FACTORS INFLUENCING TREATMENT OUTCOMES AMONG MULTI DRUG RESISTANT TUBERCULOSIS/HIV CO-INFECTED PATIENTS IN DAR ES SALAAM REGION AND KIBONG'OTO INFECTIOUS DISEASE HOSPITAL IN KILIMANJARO REGION, TANZANIA

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Factors Influencing Treatment Outcomes among Multi Drug Resistant Tuberculosis/HIV Co-Infected Patients in Dar Es Salaam Region and Kibong'oto Infectious Disease Hospital in Kilimanjaro Region, Tanzania

By

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled: **''Factors influencing treatment outcomes among multidrug resistant tuberculosis/HIV co-infected patients in Dar es salaam region and Kibong'oto Infectious Disease Hospital in Kilimanjaro region, Tanzania'',** in (partial) fulfillment of the requirements for the degree Master of Science (Applied Epidemiology) of Muhimbili University of Health and Allied Sciences.

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Date: _____

DECLARATION AND COPYRIGHT

I, **Sarah Gibson**, declare that this **dissertation** is my original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature……. **Date**….....

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DEDICATION

This work is dedicated to my fine family; my husband Mr. Gasper Said Kimario, my lovely daughter Laura Gaspar Kimario and my dear son Jonathan Gaspar Kimario for their prayers and support throughout the course. They have all been missing my attention and my presence during the field works but they have always been tolerant and loving. May God bless you always

ABSTRACT

Background: Multidrug resistant Tuberculosis is a public health problem that is increasing yearly. Sub-Saharan Africa is home to about 72% of the estimated burden of multidrug resistant tuberculosis among HIV co-infected patients. In Tanzania, 534 multidrug resistant tuberculosis cases were notified in the year 2019 and 28% of them were HIV positive. However, HIV co-infection escalates and make multi drug resistant tuberculosis (MDTR) worse. Current responses include the World Health Organization commitment to reduce unfavorable outcome and especially among multidrug resistant tuberculosis/HIV co-infected patients who are the most affected. At the same time, limited information is available to make real time plans and strategies to achieve the goal of 90% favorable outcome by 2030. Our study aimed at determining treatment outcomes and factors influencing unfavorable treatment outcome among MDRTB/HIV.

Objectives: To determine treatment outcomes and influencing factors among HIV co-infected multidrug resistant tuberculosis patients in Dar es Salaam region and Kibong'oto Infectious Disease Hospital in Kilimanjaro region from 2009 to 2017 and each patient evaluated for treatment outcome from 2011 to 2019.

Methods: We conducted a retrospective cohort study involving MDRTB/HIV co-infected patients from the MDRTB database aged ≥ 15 years from Dar es Salaam region and Kibong'oto Infectious Disease Hospital in Kilimanjaro region. The study included analysis of patients registered in the MDRTB/HIV co-infected register between 2009 and 2017 and who were censored from 2011 to 2019 to determine the treatment outcome. The outcome was favorable if the patient was declared cured or completed treatment. The outcome was unfavorable if the outcome was died, lost to follow-up or the treatment failed. Independent variables included individual social-demographic characteristics, clinical as well as health system characteristics. Quantitative variables were expressed in mean and standard deviation; qualitative variables were expressed in frequency and percentage using STATA. Cox proportion hazard model was used to determine the risk of unfavorable outcome and factors associated with increased risk of

unfavorable multidrug resistant tuberculosis treatment outcomes. In addition, Kaplan Meier survival analysis determined time to occurrence of unfavorable treatment outcomes and cox proportional hazard regression to determine. A p-value of less than 5% was considered to be statistically significant.

Results: A total of 212 multidrug resistant tuberculosis/HIV patients were enrolled in the study out of 247 patients that were present in the database. The proportion whose outcome was unfavorable was 19% while the incidence rate of unfavorable treatment outcomes was 10.4/1000 person-months and occurred mostly in the initial 10 months from treatment start. Factors found to increase the risk of unfavorable treatment outcomes among Multidrug resistant tuberculosis/HIV patients were underweight (aHR 4.50, 95% CI 2.24 to 9.05, $p < 0.001$), severe anaemia (aHR 5.13, 95% CI 1.41 to 18.57, $p = 0.013$), renal insufficiency (aHR 2.7 95% CI 1.20 to 6.05, $p = 0.016$) and non-communicable comorbidities (aHR 3.00, 95%CI 1.25 to 7.19, $p = 0.013$)

Conclusion: Results from the study enlightened that, the unfavorable outcome was 19%. This is higher than the World Health Organization recommended proportion of below 10%. Most of unfavorable outcomes occurred during the intensive treatment phase and were significantly influenced by severe anemia, low body mass index, renal impairment and non-communicable comorbidities. If the interventions planned and by National Tuberculosis and Leprosy Control Program targets to address factors that increase the risk of unfavorable MDRTB treatment outcomes among MDRTB/HIV co-infected patients the goal to improving treatment success rate will be achieved by 2030.

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LIST OF ABBREVIATIONS

ART	Ante retroviral Therapy
BMI	Body mass Index
DMO	District Medical Officer
DRTB	Drug Resistant Tuberculosis
DST	Drug Sensitivity Test
ECG	Electrocardiography
HIV	Human Immunodeficiency Virus
INH	Isoniazid
KIDH	Kibong'oto Infectious Disease Hospital
MDRTB	Multidrug Tuberculosis
MDRTB/HIV	Multidrug resistant tuberculosis with Human Immunodeficiency Virus co-infection
MOHCDGEC	Ministry of Health Community Development, Gender, Elderly and Child
NTLP	National Tuberculosis and Leprosy Program
RFT	Renal Function Test
RIF	Rifampicin
RR	Rifampicin Resistance
TB	Tuberculosis
TFELTP	Tanzania Field Epidemiology and Laboratory Training Program
WBC	White Blood Cells
WHO	World Health Organization
XDR-TB	Extremely Drug resistant Tuberculosis

DEFINITIONS OF TERMS

Cured

A multidrug resistant tuberculosis patient who has completed treatment without evidence of treatment failure and who has two or more consecutive negative cultures taken at least 30 days apart, after the intensive phase

Death

It is defined as mortality for any reason during multidrug resistant tuberculosis treatment

Extensively Resistant Tuberculosis (XDR-TB)

Is a drug resistant Tuberculosis with resistance to any fluoroquinolone (levofloxacin, moxifloxacin) and any of the injectable second-line TB drugs (capreomycin, kanamycin, and amikacin).

Favorable MDRTB treatment outcomes

Is the broad classification of treatment outcomes that includes MDRTB patients who were cured and patients who completed treatment but were not declared cured

Lost to follow up

This is when multidrug resistant tuberculosis treatment has been interrupted for two consecutive months or more.

Mono resistant Tuberculosis;

This is a form of tuberculosis, which is resistant to any single drug of the first-line anti-tuberculosis medications

Multidrug resistant treatment outcome

It is an evaluation done to a Multidrug Resistant Tuberculosis patient at end of two years following initiation and use of multidrug resistant tuberculosis treatment for at least 20 months

Polyresistant Tuberculosis;

A form of tuberculosis that is resistant to more than one first-line anti-tuberculosis drug other than both Rifampicin, and isoniazid.

Treatment completed

This is when a multidrug resistant tuberculosis patient has completed treatment but did not meet the definition for cured due to a lack of bacteriological results

Treatment failure

This is treatment terminated or a need for permanent regimen change of at least two anti-TB drugs due to an adverse drug reaction, or lack of culture conversion by the end of the intensive phase, or bacteriological reversion in the continuation phase after conversion to negative after intensive phase, or evidence of additional acquired resistance to fluoroquinolones or second-line injectable drug;

Unfavorable multidrug resistant tuberculosis treatment outcomes

Is the broad classification of tuberculosis treatment outcomes that includes patients who either died due to any cause during multidrug resistant tuberculosis treatment, lost to follow up, or patients who had treatment failure.

CHAPTER ONE

INTRODUCTION

1.1 Background

Recent global reports revealed that 10 million people were suffering from tuberculosis globally of whom 25% lived in Sub-Saharan Africa (1). Among them, a substantial number (82,166) were reported from Tanzania (2).

Drug resistant tuberculosis (DR-TB) is caused by Mycobacterium Tuberculosis that is resistant to at least one first-line anti-TB drug. Multidrug Resistant Tuberculosis (MDRTB) is a form of drug resistant tuberculosis that is resistant to both Rifampicin and Isoniazid which are the key first-line drugs. Other forms of drug resistant tuberculosis are polyresistant TB, Mono-resistant TB, extensively resistant TB (XDR-TB) and Rifampicin-resistant Tuberculosis. Rifampicin resistance is a proxy for multidrug resistant tuberculosis as it mostly occurs concomitantly with isoniazid resistance (1,3–7). Globally, 456, 426 people have recently been reported to have tuberculosis with HIV co-infection (3). In the Africa region, the burden of TB and HIV co-infection is un-proportionally high as it is home to 70% of the TB/HIV co-infected cases (5,8). The emergence of multi drug resistant tuberculosis and HIV co-infection interaction impacts negatively TB case management, as well as case outcome and program cost resulting in a global complex problem.

Multidrug resistant tuberculosis is curable, having two regimens available for treatment, a shorter-term multidrug resistant tuberculosis treatment regimen used for 9 to 11 months and a longer-term also called individualized (conventional) treatment regimen that takes at least 20 months (9–11). To eliminate TB transmission, World Health Organization has recommended a treatment success rate of above 90% for multidrug resistant TB (2,3). Treatment outcome data for people with multidrug resistant tuberculosis show a global treatment success rate of 57%; and 64% in the Africa region for the 2017 cohort (3); whereas in Tanzania, the treatment success rate for multidrug resistant tuberculosis has been reported to be 83%. This treatment success rate is higher than the global and African rates but is still lower than that recommended by World Health Organization (WHO) (2,6).

The burden of multidrug resistant tuberculosis has been reported to increase yearly whereby, in the year 2019 a total of 206,030 Multidrug Resistant Tuberculosis (MDR/RR-TB) cases were notified globally, which was a 10% increase from 2018 notified cases (3). In Africa 29,155 multidrug resistant tuberculosis cases were notified in 2019 that was a 15% increase in cases compared to those notified in 2018 (3,12). Rising multidrug resistance was also reported in Tanzania, where the number of cases rose by 16% to 534 multidrug resistant tuberculosis cases in 2019 (2).

The then emergence of HIV epidemic reversed the downward trend of Tuberculosis and thus fueling the Tuberculosis to new epidemic proportions adding another complexity dimension to the Tuberculosis multidrug resistance. Tuberculosis and HIV have a dynamic interaction in which TB causes progression of HIV infection to disease while HIV increases the body susceptibility to TB infection including multidrug-resistant tuberculosis (4). In addition, sub-Saharan Africa is home to 72% of multidrug resistant tuberculosis patients with HIV co-infection globally (13). In Tanzania, the burden of TB/ HIV co-infection in the year 2019 was 24% whereas, HIV co-infection among multidrug resistant tuberculosis patients for the same year was reported to be 28% (2).

Management of multidrug resistant tuberculosis has been challenging especially in Africa where the HIV epidemic is high. Patients with multidrug resistant tuberculosis and HIV co-infection have been experiencing unfavorable treatment outcomes more as compared to MDRTB patients who are HIV negative (14). Despite the interaction, each requires a different treatment modality while the HIV co-infection exacerbates the TB drug resistance creating a very complex problem that needs concerted planning and management(15). However, little information on factors contributing to treatment outcomes among HIV co-infected patients is available despite its public health importance.

1.2 Problem statement

Multidrug resistant Tuberculosis among HIV co-infected patients is on the rise and remains a significant public health problem of which 72% are found in Sub-Saharan Africa (3,13). An increasing trend is also observed in Tanzania whereby 534 multidrug resistant tuberculosis HIV co-infected cases were reported in the year 2019; this was an increase of 16% compared to cases notified in 2018 (2,16).

Tuberculosis/HIV co-infection is associated with poor disease outcomes and even worse in the case of multidrug resistant tuberculosis (17,18). A study in India reported that in a total of 787 study participants, 4% were HIV co-infected. Among the multidrug resistant tuberculosis patients who were HIV co-infected, 62% had unfavorable treatment outcomes (7). Another study was done in Zimbabwe that revealed that 47.1% of multidrug resistant tuberculosis patients enrolled in a study were HIV co-infected and 65% of them had unfavorable treatment outcomes, particularly death (11). In a study done in Kilimanjaro, at Kibong'oto Infectious Disease Hospital involving 193 patients, it was observed that being HIV-positive was one of the predictors of poor treatment outcome; whereby among 13 multidrug resistant tuberculosis patients who died, 9 (69%) were HIV-positive (19). In addition to the interaction, each requires a different treatment modality while the HIV co-infection exacerbates the TB drug resistance the ensuing disease severity and chronicity create a complex problem leading to increased burden and in need of innovative concerted strategies for planning and management(15).

The global efforts to escalate the TB epidemic include the WHO end TB strategy by 2035. The strategy includes efforts to ensure early detection of Multidrug Resistant Tuberculosis by use of gene X-pert machines and enrolment to effective multidrug resistant tuberculosis medications provision of treatment support, as well as an effective screening of contacts and high-risk groups. Regardless of the efforts, there is still a low treatment success rate both globally and in Tanzania (2,3). Thus, there is a need for real-time data for regular monitoring to timely intervene as need shall be to be on track to achieve the End Tuberculosis epidemic by 2030. However, there is a dearth of detailed information on current outcomes and the correlates of the low treatment success to enable planning efforts to scale up strategies to increase treatment success.

This study aims at determining the treatment outcomes, and factors influencing the treatment outcomes among multidrug resistant tuberculosis patients co-infected with HIV.

1.3 Conceptual framework

Treatment outcomes among multidrug resistant tuberculosis with HIV co-infection are determined by multiple factors which might include socio-demographic, clinical, adherence and health services factors (6,14,20). The socio-demographic characteristics in this study included age, sex, occupation, and smoking/drug abuse. Clinical factors at the start of multidrug resistant tuberculosis treatment and during treatment that predicted treatment outcomes included ART initiation, previous TB treatment history, and body mass index, co-morbid conditions like Diabetes Mellitus, sputum culture conversion, anemia, renal dysfunction, HIV viral suppression, and presence of serious treatment adverse events. Adherence factors like treatment interruptions, family and social support may also determine the multidrug resistant tuberculosis treatment outcomes. Health services factors that may influence treatment outcomes include the availability of health information, uninterrupted multidrug resistant tuberculosis drug supply, sustainable financing, and social protection, financing mechanisms for multidrug resistant tuberculosis services, health workforce providing patient-centered services. In this study, health care services factors were not included because these factors are not present in the manual multidrug resistant tuberculosis register and in patients' clinical files which were used as data sources.

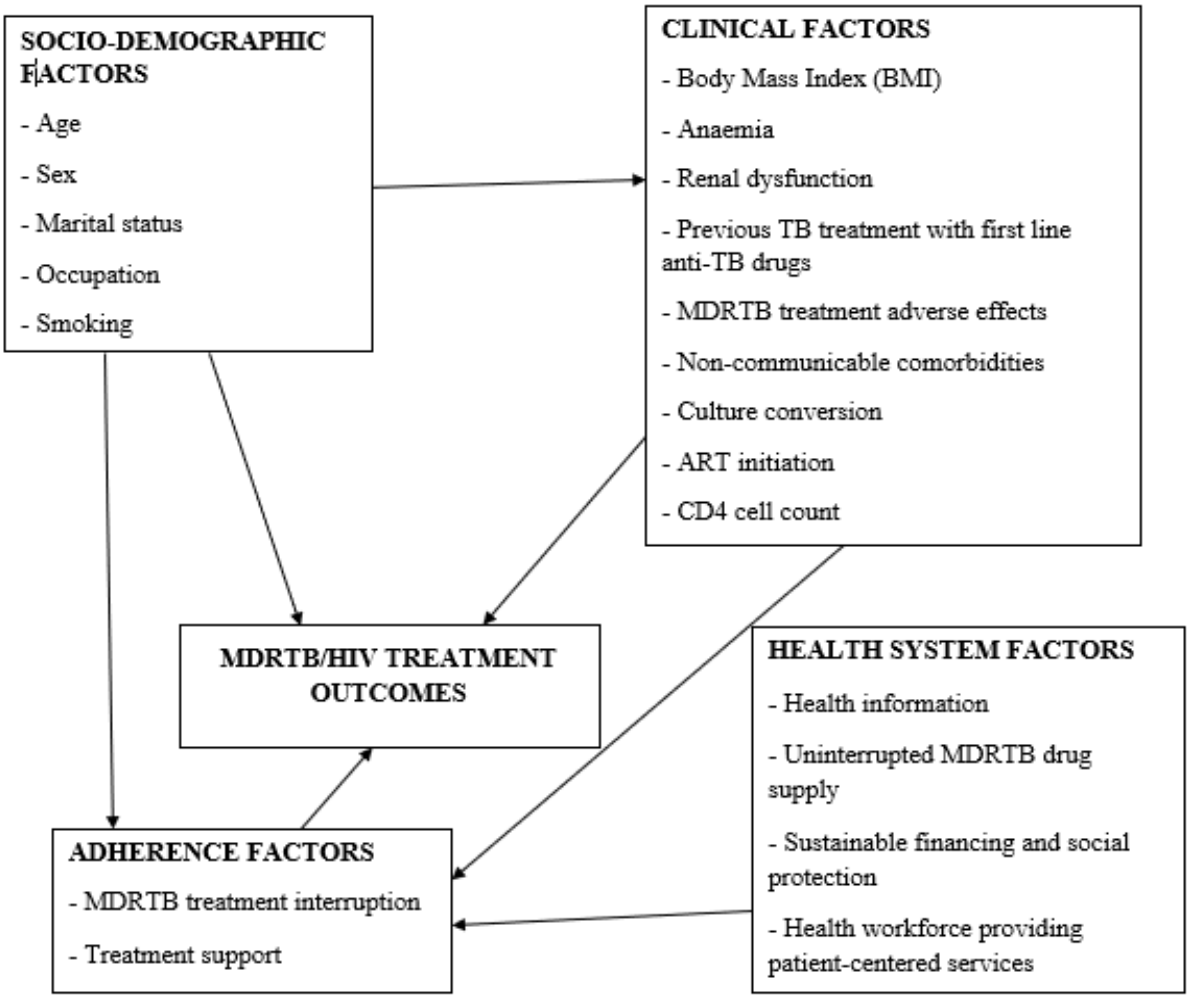

Figure 1: Conceptual framework showing factors for multidrug resistant tuberculosis treatment outcomes

1.4 Rationale

The ongoing HIV epidemic and the increasing number of patients with drug-resistant tuberculosis have posed a challenge to efforts towards global TB control through the WHO End TB strategy that aims at halting Tuberculosis by 2035 (4). In Tanzania, there is little information on current outcomes and correlates of unfavorable treatment outcomes among MDRTB/HIV patients. Results from this study will help the National tuberculosis control Program (NTLP) to make an informed decision on MDRTB patients' management policies and strategies aimed at improving treatment outcomes among HIV co-infected multidrug resistant tuberculosis patients.

Understanding the rate of occurrence of unfavorable outcomes will help to monitor the performance of various interventions against multidrug resistant tuberculosis with HIV co-infection targeting the period when most unfavorable treatment outcomes occur. It will also add to the body of knowledge among health care providers on the importance of increased suspicious index on early diagnosis and timely initiation of both ART and multidrug resistant tuberculosis treatment.

1.5 Research questions

1.5.1Broad research question

What are the treatment outcomes and influencing factors in MDRTB patients co-infected with HIV?

1.5.2 Specific research questions

1. What is the rate of occurrence of unfavorable treatment outcomes in multidrug resistant tuberculosis/HIV co-infected patients?
2. What are the factors that increase the risk of unfavorable outcomes among multidrug resistant tuberculosis patients co-infected with HIV?
3. What is the time to occurrence of unfavorable treatment outcomes among multidrug resistant tuberculosis/HIV co-infected patients?

1.6 Objectives

1.6.1 Broad objective

To determine treatment outcomes and influencing factors among HIV co-infected multidrug resistant tuberculosis patients in Dar es Salaam region and Kilimanjaro Infectious Disease Hospital in Kilimanjaro region from 2009 to 2017 to generate evidence for barriers to better outcomes among MDRTB patients

1.6.2 Specific objectives

1. To determine the incidence rate of unfavorable treatment outcomes among HIV co-infected multidrug resistant tuberculosis patients.
2. To describe factors predicting increased risk of unfavorable outcomes among HIV co-infected multidrug resistant tuberculosis patients.
3. To estimate time to occurrence of unfavorable treatment outcomes among HIV co-infected multidrug resistant tuberculosis.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Overview

Multidrug resistant tuberculosis is a public health concern worldwide with notified multidrug resistant tuberculosis cases been increasing yearly (1,3). The ongoing HIV epidemic increases the risk of Tuberculosis and in turn, increases the number of Tuberculosis cases and consequently increases the number of patients with drug-resistant tuberculosis. Tuberculosis and HIV have a dynamic interaction in which TB causes progression of HIV infection to disease while HIV increases the body susceptibility to TB infection and also the likelihood of multidrug resistant tuberculosis (4). The HIV and Tuberculosis interaction results in a complex problem which makes achieving the goal of Ending Tuberculosis epidemic by 2030 unlikely thus requiring innovative strategies to achieve the anticipated goal.

World Health Organization's recent report revealed that multidrug resistant tuberculosis cases globally were 206,030 and of whom 29,155 lived in Africa (3). On the other hand, another study done in sub-Saharan African countries revealed that the burden of multidrug resistance among HIV co-infected tuberculosis patients was 72% (13). A similar increasing trend was observed in Tanzania as it was revealed that multidrug resistant tuberculosis among HIV co-infected patients' notification increased from 449 in 2018 to 534 in 2019(2).

Despite global efforts to eliminate multidrug resistant tuberculosis through early diagnosis, notification, and early initiation to effective treatment, there are still low treatment success rates (2,3). Studies that were done in China and the Netherlands revealed variability in successful treatment outcomes ranging from as low as 30% to as high as 80% (21,22). More than 25% of multidrug resistant tuberculosis patients have been reported to experience unfavorable outcomes which are more among HIV co-infected multidrug resistant tuberculosis patients (17,18).

2.2 Factors associated with treatment outcomes in HIV co-infected multidrug resistant tuberculosis patients

This section presented factors associated with multidrug resistant tuberculosis treatment outcomes among HIV co-infected Tuberculosis patients. The factors were categorized into patient, family, clinical, and health system; the following is a discussion of each of them.

2.2.1 Social demographic characteristics:

Age and sex

Age could be associated with the likelihood of the treatment outcome among HIV co-infected patients as revealed among some studies. A study done in Zimbabwe revealed that the likelihood of unfavorable treatment outcome among HIV co-infected multidrug resistant tuberculosis patients was more than twice among patients who were aged 25 years compared to those who were younger (14). Also, in another study done in South Africa, females were less likely to have an unsuccessful treatment outcome as compared to males (17). Thus, it is possible that being a female and older one is inclined to be carrying out a lot of responsibilities in addition to lower or lack of income and therefore unable to follow treatment diligently resulting in a poor outcome.

Smoking among multidrug resistant tuberculosis patients with HIV co-infection

A study in Kilimanjaro, Tanzania revealed that cigarette smoking was associated with unfavorable treatment outcome among HIV co-infected multidrug resistant tuberculosis patients. Patients who smoked were 5 times more likely to experience unfavorable treatment outcome compared to non-smokers (19). A similar association of smoking was also observed in a study done in the Netherlands whereby patients who smoked were more than 6 times likely to experience unfavorable treatment outcome compared to non-smokers among HIV-co-infected multidrug resistant tuberculosis (22).

2.2.2 Clinical factors influencing multidrug resistant tuberculosis treatment outcomes:

ART initiation

Antiretroviral therapy initiation to HIV-positive clients long before having multidrug resistant tuberculosis disease or after being diagnosed with multidrug resistant tuberculosis/HIV co-infection can influence treatment outcomes. HIV co-infected Tuberculosis patients have to persevere the double care obligation to adhere to HIV Antiretroviral treatment while also adhering to the multi-drug resistant tuberculosis treatment. Consequently, the demands of either treatment, potential adverse reactions, and resource and time limitation create a complex situation enhancing unfavorable outcomes. This has been asserted in a study done in South Africa whereby patients who received ART before commencing multidrug resistant tuberculosis treatment were 2 times more likely to experience unfavorable treatment outcomes compared with those who initiated ART after commencement of multidrug resistant tuberculosis treatment (23). A multi-country study done in sub-Saharan Africa involving multidrug resistant tuberculosis/HIV co-infected patients revealed that the median time of ART initiation before the start of multidrug resistant tuberculosis treatment was 7 months as compared to one month among those who started ART treatment after the start of multidrug resistant tuberculosis treatment (14). Thus, there was a long delay in initiation of treatment among those HIV co-infected multidrug Tuberculosis resistant patients resulting in an enhanced unfavorable outcome.

Anemia

Nutrition at baseline including the level of hemoglobin would predict the outcome. Anemia was associated with nutritional and immunological deficiencies which could also enhance the likelihood of an unfavorable outcome. Such thinking is supported by a recent study in South Africa which revealed that HIV co-infected multidrug resistant tuberculosis patients with severe anemia had 5 times higher likelihood of experiencing treatment failure compared to patients who had normal hemoglobin levels (OR 4.72, 95 % CI 1.47–15.08, p = 0.009), results were statistically significant. (23).

CD4 cell count

Markers of HIV severe progression disease is the declining CD4 which also signals the interaction with TB and is also a good predictor of unfavorable outcome. A study done in South Africa had a similar observation that multidrug resistant tuberculosis/HIV co-infected patients with a CD4 count of ≥351 cells/mm3 are less likely to have unfavorable MDRTB treatment outcomes (OR: 0.46; CI: 0.42-0.52) as compared to those with a CD4 count ≤200 cells/mm3 (10). However, on the contrary, a study done in Tanzania revealed that there was no significant relationship of unfavorable treatment outcome among multidrug resistant tuberculosis patients whose CD4 was less than 200 cells/ul compared to those whose CD4 cell count was or above 200cells/ul (19). The inconsistency could be explained by the presence of confounders that were not accounted for since literature supporting the relationship with CD4 is overwhelming.

Body Mass Index (BMI)

Another marker of HIV progression to disease and consequently the likelihood of unfavorable outcome is poor nutrition and which low BMI is the manifestation. This is supported by a study done in Lesotho which observed that multidrug resistant tuberculosis/HIV patients who had severely low BMI were 5 times more likely to unfavorable treatment outcomes compared to those patients with normal BMI (24). This was also revealed in a study done in India whereby multidrug resistant tuberculosis patients who were underweight (BMI < 18.5 kg/m^2) showed an increased risk of the unfavorable outcome as compared to those with normal BMI (18.5 to 24.5 kg/m^2) (7).

History of Previous Tuberculosis treatment

The risk of unfavorable multidrug resistant tuberculosis treatment outcome increases in patients who are in the re-treatment category whereby these patients had previously been treated with first-line anti tuberculosis treatment. The assumption is supported by a study that was done in Zimbabwe which reported that multidrug resistant tuberculosis patients with HIV co-infection who were once infected with drug-sensitive tuberculosis and got treated with first-line anti-tuberculosis drugs before they were infected with multidrug resistant tuberculosis, had more than 4 times risk of experiencing unfavorable outcomes as compared to multidrug resistant

tuberculosis patients who had never used first-line anti-tuberculosis medications (11). Also, a study in Sudan revealed that multidrug resistant tuberculosis patients who were in the TB re-treatment category were 5 times more likely to have unfavorable treatment outcome as compared to multidrug resistant tuberculosis patients from a new multidrug resistant tuberculosis category (25).

Poor treatment outcomes among HIV co-infected multidrug resistant tuberculosis patients were also influenced by the presence of non-communicable comorbid conditions. This was revealed in a study in Johannesburg, South Africa that the presence of other diseases among MDRTB/HIV patients had 2 times the likelihood of unfavorable outcome as compared to multidrug resistant tuberculosis/HIV patients without other comorbidities (23).

2.2.3 Adherence factors

Treatment adherence is a factor that influences treatment outcome. To enhance favorable treatment outcomes, it requires the presence of treatment support as well as non-interruption of treatment. A study from e-journal databases observed that there were 2 times encouraging improvement in treatment success rate when treatment support was integrated into multidrug resistant tuberculosis treatment (26). A study in Ethiopia revealed that multidrug resistant tuberculosis patients with HIV co-infection who had treatment interruptions had two times increased risk of unsuccessful treatment outcomes as compared to patients who adhered well to multidrug resistant tuberculosis treatment (27). Thus, this study aims at establishing currently the magnitude of unfavorable treatment outcome among HIV co-infected multidrug resistant tuberculosis as inputs to strategies to improve outcomes.

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study setting and design

It was a retrospective cohort study design conducted using two sources of secondary data the HIV co-infected multidrug resistant tuberculosis treatment registers and individual patient clinical files of HIV co-infected multidrug resistant tuberculosis patients. The study was conducted at the two multidrug resistant tuberculosis treatment services sites one from Dar es Salaam Region and the second was Kibong'oto Infectious Disease Hospital in Kilimanjaro.

Tanzania has 30 regions is subdivided into districts that have facilities providing TB services including multidrug resistance services at the regional level.

Dar es Salaam is one of the regions in Tanzania providing multidrug resistant tuberculosis services. According to the 2012 population and housing census, Dar es Salaam region had a total of 1,393 km^2 and 4,364,541 population (28). It consists of five Municipal councils, namely, Kinondoni, Temeke, Ilala, Ubungo and Kigamboni. These Municipal councils are referred to as regions by the National TB and Leprosy Program whereby Ilala is further divided into Ilala I and Ilala II making a total of 6 NTLP regions in Dar es Salaam. Since the start of the multidrug resistant tuberculosis treatment Program in Tanzania in 2009, Dar es Salaam region has been contributing 25- 40% of all notified multidrug resistant tuberculosis cases yearly. Dar es Salaam region has 29 NTLP districts present in five municipal councils. Each NTLP district has at least one multidrug resistant tuberculosis treatment initiation center which has been functional since 2016 when decentralization started.

Kibong'oto Infectious Disease Hospital (KIDH) is located in the northern part of Tanzania in Kilimanjaro region. It was established in 1926 as a TB sanatorium. It started providing multidrug resistant tuberculosis treatment services in 2009 whereby, all diagnosed multidrug resistant tuberculosis cases were admitted and treated at the Kibong'oto Infectious Disease Hospital. The hospital has currently remained a referral hospital for complicated multidrug resistant tuberculosis cases requiring admission as most facilities are now offering multidrug resistant tuberculosis ambulatory services following decentralization.

The selection of these two study sites was based on the fact that Dar es Salaam Region contributes to 25-40% of all MDRTB cases notified yearly and was the first region to provide ambulatory MDRTB services following decentralization of MDRTB services whereas Kibong'oto Infectious Disease Hospital has been receiving MDRTB cases that cannot afford ambulatory services from all over the country including those from Dar es Salaam region (2).
To improve access to services and quality multidrug resistant tuberculosis treatment were decentralized in 2016, it was done through capacitating 111 health facilities (from dispensary to hospital levels) all over the country to enable the provision of ambulatory multidrug resistant tuberculosis services including diagnosis by gene X-pert machines in some of these facilities. Central support included timely delivery of needed reagents and medications to ensure that diagnosis and treatment of multidrug resistant tuberculosis are provided free of charge.

Diagnosed multidrug resistant tuberculosis patients are registered in a multidrug resistant tuberculosis register which has personal particulars (name, age, sex, TB registration number, address, treatment supporter/contacts), enrollment date, Drug resistance registration group (new or previously treated), baseline investigation (sputum smear results, culture results, X-pert results), Drug Sensitivity test (DST) and Type of resistance (Rifampicin Resistance (RR), Multidrug Resistance (MDR) and Extensive Drug Resistance (XDR)), treatment regimen (individualized long or shorter regimen), TB/HIV details (date tested, results, Antiretroviral Therapy (ART) start date and Cotrimoxazole (CPT) start date), drug adverse effects, transfer details and treatment outcomes (cured, treatment completed, lost to follow up, died and treatment failure). Along with registration in a multidrug resistant tuberculosis register, a clinical file is opened which has additional information apart from those present in a multidrug resistant tuberculosis register. These include; weight monitoring, laboratory monitoring (hemoglobin level, Renal Function Test (RFT), Liver Function Test (LFT), CD4 count, serum electrolytes, uric acid and White Blood Cells (WBCs)), bacteriology monitoring (smear results, culture results), Chest X-ray and Electro Cardiogram (ECG) monitoring; drug administration and medical diagnosis other than tuberculosis. The assessments are done as pre-treatment evaluations for all patients to determine which regimen a patient is to be initiated on.

3.3 Study population

The study used data from multidrug resistant tuberculosis registers including all HIV co-infected multidrug resistant tuberculosis patients aged 15 years and above in Dar es Salaam region and KIDH in Kilimanjaro who were enrolled in treatment from 2009 to 2017 and each patient evaluated for treatment outcome from 2011-2019.

3.4 Sample size and power of the study

From the NTLP database, there were 247 MDRTB/HIV patients of which 212 patients who met study criteria were included in the analysis. Among 212 MDRTB/HIV patients studied, 8% had non-communicable comorbid conditions; The power of the study was calculated by Open epi calculator whereby non-communicable comorbid disease was used as an exposure variable. HIV co-infected Multidrug resistant tuberculosis/HIV patients with non-communicable comorbidity conditions were grouped as exposed while those without non-communicable comorbid conditions were grouped as an unexposed group. A two-sided 95% confidence interval was considered and the proportion of exposed with the outcome (P1) was 52% while the proportion of unexposed with outcome was 8%. The power of the study was found to be 99.95% (29).

3.5 Sampling technique

Multidrug resistance tuberculosis manual register, which includes all patients enrolled for treatment was used as a sampling frame. These registers were available and used at Health facilities offering multidrug resistant tuberculosis services in Dar es Salaam region and at Kibong'oto Infectious Disease Hospital (KIDH).

3.6 Inclusion and exclusion criteria

3.6.1 Inclusion criteria

- All multidrug resistant tuberculosis patients who were HIV co-infected, with documented multidrug resistant tuberculosis treatment outcomes aged 15 years and above who were enrolled for treatment from 2009 to 2017, and each patient was evaluated for treatment outcomes starting 2011 to 2019.

- All multidrug resistant tuberculosis patients who were HIV co-infected, with baseline drug sensitivity test results to confirm drug resistance.

3.6.2 Exclusion criteria

- All Multidrug resistant Tuberculosis patients who were HIV co-infected aged 15 years and above, with missing clinical files or with clinical a file which has no documents within them.
- All Multidrug resistant Tuberculosis patients who were HIV co-infected with missing age

3.7 Study variables:

In this study, both the dependent and independent variables were included and measured.

3.7.1 Dependent Variable

These were the multidrug resistant tuberculosis treatment outcomes among HIV co-infected patients which were classified into favorable and unfavorable outcomes. Favorable outcome was measured by documentation of cured or treatment completed in a register or patient clinical file while the unfavorable outcome was measured by documentation of death, lost to follow up, or treatment failure.

3.7.2 Independent Variables:

These included the socio-demographic, clinical characteristics, and adherence that would influence the treatment outcomes among multidrug resistant tuberculosis patients co-infected with HIV. The socio-demographic characteristics included age, sex, marital status, occupation, and smoking. Smoking status was measured by ‘yes’ or ‘no’ options as it was difficult to quantify the amount and frequency of smoking from the already collected information present in the multidrug resistant tuberculosis register and the individual patient clinical file. The implication of measuring smoking status by yes or no responses is that I would not give the true effect (may overestimate the effect) smoking has on multidrug resistant tuberculosis treatment outcomes. Marital status was categorized as living with a partner or with no partner whereas occupation was categorized as formal employment, informal employment, student, peasant, and

others. Formal employment included teachers, engineers, technicians, secretaries, drivers, cleaners. Informal employment included miners, fishers, business, petty trade, self-employed, tailor, gardener. The others category included all those documented as housewives, not working, retired persons, and those whose occupations were not documented.

The clinical factors influencing treatment outcomes were assessed at the start of multidrug resistant tuberculosis treatment due to the availability of complete patients' information at baseline except for the body mass index that had complete information available both at the beginning and at end of treatment. These factors included ART initiation, body mass index, chronic non-communicable co-morbid like diabetes mellitus, cancers, liver diseases, cardiovascular diseases (hypertension, congestive cardiac failure). Other factors were previous TB treatment history, treatment adverse event, culture conversion, anemia, immune status (by CD4 cell count), and renal dysfunction.

Body mass index is the value derived from the weight and height of a person and it's an indicator of body fatness. In this study, it was categorized as normal if ranged between 18.5 to 24.9 kg/m2, underweight if below 18.5kg/m2, and overweight/obese if equal to or above 25kg/m2 (30). Anemia is a condition in which there is a deficiency of red cells or hemoglobin in the blood, resulting in pallor and weariness. In this study, anemia was measured by use of hemoglobin level readings and was interpreted according to the sex of the study participant. In Females, the hemoglobin level of equal or above 12g/dl was considered as no anemia (normal), mild anemia if the hemoglobin level was between 11g/dl to 11.9g/dl, moderate anemia if hemoglobin level was between 8 to 10.9g/dl and severe anemia if hemoglobin level was below 8g/dl. In males, a hemoglobin level of above or equal to 13g/dl was considered no anemia (normal hemoglobin), whereas a hemoglobin level of 11g/dl to 12.9g/dl was considered mild anemia. Those with hemoglobin levels between 8g/dl to 10.9g/dl were considered to be having moderate anemia while those with hemoglobin levels below 8g/dl were considered to be having severe anemia (31).

Timing for ART initiation was elicited whereby it was measured by ART initiation before the start of multidrug resistant tuberculosis treatment or after the start of multidrug resistant tuberculosis treatment. The presence of non-communicable co-morbid conditions was measured by ‘yes’ or ‘no’ options as well as mentioning of actual non-communicable co-morbid condition a multidrug resistant tuberculosis/HIV co-infected patient has. Immune suppression status was assessed by the CD4 cell counts levels. The CD4 cell count of above 500cells/mm^3 was considered normal, CD4 cell count between 350 to 500cells/mm^3 was taken as mild immune suppression, CD4 cell count of 200 to 349 cells/mm^3 as advanced immune suppression, and CD4 count of below 200cells/mm^3 was considered severe immune suppression (32).

Sputum culture conversion was defined as two consecutive negative cultures, collected at least 30 days apart. In this study, it was categorized as an early conversion if it occurred within 6 months from the start of multidrug resistant tuberculosis treatment and late conversion if occurred more than 6 months from the start of multidrug resistant tuberculosis treatment (33). The multidrug resistant tuberculosis treatment adverse events were measured as ‘yes’ if adverse effects were present and ‘no’ if adverse events were absent. Events that were considered as adverse events are gastrointestinal disturbances (vomiting, gastritis), dermatological conditions (skin rash, itching, Steven-Johnson syndrome), ototoxicity, hepatotoxicity, peripheral neuropathy, nephrotoxicity, psychosis, depression, gynecomastia, visual disorders (34,35).

The presence of previous TB treatment history in a multidrug resistant tuberculosis patient was measured by ‘yes’ or ‘no’ options whereby; ‘yes’ indicated a positive TB treatment history by using the first-line TB treatment regimen and 'no' indicated absence of the previous history of TB treatment by using the first line anti TB drugs. Renal dysfunction is the insufficiency of kidneys to remove wastes and extra water from blood or the inability from keeping the body's chemicals in balance. In this study, renal dysfunction was measured by assessing the blood creatinine levels. Serum creatinine level of 0.8 to 1.21mg/dl and 0.8 to 1.4mg/dl was considered normal for women and men respectively. Blood creatinine level above 1.2mg/dl in women and above 1.4mg/dl in men was considered abnormal (high) (36).

Adherence factors influencing treatment outcomes included treatment interruption and family support. Family support for multidrug resistant tuberculosis patients was assessed by documentation of treatment supporters in individual patient clinical files. The options 'yes' for the presence of treatment supporters and 'no' for the absence of treatment supporters were used to measure the family support. Intermittent treatment interruption was measured by the number of days a multidrug resistant tuberculosis patient missed the medications during treatment. Short treatment interruption was referred to as interruption of multidrug resistant tuberculosis treatment for at least one day at any time during the treatment course while serious treatment interruption will be an interruption of treatment lasting more than two consecutive weeks but less than two consecutive months (27).

3.8 Data collection procedure and tools

Data extraction tool was constructed to enable the collection of study data whereby the sheet was used to fill both demographic and clinical data. The tool was developed in light of study variables that were obtained from previous studies. There were two data sources from which data was extracted using a standard pretested tool. The tool had two main sections one for each of the following:

Manual register

This included both demographic and clinical data. The information included in the register that was required for the study were name, treatment registration number, age, sex, patent's address, baseline sputum investigations, patient's HIV status, date of multidrug resistant tuberculosis treatment start treatment outcome, and the date of treatment outcome.

Patient’s care clinical file

This is a hard card that contain demographic, clinical and adherence information. It also allows for attachment of MDRTB card, clinical notes, investigation results and daily dotting forms. Patient’s clinical files were used to obtain information that were missing from multidrug resistant patients’ registry due to inadequate documentation as well as to extract information that were not present in registry. The information that was in patient’s care clinical file but not available in MDRTB registry was occupation, next of kin name and address, height, weight,

clinical investigations results (Hb level, creatinine, CD4 cell count, etc.), radiological investigations, comorbidities history, treatment side effects records, daily dotting charts.

Four research assistants who were involved in providing multidrug resistant tuberculosis health services were recruited to assist in data collection whereby three assistants were used in Dar es Salaam region as it required to collect data from health facilities, and one research assistant was involved in data collection at Kibong'oto Infectious Disease Hospital. The selection was based on availability, adequate experience, and knowledge relevant to research and subject matter. One-day orientation was done to them focused on the aim of the study, methodology, data needs and administration of the data extraction tool, and how to handle it. It also included an introduction to research ethics as well as daily logistics information before the start of data collection.

3.9 Validity and reliability

Before data collection, the data extraction tool was pre-tested in Bagamoyo District Hospital which was one of the multidrug resistant tuberculosis treatment initiation facilities in Pwani region. The manual register at the facility where the pre-test was done was used to identify the multidrug resistant tuberculosis/HIV, co-infected patients. The multidrug resistant tuberculosis registration numbers of patients identified from the register were used to retrieve the clinical files of respective patients. The individual patient's information from both registers and clinical files was filled in a data extraction tool and later transferred into an excel spreadsheet. This was done to ensure the validity and clarity of the research tool in collecting the required information and subsequently, corrections to the tool were made before undertaking the study. The pre-test results were not included in the final study analysis.

3.10 Data management and analysis

3.10.1 Data cleaning

After data extraction, data were checked for completeness, consistency, and legibility. An excel data capturing file was prepared and tested. Data from the extraction sheet was entered into the prepared excel data capturing sheet in duplicate to minimize transcription errors followed by data cleaning. The data cleaning process included inspection of columns for each of the 39 variables that were present in a dataset of 215 observations. It was made sure that each of the 39 variables appeared in a column and each of the 215 observations appeared in a row. Three variables i.e., CD4 cell count in the course of multidrug resistant tuberculosis treatment, viral load test results at the start of multidrug resistant tuberculosis treatment, and viral load test results in the course of multidrug resistant tuberculosis treatment were dropped as more than 70% of the observations did not have the values filled. Also, three observations which are observations with code (serial number) 6, 9, and 37 were dropped as data was incorrectly entered, including 2018 as the year of treatment start, which was not in the inclusion criteria for the study thus a dataset remained with 36 variables with a total of 212 observations that were used in the analysis. All numeric fields were ensured that they were all numbers while fields with missing values within the dataset were left blank. Spellings and formatting irregularities including changing all capital letters into small letters, as well as data format for the variables; date of multidrug resistant tuberculosis treatment start, date of HIV test, date of ART start, and date of multidrug resistant tuberculosis treatment outcomes, were made consistent and in a format that was possible to be read by Stata software.

Missing values in this dataset were handled by imputation in Stata version 15 (Stata Corp., Texas USA). In the dataset of 212 observations, 10 variables had missing values, 5 of which were continuous variables. A high proportion of missing values was with CD4 cell count variable 16 (7.5%), culture results in 13(6.1%), and smoking 8 (3.4%). Others had missing values that ranged between 1(0.5%) and 4 (1.9%). The nature of missingness in these variables was completely missing at random as there was no systematic relationship that made some data more likely to be missing than others and the method chosen for imputation was imputation by regression method which has an advantage of increasing data variability as imputation is done

multiple times for the same variable considering all other variables and thus it reduces bias in results.

In Stata, the imputation was done in several steps whereby the data was first declared to be 'mi' set data then imputation was done. At the imputation step, continuous variables with missing values were imputed through the linear regression model; while for the categorical variables which had binary responses, the logistic regression model was run to create an imputed dataset. After the imputations for both continuous and categorical variables that had missing values, an estimation step was done for each imputation, here the logistic regression model was used because the outcome of interest for the study (multidrug resistant tuberculosis treatment outcomes among HIV co-infected patients) was binary. The results obtained from the estimation step were then combined into single multiple imputation results which updated the dataset that has been used for analysis

3.10.2 Data analysis

To facilitate analysis and enable computation of dichotomous effect measures, the outcome variable was grouped into two categories; favorable treatment (cured and treatment completed) and unfavorable treatment outcomes (died, defaulted/lost to follow up, and treatment failure). Quantitative variables were expressed by means and standard deviations (m ± SD) if normally distributed and by median and inter-quartile range if data are skewed. Qualitative variables were described by frequencies (n) and percentages (%).

Survival time data setting using the Stata commands was done based on the time from the start of treatment to unfavorable outcome (hazard time). Cox proportional hazard regression model was fitted to determine factors that had increased hazard of unfavorable outcomes among multidrug resistant tuberculosis patients. The model assumed that the hazards of any covariates were proportional over time i.e., the ratio between hazards was the same at any time t.

The test for proportional hazard assumptions was done based on Schoenfeld residuals whereby the global test for the model showed a chi-square test value of 5.61, degree of freedom was 9 and p-value was 0.7785. The Cox proportional hazard model was suitable for this study as there was a non-significant relationship between residuals and time, with p-value = 0.7785. Factor

predicted increased hazard of unfavorable outcomes among HIV co-infected multidrug resistant tuberculosis patients if the statistical significance p-value was less than 0.05. The independent factors (smoking, treatment supporters, BMI, anemia, comorbid conditions, and renal dysfunction) that were entered into regression analysis were tested for multicollinearity. No multicollinearity was found as each factor in the model had a variance inflation factor (VIF) of one. Kaplan-Meier survival analysis was used to estimate the duration to the occurrence of unfavorable outcomes from the time of commencement of multidrug resistant tuberculosis treatment.

3.11 Ethical consideration

Ethical clearance with number MUHAS-REC-01-2021-467 was obtained from Muhimbili University of Health and Allied Sciences (MUHAS) Research and Ethics Committee (see Appendix 2). Patients' record privacy and confidentiality were observed by using codes only instead of patient names or multidrug resistant tuberculosis registration number. Consent for patients' participation was not sought as routinely collected data were used.

Permission to use program data to conduct the study was obtained from National Tuberculosis and Leprosy Program (Appendix 3). It was also obtained from Dar es Salaam Regional and Districts' administrative as well as Kibong'oto Infectious Disease Hospital administration (Appendix 4)).

CHAPTER FOUR

4.0 RESULTS

Figure 2 presents the flow of patients in the selection process starting with 166 from Kibongoto and 81 from Dar es salaam (Figure 2). Finally, a total of 212 patients were included in the analysis as others were dropped for not meeting the inclusion criteria for the study (Figure 2).

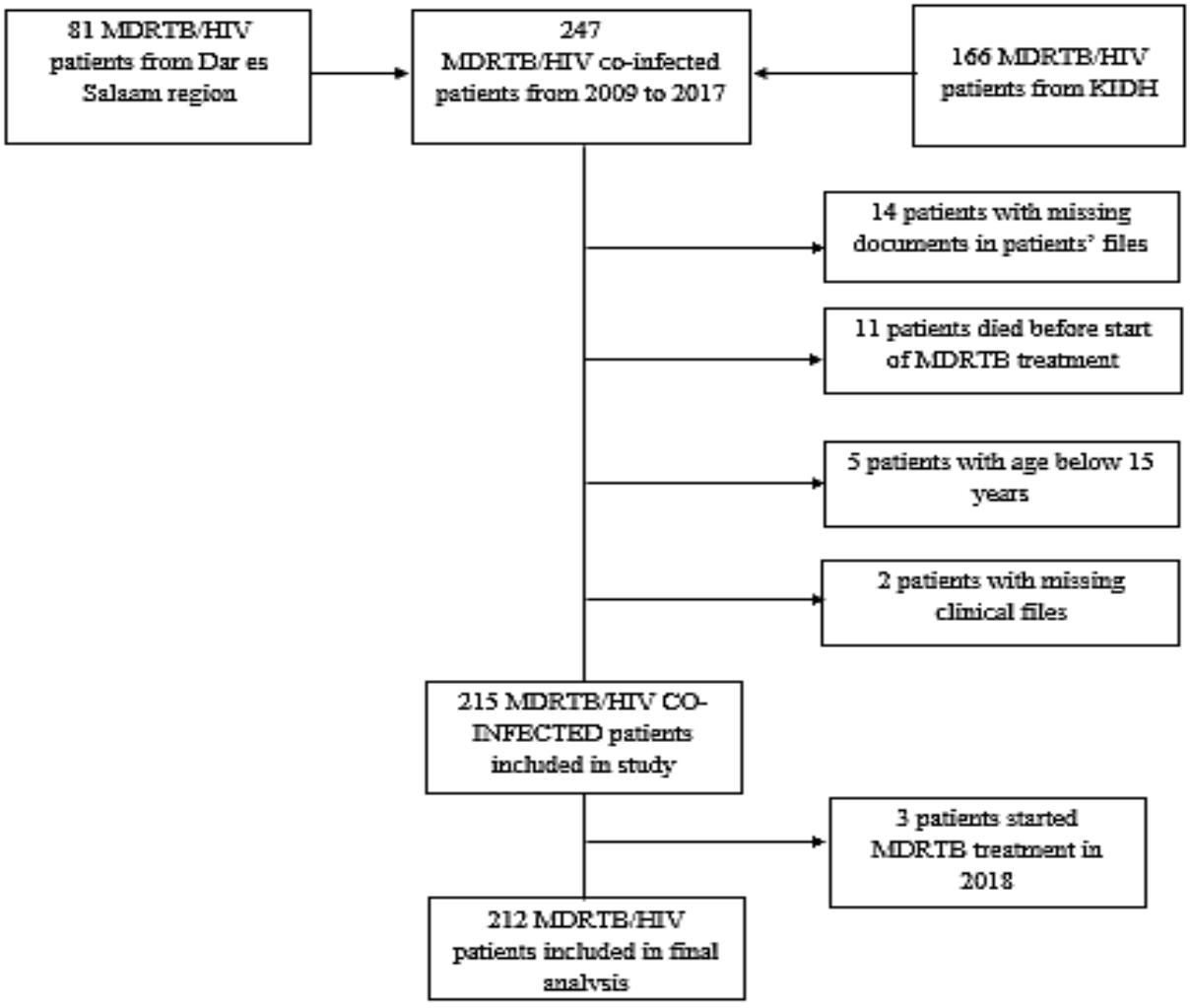

Figure 2: Patient flow chart showing exclusion criteria from the study

The study included 212 participants of whom most 137 (65%) were from Kibong'oto Infectious Disease Hospital, mean age was 39.8 years (sd=10.02). Also, most 156 (71.7%) were in the age group 30-49 years. In addition, the majority 124 (58.49%) were males while 127(59.91%) lived with partners and a few 49(21.23%) had a history of smoking (Table 1).

Table 1: Socio-demographic characteristics of multidrug resistant tuberculosis /HIV patients

Variable	**Frequency (n)**	**Percentage (%)**
Age group		
16 - 29	26	12.3
30 - 49	156	71.7
≥ 50	34	16
Sex		
Male	124	58.5
Female	88	41.5
Marital status		
No partner	85	40.1
With partner	127	59.9
Occupation		
Student	9	4.2
Peasant	70	33
Formal employment	42	19.8
Informal employment	58	27.4
Others	33	15.6
Smoking		
No	167	78.8
Yes	45	21.2

In this study, a history of previous tuberculosis treatment with first-line anti-TB drugs was reported by 137 (64.62%) of patients. The majority 192(90.6%) received support from others on treatment and care while many 211(99.5%) were currently on ART (Table 2).

Table 2: Adherence and clinical characteristics of HIV co-infected multidrug resistant tuberculosis patients

Variable	Frequency (n)	Percentage (%)
Treatment supporter		
No	20	9.4
Yes	192	90.6
Treatment interruptions		
Short interruptions	70	33
Serious interruption	15	7.1
No interruption	127	59.9
BMI at baseline		
Underweight	111	52.4
Normal	88	41.5
Overweight/Obese	13	6.1
BMI at end of treatment		
Underweight	43	20.3
Normal	133	62.7
Overweight/Obese	36	17
Treatment registration group		
New	75	35.4
Previously treated	137	64.6
Culture conversion		
Early	202	95.3
Late	10	4.7
ART use		
No	1	0.5
Yes	211	99.5
ART initiation		
Before MDRTB treatment	153	72.2
After MDRTB treatment start	59	27.8
Immune status by CD4 cell count		
Normal	30	14.2
Mild suppression	30	14.2
Advanced suppression	66	31.1
Severe suppression	86	40.6

Anemia by hemoglobin level		
Normal	55	26.1
Mild anemia	44	20.9
Moderate anemia	73	34.6
Severe anemia	39	18.5
Renal insufficiency by creatinine level		
No	183	86.3
Yes	29	13.7
Treatment adverse effects		
No	146	68.9
Yes	66	31.1
Comorbid conditions		
No	195	92
Yes	17	8
Treatment adverse effects		
No	146	68.9
Yes	66	31.1

4.1 Treatment outcomes among HIV co-infected multidrug resistant tuberculosis patients

Among 212 study participants most 172 (81.13%) their treatment outcome was declared favorable. Favorable outcomes were two and included those who were declared cured 100 (47.17%) and those who were declared that treatment was completed 72 (33.96%). Of those with unfavorable multidrug resistant tuberculosis treatment outcomes, death was 36 (16.98%), treatment failure 1 (< 1 %) and lost to follow up 3 (1.42%) (Figure 3)

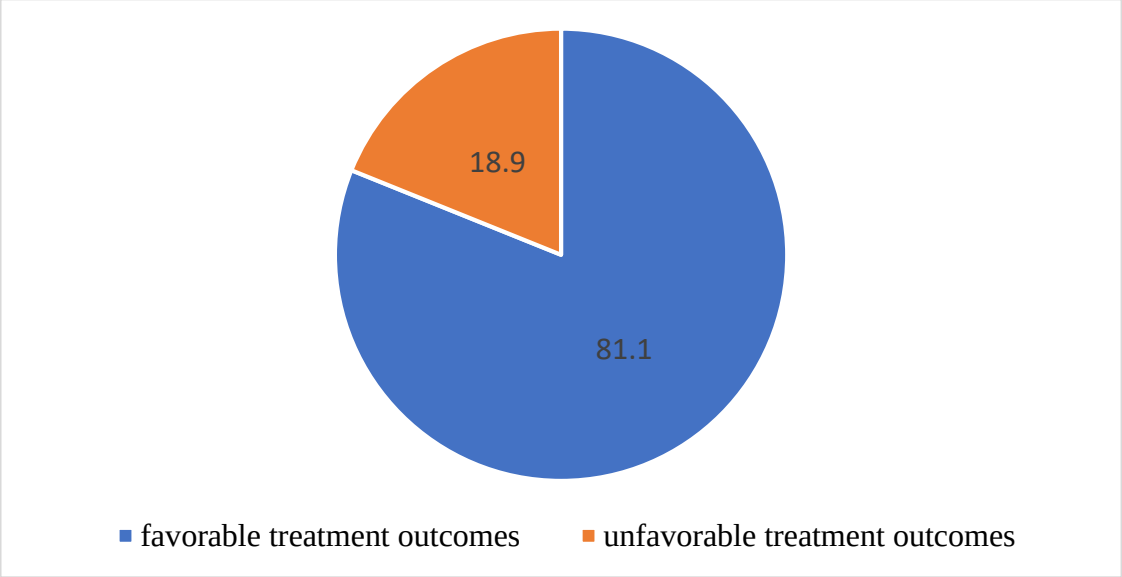

Figure 3: Multidrug resistant tuberculosis treatment outcomes among HIV co-infected patients

4.2 Incidence rate of unfavorable treatment outcomes among MDRTB/HIV patients

The follow-up time for the 212 study participants was 3841.4 person-months. During the follow-up period, 40 HIV co-infected multidrug resistant tuberculosis patients experienced unfavorable outcomes. This reveals that the incidence of unfavorable outcomes was 10.4 per 1000 person-months among HIV co-infected multidrug resistant tuberculosis patients under treatment.

4.3 Factors with increased risk of unfavorable multidrug resistant tuberculosis treatment outcomes

Table 3 presents the bivariate and multivariate cox hazard regression analysis that was done to identify factors that had increased the hazard of having unfavorable outcomes among multidrug resistant tuberculosis patients who are co-infected with HIV. The adjusted hazard ratio (AHR) of unfavorable treatment outcomes among those who were underweight as compared to those who had normal BMI was 4.50 (95% CI 2.24 – 9.05) and the p-value was< 0.001. Patients with severe anemia compared to those with normal hemoglobin their AHR was AHR 5.13 (95% CI 1.41 – 18.57) and p-value 0.013. Also, renal insufficiency as revealed by abnormal creatinine levels was associated with outcome, for those with renal insufficiency compared to those with

normal renal function the AHR was 2.7 (95% CI 1.20 – 6.05) and p = 0.016. The study also showed that those patients with other comorbid conditions compared to those without their AHR was 3.00 (1.25 – 7.19) p = 0.013

Table 3: Cox proportional hazard regression analysis of factors with risk of unfavorable treatment outcomes

Variable	Treatment outcome		Bivariate Analysis		Multivariable Analysis	
	Unfavorable n (%)	Favorable n (%)	Hazard ratio (95% CI)	p-value	Adjusted hazard ratio (95% CI)	p-value
Smoking						
Yes	14(31.1)	141(84.4)	2.42(1.26-4.67)	0.008	1.99(0.95-4.16)	0.065
No	26(15.6)	31(68.9)	1		1	
Treatment supporter						
Yes	32(16.67)	160(83.3)	1		1	
No	8(40)	12(60)	2.96 (1.36-6.4)	0.006	1.86 (0.77-4.52)	0.166
BMI at end of treatment						
Normal	16(12)	111(88)	1		1	
Underweight	22(51.2)	21(48.8)	5.45(2.85-10.42)	<0.001	4.5 (2.24-9.05)	**<0.001**
Overweight/Obese	2(5.6)	34(94.4)	0.45 (0.10-1.99)	0.298	0.57 (0.12-2.55)	0.466
Anemia by hemoglobin level						
Normal	3(5.5)	52(94.6)	1		1	
Mild anaemia	5(11.1)	39(88.6)	2.10 (0.50-8.83)	0.309	1.61 (0.38-6.88)	0.514
Moderate anaemia	15(20.3)	59(79.7)	3.77 (1.08-13.11)	0.036	2.34 (0.66-8.31)	0.187
Severe anemia	17(43.6)	22(56.4)	10.91(3.19-37.30)	<0.001	5.13 (1.41-18.57)	**0.013**
Renal insufficiency by creatinine level						
Yes	9(31)	20(69)	1.93 (0.91-4.07)	0.084	2.7(1.20-6.05)	**0.016**
No	31(16.9)	152(83.1)	1		1	
Comorbid conditions						
Yes	9(52.9)	8(47.1)	4.89 (2.31-10.32)	<0.001	3.00 (1.25-7.19)	**0.013**
No	31(15.9)	164(84.1)	1		1	

Figure four (4) shows chronic non-communicable comorbid conditions that were present among

17 MDRTB/HIV patients. These diseases were diabetes mellitus, hypertension, Kaposi's sarcoma. Others were lymphoma, asthma, epilepsy, sickle cell disease, and Condylomata accuminata

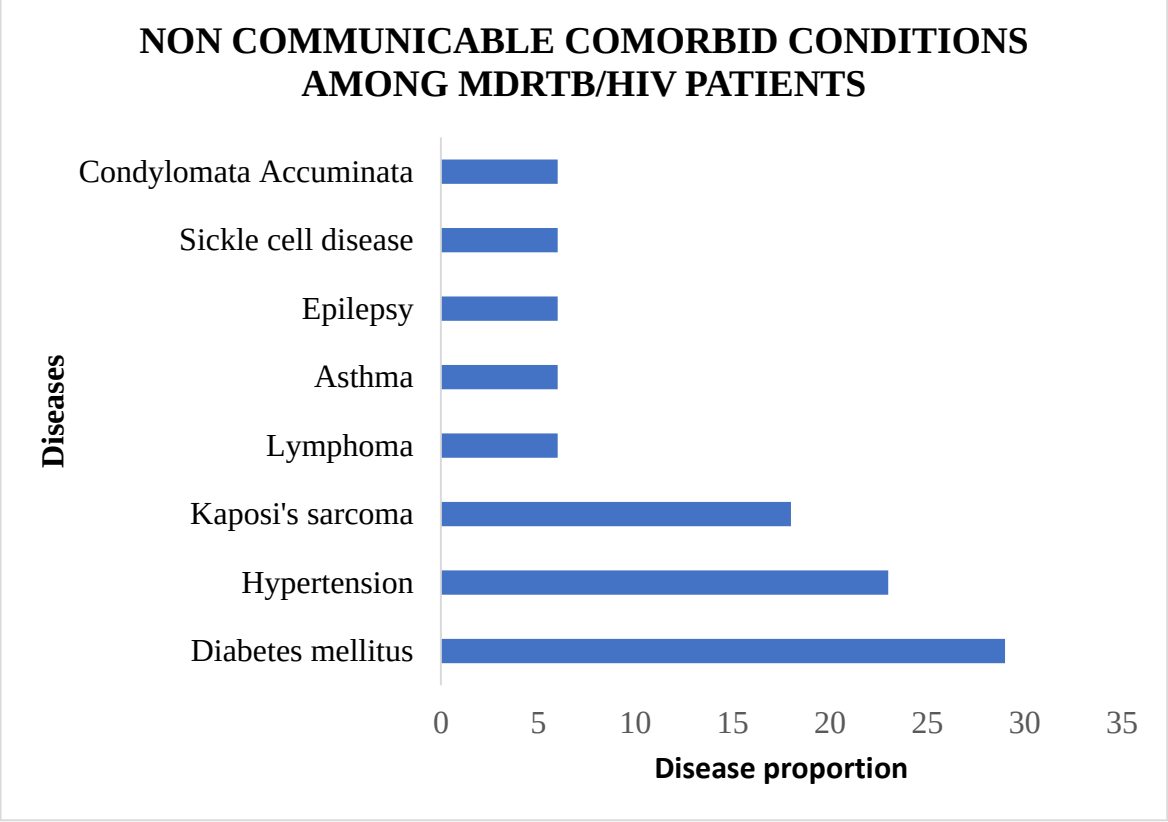

Figure 4: Proportion of non-communicable comorbid conditions among MDRTB/HIV patients

4.4 Time to occurrence of unfavorable treatment outcomes among multidrug resistant tuberculosis/HIV patients

A total of 40 (18.9%) among 212 multidrug resistant tuberculosis/HIV patients who were initiated on multidrug resistant tuberculosis treatment succumbed to unfavorable outcomes during the follow-up period. In a single group survival analysis, the study observed that the probability of failure was 0.12 (95% CI 0.09-0.18) at 10 months and increased to 0.18 (95% CI 0.14-0.24) at 20 months of follow up. Of all 40 unfavorable outcomes, 25 (62.5%) events occurred within the first 10 months from the commencement of multidrug resistant tuberculosis treatment (Figure 5).

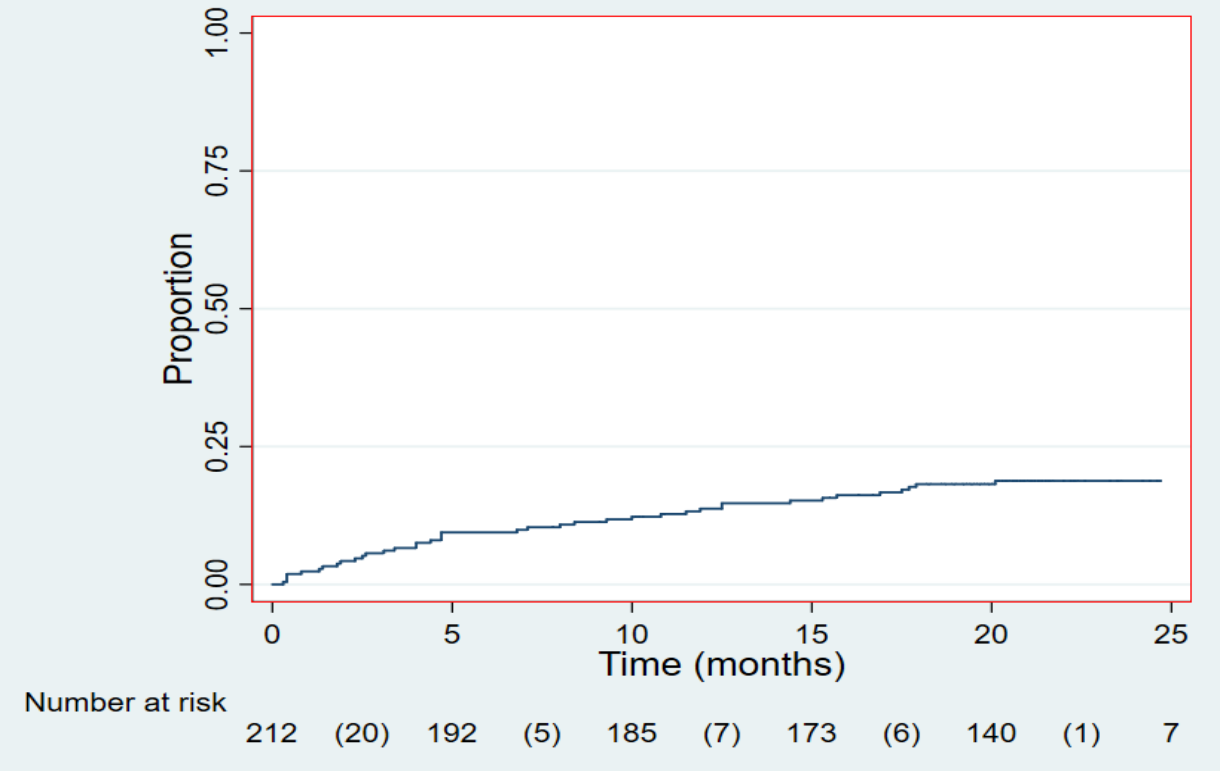

Figure 5: Kaplan Meier failure estimate curve showing unfavorable outcomes of MDRTB/HIV patients since the commencement of multidrug resistant tuberculosis treatment

Number in brackets () indicates the failure events.

The study also showed that the probability of unfavorable outcomes in multidrug resistant tuberculosis patients with HIV co-infection who had chronic non-communicable comorbid conditions were 0.35 (95% CI 0.18-0.62) and 0.53 (95% CI 0.32-0.77) at 4 and 20 months respectively, compared to patients who had no comorbid conditions with proportions 0.05 (95% CI 0.03-0.09) and 0.15 (95% CI 0.11-0.21) at 4 and 20 months respectively. This relationship was statistically significant with a p-value <0.001. (Figure 6)

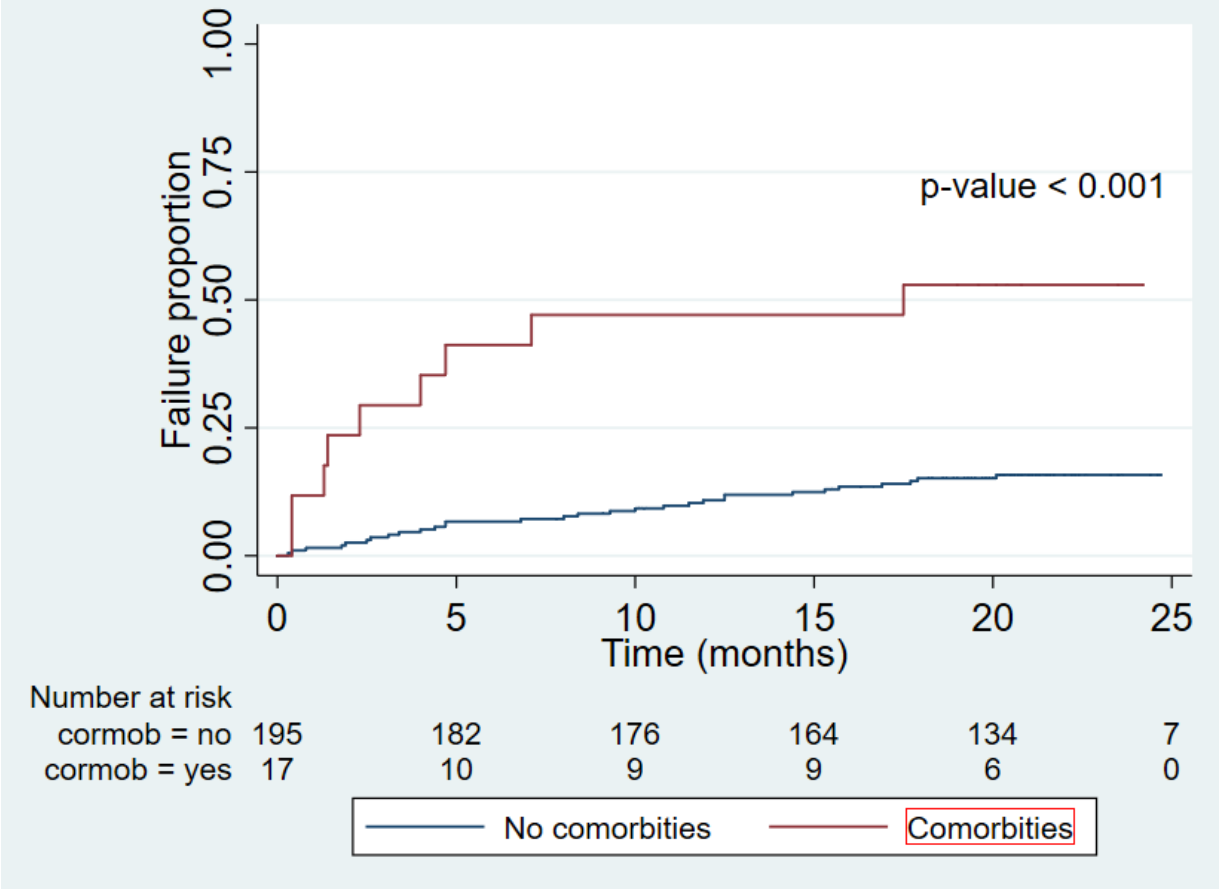

Figure 6: Kaplan Meier failure estimate curve showing unfavorable outcomes probabilities by comorbid conditions

Figure 7 describes the relationship of BMI and time to occurrence of unfavorable outcomes whereby the probability of unfavorable events at 10 and 20 months were 0.34 (95% CI 0.23-0.51) and 0.51(95% CI 0.37-0.67) respectively among multidrug resistant tuberculosis patients co-infected with HIV who were underweight compared to patients who had normal BMI. The relationship was statistically significant with a log-rank p-value <0.001

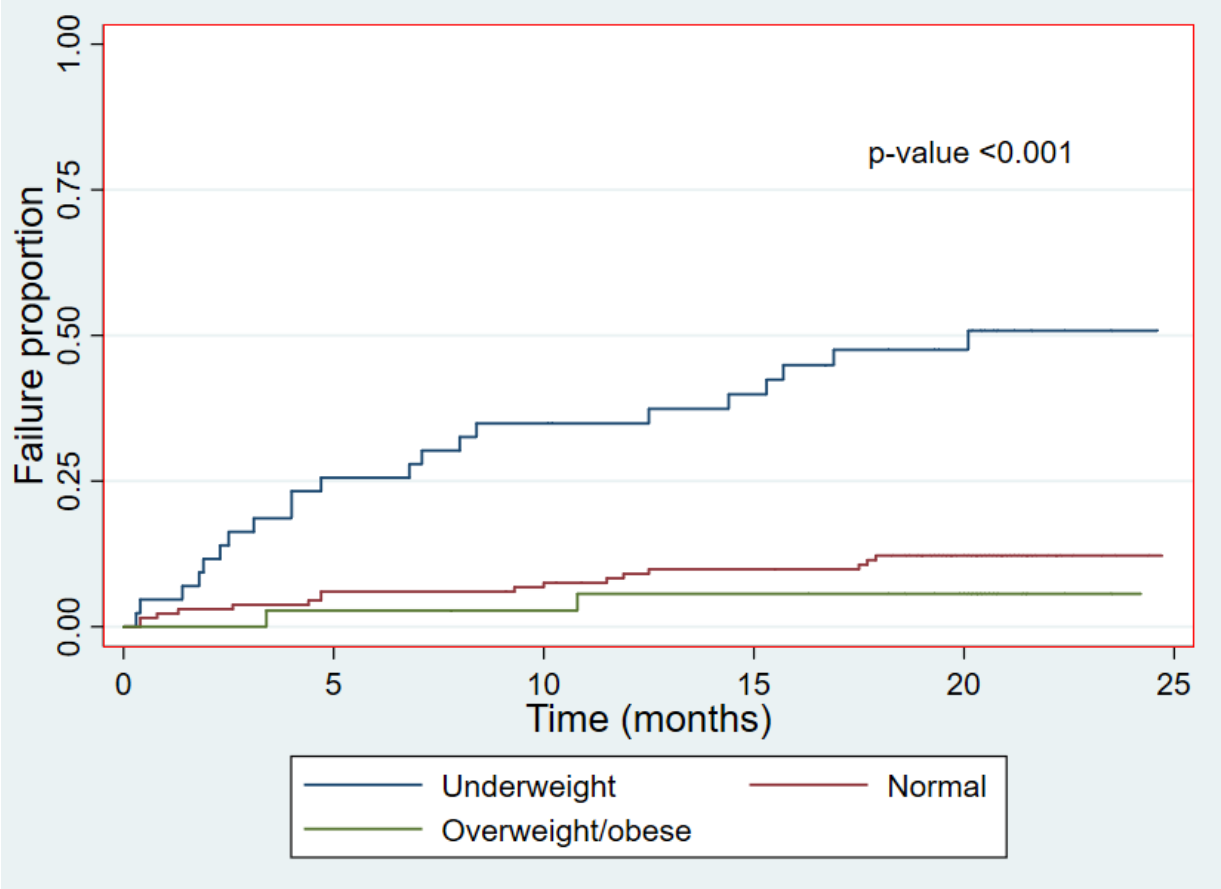

Figure 7: Kaplan Meier failure estimate curve showing unfavorable outcomes probabilities by body mass index

CHAPTER FIVE

5.0 DISCUSSION

The study aimed at determining treatment outcomes among HIV co-infected multidrug resistant tuberculosis patients undergoing treatment in two centers in Tanzania. The incidence of unfavorable outcome was moderate, however factors that significantly predicted increased risk of unfavorable outcome were severe anemia, and underweight, renal disease, and comorbid conditions. Other significant findings included time to occurrence of unfavorable treatment outcomes whereby most of the outcomes occurred during the initial 10 months of multidrug resistant tuberculosis treatment start.

The proportion of HIV co-infected multidrug resistant tuberculosis experiencing favorable treatment outcome was 81%. This was an achievement that was higher than the WHO target of at least 75% treatment success of drug resistant tuberculosis(37). A similar finding has been reported in a multicenter cohort study done in Abkhazia, Armenia, Columbia, Kenya, and Swaziland (14). The outstanding performance could be due to conducive program factors which might include motivated staff, availability of resources, environment, and good quality of care to patients leading to high-grade treatment adherence. This assertion is supported by observations that good adherence to treatment is key to reducing unsuccessful and costly individual health outcomes as well as in preventing transmission of multidrug resistant tuberculosis(38,39). On the contrary, a study in sub-Saharan Africa revealed a high proportion of unfavorable MDRTB treatment outcome among HIV co-infected patients(13). The difference in findings could be explained by differences in program performances as well as the presence of impeding factors between countries.

The incidence rate of multidrug resistant tuberculosis unfavorable treatment outcomes

The study established that the incidence rate of multidrug resistant tuberculosis unfavorable treatment outcomes among was 10.4 per 1000 person month. This finding accords with an earlier report from Ethiopia which showed an incidence rate of 10.6 (95% CI: 8.58, 13.11) per 1000 person-month (40). However, the incidence rate in this study was higher compared to the incidence rate that was reported from a study that was done in East Europe (41). The higher incidence rate of

unfavorable treatment outcomes in this study could be due to differences in geographical location from where studies were conducted. Also, this could be explained by the reasons that adverse effects from multidrug-resistant tuberculosis treatment and ART may be most acute and serious during the intensive treatment phase a period during which most patients experienced unfavorable outcomes in this study. Secondly, diagnosis of multidrug resistant tuberculosis and presence of HIV infection may create psychological disturbances that may interfere with treatment adherence resulting in unfavorable outcomes(42)

Factors predicting increased risk of unfavorable MDRTB treatment outcomes

Despite the proportion of unfavorable treatment outcome being comparably low in our study, it is still higher than the WHO recommended proportion. One of the factors that increased the risk of unfavorable outcome was underweight. This was also observed in a similar study that was done in South Africa, Lesotho, and Peru (23,24,43). Unfavorable outcome among HIV co-infected multidrug resistant tuberculosis patients who were underweight was higher compared to those who were normal. This could be due to nutritional body deficiencies including poor immune responses compromising body defenses leading to severe disease and back to more severe disease and then unfavorable outcome. This could be a reverse phenomenon which is supported by recent studies which asserted that underweight MDRTB/HIV patients have a weaker immune system and are more predisposed to other opportunistic infections. At the same time, the immune response requires adequate nutrition and energy stores to function at maximum capacity therefore it becomes weak consequently amplifying the illness severity and subsequent the unfavorable outcome (44,45).

The study also revealed that severe anemia increased the risk of unfavorable outcomes among HIV co-infected multidrug resistant tuberculosis patients. Anemia is a consequence of ongoing deficiencies which as anemia becomes severe the underlying problem also becomes more serious leading to an unfavorable outcome. Similar findings were observed in studies that were done in Lesotho and South Africa (23,24,46,47). This

could be related to the late presentation of patients to health facilities for tuberculosis treatment, nutritional deficiency, failure of iron utilization by the body.

We found that non-communicable comorbid conditions increased the risk of unfavorable outcome among MDRTB/HIV patients. Findings were consistent with studies done in South Africa, Nigeria, and Ethiopia (40,48). This could be due to the reason that patients with other non-communicable comorbidity require treatment regimen modifications based on their clinical states and face increased pill burden. The presence of comorbidity and MDRTB/HIV may then affect adherence to ART and multidrug resistant tuberculosis treatments.

In our study, we also found that renal insufficiency among multidrug resistant tuberculosis patients with HIV co-infection increased the risk of unfavorable outcome. A similar finding was observed in Indonesia whereby kidney impairment was associated with unfavorable outcome (49). Based on the literature, multidrug resistant tuberculosis treatment dosing or interval between dosing should be adjusted in multidrug resistant tuberculosis patients with poor kidney function i.e., creatinine clearance of less than 30mls/minute (50).

Time to occurrence of unfavorable multidrug resistant tuberculosis treatment outcomes

Our study elucidated that, probabilities of unfavorable treatment outcome in MDRTB/HIV patients were 0.35 and 0.52 at 4 and 20 months respectively among patients who had other comorbid conditions. It also showed that probabilities of unfavorable outcomes in patients with low body mass index were 0.34 and 0.51 at 10 and 20 months of follow up respectively. A similar finding was observed in a study that was done in Ethiopia (51). The shorter time to unfavorable treatment outcome among multidrug resistant tuberculosis/ HIV co-infected patients in this study could be due to lower body mass index at the start of multidrug resistant treatment and also due to undiagnosed or unproperly managed non-communicable conditions both of which plays a role in weakening the body’s immunity thence less response to treatment.

5.1 Limitations

Because data were collected retrospectively, there were missing data for some of the variables. These missing data were handled by imputing variables that had missing data multiple times in Stata. Variables that showed a significant proportion of missing values were CD4 cell count, culture results, smoking. Despite the limitations, this study has been able to show the proportion of treatment outcomes among multidrug resistant tuberculosis patients who are HIV co-infected. Despite the higher favorable treatment outcome noted in our study, the proportion of unfavorable treatment outcome is still higher than the recommended proportion by National Tuberculosis and Leprosy control program. The study has also shown the rate at which unfavorable outcomes do occur among multidrug resistant tuberculosis patients co-infected with HIV thus pinpointing the area of focus by the program in managing the HIV co-infected patients. Furthermore, a study has elucidated factors that increase the risk of multidrug resistant tuberculosis/HIV co-infected patients experiencing unfavorable outcomes which when promptly addressed will further decrease the proportion of unsuccessful treatment outcomes.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

The 19% proportion of unfavorable outcome noted in this study, was still higher than the World Health Organization recommended proportion of less than 10% among multidrug resistant tuberculosis patients. The rate of occurrence of unfavorable treatment outcome among HIV co-infected multidrug resistant tuberculosis patients was 10.4 per 1000 person-months and most of them occurred during the intensive treatment phase. This was within the first ten months from the commencement of multidrug resistant tuberculosis treatment. Factors that increased the risk of unfavorable outcomes among multidrug resistant tuberculosis patients with HIV co-infection were low body mass index, severe anemia, renal insufficiency, and presence of non-communicable comorbid conditions.

6.2 Recommendations

The observed higher incidence rate of unfavorable treatment outcome in our study still calls for continued efforts by the National Tuberculosis and Leprosy Control Program towards a further decrease of unfavorable outcomes which are either death, treatment failure or lost to follow-up. Interventions planned by National Tuberculosis and Leprosy Control Program should focus on addressing factors that increase the risk of unfavorable MDRTB treatment outcomes among MDRTB/HIV co-infected patients whereby by so doing the aim of reaching a goal of more than 90% treatment success rate will be achieved. Managing multidrug resistant tuberculosis/HIV co-infected patients with other co-morbid conditions is challenging. However, early diagnosis, appropriate treatment, psychosocial support as well as adequate monitoring of patients with required investigations are vital in achieving good treatment outcomes. NTLP through responsible clinicians in facilities providing multidrug resistant tuberculosis services should ensure for provision of patient-centered treatment services targeting improving patients' wellbeing as well as multidrug resistant tuberculosis treatment outcomes. Programmatic management of drug resistant tuberculosis should also consistently focus on nutritional support to improve patients' treatment outcomes as most patients with persistent low BMI in the course

of multidrug resistant tuberculosis treatment experience unfavorable multidrug resistant tuberculosis treatment outcomes.

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APPENDICES

Appendix I: Data extraction tool

MDRTB TREATMENT OUTCOMES - DATA EXTRACTION TOOL

S/N	DESCRIPTION	KEY (tick in an appropriate box)	COMMENTS
PERSONAL DETAILS			
1	Patient ID/Code …….		
2	Age (Years)		……
3	Sex	Male ☐ Female ☐	
4	Weight at treatment initiation in Kilograms (kg)		…….
5	Weight at end of treatment in Kilograms (kg)		…….
6	Height in centimeters (cm)		…….
7	Marital Status	Single ☐ Married ☐	
8	Occupation		
9	Does a patient have a treatment supporter	Yes ☐ No ☐	
10	Smoking	Yes ☐ No ☐ Not documented ☐	

11	MDR-TB registration group	New ☐ Previously treated for drug sensitive TB ☐	
ENROLLMENT DETAILS			
12	Date of start of MDR-TB treatment		……
BASELINE INFORMATION			
13	Sputum Results at the start (baseline)	Negative ☐ scanty ☐ + ☐ ++ ☐ +++ ☐	
14	Gene X-pert results	RR ☐ MDR ☐	
15	Culture results	Positive ☐ Negative ☐	

TREATMENT REGIMEN			
16	MDR-TB treatment regimen received	Shorter regimen ☐ Standardized regimen ☐ Individualized long regimen ☐	
TB/HIV INFORMATION			
17	Date of HIV testing		……
18	ART started	Yes ☐ No ☐	if yes, date ART started ……

19	Was ART initiated before the start of MDRTB treatment	Yes ☐ No ☐ Not initiated at all ☐	
20	CD4 count at the time of MDR-TB treatment initiation		……
21	CD4 cell count (final reading)		…….
22	Viral load results (first reading during MDRTB treatment)		……
23	Viral load results (subsequent/ final reading)		……
24	The patient experienced MDRTB drugs adverse events	Yes ☐ No ☐	If Yes, mention …… …… ……...
	LABORATORY MONITORING		
25	Renal function test (Creatinine level)		……
26	Liver function Test (AST, ALT)		ALT: ……. AST: …….
27	Hemoglobin level		…….
	BACTERIOLOGY MONITORING		
28	The month of sputum smear results conversion		……..

29	The month of sputum culture conversion		……..
CO-MORBID CONDITIONS			
30	Presence of medical diagnosis other than HIV with Tuberculosis	Yes ☐ No ☐	
	If yes, what is the medical diagnosis (mention)		
TREATMENT INTERRUPTIONS			
31	Number of days drugs missed	Consecutive ☐ Non-consecutive ☐ Dose not missed ☐	number of days ……..
EVALUATION			
32	Treatment outcomes	Cured ☐ Treatment complete ☐ Died ☐ Defaulter/LTF ☐ Treatment failure ☐	
33	Date of treatment outcome		……

Appendix II: Ethical clearance approval

UNITED REPUBLIC OF TANZANIA

MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

OFFICE OF THE DIRECTOR - RESEARCH AND PUBLICATIONS

Ref. No.DA.282/298/01.C/ Date: 21/01/2021

MUHAS-REC-01-2021-467

Sarah Gibson
MSc. Applied Epidemiology,
School of Public Health and Social Sciences
MUHAS

RE: APPROVAL FOR ETHICAL CLEARANCE FOR A STUDY TITLED: FACTORS INFLUENCING TREATMENT OUTCOMES AMONG MULTIDRUG RESISTANT TUBERCULOSIS/HIV CO- INFECTED PATIENTS IN DAR ES SALAAM REGION AND KIBONG'OTO INFECTIOUS DISEASE HOSPITAL IN KILIMANJARO REGION

Reference is made to the above heading.

I am pleased to inform you that the Chairman has on behalf of the University Senate, approved ethical clearance of the above-mentioned study, on recommendations of the Senate Research and Publications Committee meeting accordance with MUHAS research policy and Tanzania regulations governing human and animal subjects research.

APPROVAL DATE: 21/01/2021
EXPIRATION DATE OF APPROVAL: 20/01/2022

STUDY DESCRIPTION:
Purpose:
The purpose of this retrospective cohort study is to determine treatment outcomes and factors influence them; among MDRTB patients with HIV co-infection in Dar es Salaam and Kilimanjaro Infectious Disease Hospital in Kilimanjaro Region.

The approved protocol and procedures for this study is attached and stamped with this letter, and can be found in the link provided: https://irb.muhas.ac.tz/storage/Certificates/Certificate%20-%20301.pdf and in the MUHAS archives.

Appendix III: Permission to use program data for the study

THE UNITED REPUBLIC OF TANZANIA
MINISTRY OF HEALTH, COMMUNITY DEVELOPMENT, GENDER, ELDERLY AND CHILDREN

Telegrams.. "AFYA", DODOMA
Telephone: + 255 026 2323267
Email: ps@afya.go.tz
(All Letters should be addressed to The Permanent Secretary)

Government City - Mtumba,
Afya Road/Street,
P. O. Box 743,
40478 DODOMA.

Ref. No. GA.134/425/04D/30 **15th December, 2020**

Dr. Candida Moshiro,
Head, Epidemiology and Biostatistics Department,
School of Public Health and Social Sciences, (MUHAS),
P.O. Box 65015,
DAR ES SALAAM.

REF: REQUEST FOR MDRTB DATA FOR ANALYSIS AND PUBLICATION.

Reference is made to the above heading.

We acknowledge receiving your letter dated 13rd October, 2020, requesting for the approval of accessing the MDRTB data for the purpose of dissertation research to be conducted by Ms. Sarah Gibson. The study titled: "Factors influencing treatment outcomes among multidrug Resistant Tuberculosis/HIV co-infected patients in Dar es Salaam Region and Kibong'oto Infectious Disease Hospital in Kilimanjaro", will be under the Master of Science in Applied Epidemiology (MSc.AE) degree programme.

With this letter, the Ministry through the National Tuberculosis and Leprosy Programme is happy to inform you that the approval is granted and requires the student to work in close collaboration with the Programme mentors who will facilitate her with the required data, mentorship and further technical assistance on Programmatic information. With this regard, we would like to introduce you to Dr. Webhale Ntagazwa; Mobile No. 0744 029 829, Research Coordinator – NTLP and Mr. Emmanuel Nkiligi; Mobile No. 0713 604 812, Data Manager – NTLP who will assist the student throughout the study.

Thank you for your continued collaboration.

Edward N. Mbanga
ACTING PERMANENT SECRETARY (HEALTH)

The PI is required to:

1. Submit bi-annual progress reports and final report upon completion of the study.
2. Report to the IRB any unanticipated problem involving risks to subjects or others including adverse events where applicable.
3. Apply for renewal of approval of ethical clearance one (1) month prior its expiration if the study is not completed at the end of this ethical approval. You may not continue with any research activity beyond the expiration date without the approval of the IRB. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.
4. Obtain IRB amendment (s) approval for any changes to any aspect of this study before they can be implemented.
5. Data security is ultimately the responsibility of the investigator.
6. Apply for and obtain data transfer agreement (DTA) from NIMR if data will be transferred to a foreign country.
7. Apply for and obtain material transfer agreement (MTA) from NIMR, if research materials (samples) will be shipped to a foreign country,
8. Any researcher, who contravenes or fail to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine as per NIMR Act No. 23 of 1979, PART III section 10 (2)
9. The PI is required to ensure that the findings of the study are disseminated to relevant stake holders.
10. PI is required to be versed with necessary laws and regulatory policies that govern research in Tanzania. Some guidance is available on our website https://drp.muhas.ac.tz/.

Dr. Bruno Sunguya
Chairman, MUHAS Research and Ethics Committee

Muhimbili University of Health and Allied Sciences
DIRECTOR Research & Publications Box 65001

Cc: Director of Postgraduate Studies

Appendix IV: Permission to conduct the study at KIDH and in Dar es Salaam Region

UNITED REPUBLIC OF TANZANIA
MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY
MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR – POSTGRADUATE STUDIES

In reply quote;

Ref. No. HD/MUH/T.813/2019

26th January, 2021

The Director,
Kibong'oto Infectious Disease Hospital
P.O. Box 12,
SANYA JUU. KILIMANJARO

Re: INTRODUCTION LETTER

The bearer of this letter is Sarah Gibson, a student at Muhimbili University of Health and Allied Sciences (MUHAS) pursuing MSc. Applied Epidemiology.

As part of her studies she intends to do a study titled: "***Factors Influencing Treatment Outcomes Among Multidrug Resistant Tuberculosis/HIV Co-Infected Patients in Dar es Salaam Region and Kibong'oto Infectious Disease Hospital in Kilimanjaro Region***."

The research has been approved by the Chairman of University Senate.

Kindly provide her the necessary assistance to facilitate the conduct of her research.

We thank you for your cooperation.

Ms. Victoria Mwanilwa
For: DIRECTOR, POSTGRADUATE STUDIES

cc: Dean, School of Public Health and Social Sciences, MUHAS
cc: Sarah Gibson

9 United Nations Road; Upanga West; P.O. Box 65001, Dar Es Salaam: Tel G/Line: +255-22-2150302/6; Ext. 1015; Direct Line:+255-22-2151378;Telefax:+255-22-2150465,E-mail dpgs@muhas.ac.tz;Web:https://www.muhas.ac.tz

UNITED REPUBLIC OF TANZANIA
MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY
MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR – POSTGRADUATE STUDIES

In reply quote;

Ref. No. HD/MUH/T.813/2019 26th January, 2021

The Regional Administrative Secretary,
P.O. Box 5429
DAR ES SALAAM.

Re: INTRODUCTION LETTER

The bearer of this letter is Sarah Gibson, a student at Muhimbili University of Health and Allied Sciences (MUHAS) pursuing MSc. Applied Epidemiology.

As part of her studies she intends to do a study titled: "***Factors Influencing Treatment Outcomes Among Multidrug Resistant Tuberculosis/HIV Co-Infected Patients in Dar es Salaam Region and Kibong'oto Infectious Disease Hospital in Kilimanjaro Region.***"

The research has been approved by the Chairman of University Senate.

Kindly provide her the necessary assistance to facilitate the conduct of her research.

We thank you for your cooperation.

Ms. Victoria Mwanilwa
For: DIRECTOR, POSTGRADUATE STUDIES

cc: Dean, School of Public Health and Social Sciences, MUHAS
cc: Sarah Gibson

9 United Nations Road; Upanga West; P.O. Box 65001, Dar Es Salaam: Tel. G/Line: +255-22-2150302/6; Ext. 1015; Direct Line:+255-22-2151378;Telefax:+255-22-2150465;E-mail:dpgs@muhas.ac.tz;Web:https://www.muhas.ac.tz

JAMHURI YA MUUNGANO WA TANZANIA
WIZARA YA AFYA, MAENDELEO YA JAMII, JINSIA, WAZEE NA WATOTO

MKOA WA DAR ES SALAAM
Anwani: "Afya"
Simu: 022 – 2861903

Unapojibu tafadhali taja

KUMB. MoHCDGEC/ARRH/R.1/XII/64

HOSPITALI YA RUFAA YA MKOA
AMANA
S.L.P. 25411
DAR ES SALAAM.

22/02/2021

Katibu Tawala Mkoa,
S.L.P. 5429,
DAR ES SALAAM.

YAH: RUHUSA YA KUFANYA UTAFITI NDUGU SARAH GIBSON

Tafadhali husika na kichwa cha habari hapo juu na rejea barua yako ya tarehe 17/02/2021.

2. Uongozi wa hospitali ya rufaa ya Mkoa Amana umekubali kumruhusu mtajwa hapo juu kufanya utafiti kwa masharti yafuatayo; kwamba Ndugu Sarah Gibson atatakiwa kuwasilisha taarifa ya utafiti wake ili hospitali iweze kutumia taarifa hiyo kwa utatuzi wa changamoto.

3. Nashukuru kwa ushirikiano wako,

Dr. Rose Ntambuto
Kny; MGANGA MFAWIDHI
HOSPITALI YA RUFAA YA MKOA – AMANA

Kny: MGANGA MFAWIDHI
HOSPITALI YA RUFAA YA MKOA AMANA
S.L.P. 25411
DAR ES SALAAM

UBUNGO MUNICIPAL COUNCIL

ALL CORRESPONDENCES TO BE ADDRESSED TO THE MUNICIPAL DIRECTOR

Tel: 0222 - 926341
Fax: 0222 - 926342
Email: info@ubungomc.go.tz
Website: www.ubungomc.go.tz

In reply please quote:

Ref. No. UMC/R.6/01/10

P.O. BOX 55068
DAR ES SALAAM

Date: 08th February 2021

SINZA HOSPITAL,
MBEZI HEALTH CENTER,
MAKURUMLA HEALTH CENTER,
MSEWE DISPENSARY.

REF; RESEARCH PERMIT

Refer the heading above.

DMO'S office is pleased to inform your health facility that **Dr. Sarah Gibson** who is from Muhimbili University of Health and Allied Sciences, has been given a permit to perform the research work in your facility starting from **04th February 2021** to **19th March 2021**. The research is tittled **"FACTOR INFLUENCING TREATMENT OUTCOMES AMONG MULTI DRUG RESISTANT TUBERCULOSIS/HIV Co - infected patients in Dar Es Salaam".**

Kindly receive and provide the necessary assistance in order to enable the student to fulfill the ctivities comfortably.

Best wishes.

Dr. Peter J. Nsanya
MUNICIPAL MEDICAL OFFICER
UBUNGO MUNICIPAL COUNCIL

N.B. Please share research report with **MMOH** office at the end of your study

TEMEKE MUNICIPAL COUNCIL

ALL COMMUNICATIONS TO BE ADDRESSED TO MUNICIPAL DIRECTOR

P.O.Box. 45232
Tel: 2850142

TEMEKE MUNICIPAL MEDICAL
OFFICE OF HEALTH
DAR ES SALAAM
TANZANIA.

Date: 23/2/2021

INCHARGES
- MBAGALA RANGITATU HOSP
- YOMBO VITUKA HC
- TANDIKA RELI DISP
- KIZUIANI DISP

REF; PERMISSION TO CONDUCT HEALTH RESEARCH ACTIVITIES IN TEMEKE MUNICIPALITY.

Please refer to the above heading.
Extension of Permission has been granted to Mr./Mrs./Ms./Prof./Dr. SARAH GIBSON from (Institution) MUHAS Address 65001 DSM to Tel. No to collect data for research work in your area.

The research title is
FACTORS INFLUENCING TREATMENT OUTCOMES AMONG MULTIDRUGS RESISTANT TUBERCULOSIS/HIV CO-INFECTED PATIENTS'

She/he has submitted the proposal for the mentioned study to the MMOH Office as a pre-condition prior to authorisation.

The researchers have been instructed and agreed to submit the research progress reports and final results to the MMOH prior to any publications.

Data collection will restart on 24/2/2021 to 19/3/2021
Sample size 134

This research work is part of Academic fulfilment for Diploma/Advanced Diploma/Degree/master /PhD it is part of ongoing research in your institution

I am kindly requesting you to give him/her the necessary assistance so as to accomplish this task timely.

Yours Sincerely

AGNES KYAMBA
For; Temeke Municipal Medical Officer of Health

FOR MUNICIPAL MEDICAL OFFICER
OF HEALTH
TEMEKE

KINONDONI MUNICIPAL COUNCIL

ALL CORRESPONDENCES TO BE ADDRESSED TO THE MUNICIPAL DIRECTOR

Tel: 2170173
Fax: 2172951

In reply please quote:

Ref. No. KMC/HEALTH/RP.10.15

DISTRICT MEDICAL OFFICER,
KINONDONI MUNICIPAL COUNCIL
P. O. Box 61665,
DAR ES SALAAM

Date: 10/02/2021

HEALTH FACILITY INCHARGES
MAGOMENI HEALTH CENTER,TANDALE HC&TEGETA DISPENSARY
P.O.BOX 61665
DAR ES SALAAM.

RE: RESEARCH PERMIT

Refer to the heading above,

The DMO's Office is pleased to inform you that **SARAH GIBSON** under **MUHAS** has been given a permit to perform the Research at your Facility, after verification of ethics clearance and other necessary field document.

The study will be conducted within 19 days period from 10th of February, 2021.

The research title of the study is "**FACTORS INFLUENCING TREATMENT OUTCOMES AMONG MULTDRUG RESISTANT TUBERCULOSIS/HIV CO-INFECTECTED PATIENTS IN DAR ES SALAAM REGION AND KIBON'GOTO INFECTIOUS DISEASE HOSPITAL IN KILIMANJARO REGION**"

Kindly receive and provide him with all necessary assistance to enable him to fulfill the activities comfortably.

Regards,

Dr. Ezra Ngereza
FOR: MUNICIPAL MEDICAL OFFICER OF HEALTH
KINONDONI MUNICIPAL COUNCIL

THE UNITED REPUBLIC OF TANZANIA
President's Office
REGIONAL ADMINISTRATION AND LOCAL GOVERNMENT

DAR ES SALAAM REGION
Phone Number: 2203158
Fax number: 2203158
email: ras@dsm.go.tz
website: www.dsm.go.tz

In reply please quote:
Ref. No. .....

REGIONAL COMMISSIONER'S OFFICE,
3 RASHID KAWAWA ROAD,
P.O. BOX 5429,
12880 DAR ES SALAAM

1ST FEBRUARY 2021

District Administrative Secretary,
KIGAMBONI.....,
P. O. Box .....,
DAR ES SALAAM.

RE: RESEARCH PERMIT

Prof/Dr/Mrs./Ms/Miss ...SARAH.....GIBSON..... is student/**Research** from MUHIMBILI UNIVERSITY OF HEALTH (MUHAS) has been permitted to undertake research on ..FACTORS...INFLUENCING..TREATMENT. OUTCOMES..AMONG...MULTIDRUG...RESISTANT...TUBERCULOSIS./.H.I.V..... CO-INFECTED...PATIENTS...IN..DAR-ES-SALAAM...REGION...AND KIBONGOTO INFECTIOUS....DISEASE....HOSPITAL...IN.....KILIMANJARO...REGION..... From...2ND FEBRUARY..... 2021 to ....13TH MARCH.....2021.

I Kindly request your good assistance to enable her/his research.

.....
For; **REGIONAL ADMINISTRATION SECRERTARY**
DAR ES SALAAM

Copy: Municipal Director,
...KIGAMBONI.....
DAR ES SALAAM.

" Principal/Vice Chancellor
...MUHAS.....

THE UNITED REPUBLIC OF TANZANIA
President's Office
REGIONAL ADMINISTRATION AND LOCAL GOVERNMENT

DAR ES SALAAM REGION
Phone Number: 2203158
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In reply please quote:
Ref. No. .....

REGIONAL COMMISSIONER'S OFFICE,
3 RASHID KAWAWA ROAD,
P.O. BOX 5429,
12880 DAR ES SALAAM

1st of February 2021

District Administrative Secretary,
ILALA .....,
P. O. Box .....,
DAR ES SALAAM.

RE: RESEARCH PERMIT

Prof/Dr/Mrs./Ms/Miss ..Sarah Gibson..... is student/Research from ...Muhimbili University of Health (MUHAS).... has been permitted to undertake research on ..Factors influencing treatment outcomes ..among Multi Drug Resistant Tuberculosis/HIV co-infected patients in Dar es salaam Region and Kibong'oto Infectious Disease Hospital in Kilimanjaro Region .....
.....
From 2nd of February ..... 2021 to ...19th of March.....2021.

I Kindly request your good assistance to enable her/his research.

.....
For; REGIONAL ADMINISTRATION SECRERTARY
DAR ES SALAAM

Copy: Municipal Director,
ILALA
.....
DAR ES SALAAM.

" Principal/Vice Chancellor
MUHAS
.....