosis mycobacteraemia makes the diagnosis of tuberculosis in these patients a challenge.*

METHODOLOGY: *This was a cross-sectional study which was done by analyzing data from 199 HIV positive patients enrolled in two randomized control studies; the Simplified Severe Sepsis Protocol (SSSP) and SSSP-2 and data from 2 patients enrolled independently. Participants were adults who met the inclusion criteria for severe sepsis. Baseline data was collected on demographic and laboratory characteristics including blood cultures for tuberculosis and aerobic organisms.*

RESULTS: *The prevalence of tuberculosis mycobacteraemia in the study population was 34.8%.The study population was generally underweight but the population with tuberculosis mycobacteraemia had a significantly lower mid-upper arm circumference (MUAC) than the population without (20.2[SD: 2.4] vs 21.4 [SD: 3.8] cm; p=0.01).There was a higher proportion of patients with tuberculosis mycobacteraemia in patients who were not on anti-retroviral therapy (ART) compared to those on ART (p=0.01). The study population was generally anaemic with mean haemoglobin of 8.0(SD: 3.0) g/dl but the tuberculosis mycobacteraemia group had significantly lower haemoglobin. The population with tuberculosis mycobacteraemia had a significantly lower median CD4 count compared to the population without (44cells/dl vs 56 cells/dl; p=0.01). Aerobes were isolated in 20.4% (41) of the study population. The commonest isolate was Staphylococcus aureus 5% (10). Factors that were independently associated with tuberculosis mycobacteraemia include low MUAC, unknown ART history, low albumin and low sodium.*

CONCLUSION: *Tuberculosis mycobacteraemia is very common in HIV infected patients with severe sepsis. Low CD4 count, albumin, sodium levels and low MUAC were independently associated with tuberculosis mycobacteraemia in patients with severe sepsis. Severe anaemia was not independently associated with tuberculosis mycobacteraemia.*

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ABBREVIATIONS

ACCP	-	American College of Chest Physicians
AIDS	-	Acquired Immunodeficiency Syndrome
AITRP	-	AIDS International Training Research Program
ALT	-	Alanine amino Transferase
AMEU	-	Adult Emergency Medical Unit
AST	-	Aspartate amino Transferase
ART	-	Anti-Retroviral Therapy
BCG	-	Bacillus-Calmette Guerin
^{o}C	-	Degrees Celsius
CD4	-	Cluster of Differentiation 4
CXR	-	Chest X-Ray
FBC	-	Full Blood Count
HAART	-	Highly Active Anti-Retroviral Therapy
HIV	-	Human Immunodeficiency Virus
IFN	-	Interferon
IL-1	-	Interleukin-1
IL-2	-	Interleukin-2
IL-4	-	Interleukin-4
IL-6	-	Interleukin-6
IL-8	-	Interleukin-8
IL-10	-	Interleukin-10
LAM	-	Lipoarabinomannan

ABBREVIATIONS contd.

MUAC	-	Mid Upper Arm Circumference
MPT-64	-	Mycobacterium Tuberculosis Protein 64
mRNA	-	Messenger Ribonucleic Acid
OR	-	Odds Ratio
p- Value	-	Probability value
SCCM	-	Society of Critical Care Medicine
SIRs	-	Systemic Inflammatory Response Syndrome
SSSP	-	Simplified Severe Sepsis Protocol
SSSP-2	-	Simplified Severe Sepsis Protocol-2
TB	-	Tuberculosis
TGF	-	Transforming Growth Factor
TNF	-	Tumor Necrosis Factor
UNZABREC	-	University of Zambia Biomedical Research Ethics Committee
USA	-	United States of America
UTH	-	University Teaching Hospital
WHO	-	World Health Organization

TABLE OF CONTENTS **PAGE NUMBER**

1. INTRODUCTION

Severe sepsis is one of the leading causes of death among hospitalized HIV positive patients in sub-Saharan Africa (Bane et al. 2003). Disseminated tuberculosis is recognised as one the leading causes of severe sepsis among HIV infected patients and significantly affects short term and long term survival among this population of patients (Arthur G et al. 2001). In industrialized countries mycobacteraemia is caused by organisms of the Avium complex and in developing countries mycobacteraemia is principally caused by *Mycobacterium tuberculosis* (von Reyn 1999).

Tuberculosis mycobacteraemia may go unrecognised among febrile hospital patients in less developed countries where both *Mycobacterium tuberculosis* and HIV are prevalent (Archibald et al. 1999).Many patients with tuberculosis have advanced HIV disease with CD4 counts less than 100 cells/ul and most do not present with the classical signs. These patients are also susceptible to other pulmonary infections that can mimic tuberculosis. The typical clinical symptoms of tuberculosis have been defined as weight loss, cough or fever of longer than two weeks duration or haemoptysis. Subtle or unusual presentation of tuberculosis has been responsible for the delays in the diagnosis of tuberculosis in most patients with HIV (Greenway et al. 2002). Standard mycobacterium cultures may take four weeks to detect mycobacterium in blood and automated cultures may take 2-3 weeks (Rhoner 1997). This makes tuberculosis a diagnostic challenge in these patients, especially in resource limited countries like Zambia where capacity to do cultures is limited to a few centres.

Studies in the region have also documented haematological and biochemical changes in patients with tuberculosis (Charles et al. 2001). This study analysed data from 201 HIV positive patients admitted with severe sepsis at the University Teaching Hospital in Lusaka, Zambia to determine if severe anaemia is independently associated with tuberculosis mycobacteraemia.

2. LITERATURE REVIEW

SEPSIS

Sepsis is defined as an infection with concurrent systemic response.

The systemic inflammatory response (SIRS) to a variety of response is manifested by two or more of any of the following:

- Temperature >38 or <36 degrees centigrade (°C)
- Heart rate > 90 beats/minute
- Respiratory rate > 20 breaths/minute
- White blood cells >12000 cells /mm^3 or < 4000cells/mm^3 or 10% immature band form.

The current definition of sepsis was arrived at in 1992 by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) consensus conference (Levy et al. 2003).

Severe sepsis occurs when sepsis is associated with tissue hypo-perfusion manifested as hypotension, lactic acidosis or organ dysfunction such as altered mental state, oliguria (urine output less than 0.5ml/kg/hour) or creatinine more than 120umol/l or hyperbilirubinaemia. Severe sepsis with hypotension along with poor perfusion despite adequate fluid resuscitation is called septic shock.

(Bone et al.1992).

Pathophysiology of Sepsis

The pathophysiology of sepsis is complex, it is often described as an auto- destructive process that permits the extension of a normal pathophysiological response to infection to involve normal tissues (Hotchkiss R S et al. 2003).The normal host response to infection serves to localize and control bacterial invasion and to initiate bacterial repair of injured tissue. This inflammatory response is normally accompanied by activation of circulating and fixed phagocytic cells and by generation of pro-inflammatory and anti-inflammatory

mediators. Activated polymorphs secrete mediators at the site of infection which causes local inflammation. Macrophages secrete tumor necrosis factor (TNF) and interleukins (IL) into the cell environment which increase the release of other inflammatory cytokines including IL-1, IL-2, IL-6, IL-8, IL-10, IFN (Interferon) and eicosanoids. This leads to continued activation of polymorphs, macrophages lymphocytes. The net effect is clearing of bacteria which are followed by tissue repair (Oberholzer C et al. 2000).

A balance normally exists between the pro-inflammatory and anti-inflammatory mediators and when the equilibrium is lost, these mediators exert systemic effects.

The significant consequent of a systemic inflammatory reaction include endothelial damage, microvascular dysfunction and impaired tissue oxygenation and organ injury. The consequence of excessive anti-inflammatory response includes anergy and immunosuppression. Pro and anti-inflammatory response may interfere with each other creating a state of immunologic dissonances (Schulte W et al. 2013).

Severe sepsis and HIV

Severe sepsis has been identified as a leading cause of non-cardiac deaths among hospitalized critically ill patients in the developed world (Angus et al. 2001). Approximately 750 000 people in the United States of America suffer from sepsis with an annual incidence of 9% and with an overall mortality of 26.6%. Mortality is high especially among those patients who develop shock because such patients frequently develop multiple organ dysfunctions. In Germany the incidence of sepsis is 76-110 per 100,000 inhabitants and is responsible for 600 deaths per year (Christoph et al. 2007).

HIV infected patients are at a greater risk of developing sepsis due to their immunosuppression. Several studies from sub-Saharan Africa have demonstrated a high prevalence of bacteraemia among hospitalized HIV infected patients with sepsis. In Lusaka, Chimese et.al 2012, documented a prevalence of 21% in a cohort of 161 patients which was

predominantly (68%) HIV positive while in Uganda, Jacob et al. 2009, noted that bacteraemia was prevalent in 18.9% of the patients with severe sepsis. A systematic review of studies looking at community acquired blood stream infections in HIV infected show a regional bacteraemia prevalence of 16-21% .Patients with untreated bloodstream infections rapidly become very ill, then severe sepsis sets in and they die. In hospital and post discharge death rates among these patients is as high as 7-47% (Huson A M et al. 2013).

A spectrum of pathogens causes bacteraemia in hospitalized HIV positive patients. A prospective study of causes of febrile illness among in-hospital patients in Tanzania evaluated 517 patients admitted with febrile illness; of whom 282 were HIV infected (Archibald et al. 1998).The study noted that 28% of the study participants had bacteraemia. Bacteraemia was more common in HIV positive infected patients where 81% had bacteraemia. Among those with positive blood cultures the commonly isolated pathogens were: *Mycobacterium tuberculosis* (39%), Non-salmonella typhi (19*%), Streptococcus pneumonia*e (11%), S*taphylococcus aureus* (8.3%) and malaria (9%).The study also noted polymicrobial infection (where more than one pathogen was isolated) in 10 of the study patients of whom 8 were HIV infected.

Severe sepsis and Tuberculosis

Tuberculosis is the leading cause of death among HIV positive patients in the world (WHO 2004). Sepsis due to tuberculosis occurs more commonly in the late stages of HIV disease. Many HIV patients with tuberculosis mycobacteremia have active disease which may cause sepsis (McDonald et al. 1999). Simple diagnostic tests such as chest x-ray and sputum smear are important in recognizing active tuberculosis (Mtei L et al. 2005)

In the USA, bacteraemia due to tuberculosis was uncommon until its recognition among AIDS patients (Barnes and Arevelo 1987). A 2 year prospective study in Brazil evaluated the main risk factors for in- hospital mortality and impact of severe sepsis on shorter and long term survival among HIV/AIDS patients. The study observed that among the 88 critically ill patients admitted to intensive care unit, severe sepsis was noted in 50% of the patients and in-hospital mortality was 49%. *Mycobacterium tuberculosis* was isolated in 14% of the patients;

other organisms isolated included *Pseudomonas aeruginosa* (23%), *Staphylococcus aureus* (20%) and *Klebsiella pneumoniae* in 14% of the patients (Japiassu et al. 2010). In Cambodia, Thailand and Vietnam, 2009 HIV patients were evaluated for the risk factors and prevalence of blood stream infections. The study observed a 2.9% prevalence of blood stream infections and noted that *Mycobacterium tuberculosis* accounted for 54%, fungi 22% and bacteria only 16%.The risk factors noted for tuberculosis were, low CD4 count, fever, abnormal chest X-ray and signs and symptoms of abdominal illness (Varma et al. 2010).

Several studies in Africa looking at blood stream infections among HIV positive patients have documented a high prevalence of tuberculosis mycobacteraemia.

A study by Jacob S T et al. 2009 in Uganda evaluated the management and outcomes in a cohort of 382 patients admitted with severe sepsis. In this study, where 84% of the participants were infected with HIV, gram positive or gram negative bacteraemia was observed in 19% of the study population. The study further noted that mycobacteraemia was present in 22% of the 249 the patients (with available cultures) of which 10% was due to tuberculosis mycobacteraemia and the remainder was due to non-tuberculous mycobacteraemia. Organisms isolated from aerobic cultures were non-typhoid salmonella in 20%, S*taphylococcus aureus* in 12% and *Streptococcus pneumoniae* in 6% of the study patients. A follow up study (Jacob S T et al. 2013) involving 368 HIV infected patients with severe sepsis observed that 23% of the patients had tuberculosis mycobacteraemia. A study in Malawi on causes of febrile illness in hospitalized patients observed that mycobacterium was the commonest cause of blood stream infection (17% of the 344 study patients). Strong predictors of mycobacteraemia were noted to be the diagnosis of AIDS, anaemia, chronic cough and chronic fever (Lewis et al. 2002).

A descriptive cross-sectional study was done in Lusaka, to compare prevalence of mycobacteremia due to *Mycobacterium tuberculosis*, *Mycobacterium bovis* and Bacillus Calmette–Guerin (BCG) in hospitalized HIV infected patients of whom 344 were adults and

387 were children. The study observed that 11% of the adults and 2% of the children had mycobactereamia with one of these organisms. *Mycobacterium tuberculosis* was the commonest isolated organism in both groups of patients while mycobacteremia due to *Mycobacterium bovis* and BCG were rare in the study groups (Richard et al. 2001).

Haematological and Biochemical changes in Tuberculosis

Haematological and biochemical changes are common in tuberculosis and may be valuable aids to diagnosis. Tuberculosis is a chronic inflammatory disease; it causes elevation of inflammatory cytokines such as IL-1, TNF and TGF. Elevated levels of IL-1 and other cytokines increase synthesis of hepcidin from the liver which impairs mobilization of iron from the reticuloendothelial cells. These cytokines have also been observed to inhibit colony forming units which later develop into erythroblasts and also impair erythropoiesis by impairing erythropoietin mRNA transcription. By this way tuberculosis causes anaemia of chronic inflammation (Weiss et al. 2005).

A prospective study in South Africa of haematological and biochemical abnormalities in 245 patients with tuberculosis noted anaemia in 60% of the study patients. Neutrophilia and leucocytosis occurred in 40%, lymphopaenia in 17% and monocytopaenia in 50% of the patients. Hyponatraemia was observed in 40% and hypoalbuminaemia in 72% of the patients. One third of the patients had elevated alkaline phosphatase and lactate dehydrogenase (Charles et al. 1989). Pancytopenia is a common finding in patients with disseminated tuberculosis (Singh et al. 2001). A study in Uganda evaluated 395 patients (50% of whom had HIV infection) admitted to hospital for prevalence of and morphological types of anaemia.

The prevalence of anaemia in the study population was 64.6%. Anaemia in this study was defined as haemoglobin <11g/dl in female and <12gdl in male adult patients .The study noted that 31.8 % had normocytic normochromic anaemia and the remainder had hypochromic microcytic anaemia. The study observed that 22.7% of the patients with

anaemia had a clinical diagnosis of tuberculosis on admission (Mukaya et al. 2009). However, there was no microbiological confirmation of tuberculosis in the study patients.

A study in Malawi looked at treatable factors associated with severe anaemia in a cohort of 105 patients admitted to a hospital. The proportion of HIV infected patients in the study population was 79%. Definite or probable tuberculosis was diagnosed in patients with severe anaemia in 37% of the patients. Other factors were parasitic infections 32% and Malaria in 14% of the patients particularly HIV negative patients. Tuberculosis was observed in 43% of the HIV infected and in 14% of the HIV negative patients (Lewis et al. 2005).

Tuberculosis and Wasting

Individuals at all stages of HIV disease are at risk of nutritional deficiencies and nutritional status is strong predictor of disease progression (Swaminathan et al. 2008). Tuberculosis which is the most common opportunistic infection in HIV patients is also associated with weight loss and hypoalbuminaemia. Co-infection of tuberculosis with HIV has synergistic effect on wasting. A study among patients with severe sepsis in Uganda observed wasting and albumin levels are associated with *Tuberculosis Mycobactereamia* (Jacob S T et al. 2013). Pro-inflammatory cytokines have been recognised as causative agents that eventually result in tuberculosis associated wasting. Leptin has emerged as a key mediator of metabolism and it reports the status of body energy stores to the feeding centre. It has been suggested that leptin mediates anorexia in chronic inflammatory states. In tuberculosis, leptin levels are increased and there is also an associated increase in concentration of TNF-alpha which increases energy expenditure (Schwenk et al. 2003).

3. STATEMENT OF THE PROBLEM

Mycobacterium tuberculosis is a very common problem among HIV infected patients. In advanced HIV disease *Mycobacterium tuberculosis* may frequently present as sepsis. Mortality in patients with tuberculosis mycobacteraemia is very high. A study by Jacob et al.

2013 observed that 30 day mortality in HIV infected patients with mycobactereamia and severe sepsis was as high as 53%.

Unusual presentation of tuberculosis in advanced HIV disease may result in delays in the diagnosis and treatment of the disease (Greenway et al 2002). Lack of early recognition of tuberculosis compounded by associated factors leads to clinical deterioration and poor outcomes.

4. STUDY JUSTIFICATION

In the sub-Saharan region tuberculosis is a commonly isolated pathogen among HIV infected patients admitted with severe sepsis. Diagnosis of tuberculosis in these patients is often delayed for several reasons. Patients may be too sick to produce sputum and clinicians would therefore wait for empirical antibiotic response. Disseminated tuberculosis is often sputum positive. Standard cultures for tuberculosis take 2-4 weeks and in the Zambian setting the capacity to do these cultures is only limited to a few centres. The delays in time to diagnosis also delays initiation of treatment of these patients for tuberculosis.

A study to determine factors (especially severe anaemia) associated with tuberculosis mycobacteraemia in HIV positive patients presenting with severe sepsis would help clinicians in early identification of patients with tuberculosis and subsequently lead to early treatment initiation.

5. OBJECTIVES

General Objective

To establish the prevalence and factors that are associated with tuberculosis mycobacteraemia among HIV infected patients admitted with severe sepsis.

Specific Objectives

1. To estimate the prevalence of tuberculosis mycobacteraemia among HIV infected patients admitted with severe sepsis.
2. To ascertain the prevalence of other blood stream infections in HIV positive patients admitted with severe sepsis.
3. To determine whether severe anaemia is independently associated with tuberculosis mycobacteraemia among HIV positive patients admitted with severe sepsis.
4. To identify other factors that are significantly associated with tuberculosis mycobacteraemia in HIV positive patients admitted with severe sepsis.

6. NULL HYPOTHESIS

Severe anaemia (haemoglobin <7g/dl) is not independently associated with tuberculosis mycobacteraemia among HIV positive patients with severe sepsis.

7. METHODOLOGY

STUDY DESIGN

This was an observational cross-sectional study that combined secondary data from two studies: the Simplified Severe Sepsis Protocol (SSSP) and the Simplified Severe Sepsis Protocol-2 (SSSP-2) studies, together with data that was obtained independently using the same inclusion criteria as the SSSP study. The SSSP and SSSP-2 studies assessed the performance and cost of a simple treatment protocol, developed by the investigators, for severe sepsis. The two studies had similar inclusion criteria but the only difference between the two was that the SSSP-2 included only septic patients who were hypotensive and excluded patients who had respiratory failure (Respiratory rate >40 breaths/minute).

The studies were randomized controlled trials which were done at the Adult Emergency Medical unit of the University Teaching Hospital, the largest health institution that provides tertiary care to the country. The two studies had approval from the University of Zambia Biomedics Research Ethics Committee (UNZABREC) REF. Nos.: 009-08-11 for SSSP and 008-06-12 for SSSP-2.

This study had an independent approval from UNZABREC, REF. No: 001-02-13.

PATIENT RECRUITMENT

Patients above 18 years of age were screened and enrolled in the study from the Adult Medical Emergency Unit (AMEU) every day, during week days if they met the inclusion criteria.

INCLUSION CRITERIA

i. Above age of 18 years
ii. HIV positive
iii. Suspected or confirmed infection.
iv. Two or more of the following: axillary temperature> 38 degrees or <36 degrees; heart rate >90b/min, respiratory rate >20/min, Leukocytosis >12000 leukocytes/mm.
v. Evidence of one or more signs of end-organ dysfunction such as hypotension defined as systolic blood pressure of ≤90mm Hg or a mean arterial pressure (MAP) of <65mmHg,altered mental state, oliguria (urine <0.5ml/kg/l), severe respiratory distress (Respiratory rate>40 /min), creatinine more than 120umol/l, hyperbilirubinaemia (total bilirubin >17umol/l) or thrombocytopenia (platelets <100,000u/l).
iv. Consent given by the patient or by the next of kin if patient did not have capacity to give consent.

Inclusion criteria for this were similar to the SSSP and SSSP-2 studies but we only followed up the HIV positive patients in this study.

EXCLUSION CRITERIA

The exclusion criteria for this study were similar to the SSSP and SSSP-2 studies which were as follows:

i. Patients with gastrointestinal bleeding
ii. Patients requiring immediate surgery
iii. Suspected to have heart failure patients
iv. Renal failure patients and
v. Patients who were unable to give consent.

This study additionally excluded the following patients:

vi. Patients on treatment for tuberculosis at the time of admission.

vii. Patient with history of acute blood loss, not necessarily from gastrointestinal bleeding.

viii. Patients with a history of blood transfusion in last the 3 months.

ix. Patients with stroke and those with neuromuscular disorders

x. Patients with intentional weight loss

SAMPLE SIZE

A study in Malawi by Lewis et al. 2005 looking at treatable factors associated with severe anaemia noted that 43% of HIV positive patients had *Mycobacterium tuberculosis*. The Ugandan severe sepsis study (Jacob et al. 2009) observed that 22% of patients with severe sepsis had tuberculosis mycobacteraemia. Assuming that these were the proportions of the disease in the exposed and in the non-exposed respectively, we calculated sample size using OpenEpi software.

A minimum sample size of 205 patients would have a power of 80% at chi-square significance of 5% to determine if there was any significant association between severe anaemia and tuberculosis mycobacteraemia among HIV patients admitted with severe sepsis. The final figure also allowed for a 10 % attrition rate and for limited data or missing laboratory data.

VARIABLES MEASURED

Dependent Variable

The dependent variable for this study was the demonstration of tuberculosis mycobacteraemia by a positive blood culture in HIV positive patients with severe sepsis with a confirmatory MPT4 antigen test for *Mycobacterium tuberculosis.*

Independent Variables

Numerous independent variables were measured which included demographic characteristics such as age and sex of the study participants. The other variables measured included: FBC, CD4 count, CXR report, and sputum microscopy result, fever and cough of any duration, whether the patient is on HAART or not and if on HAART, the duration of treatment. Biochemical variables included alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, urea, creatinine, sodium and potassium.

MICROBIOLOGY

Approximately 1- 5ml of blood was aseptically collected and inoculated in BACTEC Myco/F lytic culture vials for mycobacteria culture within one hour of admission. Confirmatory MPT-64 antigen test was done on positive cultures to differentiate *Mycobacterium tuberculosis* from non-tuberculous mycobacterium. For pathogens other than tuberculosis 8-10ml of blood was aseptically inoculated into a BACTEC blood culture bottle. Bacteraemia was defined as isolation of an organism from the blood culture bottle.

STUDY DEFINITIONS

Severe Anaemia

In this study severe anaemia was considered to be haemoglobin < 7g/dl, moderate anaemia as haemoglobin between 7-10g/dl and anaemia as haemoglobin between 10g/dl to normal limit for age and sex (WHO, UNICEF 1998).

Wasting

In an analysis and extrapolation of data from nine different surveys in Asia, Africa and the pacific, a series of mid upper arm circumference (MUAC) cut-off points have been identified to allow the screening of adults under extreme conditions. Wasting is MUAC < 20.0cm and 19.0 cm for men and women respectively and corresponds to a Body Mass Index (BMI) of <13.0 Extreme wasting is MUAC <17.0cm for men and <16.0cm for women and corresponds

to a BMI of about 10 (Ferro-Luzzi et al.1996). For this cross-sectional study we used MUAC <20.0cm and <19.0 cm for men and women respectively to define wasting.

8. DATA ANALYSIS

Data for 201 participants enrolled in the study was transcribed to a Microsoft excel (2010) spread sheet and imported into SPSS version 16.0 for analysis.

Continuous variables were summarized as means and standard deviations for normally distributed and medians and interquartile ranges for non-parametric data. Categorical variables were expressed as proportions and summary of Odds Ratios (OR). The Chi-square test was used to examine the association between the independents variables and the dependent variable. The Student t-test was used to examine the association between normally distributed independent variables and the dependent variable, while the Mann-Whitney U test was used for non- parametric data. An association was considered to be significant if the p value was less than 0.05 (one tailed).

Bivariate logistic regression was used to determine predictors of tuberculosis mycobacteraemia using all the independent variables and tuberculosis mycobacteraemia outcome result as the dependent variable. A multivariate logistic regression was used to determine whether the following selected variables were independently associated with the dependent variable: haemoglobin, MUAC, CD4 count, fever of any duration, cough of any duration and wasting.

Biochemical variables included the following; serum sodium, albumin, creatinine and ALT levels. A minimum of 10 events per independent variable were considered as the maximum number of independent variables to be included in the logistic regression model.

9. RESULTS

9.1 PATIENT ENROLMENT

a. Patient Enrolment

Three hundred eighteen patients were enrolled in the SSSP and SSSP 2 studies between the period of February 2012 and September 2013.Two patients were enrolled independent of these studies. Out of the 320 participants who were assessed for eligibility in this analysis, 201 met the inclusion criteria and were included in the study. The other patients were excluded because they were HIV negative

The patient enrolment flow diagram is shown in figure 1.

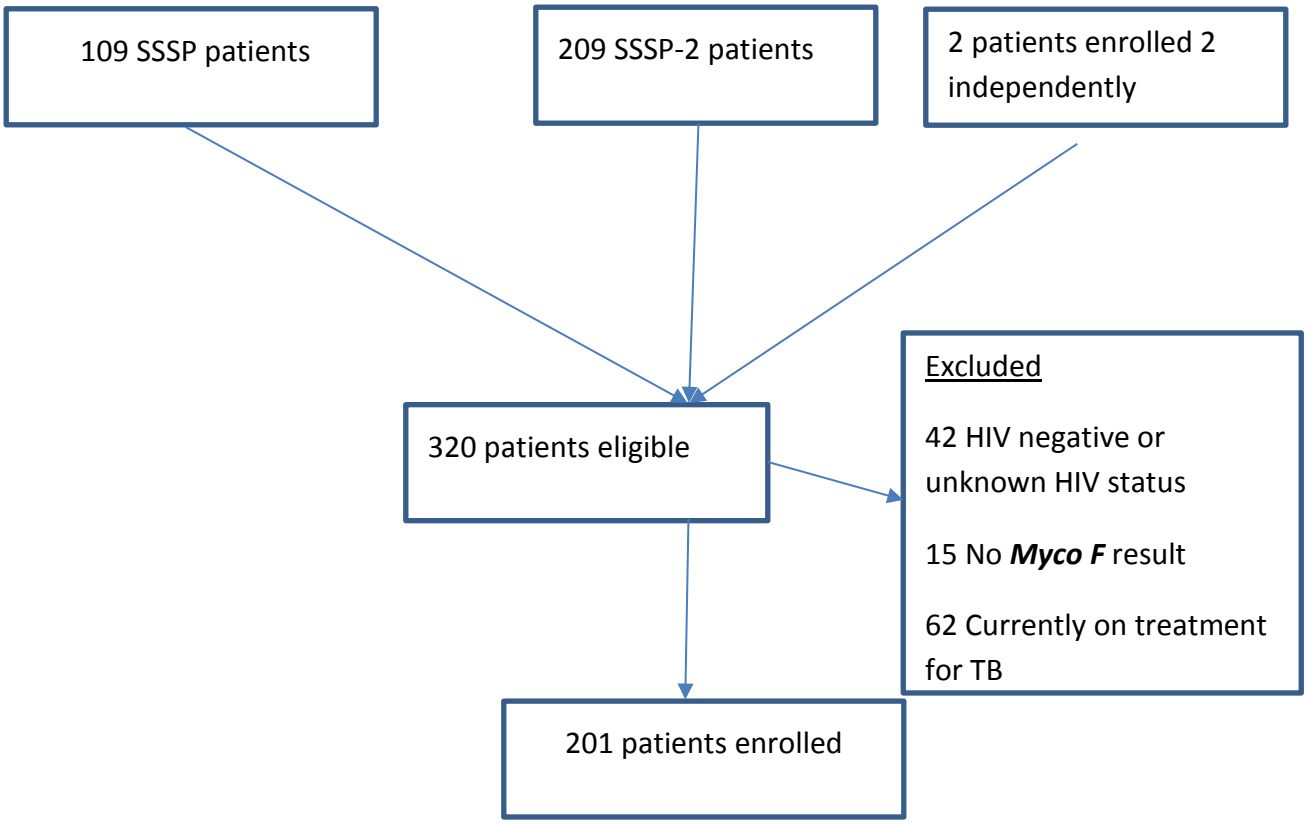


Figure 1: Flow chart for the enrolment of study participants

9.3.0. BASELINE CLINICAL AND LABORATORY CHARACTERISTICS

9.3.1. BASELINE CLINICAL FEATURES

a. Demographics

The mean age of the 201 study participants was 32.3(SD: 9.5) years .There were 103(51.2%) males.

b. Clinical features

Cough of any duration was a clinical presentation in 139(69.2%) of the patients, fever of any duration was reported by 150(74.6%) while weight loss was reported by 186(92.5%) participants. Slightly over half, 109(54.2%), of the study population were not on anti-retroviral therapy. The median duration of ART, for patients who were on treatment, was 3.5 months. The mean MUAC for the study patients was 21.0(SD: 3.4) cm and 60(30%) of the patients had been treated for tuberculosis in the past. Chest x-rays were available in 104(51.7%) of the patients with 72(35.8%) of them being reported as having some form of pulmonary infection. Sputum was available only in 27(13.4%) participants with 11 having *Mycobacterium tuberculosis* reported on microscopy. Tuberculosis treatment was started in 73(36.3%) of the study participants and the median time to tuberculosis treatment was 3.0 days.

The overall clinical characteristics are summarized in table 2, column (a).

9.3.2. BASELINE LABORATORY FEATURES

a. Laboratory features

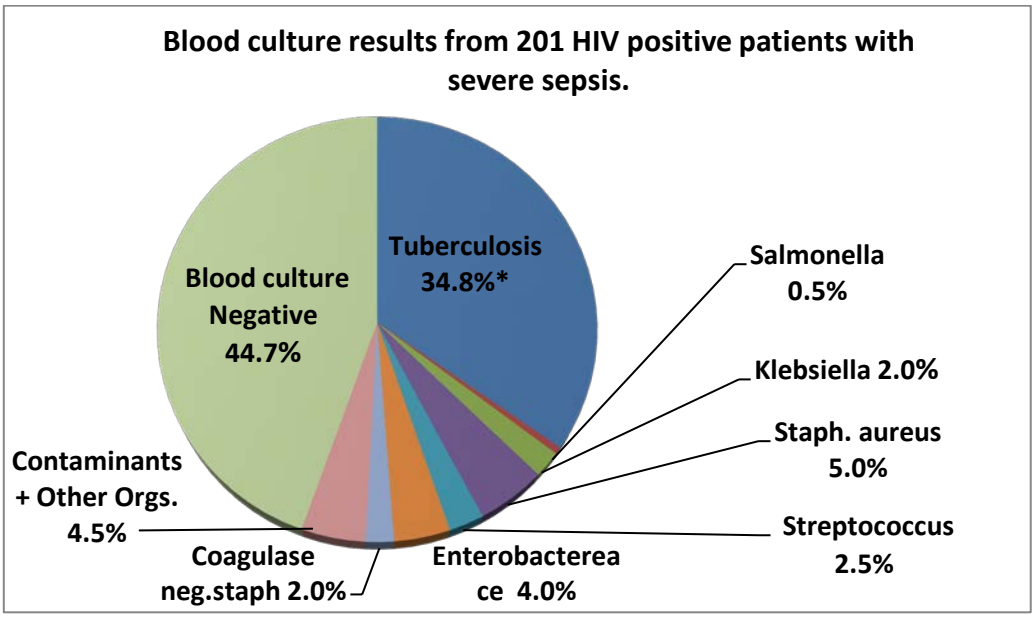
The mean hemoglobin for the study patients was 8.0 g/dl (SD: 3.0). FBC data was missing in 39 patients .The prevalence of severe anaemia (Hb≤7.0 g/dl) in this study population was 31.2%.Data for CD4 was available in 160 patients and the median CD4 count was 51 cells /ul (IQR: 20-136) and the mean albumin was noted to be 24.7 g/L (SD: 12.3) from the available data in 146 patients.

The overall laboratory features are summarized in table 3, column (a)

9.2. PREVALENCE OF MYCOBACTERAEMIA AND OTHER ORGANISMS

Tuberculosis mycobacteraemia was detected in 70(34.8%) of the 201 patients. The prevalence of all other organisms was 20.4% and the commonly isolated organisms were; *Staphylococcus aureus* 10(5.0%), *Streptococcus* 5(2.5%), *Klebsiella* 4(2.0%) and *E. Coli* 2(1.0%). Other organisms isolated included *Salmonella typhi*, Non-Salmonella typhi, *Pseudomonas aeruginosa*, *Enterobacter* and *Cryptococcus* making up the remainder of the isolates. Coagulase negative *Staphylococcus* was isolated in 5(2.5%). Approximately 8(4.0%) were deemed contaminants as diptheroids and gram positive rods were isolated. In 90(44.7%) study patients, no organism was isolated.

Concomitant tuberculosis mycobacteraemia and aerobic bacteraemia was observed in 8(4.0%) of the 201 participants. Of 8 the patients with co-infection with tuberculosis, *Staphylococcus aureus* was present in 4 patients, 2 had *Coagulase negative staphylococcus* and *Streptococcus viridans* while *Enterobacter aeruginosus* was isolated in the remaining 2 patients.



*The tuberculosis specimen includes the 8 (4%) co-infections with other organisms with detailed breakdown in figure 3. Further, contaminants 8 (4.0%) together with other organisms (0.5%) made up 4.5 % of the isolates.

Figure 2: Pie chart of organisms isolated from blood culture

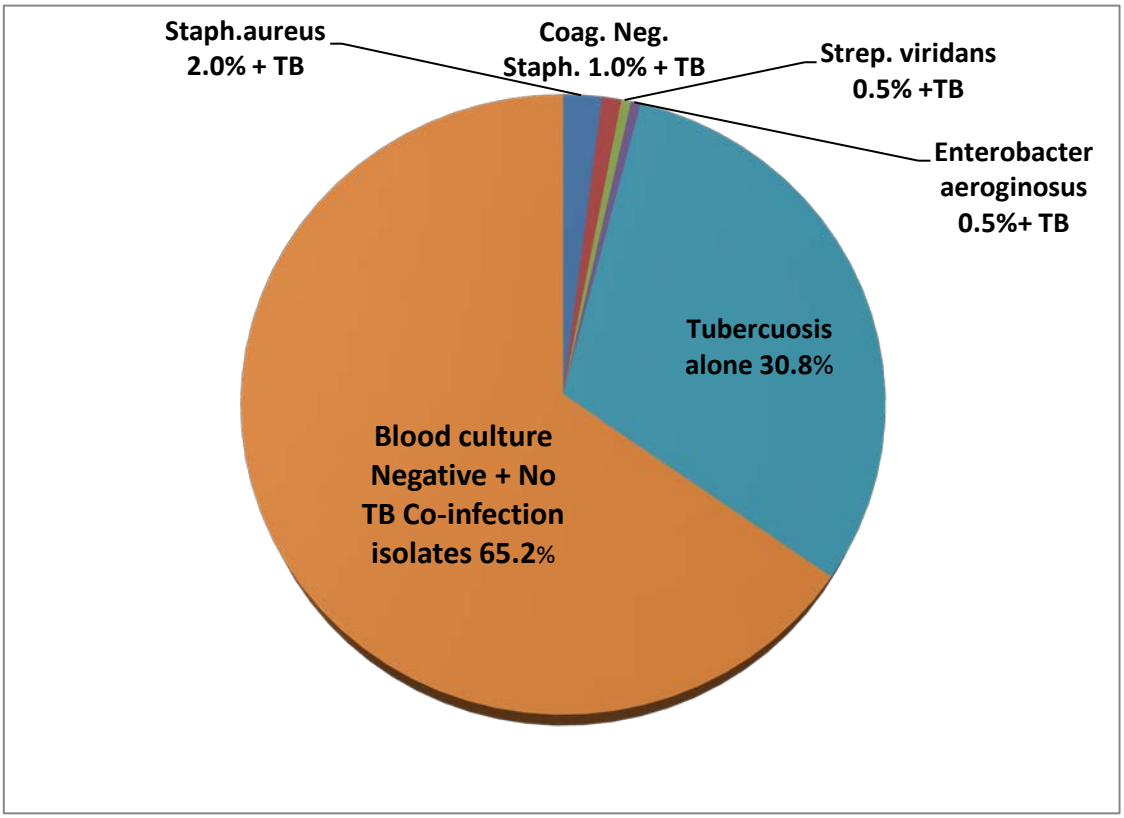


Figure 3: Pie chart showing details for *Tuberculosis mycobacterium* co-infection with other organisms

Table 1: Routine blood culture findings in 201 HIV infected patients with severe sepsis*

NEGATIVE BLOOD CULTURE n(%)	**160(79.6)**
POSITIVE BLOOD CULTURE n(%)	**41(20.4)**
PATHOGENS	
Gram positives n(%)	
Staphylococcus aureus	10(5.0)
Streptococcus pneumoniae	2(1.0)
Strep. viridans	1(0.5)
Other Strep. sp	2(1.0)
Gram Negatives n(%)	
E.Coli	2(1.0)
Salmonella Typhi	1(0.5)
Non-Salmonella Typhi	1(0.5)
Undetermined Salmonella sp.	1(0.5)
Klebsiella (+ Coagulase negative Staph. aureus)	4(2.0)
Pseudomonas aeroginosum	1(0.5)
Acinetobacter (+ Klebsiella)	1(0.5)
Enterobacter aeruginosa	1(0.5)
Enterobacter agglomerans	1(0.5)
OTHER PATHOGENS n(%)	
Cryptococcus	1(0.5)
POSSIBLE PATHOGENS n(%)	
Coagulase negative staph. aureus	4(2.0)
CONTAMINANTS n(%)	
Corynebacteria	1(0.5)
Diphtheroids	3(1.5)
Gram positive rods	2(1.0)
Mixed Growth	2(1.0)
Total n(100%)	**201(100)**

*Excludes Myco/F results

Table 2: Baseline characteristics of clinical features

Characteristics Study population	(a) ALL n=201	(b) No Tuberculosis mycobactereamia n=131	(c) Tuberculosis mycobactereamia n=70	p-value	Statistical Test
Demography					
Age in years (mean)	35.3(9.5)	34.7(9.0)	36.2 (10.0)	0.32	Students t-Test
Sex (male %)	103(51.2)	62(47.3)	41(58.6)	0.13	Chi-Square
Clinical Features					
Cough (%)	139(69.2)	89(67.9)	50(71.4)	0.61	Chi-Square
Fever (%)	150(74.6)	93(71.0)	57(81.4)	0.10	Chi-Square
Weight loss (%) No weight loss (%)	186(92.5) 15(7.5)	118(90.1) 13(9.9)	68(97.1) 2(2.9)	0.06	Chi-Square
[β] Not on ART (%) Unknown ART history (%) On HAART (%)	90(45.8) 19(9.5) 92(45.8)	57(43.8) 7(5.4) 66(50.8)	32(45.7) 12(17.1) 26(37.1)	**0.01**	Chi-Square
[β] Duration on ART in months (median)	3.5(IQR: 0.77 – 24.0)	9.0(IQR: 2.0 - 36.0)	9.0(IQR: 0.56 – 2.0)	**<0.01**	Mann- Whitney U Test
[β] History of TB n (%)	60(30.0)	48(36.6)	12 (17.1)	**0.01**	Chi-square
[β] MUAC (Mean {SD} cm)	21.0(3.4)	21.4(3.8)	20.2(2.4)	**0.01**	Students t-Test
Submitted sputum n (%)	27(13.4)	19(14.5)	8(11.4)	0.33	Chi-Square
CXR available n (%)	105(51.7)	63(48.1)	42(60.0)	0.64	Chi-Square
CXR suggestive of Pulmonary infection n (%)	72(35.8%)	45(34.3)	27(38.6)	0.27	Chi-Square
Started on ATT n (%) in Hospital	73(36.3)	42(32.1)	31(44.3)	0.09	Chi-Square
Median Time (days) to ATT	3.00(1.75-5.00)	2.0(2.0 – 4.0)	2.5(4.0 – 8.0)	0.50	Chi-Square

[β] ***Statistically significant***

Table 3: Baseline Characteristics for Laboratory findings

Study population	(a) ALL n=201	(b) No Tuberculosis mycobactereamia n=131	(c) Tuberculosis Mycobactereamia n=70	p value	Statistical Test
Laboratory characteristics					
β Haemoglobin in g/dl(mean [SD])	8.0(3.0)	8.4(3.1)	7.20(2.3)	**0.01**	Students t-Test
Severe Anaemia n (%) (Hb≤7.0 g/dl)	64(31.2)	40(30.5)	24(34.3)	0.47	Chi-Square
β White Blood Cells x 10^3/ml (mean [SD])	6.7(4.9)	7.29 (5.1)	5.54(4.2)	**0.03**	Students t-Test
Platelets x 10^3/ml (median[IQR])	143(IQR: 77-249)	261(153 – 432)	89(40 – 180)	0.07	Students t-Test
Creatinine umol/L (median[IQR])	111(IQR: 77-212)	107.0(78.0 – 233.0)	120(76.50 – 186.0)	0.93	Mann-Whitney U Test
Albumin in g/L (mean[SD])	24.7(12.3)	25.86(14.1)	22.10(5.9)	0.08	Students t-Test
β Sodium in mmol/L (mean[SD])	130(8.0)	131.7(6.9)	128.0(9.0)	**0.03**	Students t-Test
Potassium in mmol/L (mean[SD])	4.00(0.9)	3.93(0.9)	4.15(1.0)	0.13	Students t-Test
ALT in U/L (median[IQR])	24.0(IQR: 11.0-47.7)	22.6(6.0 – 81.1)	19.0(19 – 21.5)	0.71	Mann-Whitney U Test
AST in U/L (mean[SD])	63.5(IQR: 31.75-134.8)	29.0(14.4 - 79.4)	76.0(72.0 - 77.0)	0.45	Mann-Whitney U Test
β CD4 Count (median[IQR]) Cell/ul	51(IQR: 20-136)	56(IQR :18 - 184)	44(IQR: 26 - 64)	**<0.01**	Mann-Whitney U Test
Blood culture positive For aerobic organisms n (%)	41(20.4)	33(25.2)	8(11.4)	0.06	Chi-Square
βSputum positive for AAFB	11(5.5)	4(3.0)	7(10.0)	**0.01**	Chi-Square

β Statistically significant

9.3.3. COMPARISON BETWEEN TUBERCULOSIS MYCOBACTERAEMIA AND NON TUBERCULOSIS MYCOBACTERAEMIA POPULATIONS

i. Demographic and Clinical Features

The demographic characteristics of the patients with and those without tuberculosis mycobacteraemia is summarized in table 2, columns (b) and (c) respectively.

a. Demographics

The demographic characteristics between participants with tuberculosis mycobacteraemia and those without were similar. The mean age for the tuberculosis mycobacteraemia and the non-tuberculosis mycobacteraemia participants were similar (34.8{SD: 9.0} vs 36.2{10.0} years, p=0.32).The proportion of males and female between the two groups were also similar.

b. Clinical features

There was a high proportion of participants in the group with tuberculosis mycobacteraemia who reported weight loss, though this was not significant (118{90.1%} vs 68{97%}, p=0.06). For participants on anti-retroviral therapy, those with tuberculosis mycobacteraemia had a significantly shorter duration of time on treatment for HIV compared to those without mycobacteraemia (9.0{IQR: 0.56 – 2.0} vs. 9.0{IQR: 2.0 – 36.0} months, p <0.01). But the median duration of time on treatment was the same for the two groups. Though not significantly different, there was a higher proportion of participants with tuberculosis mycobacteraemia among the group who were not on ART compared to those on ART (44{62.9%} vs. 26{37.1%}, p=0.07).The participants with tuberculosis mycobacteraemia had a significantly lower MUAC compared to those without (21.4{SD: 3.4} vs 20.20 {SD: 2.40} cm, p=0.01).

There was a statistically significant difference between the two groups with regards to the past medical history of tuberculosis. There was a higher proportion of mycobacteraemia

among the participants without a history of treatment for tuberculosis (48{36.6%} vs 12{17.1%}, p =0.01). From the 105 patients with available chest x-rays, 72 participants had x-rays suggestive of pulmonary infection. There was no statistically significant difference in the chest X-ray findings between the group with tuberculosis mycobacteraemia and those without (27{38.6%} vs 45{34.3%}; p=0.65). Though not statistically significant, 42(32.1%) of the participants were started on treatment for tuberculosis in the group without tuberculosis while 31(44.3%) in the group with tuberculosis mycobacteraemia were started on treatment (p=0.09). There was no statistical difference between the two groups in terms of time to starting tuberculosis treatment.

ii. Laboratory characteristics

The laboratory characteristics of patients with and those without tuberculosis mycobacteraemia are summarized in table 3, columns (b) and (c).

Participants with tuberculosis mycobactereamia had a significantly lower mean haemoglobin compared with those without (8.4{SD: 3.1} vs 7.2{SD: 2.3} g/dl, p=0.01). Between the two comparison groups, severe anaemia (Hb ≤ 7.0g/dl) was observed in 40(31.2%) of the participants without tuberculosis mycobacteraemia and in 34(34.3%) of participants with mycobactereamia, a non-significant difference (p=0.47). Participants with tuberculosis mycobacteraemia had a significantly lower white cell count compared the participants without (7.3 $x10^3$ vs 5.2 $x10^3$, p=0.03). Although the platelet count was not significantly different between the two comparison groups, the group with tuberculosis mycobacteraemia had lower mean platelet count (261$x10^3$ vs 89 $x10^3$, p=0.07).The mean sodium level was significantly lower in the group with tuberculosis mycobacteraemia (128 {9.0} vs 131.7{6.9} mmol/L, p=0.03.) .The CD4 count was significantly different between the two comparison groups with the tuberculosis mycobacteraemia group having a lower median CD4 count (56{18-184) vs 44 {26-64), p <0.01).A high proportion of patients who were sputum smears positive also had tuberculosis mycobacteraemia compared to those without mycobacteraemia 11[10.0%] vs (4 {3.0%} ; p=0.01).

Table 4: Bivariate and Multivariate analysis of factors associated with *tuberculosis mycobacteraemia* in HIV positive patients with severe sepsis

Variable	Bivariate Analysis (OR, 95% CI)	p-value	Multivariate Analysis (OR, CI 95%)	p-value
Clinical features				
Age (years)	1.01 (0.98-1.05)	0.30	1.02(1.00-1.06)	0.11
Sex (Females Vs Males)	0.64 (0.35-1.14)	0.13	0.68(0.35-1.31)	0.25
Cough	1.12 (0.62-2.23)	0.60	1.20 (0.57-2.49)	0.65
Fever	1.78 (0.88-3.64)	0.11	1.44 (0.64-3.22)	0.37
$^{\beta\beta}$ MUAC per cm	0.89 (0.97-1.04)	**0.02**	0.85 (0.76-0.95)	**<0.01**
Pre-ART	1.4 (0.75-2.62)	0.29	1.5 (0.73-3.11)	0.26
$^{\beta\beta}$ Unknown ART History*	4.3(1.54-12.27)	**<0.01**	5.0(1.60-15.70)	**<0.01**
$^{\beta\beta}$History of TB	0.40 (0.20-0.79)	**0.01**	0.40(0.19-0.88)	**0.02**
Laboratory Characteristics				
$^{\beta}$ Haemoglobin g/dl	0.86 (0.77-0.97)	**0.02**	0.92 (0.75-1.13)	0.44
Severe Anaemia (Hb≤7.0 g/dl)	1.26 (0.65-2.43)	0.50	1.13 (0.40-3.19	0.82
$^{\beta}$ Sodium mmol/l	0.93 (0.89-0.98)	**<0.01**	0.93 (0.87-1.00)	0.05
Potassium mmol/l	1.20 (0.92-1.80)	0.95	1.28 (0.56-1.10)	0.13
$^{\beta}$Albumin g/l	0.95 (0.91- 0.10)	0.06	0.91 (0.85-0.99)	**0.02**
Creatinine umol/l	1.00 (0.99-1.00)	0.34		
$^{\beta}$CD4 Count cells/ul	1.00 (0.99-1.00)	**0.02**	1.00 (0.39-1.08)	0.09
ALT U/l	1.00 (0.98-1.00)	0.26		

$^{\beta\beta}$ Statistically significant in both the Univariate and Multivariate logistics regression analysis

$^{\beta}$ Statistically significant in the Univariate or Multivariate analysis

***Unknown ART history compared to those taking ART**

9.3.4. BIVARIATE LOGISTICS REGRESSION ANALYSIS

A Bivariate logistics regression analysis was performed to find out which factors were associated with tuberculosis mycobacteraemia .The factors that were significantly associated with tuberculosis mycobacteraemia were: MUAC (OR 0.89; CI 95% 0.97-1.04; p =0.02), unknown ART history (OR 4.3; CI 95% 1.54-12; p<0.01) and a history of being treated for tuberculosis previously OR 0.4; CI 95% 0.20-0.70; p= 0.01. Other factors that were significantly associated with tuberculosis mycobacteraemia in our study were: haemoglobin level (OR 0.89; CI 95% 0.77-0.97; p=0.02, CD4 count (OR 1.00; CI 95% 0.99-1.00; p= 0.02) and the level of sodium (OR 0.93; CI 95% 0.89-0.98; p<0.01). Male patients are more likely to develop tuberculosis mycobacteraemia than female patients, though this was not statistically significant, (OR 0.64; CI 95% 0.35-1.14; p=0.13). A patient with fever of any duration is 1.7 more likely to have tuberculosis mycobacteraemia in comparison with a patient without, this was not statistically significant (p=0.11).

MULTIVARIATE LOGISTICS REGRESSION ANALYSIS

A multivariate logistics regression analysis was done using pre-selected variables in the clinical and laboratory features to determine whether these variables were independently associated with tuberculosis mycobacteraemia. Clinical Factors that were independently associated with tuberculosis mycobacteraemia were: MUAC (OR 0.85; CI 95% 0.76-0.95; p=<0.01), unknown ART history (OR 5.0; CI 95% 1.6-15.7; p<0.01) and a past medical history of treatment for tuberculosis (OR 0.4; CI 95% 19-0.88; p=0.02). Among the laboratory factors, albumin levels (OR 0.91, CI 95% 0.85-0.99; p=0.02) was the only factor that was independently associated with tuberculosis mycobacteraemia. Sodium levels (OR 0.93, CI 95% 0.87-1.0; p=0.05) and CD4 count (OR 1.00; CI 95% 0.39-1.08; p=0.09) were strongly associated with tuberculosis mycobacteraemia after correction for confounders but not independently associated with tuberculosis mycobacteraemia. Severe anaemia was not independently associated with tuberculosis mycobacteraemia (OR 1.13; CI 95% 0.40-3.19; p=0.82).

10. DISCUSSION

The most notable finding of this study was the high prevalence of tuberculosis mycobacteraemia of 34.8% in a cohort of HIV positive patients admitted with severe sepsis to the University teaching hospital. This is the highest prevalence of tuberculosis mycobacteraemia than what we have seen documented in the region. The study population was generally young with a mean age of 35.3(SD: 9.5) years and the study participants were generally severely immunosuppressed with a median CD4 count of 51cells/ul (IQR: 20-136). Slightly above half of the patients were not on ART or the ART history was unknown but for those on ART, the median time on treatment was just a few months (3.5 months) implying that they were recently diagnosed with HIV. However, participants with tuberculosis mycobacteraemia had a significantly shorter duration of time on ART and their median CD4 count (44cells/ul) was significantly lower. At such low levels of CD4 count, patients are also at risk of having sepsis from bacterial infections other than tuberculosis.

In our study, severe sepsis due to bacterial infection other than tuberculosis was found in 41 (20.4%) of the study patients and the commonly isolated organism was *Staphylococcus aureus* followed by Enterobactereace and Streptococcus species *(Streptococcus pneumoniae* and *Streptococcus viridans*). This is similar to observations made by Chimese et al. (2011) in Lusaka, Zambia and by Jacob et al. (2009) in Uganda where the prevalence of bacteraemia in septic patient was 21% and the commonly isolated organism was *Staphylococcus aureus* followed by *Streptococcus pneumoniae* while in the Ugandan study the prevalence of bacteraemia was 18.9% and the commonly isolated organism was non typhoid salmonella followed by *Staphylococcus aureus* and *Streptococcus pneumoniae*. Co-infection of tuberculosis with other bacteria in patients with severe immunosuppression is not uncommon. This study observed that 8(4.0%) of the study patients had co-infection of tuberculosis mycobacteraemia with other bacteria and the commonly isolated organisms were: S*taphylococcal aureus* (4), *Streptococcus viridans* (1), *Enterobacter aeroginosus* (1) and *Coagulase negative staphylococcus* (2).

Most patients in our study presented with any of the following clinical features as the chief complaint; fever, weight loss or cough. We observed that a very high proportion of the patients 186(92.5%) presented with weight loss. There was no significant difference between the patients with tuberculosis mycobacteraemia from those without in terms of the clinical presentation mentioned above. The implication of this is that the classical clinical features of tuberculosis like fever and cough of any duration, and weight loss as reported by patients would not be enough to identify tuberculosis mycobacteraemia in most severely septic HIV infected patients. This is in contrast to the findings by Jacob et al. 2013 who found these clinical features significant. However, we noted that the mean MUAC for the study patients was very low 21.0(SD: 3.4) cm and that patients with tuberculosis mycobacteraemia had a significantly lower MUAC (just slightly above the cut off value for wasting) in comparison with the patients without. MUAC was noted to have been independently associated with tuberculosis mycobacteraemia in our study population. We know that wasting is prominent feature of tuberculosis and an indication of active disease, this could explain the significantly lower MUAC in the patients with tuberculosis mycobacteraemia.The other significant clinical finding in our study was that there was a higher proportion of patients without tuberculosis mycobacteraemia in the patients previously treated for tuberculosis in comparison to those without history treatment for *Mycobacterium tuberculosis*. The possible reason for this observation is that tuberculosis may have been identified early and adequately treated .This further means that once tuberculosis is diagnosed and treated early, it prevents dissemination of the infection and subsequent development of sepsis. Clinicians should have a high index of suspicion for tuberculosis mycobacteraemia in HIV infected patients with severe sepsis who have no history of treatment for tuberculosis.

Generally, this study population had very low mean haemoglobin but the subgroup with tuberculosis mycobacteraemia had significantly lower mean hemoglobin compared to the group without. This is similar to an observation by Jacob et al. (2013) in Uganda. The prevalence of severe anaemia was not significantly different between the two comparison

groups in our study. Two common causes of anaemia of chronic inflammation in developing countries are tuberculosis and HIV. Patients usually present with mild to moderate anaemia but for long standing causes patients may present with severe anaemia. Tuberculosis has been documented as one of the most common cause of severe anaemia in adult males and non-pregnant females, in some cases requiring admission and blood transfusion (Lewis DK et al. 2005). Haematological abnormalities found in patients with tuberculosis are varied and included leukopenia, lymphopaenia, monocytopaenia, lymphocytosis, neutrophilia and monocytosis; pancytopenia is observed in patients with milliary or disseminated tuberculosis (Singh J et.al 2001).This study did not focus on all the haematological indices apart from the haemoglobin and white cell count. In their study, Lewis et.al 2005, documented that spread of tuberculosis to the bones is common leading to bone marrow suppression. In this study, participants with tuberculosis mycobacteraemia had a significantly lower white cell count compared to the participants without ($p=0.03$). The mean platelet count for participants with tuberculosis mycobacteraemia was lower than participants without tuberculosis mycobacteraemia, though this was no significant difference ($p=0.07$). Some of our patients with tuberculosis mycobacteraemia possibly had bone marrow depression from disseminated tuberculosis. Anaemia is common in HIV infected patients and becomes frequent as the disease progresses to AIDS. This has been observed in slightly above75% of HIV infected patients in a study in Tanzania (Johannese et al. 2011) and in above 90% (Belpeirol et al. 2004) from a systematic review of literature of prevalence of anaemia in individuals with HIV. Our study population falls into the AIDS stage. The main mechanism of anaemia in HIV infected patients is chronic inflammation (Sullivan et. al 1988). Other mechanisms include direct depression of erythropoiesis by the HIV itself, diffuse fibrosis of the bone marrow cavity and co-infection with the Parvovirus B19 causing pancytopenia. Immunosuppressed patients lack protective antibodies to clear the Parvovirus B19 (Koduri PR, 2000). Another factor that may play a role is the nutritional deficiencies due to poor intake and malabsorption.

The patients with tuberculosis mycobacteraemia had two important factors that are known to cause anaemia, tuberculosis itself and HIV infection. This could be the possible explanation for the significantly lower haemoglobin observed in the participants with tuberculosis mycobacteraemia in comparison to the group without. After adjusting for confounders, anaemia including severe anaemia (Hb < 7.0g/dl) was found not to be independently associated with tuberculosis mycobacteraemia in HIV infected patients who presented with severe sepsis

The mean sodium levels of participants with tuberculosis mycobacteraemia was significantly lower than the group without mycobacteraemia. The mean serum potassium levels in the two comparison groups were normal. Disseminated tuberculosis has been associated with adrenal insufficiency .This strong association of hyponatraemia with tuberculosis mycobacteraemia was also observed by Jacob et.al 2013. A study by Kaabwe-Yavwa et al. 2013 in Lusaka, Zambia looked at the prevalence of adrenal insufficiency in HIV infected patients presenting with hypotension and history of tuberculosis. The study observed that 94% of the patients had adrenal insufficiency (based on the measurement of serum cortisol levels) and that the patients had normal potassium levels.

Generally, the mean serum albumin level in this cohort was low but the subgroup with tuberculosis mycobacteraemia had a much lower albumin, though this was not statistically significant. However, we observed that albumin was independently associated with tuberculosis mycobacteraemia after adjusting for confounders in a multivariate logistics regression analysis. Albumin is an acute protein that decreases during inflammation. HIV infection causes chronic inflammation and is a possible cause of hypoalbuminaemia in our study population. The subgroup with tuberculosis mycobacteraemia had an additional inflammatory illness, tuberculosis itself, which could explain the much lower albumin observed compared to the subgroup without tuberculosis mycobacteraemia. In India Alvarez-Uria et.al (2013), explored the usefulness of serum albumin in predicting tuberculosis and observed a positive predictive value of 89% for serum albumin <23g/l .

About half of the participants were able to do chest x-rays and 72(68.6%) of the available 105 chest x-rays had features suggestive of pulmonary infections as reported by the attending physician. The chest x-ray finding in participants with tuberculosis mycobacteraemia was not significantly different from the group without. The chest x-ray findings in our study included milliary mottling, pleural effusion, hilar lymphadenopathy and non-specific infiltrates. Patients with advanced HIV disease could have tuberculosis with non-specific chest x-ray findings as has been documented by von Reyn et.al 2011, these findings can be subtle infiltrates, micro-nodular infiltrates or indeed pleural effusions. The sensitivity of Chest X-ray in identifying tuberculosis mycobacteraemia in HIV positive with severe sepsis was observed to be 77% by Jacob et.al 2013 in Uganda.

11. STUDY LIMITATIONS

The study had a number of limitations:

The results of this study are limited to HIV infected patients with severe sepsis admitted to hospital in regions where prevalence of tuberculosis high.

Data for haemoglobin was available in 162 patients, 160 patients had CD4 count while 146 had data for Albumin available.

Only half of the participants were able to do chest x-rays because most of them were too ill to be moved to the radiology department and the portable X-ray machine was not functional in the emergency unit at the time of the study.

Due to logistical problems, we were only able to do one blood culture for aerobes and we could not do sensitivity tests on all the isolates. We could not ascertain whether some isolates like coagulase negative staphylococcus was a pathogen or contaminant as this would have required collection of a set of 2 or 3 blood cultures to ascertain. The gold standard for this study was a positive mycobacterial culture. Thus patients with Non-bacteraemia tuberculosis could not be identified.

12. CONCLUSION

Tuberculosis mycobacteraemia seem to be very common in patients with advanced HIV disease who have severe sepsis. Most patients with tuberculosis mycobacteraemia presented with wasting, cough and fever as their main complaint. However, these symptoms were not specific to patients with tuberculosis mycobacteraemia alone. Patients were generally anaemic; however, severe anaemia was not independently associated with tuberculosis mycobacteraemia. In our study, the factors that were independently associated with tuberculosis mycobacteraemia were: MUAC, low albumin, a past medical history of treatment and unknown ART history.

Chest x-ray findings in HIV infected patients with severe sepsis who have tuberculosis mycobacteraemia are not significantly different from those who do not have. Diagnosing tuberculosis mycobacteraemia HIV infected patients with severe sepsis remains a largely difficult problem. Clinicians need to have a high index of suspicion for tuberculosis mycobacteraemia in HIV positive ART naïve patients with severe sepsis who present with the following; wasting, low sodium and albumin levels and non-specific clinical symptoms.

13. RECOMMENDATIONS

1 .Given the difficulties of diagnosis of tuberculosis in septic HIV positive patients there is need to look at quicker, easy and reliable methods of diagnosis of tuberculosis even in resource limited settings .We must explore the utility LAM and Gene X pert as part of the point of care test in all health institution for HIV positive patients with severe sepsis

2. All patients with advanced HIV disease should be aggressively screened for tuberculosis

3. Most of the study patients had severe immunosuppression, a reflection of late presentation among our patients; therefore we must do more on health education for our patients to present early.

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APPENDICES

APPENDIX 1: Data Collection Sheet for Clinical characteristics of Study patients

ASSOCIATION OF SEVERE ANAEMIA WITH TUBERCULOSIS MYCOBACTEREMIA AMONG HIV PATIENTS ADMITTED WITH SEVERE SEPSIS

PATIEN NAME (SURNAME)..... GIVEN NAME..... FILE NO.....

CRF 01: CLINICAL CHARACTERISTICS OF STUDY PATIENTS

	QUESTION	**ANSWER**	**CODE**	
01	DATE OF ENROLMENT	...../...../.....		
02	IDENTIFICATION NUMBER	.....		
03	AGE	..... YEARS		
04	SEX	M..... F.....	0 1	
05	PRESENCE OF COUGH	NO..... YES.....	0 1	
06	COUGH >2 WEEKS	YES NO	1 0	
07	PRESENCE OF FEVER	NO..... YES.....	0 1	
08	FEVER <2 WEEKS FEVER >2WEEKS	NO YES	0 1	
09	PAST MEDICAL HISTORY OF TB	NO YES	0 1	
10	HISTORY OF TB CONTACT	NO YES	0 1	
11	HAART	NO..... YES.....	0 1	
12	DATE OF INITIATION OF HAART	...../...../.....		
13	IF ON HAART BASELINE CD4 COUNT	.....		
14	CO-MORBIDITIES	DIABETES MELLITUS MALIGNANCY OTHERS.....		Circle
15	Alcohol >6 months Smoking >6months	NO..... YES..... NO..... YES	 0 1 0 1	

APPENDIX 2: Data Collection Sheet for Laboratory and Chest X- Results

Name (Surname).....Given Name.....File No.....

CRF 02: LABORATORY AND RADIOLOGICAL FINDINGS IN THE STUDY PATIENTS

	VARIABLE	RESULT	CODE
01	DATE OF ENROLMENT	...../...../.....	
02	IDENTIFICATION NUMBER	.....	
03	MUAC	……	
04	FBC	Hb..... WBC..... PLT..... MCV.....	
05	BIOCHEMISTRY	Creatinine..... Urea..... Na..... K..... Bicarbonate..... Albumin..... ALT..... Total Bilirubin.....	
06	Sputum for AAFB.	Unable to produce..... Negative..... Positive.....	0 1 2
07	Blood Culture for Mycobacteria	Negative..... Positive.....	0 1
08	PCR for Culture Positive for Mycobacterium	Non-Tuberculous..... Tuberculosis.....	0 1
09	Blood culture for other bacterial organisms	Salmonella..... Streptococcus..... Staphylococcus aureus..... Klebsiella Other..... No Isolate.....	0 1 3 4 5 6 7
10	CD4 Count NOT AVAILABLE	....	0 1
11	DATE OF INITIATION OF ATT	...../...../.....	
12	CXR REPORT	Not performed..... Normal ..... Infiltrates..... Apical Infiltrates..... Bilateral Infiltrates..... Hilar adenopathy..... Milliary TB.....	0 1 2 3 5 6 7

APPENDIX 3: INFORMATION SHEET FOR PARTICIPANTS WHO ARE ELLIGIBLE FOR THE STUDY

Study title: Association of severe anaemia with tuberculosis mycobacteremia in HIV positive patients admitted with severe sepsis at the University teaching hospital, Lusaka.

Principal investigator: Dr. Levy Muchemwa

Institution: University teaching hospital, department of Internal Medicine, P/Bag RW 11X Lusaka

You are being asked to participate in this research being conducted by Dr. Levy Muchemwa, a Master of Medicine student from the department of internal medicine. The results will contribute to the thesis for my Master of Medicine degree and also to knowledge about the care of HIV patients with severe sepsis.

Purpose of the study

The purpose of this study is to investigate association of severe anaemia with blood stream tuberculosis among HIV positive patient with severe sepsis who are admitted to the university teaching hospital. Bacteria present in blood may cause a serious infection called sepsis and tuberculosis commonly causes sepsis in HIV patients.

Procedure

If you agree to take part in the study:

- We will get information on the duration of your illness
- We will measure the mid-upper arm circumference
- About 8-10 mls of blood will be drawn to test for infections
- An additional 4- 6mls of blood will be collected to check how strong your immunity is (CD4 count-2mls) if not done already, also to check for the level of blood (Full blood count-2mls) blood to tests the functioning of the kidneys and the liver (2mls)
- Blood will be drawn once at the time of enrolment
- Your doctors may additionally draw blood for tests which they feel will be required
- You will also be required to submit sputum to check for tuberculosis and other infections
- You will also be required to do a Chest X-ray

Potential risks and discomfort

- The procedures mentioned above carry minimal risks:
- Blood collection may cause pain at the collection site
- Blood will be collected by the doctor, the principal investigator
- Infection at the site of collection rarely occurs (<1%), to prevent such problems the doctor will collect blood
- Exposure to X-rays has minimal risks if, not repeatedly done

Potential benefits to Participants/Society

The laboratory tests outlined above will be done and made available on the file for the participant as soon as we get them, meaning that we will quickly follow up the results for you. The study may not be directly beneficial to the patient, however the results of the study has potential benefits to society in that it may improve the diagnosis of tuberculosis in HIV positive patients with severe sepsis and consequently contribute to decrease in mortality in these patients

Payment for participating in the study

You will not be paid for participating in this study.

Confidentiality

Data for this study will be kept confidential under lock and key. Only the researcher and the supervisors will have access to the information. In the event of publication of the research, no personally identifying information will be disclosed.

Participants Rights

By consenting to participate in this study, you do not waiver any of your legal rights. Giving consent means you have read or heard the information about the study and you agree to participate. You will not suffer any penalty or lose any benefits to which you are entitled by participating in the study

Right to refuse or withdraw

Participation in this study is voluntary. If you feel uncomfortable with any of the questions in the study you have the right to refuse to take part in the study .If you decide to be in the study and then change your mind; you can withdraw from the study at any point. Your decision to withdraw will not affect the standard of care that you will receive from the hospital.

If you have any questions about the study, feel free to contact the Chair of University of Zambia Biomedical Research Ethics Committee (UNZA REC), P.o. Box 50110, Ridgeway, Lusaka: Phone 0211-256067 or my number, Dr. Muchemwa **(0975697604**)

APPENDIX 4: INFORMED CONSENT FOR RESEARCH
Principal Investigator: Dr. Levy Muchemwa

Study Title: Association of Severe anaemia with tuberculosis mycobacteremia in HIV positive patients admitted with severe sepsis at the University teaching hospital, Lusaka.

Institution: University teaching hospital, department of Internal Medicine, PB RW 1X Lusaka

This informed consent applies to adults.

Participation in the study is voluntary

I have read the information provided for the study, Association of severe anaemia with tuberculosis mycobacteremia among HIV positive patients admitted with severe sepsis to the university teaching hospital, Lusaka, Zambia, as described herein. My questions have been answered to my satisfaction and i agree to take part in the study.

NAME OF PARTICIPANT : ---------- Age: ----------

SIGNATURE: ----------

THUMB PRINT: ----------

DATE: ----------

(If participant is unable to consent, next-of- kin can consent)

NAME OF NEXT OF KIN: ----------

SIGNATURE: ----------

THUMB PRINT (if illiterate): ----------

DATE: ----------

WITNESS: ----------

SIGNATURE: ----------

THUMB PRINT (if illiterate): ----------

DATE: ----------

SIGNATURE OF RESEARCHER

NAME OF RESEARCHER----------

SIGNATURE---------- DATE----------

APPENDIX 5: INFORMATION SHEET FOR PARTICIPANTS WHO ARE ELLIGIBLE FOR THE STUDY (NYANJA)

Mutu wankhani mukufufuza uku: Kugwirizana ko chepekela maningi magazi ndi Chifuwa kapena TB muli antu odwala ali ndi tulombo twa HIV omwe asungidwa ndi matenda maningi mumagazi muchipatala cha University Teaching Hospital, mu Lusaka.

Oyanganila pa kufufuza uku: Dr. Levy Muchemwa
Kabbungwe: University teaching hospital, chigawo cha Internal Medicine, P/Bag RW 11X Lusaka
Mupemphedwa kutengako mbali mukufufuza ku mene kuchitidwa ndi Dr. Levy Muchemwa amene aphunzira Master of Medicine mu chiagawo cha internal medicine. Zotulukamo mu kufufudza uku kuza thandidizra maphunziro anga a masters mu medicine degree ndiponso maphuziro akasungidwe ka odwala ali ndi tulombo twa HIV ndi matenda maningi mumagazi..

lingo lakufufuza
Lingo la kufufuza uku ndi kufuna kuziwa kugwirizana kwa kuchepakela maningi kwa magazi ndi matenda a Chifuwa kapena TB cha mu magazi mu antu odwala ali ndi tulombo twa HIV ndi kudwala kweni kweni amene ali muchipatala cha University teaching hospital.Tulombo tuli mumagazi tu lenga ku dwala kweni kweni kwa matenda mumagazi ndiponso chifuwa cha TB nthawi zambili mu anthu odwala ndi kalombo ka HIV.

Ka chitidwe
Ngati mwa bvomela kutengako mbali mu kufufudza uku:

- Tiza thenga unthenga kuziwa mwa dwala kwa nthwai bwanji
- Tiza pima dzanja lanu pamphavu
- Tidza tenga magazi okwanila 8-10 mls kuti tika pimemo matenda
- Ndiponso magazi okwanila 4- 6mls adzatengedwa kuti aka pime mphavu ya thupi yanu kuziwa chingilizo kumatenda (CD4). Ngati muna pimisa kale tiza tenga magazi kupima unyinji wa magazi mu thupi (Full blood count-2mls) ndipo tiza tenganso magazi kuti tiziwe ku sewenza kwa mafwo ndi masewenzedwa a chwindi.)
- Magazi a maphunziro awa adza tengedwa ka modzi
- A dotolo anu anga chotse magazi ena kuti apimemo zimene afuna
- Ndipo muzafunika ku peleka zinkholodwa kuti a pimemo chifwa cha TB ndi matenda ena.
- Muza funikila ku kopedwa mu chifuwa

Opsa kuli konse ndi kusanvela bwino

- Zochitidwe za chulidwa pa mwamba zili ndi ku opsa kochepakela:
- Kuchosa magazi ku pangesa kuwawa pamalo pamene a chosalapo magazi
- Magazi adza chosedwa ndi a dotolo, oyanganila pa kufufuza uku.
- Matenda pamalo pamene alasidwa sama chitika nthawi zimbili (<1%), koma chingiliza bvuto ya choncho ku chitika a dotolo azda chosa magazi.
- Ku kopewa kwa X-ray mu chifwa kuli ndi kuopyesa kochepekala ngati simuna kopedwa nthawi zambili.

Phindu lake kapena Ubwino wake kuli otengamo mbali kapena muno mudela

Zo pimidwa za chulidwa pa mwamba ziza chitidwa ndi kuzi faka mu fayelo ya bo tengamo mbali mwa musanga ,kutantauza kuti tiza konka nokukubwalesani zopezekamo kamusanga.. Phindi yo tengeko mbali kwanu simunga kuona pomwepo kuli odwala,koma zopezekamo zikonza kutendizdira mudela muku pima chifuwa cha TB muli anthu odwala ali ndi tulombo twa HIV ndi matenda ena amumagazi ndiponso kutandizdira kupeleka pasongolo zaumoyo ndi ku chepesa imfa muli odwala aba.

Malipilo pa kutengako mbali mukufufuza uku.

Dziwani kuti simuza landila ndalama kapena cina cili consa potengamo mbali muku fufudza uku.

Chisinsi

Masungidwe azisinsi Uthenga ulionse otengedwa uzasugidwa mwachisinsi ndiponso ukala mokomedwa ndi maki. Kulibe uthenga ulionse udza ulusidwa koma chabe m'sogoreri ndi uku fufudza azankhala ndimupata kuli uthenga koma kuti mwina m'sogoro kwafunika kulemba ku fufudza madzina kwa aliyense polemba mumabuku sazaziwika..

Mphamvu Za okotengako mbali

Kutengako mbali mu punzilo li uku sikukulesani kapena kukanizidwa zilizonse zofunikila kwa enu.Kuvomela kutengako mbali kutantauza kuti mwa welenga uthenga kapena za masulidwa zau uthenga otengako mbali ndipo mwa vonmela kutengako mbali. Ku kana kutenghako mbali mukufufudza uku sikuza mulesani ku sebenzesa zilizonse zofunikila kwa enu.

Mphamvu zotengako mbali kapena kusiya

Kutengako mbali mukufufudza uku ndi kozipeleka kapena ndi ufulu wanu . Nghati kuli zomwe simufuna kukambilana, muli omasuka ku kana kutengako mbali mukufufudza uku. Ngati mwavomera kutengako mbali mukufufudza uku ndi mwe omasuka kusiya panthawi ili yonse kosa sonkoneza za umoyo zimene mulandila muchipatala.

Ngati muli ndimafunso alionse pali maphuniziro awa, ndinu omasuka ku lembela kapena ku tumila kuli akumupandoku University of Zambia Biomedical Research Ethics Committee (UNZA REC), P.o. Box 50110, Ridgeway, Lusaka : Phone 0211-256067 kapena pa nambela yanga, Dr. Muchemwa (0975697604)

APPENDIX 6: INFORMED CONSENT FOR RESEARCH (NYANJA)

Oyanganila pa kufufuza uku: Dr. Levy Muchemwa

Mutu wankhani mukufufuza uku: Kugwirizana ko chepekela maningi magazi ndi Chifuwa kapena TB muli antu odwala ali ndi tulombo twa HIV omwe asungidwa ndi matenda maningi mumagazi muchipatala cha University Teaching Hospital, mu Lusaka.

Kabbungwe: University teaching hospital, chigawo cha Internal Medicine, P/Bag RW 11X Lusaka

Ichi chipepala ndi cha chisimikidzo ku akulu pazopezekamo mukufufuza
Ndawelenga uthenga wama phunziro aya paku kugwirizana ko chepekela maningi magazi ndi Chifuwa kapena TB muli antu odwala ali ndi tulombo twa HIV omwe asungidwa ndi matenda maningi mumagazi muchipatala cha University Teaching Hospital, mu Lusaka ,olembedwa umu. Mafunso anga ayankhidwa motsimikidza ndipo ndi bvomera kutengako mbali mumapuziro li.

DZINA LA OTENGAKO MBALI:
_____DZAKA:____

KUTSINDIKIDZA: _____

KUTSINDIKIZA NDI CHALA CHACHIKULU (Osapunzila): _____

TSIKU: _____

(Ngati otengako mbali sanakwanitse kusindikidza,wahcibbale anga sindikidze.)

DZINA LA WACHIBBALE: _____

KUTSINDIKIDZA: _____

KUTSINDIKIDZA NDI CHALA CHACHIKULU (Osapunzila): _____

TSIKU: _____

MBONI: _____

KUTSINDIKIDZA: _____

KUTSINDIKIDZA NDI CHALA CHACHIKULU (Osapunzila): _____
TSIKU:_____

KUTSINDIKIDZA KWA OFUFUFDZA: _____

DZINA LA OFUFUZA: _____

KUTSINDIKIDZA: ___________________________________ TSIKU :________________

Appendix 7: BUDGET

ACTIVITY	QUANTITY FOR DISSERTATION	UNIT COST	COST
RESEARCH ETHICS FEES	-	-	K500, 000.
ADMINSTRATIVE FEES 1.Reams of paper 2.Thesis preparation	 2 -	 K30,000 K400,000	 K60, 000 K400,000
RESEARCH ACTIVITIES 1.T.B blood culture bottles 2.Blood cultures for TB (PERCH2 LAB) 3. TB PCR (CIDRZ LAB) 4. Aerobic blood culture bottles 5.Blood culture for aerobes 6.FBC (HIGH COST LAB) 7. Urea,Creat, ,ALT,AST 8.Na,K, HCO3 (CIDRZ) 9.CD4 Count 10.CXR 11.RESEARCH ASSISTANTS(02)	 50 50 36 50 90 50 30 90 0 0 2	 K60,000 K0, 000 K133 120 K66,000 K10,000 K40,000 K10,000 K40,000 K0,000 K0,000 K500, 000/1 for 2months.	 K3,000,000 K0,000 K4,792,320 K3,300,000 K900,000 K2,000,000 K0,000 K3,600,000 K0,000 K0,000 K2,000,00
TOTAL			K20, 550,320.

*Costs for other patients will be covered by the SSSP/SSSP-2 project funds. The figures above reflect participants who will take part in the cross-sectional study.

Appendix 8: TIME TABLE

	DEC 2011	JAN 2012	FEB 2012	JUN 2012	JUL 2012	AUG 2012	SEP 2012	OCT 2012	NOV 2012	DEC 2012	JAN 2013	FEB 2013	MAR 2013
PRESENT TO DEPARTMENT													
CORRECTIONS SUGGESTED BY DEPT													
ENROLMENT OF PATIENTS BY MAIN STUDY (SSSP)													
ENROLMENT OF PATIENTS IN SSSP COMPLETED													
ENROLMENT OF PATIENTS IN SSSP-2 STARTS													
SUBMIT PROPOSAL TO ASSISSTANT DEAN (PG)													
PRESENTATION AT GRADUATE FORUM													
SUBMIT TO RESEARCH ETHIC COMMITTEE													
DATA COLLECTION													
WRITE DISSERTATION													
SUBMIT FINAL REPORT													