**MAKERERE UNIVERSITY**

**COLLEGE OF HEALTH SCIENCES**

**SCHOOL OF MEDICINE**

**CLINICAL EPIDEMIOLOGY UNIT**

# MORTALITY RATE AND ASSOCIATED FACTORS AMONG PATIENTS CO-INFECTED WITH DRUG RESISTANT TUBERCULOSIS AND HIV AT MULAGO HOSPITAL.


**BY**

**BAYOWA JOAN ROKANI, BBLT (Mak)**

**REG NO: 2018/HDO7/3295U**

**SUPERVISORS**

**PROF JOAN KALYANGO (BPharm, MSc Comm, MSc CEB, PhD)**

**DR JOSEPH BARUCH BALUKU (MBChB, MMED, PgDip, PCVM)**


**A DISSERTATION SUBMITTED TO MAKERERE UNIVERSITY COLLEGE OF HEALTH SCIENCES IN PARTIAL FULFULLMENT OF THE REQUIREMENT FOR THE AWARD OF A MASTERS OF SCIENCE IN CLINICAL EPIDEMIOLOGY AND BIOSTATISTICS.**

**March 2021**

## Declaration

I **Joan Bayowa Rokani,** declare that this is my original work and that to the best of my knowledge, it has never been submitted in any institution for the award a bachelor's degree.

Bayowa Joan Rokani,

Principal Investigator,

Signature..... Date.....25/03/2021.....

This dissertation has been submitted with approval of the following supervisors;

Dr. Joseph Baruch Baluku,

Physician,

Mulago National Referral Hospital Tuberculosis Unit,

Department of Internal Medicine, Division of Pulmonology,

Mulago Hospital,

P.O BOX 7051, Kampala

Signature..... Date.....25/03/2021

Ass Prof Joan Kalyango,

Director Clinical Epidemiology Unit,

Makerere University College of Health Sciences,

P.O BOX 7072, Mulago

Signature..... Date.....29/3/2021.....

## Dedication

To my parents Mr. and Mrs. Rokani, my aunt Miss Nansubuga Eve, my brothers David and Jacob and my sisters Barbra, Ritah and Angella.

## Acknowledgements

To the almighty God, without whom all this wouldn't have been possible. My exceptional appreciation and gratitude goes to my supervisors Prof Joan Kalyango and Dr Baluku Joseph for their tireless efforts, supervision, advice and guidance throughout the entire research period despite their busy schedules. Your expertise was invaluable and your feedback was insightful and it always pushed me to sharpen my thinking.

To the staff of the Clinical Epidemiology Unit; Associate Prof. Kalyango Joan, Associate Prof. Charles Karamagi, Dr Nankabirwa Joaniter, and Dr Achilles Katamba for all time they have dedicated and the knowledge and skills they have imparted selflessly to me throughout the master's program.

Exceptional gratitude goes to Makerere University Mapronano-Ace that provided funding for this research. Thank you so much. I also want to appreciate and thank my classmates; Akunzirwe Rebecca, Alupo Ann, Amutuhaire Judith, Ansiima Sheila, Bagoloire Lynn, Buhuguru Remmy, Cherop A, Cwinyaai Norman, Kivumbi Ronald, Kyaterekera Martha, Mushi Kalister (RIP), Nanyonga Stella, Nasinghe Emma, Nkugwa Ivan, Nyuma Ferdinand, Oitangor Arthur, Okello Tom, Omaido Blair, Otike Caroline, Ssebunje Jerome, Ssendikwana Emma and Zalwango Jane for the support, encouragement and the zeal that helped me to make this research a success.

I am also grateful to my parents Mr. and Mrs. Rokani, friends and family who supported me financially, socially and psychologically .Thank you. To the staff of Mulago Hospital Tuberculosis Unit who provided me with a conducive research and friendly environment through the research period. Thank you so much. Finally, I am thankful for the support of all those unmentioned individuals that played a vital role in making this write up a success.

## List of Abbreviations/Acronyms

| | |
|---|---|
| AFB | Acid fast bacteria |
| ART | Antiretroviral therapy |
| CI | Confidence interval |
| CPT | Cotrimoxazole Preventive Therapy |
| DOTs | Directly Observed Therapy-Short Course |
| DR-TB | Drug resistant tuberculosis |
| EPTB | Extra pulmonary tuberculosis |
| HIV | Human Immunodeficiency Virus |
| HR | Hazard Ratio |
| IQR | Interquartile Range |
| MDR-TB | Multi-drug resistant Tuberculosis |
| MJAP | Mulago Joint AIDS Program |
| MOH | Ministry of Health |
| NTLP | National Tuberculosis and Leprosy Program |
| PLWHA | People Living With HIV and AIDS |
| PTB | Pulmonary Tuberculosis |

| | |
|---|---|
| RR-TB | Rifampicin resistant Tuberculosis |
| TAT | Turnaround time |
| TB | Tuberculosis |
| TSR | Treatment Success Rate |
| URC | University Research Council |
| XDR-TB | Extensively drug resistant Tuberculosis |

## Operational definitions

**Mono-resistance:** resistance to one first line anti-tuberculosis drug (WHO, 2020b).

**Poly-resistance:** resistance to more than one first line anti-tuberculosis drug, other than both Isoniazid and Rifampicin combined (WHO, 2020b).

**Multidrug-resistance(MDR-TB):** resistance to at least Rifampicin and Isoniazid (WHO, 2020b).

**Extensively drug resistant TB (XDR-TB)** is defined as MDR-TB with additional resistance to any fluoroquinolone and one of the second-line anti-TB injectable agents; kanamycin, amikacin, or capreomycin (WHO, 2020b).

**New case** is defined as a newly registered episode of TB in a patient who has never been treated for TB or has taken anti-TB medicines for less than 1 month (WHO, 2020b).

**Previously treated** refers to patients who have received 1 month or more of anti-TB medicines in the past. Previously treated cases may have been treated with a first-line regimen for drug susceptible TB or a second-line regimen for drug-resistant forms (e.g. shorter MDR-TB regimen) (WHO, 2020b).

**Others** are previously treated TB cases without a treatment outcome (Nkolo et al, 2019).

**Mortality** is ratio of the total number of deaths to the total population (WHO, 2013).

**Mortality rate** is a measure of the frequency of occurrence of death in a defined population during a specified interval (WHO, 2013).

**Treatment Success -**if the TB patients were cured (negative smear microscopy at the end of the treatment and on at least one previous follow-up test) or completed treatment with resolution of symptoms (WHO, 2013).

**Lost to follow up** -A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more (WHO, 2013).

# Table of Contents

# List of figures

# List of tables

# List of appendices

# Abstract

**Introduction:** Drug resistant tuberculosis (DR-TB)/HIV co-infection remains a growing threat to public health and threatens global TB and HIV control programs. HIV is likely to worsen the outcomes of DR-TB and DR-TB is likely to worsen the outcomes of HIV despite the scale up of TB and HIV services and advances in treatment and diagnosis.

**Objective:** To determine the mortality rate and factors associated with mortality among patients with drug resistant TB/HIV co-infection at Mulago Hospital.

**Methods:** This study employed a retrospective cohort study design. It was carried out in Mulago Hospital tuberculosis unit and the eligible participants were those with DR-TB and HIV co-infection. Pre-tested structured data extraction forms were used to obtain information from the patients' medical records by trained research assistants. Data on sociodemographics, HIV and TB clinical characteristics was collected. Data were analyzed in STATA version 14.0. At univariate, data were presented in form of medians with corresponding interquartile ranges for continuous data while frequencies and percentages were used for categorical variables. Modified poisson regression with robust standard errors was used to determine relationships between the independent variables and the dependent variable (mortality) at bivariate and multivariate analysis.

**Results:** Of the 390 participants enrolled, 201(53.9%) were males with a mean age of 34.7 (±10.6) and 128 (32.8%, 95% CI=28.3-37.7%) died. ART initiation (aIRR 0.79, 95% CI= 0.71-0.88), having a BMI ≥18.5Kg/$m^2$ (aIRR 0.91, 95% CI= 0.85-0.97), having a documented patient phone contact (aIRR 0.85, 95% CI=0.76-0.97), having a MUAC ≥24.5cm (aIRR 0.83, 95% CI= 0.78-0.88) and having an adverse event during the course of treatment (aIRR 0.81, 95% CI= 0.75-0.87) were protective against mortality.

**Conclusion:** There was a significantly high mortality rate due to the DR-TB/HIV co-infection. Having a side effect, BMI ≥18.5Kg/$m^2$, starting ART and MUAC ≥24.5cm were protective against mortality. These results suggest that initiation of all HIV positive patients with DR-TB on ART and frequent monitoring of drug side effects highly reduce mortality.

# CHAPTER ONE

## 1.0 Introduction

Despite scale up of tuberculosis /HIV services and advances made in treatment and diagnosis, drug-resistant tuberculosis (DR-TB) remains a growing threat to public health and threatens global TB and HIV control (Singh et al., 2020). In 2019, an estimated 3.3% of new TB cases and 18% of previously treated cases had MDR-B/RR-TB. In absolute numbers, there were an estimated 465 000 (range, 400 000–535 000) incident cases of RR-TB while 78% had MDR-TB(WHO, 2020a).

In sub-Saharan Africa, DR-TB prevalence among new TB patients was 3.9% while that of those previously treated was 21% (Musa et al., 2017). Additionally, among previously treated TB

patients, the prevalence of DR-TB and MDR-TB was 53% and 34% respectively (Otu et al., 2017) with East Africa having an estimated burden ranging from 0.4%-4.4% among new cases and 3.9%-17.7% among recurrent TB patients (Kidenya et al., 2014).

In Uganda, DR-TB prevalence was 1.6% among newly diagnosed TB cases and 12% among previously-treated TB cases (Okethwangu et al., 2019) and the risk of TB is higher among HIV positive patients than HIV negative patients (Baluku et al., 2020; Nkolo et al, 2018a; Podlekareva et al., 2017).There is a dual potential of death due to both disease conditions. There is high mortality associated with DR-TB (Bei et al., 2018) but also mortality associated with HIV(Singh et al., 2020) due to opportunistic infections and drug related adverse reactions. HIV is also likely to worsen outcomes from DR-TB (Daftary et al., 2014) and DR-TB is likely to worsen the outcomes from HIV (Farley et al., 2011). Also, the medicines for both conditions are associated with toxicities such as: hepatotoxicity, renal toxicity (K. Schnippel et al., 2017) which have a high potential to result in death. In addition, toxicities may at times result into drug withdrawal by clinicians and affect patient drug adherence in turn affecting treatment outcomes. In Uganda, DR-TB/HIV mortality has been reported at 11.7-19% (Nkolo et al, 2019; USAID, 2018)

Among the factors found to be associated with DR-TB/HIV mortality across several studies were; age, sex, antiretroviral therapy/TB regimen, hospitalization, education, marital status, diabetes history, CD4 cell count, body mass index, time of drug initiation, change in drug regimen, malnutrition, type of treatment modality (hospital based or community based), smoking status, co-morbidity, adherence, anemia (Aljadani, Ahmed, & Al-Jahdali, 2019; Chung-Delgado, Guillen-Bravo, Revilla-Montag, & Bernabe-Ortiz, 2015; Farley et al., 2011; Gandhi et al., 2012; Hirasen et al., 2018; Mollel & Chilongola, 2017; O'Donnell et al., 2013; Salinas, Armstrong, Silk, Haddad, & Cegielski, 2017; Viana, Redner, & Ramos, 2018) and adverse drug reactions like gastrointestinal toxicity, nausea, vomiting and diarrhea), ototoxicity, kidney dysfunction, hepatic dysfunction, anemia and insomnia (Brust et al., 2013; Isaakidis et al., 2012; Lehloenya & Dheda, 2012; Sagwa et al., 2012; Schnippel, Firnhaber, Berhanu, Page-Shipp, & Sinanovic, 2017; Shean et al., 2013).

There is paucity of data in the Ugandan context as to whether the DR-TB/HIV places a person at increased risk for mortality. Whereas people have evaluated predictors of mortality in DR-TB and have found HIV to be one of them; few have evaluated predictors of mortality among those with DR-TB/HIV co-infection specifically (Kliiman & Altraja, 2010; Kurbatova et al., 2012). More still, studies about DR-TB/HIV mortality have not been carried out in the Ugandan setting.

The aim of this study was to determine the mortality rate and factors associated with mortality among patients with DR -TB/HIV co-infection so as to detect gaps in diagnosis, detection and monitoring of DR-TB to identify implementation challenges and to act as a basis for future research to close the gaps and reduce mortality from DR-TB/HIV co-infection in Uganda.

## 1.1 Problem statement

There are increasing deaths due to DR-TB/HIV co-infection. A programmatic study reported 11.7% deaths among DR-TB /HIV co-infected patients (USAID, 2018). Another study reported a 14% incidence of mortality due to DR-TB (NTLP, 2018) in 2016, and 80% of the deaths were driven by HIV infection. There were 19% deaths due to DR-TB that were reported countrywide. The deaths were more prevalent among those aged 25-34 years, HIV positive (54%) and among males (64%)(USAID, 2018).The death of these young people who could still be productive affects the Ugandan economy and greatly impacts their families' wellbeing, quality of life, social, financial and psychological state leaving them with emotional pain and grief.

The high mortality of these patients implies high level of late diagnosis yet early treatment reduces morbidity and mortality, but many people including the young people with HIV and DT-TB remain undiagnosed until late in the course of both infections. If these young people do not get diagnosed and started on treatment for DR-TB/HIV co-infection, Uganda is likely not to meet its 90–90–90 targets of reducing the HIV new infections by 2020 and 95% target in reduction of TB deaths set by WHO by 2035 .There is likely to be continued morbidity and mortality impacting individuals, health system and economy since this is the productive age group.

Additionally, second line TB drugs e.g. linezolid when combined with ART may increase immunosuppression, drug- drug interactions and lead to higher rates of toxicity, higher pill burden and greater noncompliance further worsening treatment outcomes (Arentz et al., 2012; Edelman et al., 2013). If these problems are not managed early, they may lead to catastrophic costs and increased morbidity and mortality. DR-TB/HIV co-infected patients in South Africa were more likely to die within 30 days after initiation of treatment (Gandhi et al., 2006). In Uganda, predictors of mortality in patients co-infected with DR-TB/HIV are unclear so this study determined the mortality rate and factors associated with mortality among patients co-infected with DR-TB/HIV. Exploration and analysis of death among DR-TB/HIV patients led to a clearer and specific understanding of why the deaths happened and where interventions are likely to make a difference in this context.

## 1.2 Justification

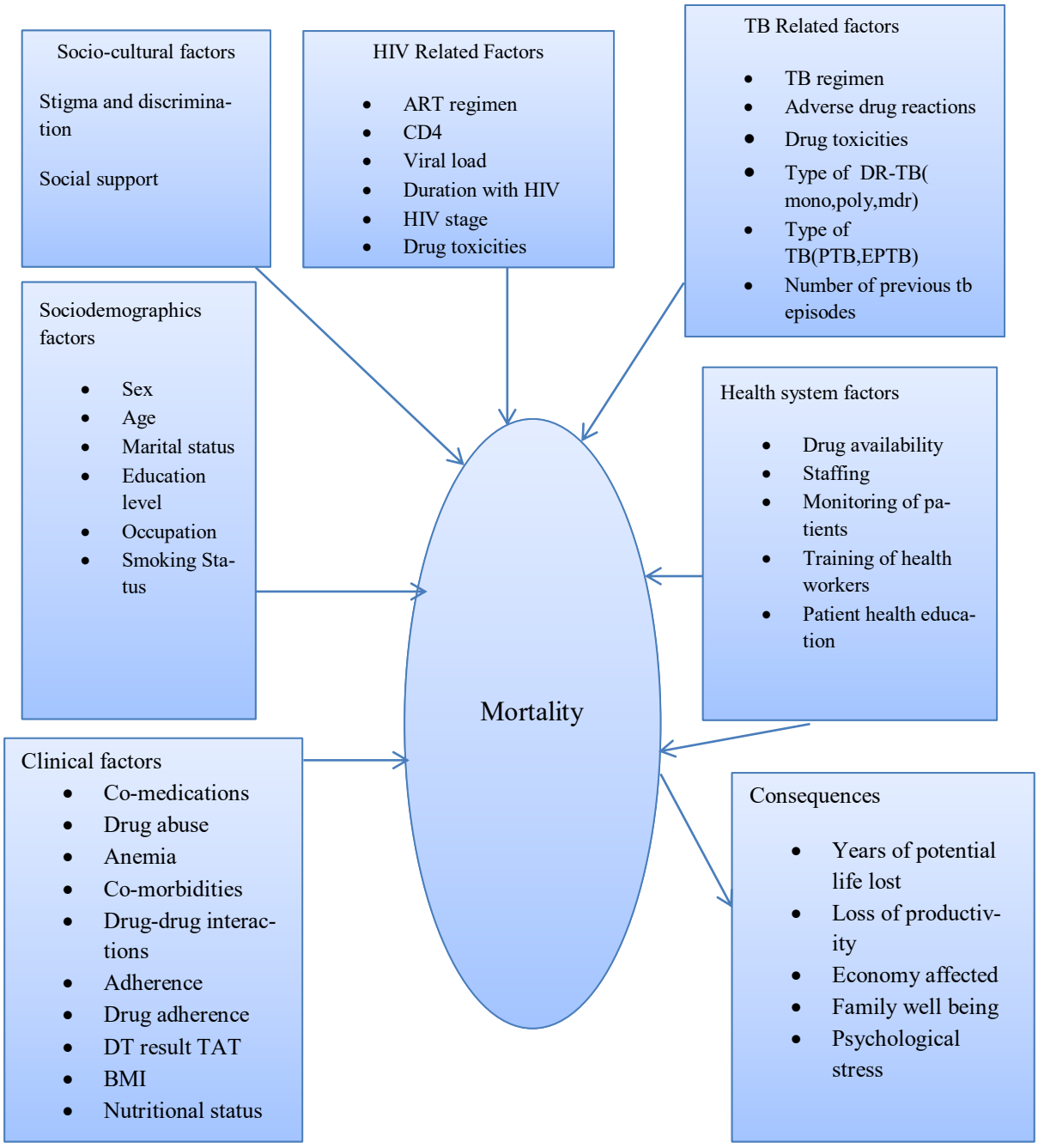
National Tuberculosis Leprosy Program (NTLP) recommends monthly and bimonthly monitoring during the intensive phase and continuation phase of DR-TB treatment respectively. Regular monitoring of any adverse drug reactions, treatment outcomes of DR-TB/HIV and understanding the specific reasons for unsuccessful treatment outcomes (mortality) is further recommended in evaluating the effectiveness of TB/HIVcontrol program. At minimum, an ordinary acid fast bacteria smear should be performed throughout treatment with confirmation of conversion on culture documenting the end of the intensive and continuation phases or in case of reversion to positive smear. However, there is inadequate monitoring as far as DR-TB/HIV is concerned. This is because of inadequate diagnostic capacity faced with irregular supply of reagents in turn causing delay in laboratory and treatment monitoring (USAID, 2018).

To date, there is a knowledge gap and limited clinical data regarding mortality rate and factors associated with mortality among patients co-infected with DR-TB and HIV.

This study will generate knowledge that will improve clinical care and management of patients co-infected with DR-TB and HIV in Uganda.

The recommendations will be used to identify modifiable factors where interventions may be most successful in increasing survival of patients and also provide basis for future studies on DR-TB/HIV co-infection in Uganda.

## 1.3 Conceptual framework




## Figure 1. Conceptual Framework

The conceptual framework postulated that social cultural factors, HIV related factors, TB related factors, socio-demographics factors, clinical factors and health system factors would influence mortality.

## 1.4 Scope of the study

This study particularly looked at sociodemographics, HIV related factors, TB related factors and clinical factors of Mulago Tuberculosis Unit patients but didn't look at socio-cultural factors, health system factors and the consequences from 1st January 2014 t0 31st December 2019.

## 1.5 Research Question

The overarching question: What is the vital status of patients co-infected with DR-TB/HIV in Mulago Hospital? What is the mortality rate and factors associated with mortality among patients co-infected with DR-TB/HIV at Mulago Hospital from 1st January 2014 to 31st December 2019?

## 1.6 Specific Research Questions

1. What is the mortality rate among patients co-infected with DR-TB /HIV in Mulago Hospital from 1st January 2014 to 31st December 2019?
2. What are the factors associated with mortality among patients co-infected with DR-TB/ Mulago Hospital from 1st January 2014 to 31st December 2019?

## 1.7 Research Objectives

## 1.8 General objective

To determine the mortality rate and factors associated with mortality among patients with DR-TB/HIV attending Mulago Hospital from 1st January 2014 to 31st December 2019?

## 1.9 Specific objectives

1. To determine the mortality rate among patients co-infected with DR-TB /HIV in Mulago Hospital.
2. To determine the factors associated with mortality among patients co-infected with DR-TB/HIV in Mulago Hospital.

# Chapter 2

## 2.0 Literature Review

### 2.1 Mortality Rate in DR-TB/HIV co-infected patients.

This section reviews the existing literature on mortality rates and associated factors among DR-TB/HIV co-infected patients done by different researchers using different study designs.

A prospective Ugandan cohort recruited 473 DR-TB patients from Arua, Mulago, Fort portal, Hoima, Mbale, Matany, Kabale and Mbarara of whom 455 had a documented HIV test result, 229 (49.9%) were co-infected and 218 (95.2%) started or continued taking ART. A mortality rate of 11.7% was reported at twelve month analysis (USAID, 2018).

An observational study of HIV co-infected patients looked at Undertreated HIV and drug-resistant tuberculosis at a referral hospital in Irkutsk, Siberia enrolled a total of 98 patients were enrolled with a median CD4 count of 147 cells/mm3 and viral load of 205 943 copies/ml. Among patients with drug susceptibility testing (DST) results, 29 (64%) were multidrug-resistant (MDR), including 12 without previous anti-tuberculosis treatment. 19 patients were on antiretroviral therapy (ART) at admission, and 10 (13% ART-naïve) were started during hospitalization. Barriers to timely ART initiation included death, in-patient treatment interruption, and patient refusal. Of 96 evaluable patients, 21 (22%) died, 14 (15%) interrupted treatment, and 10 (10%) showed no microbiological or radiographic improvement. Patients with a cavitary chest X-ray (aOR 7.4, 95%CI 2.3–23.7, P = 0.001) or central nervous system disease (aOR 6.5, 95%CI 1.2–36.1, P=0.03) were more likely to have one of these poor outcomes. The study concluded that high rates of MDR-TB, treatment interruption and death were found in an

HIV-infected population hospitalized in Irkutsk and thus recommended that there are opportunities for integration of HIV and TB services to overcome barriers to timely ART initiation, increase the use of anti-tuberculosis regimens informed by second-line DST, and strengthen out-patient diagnosis and treatment networks(Heysell et al., 2016).

A retrospective South African based study that recruited 114 patients with XDR-TB with 82 (73%) having HIV with 50 (61%) on ART, reported a 42% mortality among patients co-infected with XDR-TB and HIV. A higher number of deaths occurred among HIV-positive patients not receiving antiretroviral therapy. This study concluded that culture conversion was a major predictor of survival but was poorly predictive (51%) of successful treatment outcome (O'Donnell et al., 2013).

An average of 34.3% DR-TB/HIV mortality was reported in Abkhazia, Armenia, Colombia, Kenya, Kyrgyzstan, Swaziland and Uzbekistan, South Africa, Peru, Europe and America, Lesotho, Sub-Saharan Africa and Cambodia (Bastard et al., 2018; Chingonzoh et al., 2018; Farley et al., 2011; Gandhi et al., 2012; Hicks et al., 2014; Kawai et al., 2006; Palacios et al., 2012; Podlekareva et al., 2017; Satti et al, 2012; Satti et al., 2012; Van Hout & Hope, 2019; Walls et al., 2015).About 50% patients in 8 sites (Arua, Mulago, Fort portal, Hoima, Mbale, Matany, Kabale, Mbarara were DR-TB/HIV co-infected and of these 11.7% had died(Nkolo et al, 2019). The high case fatality rates informed a mortality audit at all centres with the deaths largely due to late presentation and co-morbidities (Nkolo et al, 2018b). Of the 365 DR-TB cases in the DR-TB initiation sites county wide in the 2016 Ugandan cohort, 54% were co-infected with HIV and 19% died (USAID, 2018). Six and twelve month's interim analysis of treatment outcomes revealed 7.8% and 12% deaths respectively.

A case control study done in South Africa recruited 123 MDR-TB and XDR-TB patients co-infected with HIV of which 78 (63%) died following diagnosis of either DR-TB or HIV and 111 (80%) had died at the end of the study. CD4 count $\leq$50 cells/mm$^3$ and resistance to all six drugs tested were the principal risk factors for mortality. Use of antiretroviral therapy (ART) was protective. This study concluded that mortality due to MDR-TB and XDR-

TB was associated with greater degree of immunosuppression and drug resistance and recommended that efforts to reduce mortality must focus on preventing the amplification of resistance by strengthening TB treatment programs, as well as reducing the pool of immunosuppressed HIV-infected patients through aggressive HIV testing and ART initiation (Gandhi et al., 2012).

A South African based prospective cohort that looked at outcomes of MDR-TB among a cohort of South African patients with high HIV prevalence enrolled 757 patients with known HIV status and were included in the final analysis. HIV infection was documented in 287 (38%). Overall, 348 patients (46.0%) were successfully treated, 74 (9.8%) failed therapy, 177 (23.4%) died and 158 (20.9%) defaulted. Patients with HIV were slightly younger and less likely to be male compared to HIV negative patients. Patients with HIV were less likely to have a successful treatment outcome (40.0 vs. 49.6; $P<0.05$) and more likely to die (35.2 vs. 16.2; $P<0.0001$). In a competing risk survival analysis, patients with HIV had a higher hazard of death (HR: 2.33, $P<0.0001$). Low baseline weight (less than 45 kg and less than 60 kg) was also associated with a higher hazard of death (HR: 2.52, $P<0.0001$; and HR: 1.50, $P<0.0001$) respectively, compared to weight greater than 60 kg. Weight less than 45 kg had higher risk of failure (HR: 3.58, $P<0.01$). Any change in treatment regimen was associated with a higher hazard of default (HR: 2.86; 95% CI 1.55–5.29, $P<0.001$) and a lower hazard of death (HR: 0.63, $P<0.05$)(Farley et al., 2011).

A retrospective cohort done in South Africa that looked at risk of death among HIV co-infected MDR-TB patients, compared to mortality in the general population recruited 1619 patients that met the eligibility criteria. Death was recorded on 1619 patients, of whom 367 (22.7%) had died within 2 years. Out of the 1413 patients that tested for HIV infection, 554 (39.2%) tested positive. Excess mortality was higher in HIV infected, compared to HIV uninfected, MDR-TB patients (adjusted excess hazard ratio, 5.6 [95% CI, 3.2–9.7]); in patients whose TB isolates' resistance to ethambutol and kanamycin was unknown (3.7 [2.1–6.2] and 4.87 [1.9–13.3], respectively versus known. There were no differences in excess mortality between age and gender of the patient, year of

diagnosis and TB history. The study concluded that adjusting for some important predictors, MDR-TB patients with HIV infection experienced higher excess mortality compared to HIV-uninfected MDR-TB patients, after accounting for the general mortality in South Africa. An appropriate, though complex method produced predictor effect estimates similar to those obtained from classical methods. Thus, the use of relative survival methods should be encouraged in the analysis of cause specific mortality, when ascertainment of cause of death is inaccurate or unknown (Manda et al., 2013).

Despite literature from all the above studies about mortality rate, there is limited information about mortality among DR-TB/HIV co-infected patients in Uganda**.**

## 2.2 Factors associated with mortality in DR-TB/HIV co-infected patients.

This section involves reviewing the existing literature on factors associated with mortality among DR-TB/HIV co-infected patients done by different researchers using different study designs. They have been divided into sociodemographics and clinical factors.

## 2.3 Sociodemographics factors

A retrospective cohort study that looked at outcomes of HIV-infected versus HIV-non infected patients treated for drug-resistance tuberculosis in a multicenter cohort based in seven countries: Abkhazia, Armenia, Colombia, Kenya, Kyrgyzstan, Swaziland and Uzbekistan. A total of 1,369 patients that had started DRTB treatment were enrolled, 809 (59.1%) had MDR-TB and 418 (30.5%) were HIV-positive. HIV-positive patients were mainly from African countries (90.1%) while HIV-negative originated from Former Soviet Union (FSU) countries. Despite a higher case fatality rate (19.0% vs 9.4%), HIV-positive MDR-TB patients had a 10% higher success rate than HIV-negative patients (64.0% vs 53.2%, p = 0.007). No difference in treatment success was found among poly drug-resistant (PDR-TB) patients. Overall, lost to follow-up rate was much higher among HIV-negative (22.0% vs. 8.4%). Older age and not receiving ART were the only factors associated with unfavorable treatment outcome

among HIV-positive patients. The study concluded that success rate of DR-TB/ HIVpositive patient remains low and requires more effective DR-TB regimen using new drugs also suitable to HIV-infected patients on ART. The study also confirmed the need of ART introduction in HIVco-infected patients (Bastard et al., 2018).

A retrospective study based in Peru that was carried out to compare mortality between MDR drug-susceptible cases of tuberculosis, and to determine risk factors associated with mortality among MDR-TB cases. A total of 1,232 patients were analyzed. The mean age was 30.9 years and 60.0% were males. Education level was associated with mortality among MDR-TB cases. This study concluded that lower education was independently associated with mortality among MDR-TB cases (Chung-Delgado et al., 2015).

A South African based prospective cohort that looked at outcomes of MDR-TB among a cohort of South African patients with high HIV prevalence enrolled 757 patients with known HIV status and were included in the final analysis. HIV infection was documented in 287 (38%). Overall, 348 patients (46.0%) were successfully treated, 74 (9.8%) failed therapy, 177 (23.4%) died and 158 (20.9%) defaulted. Patients with HIV were slightly younger and less likely to be male compared to HIV negative patients. Low baseline weight (less than 45 kg and less than 60 kg) was also associated with a higher hazard of compared to weight greater than 60 kg. Weight less than 45 kg had higher risk of failure or death (Farley et al., 2011). This study concluded that in this MDR-TB treatment program patients with HIV infection and low weight had higher hazards of death and overall treatment outcomes were poor thus recommended efforts to improve treatment for MDR-TB are urgently needed (Manda et al., 2013; van der Walt et al., 2016).

Despite all the above studies about mortality rate and associated sociodemographics factors among DR-TB/HIV co-infected patients, some factors can be modifiable to avert mortality, however, this information is lacking in Uganda.

## 2.4 Clinical factors

An observational retrospective South African based study that looked at HIV co-infection in Multi-drug and extensively drug resistant tuberculosis resulting into high early mortality enrolled 654 MDR-TB and XDR-TB cases that were diagnosed in Tugela Ferry, South Africa from 2005 to 2007. Their demographics and HIV status were abstracted from available medical records. Survival was determined from the date of sputum collection until October 2008 and correlated with year of diagnosis and drug-susceptibility test results. From 2005 to 2007, 272 MDR TB and 382 XDR-TB cases were diagnosed; HIV co-infection rates were 90 and 98%, respectively. One-year mortality was 71% for MDR-TB and 83% for XDR-TB patients; 40% of MDR-TB and 51% of XDR-TB cases died within 30 days of sputum collection. One year mortality among both MDR-TB and XDR-TB patients improved from 2005 to 2007; however, the majority of deaths still occurred within the first 30 days. One-year and 30-day mortality rates were worse with greater degree of drug resistance ($P<0.001$).This study concluded that mortality from MDR-TB and XDR-TB in this high HIV prevalence region is extraordinarily high, particularly within the first 30 days thus recommended that efforts to reduce mortality must focus on earlier diagnosis and early initiation of second-line TB and antiretroviral therapy (Gandhi et al., 2010).

A retrospective cohort study based in South Africa that looked at tuberculosis case fatality and other causes of death among multidrug resistant tuberculosis patients in a high HIV prevalence setting, enrolled 671 patients treated between 2000–2008; 59% of the cohort was HIV-infected and 33% had received ART during MDR-TB treatment. Treatment outcomes between HIV un-infected cases, HIV-infected cases receiving ART and HIV-infected without ART differed significantly ($p<0.001$).The cohort death rate was 24% for HIV infected on ART, 13% for HIV-uninfected cases and 31% for HIV-infected cases and not on ART. TB caused most of the deaths, resulting in a cohort CFR of 15%, 9% for HIV-uninfected cases and 20% for HIV-infected cases. Cohort mortality

rate due to other conditions was 2%. The study concluded that AIDS-conditions rather than TB caused significantly more deaths among HIV-infected cases receiving ART than those not (p = 0.02). The deaths among HIV-infected individuals contributed substantially to the high death rate. ART co-therapy protected HIV-infected cases from death due to TB and AIDS conditions. This study recommended that mechanisms need to be in place to ensure that HIVinfected individuals are retained in care upon completion of their MDR-TB treatment (van der Walt et al., 2016).

A retrospective study based in South Africa TB referral hospital that looked at malnutrition as being associated with unfavorable outcome and death among South African MDR-TB and HIV co-infected children enrolled 84 children (median age 8 years, IQR 4–12) with MDR-TB (n = 78) or XDR-TB (n = 6) that had initiated treatment between January 2009 to June 2010. 64 (77%) were HIV-positive and 62 (97%) received antiretroviral therapy. 66 (79%) achieved favorable treatment outcomes. Overall mortality was 11% (n= 9) at 18 months after initiation of treatment. Malnutrition (aOR 27.4, 95%CI 2.7–278.7) and severe radiographic findings (aOR 4.68, 95% CI 1.01–21.9) were associated with unfavorable outcome. New pediatric outcome definitions increased the proportion classified as cured. This study concluded that it was possible to successfully treat pediatric MDR-TB/HIV even in resource-poor settings and malnutrition was a marker for severe TB-HIV disease, and is a potential target for future interventions in these patients (Hicks et al., 2014).

A case control study done in South Africa that looked at the risk factors for mortality among MDR-TB and XDR-TB patients in a high HIV-prevalence setting enrolled 123 MDR-TB patients and 139 XDR-TB patients. Among the 123 MDR-TB patients, 78 (63%) died following diagnosis. CD4 count less than 50 (HR 4.64, p=0.01) and 51-200 cells/mm3 (HR 4.17, p=0.008) were the strongest independent risk factors for mortality. Among 139 XDR-TB patients, 111 (80%) died. CD4 count less than 50 cells/mm3 (HR 4.46, p=0.01) and resistance to all six drugs

tested (HR 2.54, p=0.04) were the principal risk factors. Use of antiretroviral therapy (ART) was protective (HR 0.34, p=0.009).This study concluded that mortality in MDR-TB and XDR-TB was associated with greater degree of immunosuppression and drug resistance. It thus recommended that efforts to reduce mortality must focus on preventing the amplification of resistance by strengthening TB treatment programs, as well as, reducing the pool of immunosuppressed HIV-infected patients through aggressive HIV testing and ART initiation (Gandhi et al., 2012).

A South African based prospective cohort that sought to assess the risk of death among HIV co-infected multidrug resistant tuberculosis patients, compared to mortality in HIV negative MDR-TB patients of South Africa , death was recorded on 1619 patients, of whom 367 (22.7%) had died within 2 years. Out of the 1413 patients that tested for HIV infection, 554 (39.2%) tested positive. Excess mortality was higher in HIV infected, compared to HIV uninfected, MDR-TB patients, in patients whose TB isolates' resistance to ethambutol and kanamycin was unknown This study concluded that adjusting for some important predictors, MDR-TB patients with HIV infection experienced higher excess mortality compared to HIV-uninfected MDR-TB patients, after accounting for the general mortality in South Africa. Thus, the use of relative survival methods should be encouraged in the analysis of cause specific mortality, when ascertainment of cause of death is inaccurate or unknown (Manda et al., 2013).

A prospective study done in a TB referral hospital in KwaZulu-Natal Province, South Africa looked at the effect of antiretroviral therapy on treatment outcomes in patients with extensively drug resistant tuberculosis (XDR-TB) HIV co-infection treatment enrolled 105 patients. Of the 105 XDR-TB patients (76.1% HIV infected) were enrolled from August 2009 through July 2011. Among HIV co-infected patients, 82.5% were on ART initially and 93.8% cumulatively over the study period. At 24 months 31.4% had a successful outcome and 68.6% had an

unsuccessful outcome with 41% mortality. ART was associated with improved mortality in HIV co-infected patients (p= 0.05), as was TB culture conversion (p <0.0001). The study concluded that despite improved HIV care, treatment outcomes and mortality were only modestly improved compared to previous South African XDR-TB/HIV treatment cohorts. Noting that this study was completed prior to introduction of new antimycobacterial agents (e.g. bedaquiline, delaminid). As new TB drugs and regimens become available it is important to monitor treatment to ensure benefits seen in clinical trials are reproduced in high-burden, low-resource settings (Yuengling et al., 2018).

A retrospective cohort study done at Sizwe Tropical Disease Hospital, Johannesburg from 2007 to 2010 that looked at treatment outcomes in MDR-TB/HIVco-infected patients on anti-retroviral therapy recruited 1200 patients. Mortality was higher (21.8 % vs. 15.4 %) among patients who started ART before initiating MDR-TB treatment compared with patients initiated on ART after commencing MDR-TB treatment (p = 0.013). Factors significantly associated with mortality included: the use of ART before starting MDR-TB treatment (OR 1.65, 95 % CI 1.02–2.73), severely underweight (OR 3.71, 95 % CI 1.89–7.29) and underweight (OR 2.35, 95 % CI 1.30–4.26), cavities on chest x-rays at baseline (OR 1.76, 95 % CI 1.08–2.94), presence of other opportunistic infections (OR 1.80, 95 % CI 1.10–2.94) and presence of other co-morbidities (OR 2.26, 95 % CI 1.20–4.21). Factors predicting failure were severe anemia (IRR (OR 4.72, 95 % CI 1.47–15), other co-morbidities (OR 2.39, 95 % CI 1.05–5.43) and modified individualised regimen at baseline (OR 2.15, 95 % CI 0.98–4.71).This study concluded that high mortality among patients already on ART before initiating MDR-TB treatment is a worrisome development. Management of adverse-events, opportunistic infections and co-morbidities in these patients is important if the protective benefits of being on ART are to be maximized. And thus recommended that there is the need to intensify intervention programs targeted at early identification of MDR-TB, treatment initiation, drug monitoring and increasing adherence among HIV co-infected MDR-TB patients (Umanah et al., 2015).

A South African retrospective study that looked at severe adverse events during second-line TB treatment in the context of high HIV co-infection enrolled 578 participants. 36.7% were categorized as low weight (≤50 kg) at DR-TB initiation. 76.0 % had no history of TB treatment prior to the current episode of RR TB. 26.8 % were diagnosed with RR TB while hospitalized, indicating poor clinical condition. 82.5 % of patients were also HIV positive, of whom 43.8 % were on ART prior to RR TB treatment and 32.1 % initiated ART with or after RR TB treatment. Median CD4 count was 114.5 (IQR: 45-246.5). Overall, 578 reports of AEs were captured for 204 patients (35.3 %) and 110 patients (19.0 %) had at least one severe AE reported. Patients with at least one AE experienced a median of 3 (IQR: 2-4) AEs per patient. HIV-positive patients with CD4 counts ≤100 cells/mm3 and those newly initiating ART were more likely to experience a severe AE (sHR: 2.76, 95 % CI: 1.30–5.84 and sHR: 3.07, 95 % CI: 1.46–6.46, respectively). This study concluded that severe AEs are common during the first 6 months of RR TB treatment and HIV-positive patients newly initiating ART have the highest sub-distribution hazard ratio for severe AE, accounting for the competing risks of death and loss from treatment (Schnippel et al., 2016).

Despite all the above studies about mortality rate and associated clinical factors among DR-TB/HIV co-infected patients, some factors can be modifiable to avert mortality, however, this information is lacking in Uganda

# Chapter 3

## 3.0 Methods

## 3.1 Study design

A retrospective cohort study design was used. Secondary data were collected from patient files and DR-TB registers from 1st January 2014 to 31st December 2019.

## 3.2 Study Setting

The study was carried out at Mulago Hospital tuberculosis unit. Mulago Hospital is a national referral and teaching Hospital. Mulago Tuberculosis unit is an urban TB center of excellence located in Mulago teaching hospital with over 800 patients both referred and those that use it as a primary health care Centre with drug resistant TB receiving care. It handles both HIV infected and non HIV DR-TB patients. The Mulago Tuberculosis unit began providing free DR-TB care in 2012 and provides other services like radiology, nursing, pharmacy, inpatient services and Counselling. The Mulago tuberculosis unit works in collaboration with Mulago Joints Aids Program (MJAP) to provide free ART for all HIV positive DR-TB patients at one stop centre. MJAP is an HIV center of excellence that provides HIV services including counseling, treatment and laboratory testing. This Mulago Tuberculosis unit receives about 71 DR-TB patients annually with 60% of them co-infected with HIV coming from different districts around Kampala and it runs a DR-TB/HIV clinic weekly on Tuesday. Patient data were captured in personal patient files and the DR-TB register. Information on sociodemographics and TB and HIV clinical factors was collected.

## 3.3 Populations

### 3.3.1Target Population

All DR-TB/HIV co-infected patients in Central Uganda.

### 3.3.2 Accessible Population

All DR-TB/HIV co-infected patients during the study period in Mulago Hospital.

### 3.3.3 Study population

All DR-TB/HIV co-infected patients from 1st January 2014 to 31st December 2019 who met the eligibility criteria. The study period was chosen in order to get a representative sufficient sample size as well as be more recent as possible. This was done by checking in the drug resistant TB patient register and their corresponding personal files.

## 3.4 Eligibility Criteria

### 3.4.1 Inclusion criteria

- Patients with laboratory confirmed DR-TB and HIV positive results
- Patients having a treatment outcome recorded.
- Patients that had attended the Mulago tuberculosis Unit between 1$^{st}$ January 2014 and 31$^{st}$ December 2019.

### 3.4.2 Exclusion criteria

- Patients with incomplete records/missing data on age, sex, BMI and treatment start date were excluded.

## 3.5 Sample size calculation

The sample size for the 1st objective was computed using Kish Leslie's formula using

$$N = \frac{Z^2{}_{\alpha/2}\, p(1-p)}{d^2}$$

Where;

- Z-alpha is standard normal value corresponding to the set confidence level , 95% confidence then Z is 1.96
- N is required sample size
- d is the tolerable sampling error (precision) = 5%
- p is the estimated proportion of the characteristic in a population similar to the one that is being studied. Mortality rate =42% (O'Donnell et al., 2013)

$$= \frac{1.96\text{^}2 * 0.42(0.58)}{0.05\text{^}2}$$

=374.3 ≈375

A sample size of 375 participants was estimated for this study.

The sample size for the 2nd objective was computed using the formula for estimating sample size for comparison of two proportions.

$$N = \frac{[Z_{\alpha/2}\sqrt{p(1-p)(1/q_1 + 1/q_2)} + Z_{\beta}\sqrt{p_1(1-p_1)\,1/q_1 + p_2(1-p_2)\,1/q_2}]^2}{(p_1 - p_2)^2}$$

Where;

- N is required sample size
- q1 is proportion of subjects with DR-TB/HIV aged less than 35years of age 57.3% (Bastard et al., 2018)
- q2 is proportion of subjects with DR-TB/HIV aged ≥35 years of age 42.7% (Bastard et al., 2018)
- Zα is standard normal value corresponding to level of significance=1.96 for 5% level of significance.
- Zβ is standard normal value corresponding to power of the study=0.84 for power of 80%.
- p1 is proportion of those less than 35 years that died of DR-TB /HIV 26.3% (Bastard et al., 2018).
- p2 proportion of those ≥35 years of age that died of DR-TB/HIV 39.7% (Bastard et al., 2018).
- p = p1q1+p2q2=0.32

N=389.3≈390

390 patients were recruited in the study.

## 3.6 Sampling Procedures

Consecutive sampling was used. Each subject meeting the inclusion criteria was selected until the required sample size was attained. This was because I was working with a limited population.

## 3.7 Study Variables

**3.7.1 Dependent Variable:** Vital status of the patient at the end of treatment which may either be dead or alive.

**3.7.2 Independent Variables -** Age, sex, body mass index (BMI), mid upper arm circumference (MUAC), viral load, adverse effects, patients phone contact, start of ART, ART regimen, sputum culture result at baseline, type of case was categorized as no history of TB treatment or history of TB treatment and time to mortality.

## 3.8 Data collection methods and tools

Data abstraction tool was used since secondary data was to be utilized. I looked through the DR-TB register and searched through for patients meeting the eligibility criteria and their corresponding personal files were got by the data custodian at Mulago Tuberculosis unit to extract the other information on variables to be studied.

The abstraction process summarized all the information about a patient from which data were extracted for analysis. This data were collected by two well-trained research assistants (nurses) who underwent training for one week prior to data collection. Ten patients' records were used for pre-testing the abstraction form by research assistants in Mubende Regional Referral Hospital. After the pretest, the researcher examined each of the already filled abstraction forms for validity and determined whether all the data variables needed had been filled to evaluate conformance and check out any discrepancies. The researcher checked each abstraction form to ensure that the patient information from patient file and TB register was consistent with that on the data abstraction form. The researcher identified any ambiguous or confusing information which was incorporated during the drafting of the forms and incase of any aspect that research assistants were not well conversant with, a retraining was conducted.

### 3.8.1 Data Management

Data were checked for completeness and correctness. Data were coded and de-identified for confidentiality purposes. Double entry of all data on the filled abstraction form was done to check for any errors. Data cleaning was done to check for accuracy, consistency, missed values and variables so as to improve data quality for analysis. Data were also backed up to prevent primary data loss and it was under restricted access and lock and key for confidentiality purposes. It was entered in EpiDATA.

### 3.8.2 Data Analysis Plan

Data were analyzed in STATA version 14.0.At univariate level, the data were presented as frequencies and percentages for categorical variables, medians with corresponding interquartile ranges and means and standard deviation for continuous variables.

At bivariate, modified poisson regression with robust standard errors with the family poisson and link log was used to determine relationships between the independent variables and the dependent variable (mortality). Independent variables with a pvalue <0.2 were taken to multivariate level for analysis. Incidence rate ratios (IRR) were the measure of association used.

At multivariate level, modified poisson regression with robust standard errors was used to determine the association between mortality and the independent variables. Independent variables with a pvalue <0.05 were the factors associated with mortality among DR-TB/HIV co-infected patients and were in the model.

Interaction was assessed in the model. After multivariate analysis, using the backward stepwise estimation, interaction terms with the independent variables in the model were formed and a full model with interaction terms and a reduced model without interaction terms were compared. A likelihood ratio test was done and the p-value checked for significance.

Confounding was assessed by running both the adjusted model and an unadjusted model and ≥10% change in the incidence rate ratios of the variable was considered a confounder. All known confounders like age, history of TB,

body mass index (from literature) were left in the study. Conclusions were drawn based on the adjusted incidence rate ratios with their corresponding 95% confidence intervals and P-values.

### 3.8.3 Data Quality Control

Training of research assistants was done to ensure they were well informed about what they were going to do. The data abstraction form was pre-tested on 10 patient records by the research assistant to check for its feasibility before the actual study took place. Double entry was done by the researcher to see if patient information on the form corresponds to that in the register or patient file to increase accuracy and a retraining was done for the research assistants in case they found any problems with filling the data abstraction form correctly.

### 3.9.0 Ethical Considerations

### 3.9.1 Permission to carry out the study

Permission to carry out the study was sought from Clinical Epidemiology Unit, Makerere University, and School of Medicine. Approval was sought from School of Medicine Research and Ethics Committee and Mulago Research and ethics committee (#REC REF 2020-063). Administrative approval was also obtained from Mulago to access patient data records (MHREC 1832).

### 3.9.2 Confidentiality

Data extracted from patient records didn't bear any patient names and was de-identified, and coded for confidentiality and safety purposes of the patients. No data was given out to any person and all data was stored on a computer with a password, which was only accessed by the researcher.

### 3.9.3 Informed Consent

An application for waiver of consent was submitted and approval was got from the School of Medicine Research Ethics Committee.

### 3.9.4 Dissemination of Results

The report was first presented to Clinical Epidemiology Unit and thereafter, a copy of the report was given to the Directorate of graduate studies and Albert cook Library as well as Mulago Tuberculosis Unit. A manuscript was prepared for online publication in a peer review journal.

# Chapter 4: Results

## 4.0 Flow of participants in the study

This study screened 412 participants with drug resistant TB/HIV co-infection. Of these, 390 (94.7%) participants aged 1-80 years were recruited into the study. 12 and 10 participants were excluded because they lacked a documented BMI results and a documented treatment start date respectively.

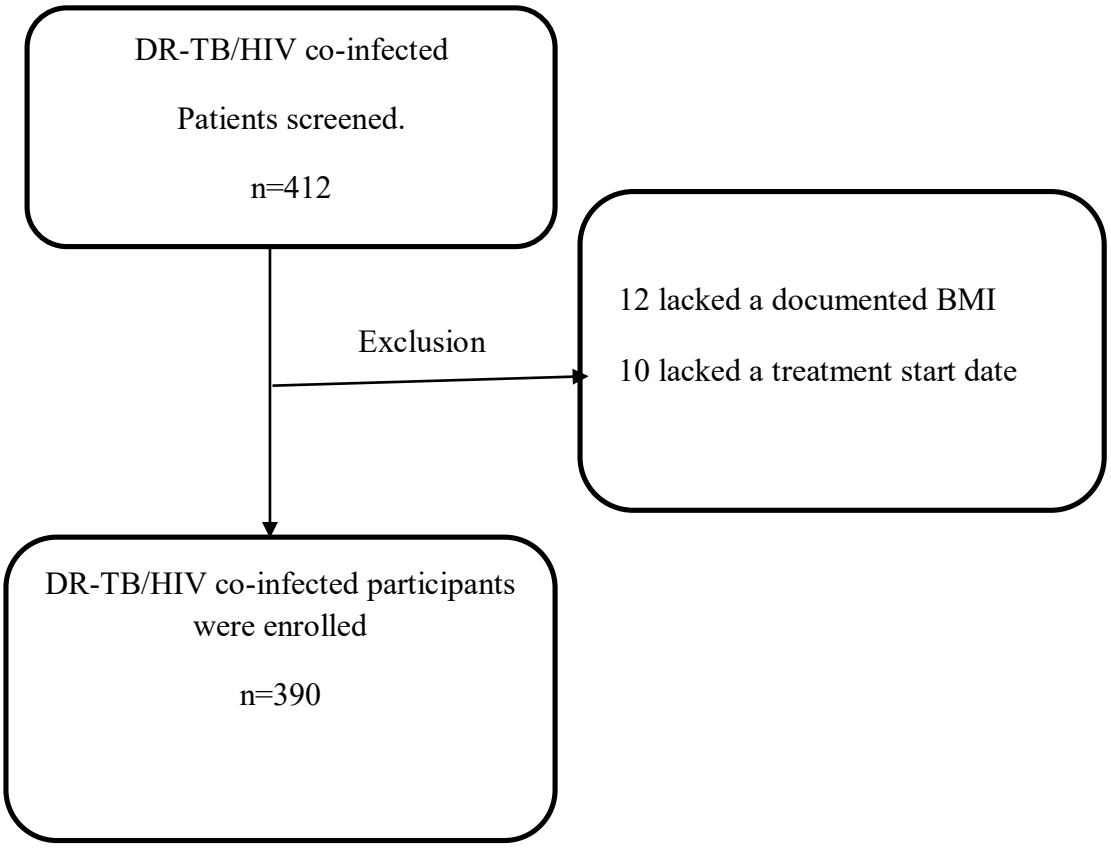



**Figure 2. Flow chart showing participant recruitment in the study**

## 4.1 Description of the study participants

The mean (SD) age at enrolment was 34.7 (± 10.6) years. Out of the 390 enrolled, 210 (53.9%) were males .Majority of the participants had their phone contacts documented 363 (93.3%) and were new cases without any history of TB treatment 203 (52.1%).Most of the participants had a positive sputum smear at baseline 161 (57.3%) with majority having an adverse event 245 (62.8%).Majority of the participants had started Antiretroviral therapy 365 (95.5%) and were taking first line Antiretroviral therapy regimen 369 (94.6%).Majority of the patients had a missing viral load result 289 (75.9%). Most of them had a body mass index (BMI) ≥18.5Kg/$m^2$ 247(63.3%) with most of them having a mid-upper arm circumference (MUAC) of <24.5cm 351(90%) as summarized in table 1 below.

**Table 1. Sociodemographic characteristics of the study participants (N=390)**

| Characteristic | Frequency (%) |
|---|---|
| **Sex** | |
| Male | 210(53.9) |
| Female | 180(46.1) |
| **Age** | |
| <35 | 220(56.4) |
| ≥ 35 | 170(43.6) |
| **Patient's Phone contact(n=389)** | |
| No | 26(6.7) |
| Yes | 363(93.3) |
| **Case** | |
| No History of TB Rx | 203(52.1) |
| History of TB Rx | 187(47.9) |
| **Sputum Culture at baseline(n=281)** | |
| Positive | 161(57.3) |
| Negative | 120(42.7) |
| **Adverse event** | |
| No | 145(37.2) |
| Yes | 245(62.8) |
| **Antiretroviral Therapy started(n=382)** | |
| No | 17(4.5) |
| Yes | 365(95.5) |
| **Antiretroviral Therapy Regimen** | |
| First line | 369(94.6) |
| Second line | 21(5.4) |
| **Viral load(n=381)** | |
| Detectable | 37(9.7) |
| Undetectable | 55(14.4) |
| Unknown | 289(75.9) |
| **BMI catergory** | |
| < 18.5 kg/m2 | 143(36.7) |
| ≥18.5 kg/m2 | 247(63.3) |
| **MAUC catergory** | |
| < 24.5cm | 351(90.0) |
| ≥24.5cm | 39(10.0) |

## 4.2 Mortality rate among drug resistant tuberculosis/HIV co-infected patients at Mulago Hospital.

The mortality rate among DR-TB/HIV co-infected patients at Mulago Hospital was 32.8% (95% CI:28.3-37.7) as shown in Figure 3 below with majority of the participants having a median time to mortality of ≤ 2.2 months (1,2).

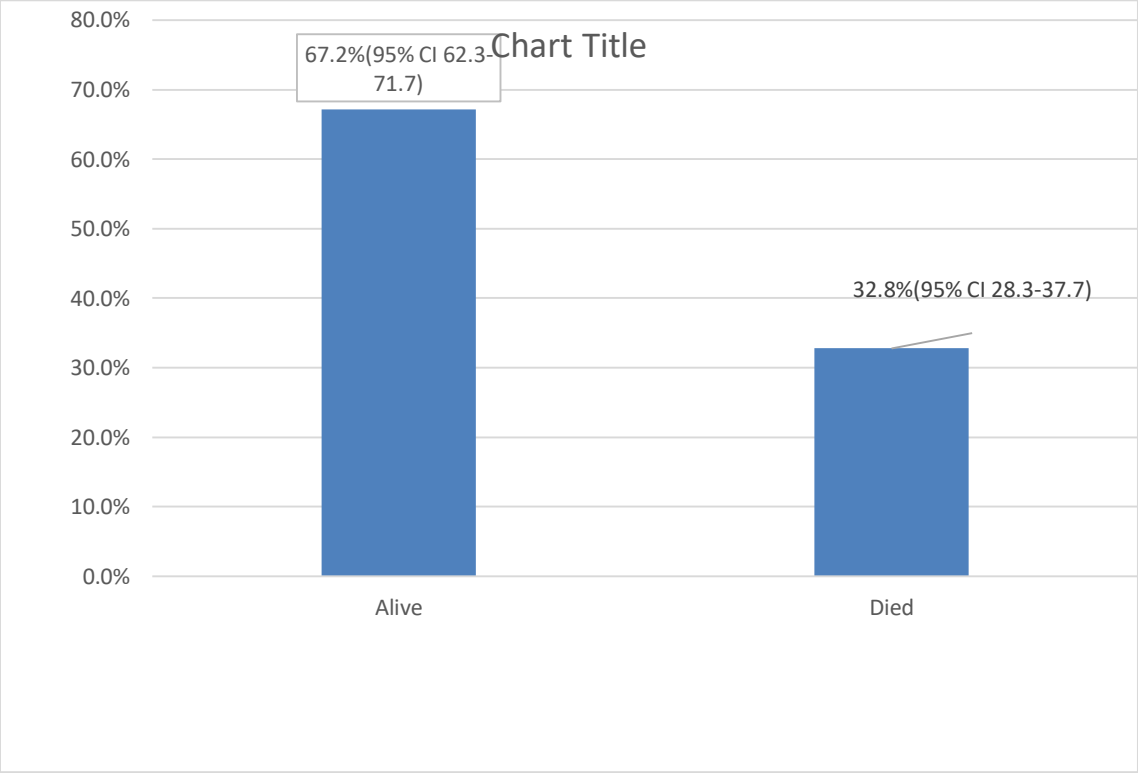



**Figure 3. Mortality rate among drug resistant TB/HIV co-infected patients in Mulago Hospital.**

## 4.3 Factors associated with mortality among drug resistant TB/HIV co-infected patients at Mulago Hospital at bivariate analysis.

At bivariate analysis, having a documented phone contact (IRR=0.8395% CI: 0.73-0.94, p-value=0.004) and experiencing an adverse event (IRR= 0.77 95% CI: 0.72-0.82, pvalue=<0.001) were protective against mortality.

Additionally, starting antiretroviral therapy (IRR=0.67 95%CI: 0.62-0.72, p-value=<0.001), being on first line antiretroviral regimen (IRR=0.89 95% CI: 0.77-1.03, p-value<0.121) and having undetectable viral load (IRR=0.77 95%CI: 0.68-0.87, p-value=<0.001), body mass index of ≥18.5 $Kg/m^2$ (IRR=0.88 95% CI: 0.82-0.94, p-value =<0.001), mid upper arm circumference of ≥24.5cm (IRR=0.73 95% CI: 0.71-0.76, p-value=<0.001 were found to be protective against mortality as shown in table 2 below.

**Table 2. Factors associated with mortality among patients co-infected with DR-TB/HIV at Mulago Hospital at bivariate analysis.**

| | Died | | | |
|---|---|---|---|---|
| **Characteristic** | **Yes n (%)** | **No n (%)** | **IRR( 95% CI)** | **Pvalue** |
| **Sex** | | | | |
| Female | 56(31.1) | 124(68.9) | 1 | |
| Male | 72(34.3) | 138(65.7) | 1.02(0.96-1.01) | 0.505 |
| **Age** | | | | |
| <35 | 77(35.0) | 143(65.0) | 1 | |
| ≥35 | 51(30.0) | 119(70.0) | 0.96(0.90-1.03) | 0.296 |
| **Patient's Phone contact** | | | | |
| No | 15(57.7) | 11(42.3) | 1 | |
| Yes | 113(31.1) | 250(68.9) | 0.83(0.73-0.94) | 0.004 |
| **Type of TB case** | | | | |
| No History of TB Treatment | 65(32.0) | 138(68.0) | 1 | |
| History of TB Treatment | 63(33.7) | 124(66.3) | 1.01(0.944-1.07) | 0.726 |
| **Sputum Culture at baseline** | | | | |
| Positive | 39(24.2) | 122(75.8) | 1 | |
| Negative | 23(19.2) | 97(80.8) | 0.96(0.89-1.04) | 0.307 |
| **Adverse event** | | | | |
| No | 80(55.2) | 65(44.8) | 1 | |
| Yes | 48(19.6) | 197(80.4) | 0.77(0.72-0.82) | <0.001 |
| **Antiretroviral Therapy started** | | | | |
| No | 16(94.1) | 1(5.9) | 1 | |
| Yes | 108(29.6) | 257(70.4) | 0.67(0.62-0.72) | <0.001 |
| **Antiretroviral Therapy Regimen** | | | | |
| First line | 124(33.6) | 245(66.4) | 1 | |
| Second line | 4(19.1) | 17(80.9) | 0.89(0.77-1.03) | 0.121 |
| **Viral load** | | | | |
| Detectable | 13(35.1) | 24(64.9) | 1 | |
| Undetectable | 2(3.6) | 53(96.4) | 0.77(0.68-0.87) | <0.001 |
| Unknown | 110(38.1) | 179(61.9) | 1.02(0.91-1.15) | 0.728 |
| **BMI at baseline** | | | | |
| <18.5kg/m2 | 63(44.1) | 80(55.9) | 1 | |
| ≥18.5kg/m2 | 65(26.3) | 182(73.7) | 0.88(0.82-0.94) | <0.001 |
| **MAUC at baseline** | | | | |
| <24.5cm | 128(36.5) | 223(63.5) | 1 | |
| ≥24.5cm | 0(0.0) | 39(100) | 0.73(0.71-0.76) | <0.001 |

## 4.4 Factors associated with mortality among drug resistant co-infected TB/HIV attending Mulago Hospital at multivariate analysis.

At multivariate analysis, having an adverse event (aIRR=0.81 95% CI: 0.80-1.15, p-value=0.001), having a documented patients phone contact (aIRR=0.85 95% CI:0.75-0.87,p-value=0.012),body mass index of ≥ 18.5Kg/m2(aIRR= 0.91 95% CI:0.85-0.97,pvalue =0.007), having started Antiretroviral therapy (IRR=0.79 95% CI:0.71-0.88,p-value=<0.001) and a mid-upper arm circumference of ≥ 24.5 cm (aIRR=0.83 95% CI:0.78-0.88, p=0.001) decreased the likelihood of death among patients that were drug resistant TB/HIV co-infected as shown in table 3 below.

**Table 3. Factors associated with mortality among patients with DR-TB/HIV in Mulago Hospital**

| Characteristic | aIRR( 95% CI) | Pvalue |
|---|---|---|
| **Age** | | |
| <35 years | 1 | |
| ≥35 years | 0.99(0.93-1.05) | 0.683 |
| **Adverse event** | | |
| No | 1 | |
| Yes | 0.81(0.75-0.87) | < 0.001 |
| **Patient's Phone contact** | | |
| No | 1 | |
| Yes | 0.85(0.76-0.97) | 0.012 |
| **BMI at baseline** | | |
| < 18.5 kg/m2 | 1 | |
| ≥18.5 kg/m2 | 0.91(0.85-0.97) | 0.007 |
| **ART started** | | |
| No | 1 | |
| Yes | 0.79(0.71-0.88) | <0.001 |
| **TB case** | | |
| No history of Treatment | 1 | |
| History of Treatment | 1.03(0.97-1.10) | 0.391 |
| **MUAC at baseline** | | |
| < 24.5cm | 1 | |
| ≥24.5 cm | 0.83(0.78-0.88) | < 0.001 |

# Chapter 5

## 5.0 Discussion

The study aimed at ascertaining the mortality rate and factors associated with mortality among DR-TB/ HIV co-infected patients at Mulago Hospital. The epidemic levels of drug resistant TB/HIV co-infection are growing threat to public health and threaten global TB and HIV control because they are associated with high mortality rates (Singh et al., 2020).Despite the new diagnostic technologies and treatment options becoming available, as well as strong global political commitment to ending TB and HIV, there are still high mortality rates among DR-TB/HIV co-infected patients.

## 5.1 Mortality rate among drug resistant TB/HIV co-infected patients.

This study reported a 32.8% (95% CI: 28.3-37.7) mortality among DR-TB/HIV co-infected patients at Mulago hospital. This implied that approximately 33 DT-TB/HIV patients died in every 100 patients with this co-infection. This is much higher than that reported by the East African Community (EAC), Uganda inclusive of 24% TB deaths (Sabiiti, 2017). This high mortality threatens Uganda's progress in the fight against TB and HIV of her goals of zero deaths from DR-TB/HIV patients as they are among the most vulnerable groups rapidly progressing to severe disease states, or even death. This study is one of the kind that investigated the mortality rate among DR-TB/HIV in Uganda. Furthermore, drug-drug interactions between second-line anti-TB drugs and ART are not well known (Dooley, Charles, & Andrade, 2008), but this could also explain the high mortality rate although there is no literature to support this finding. These findings were consistent with those reported in Lesotho (34%) (Satti et al, 2012) and38% (Singh et al., 2020).However, despite the consistency in findings, there is still a lot of effort needed in the Uganda especially in regions with high mortality rates due drug resistant TB/HIV dual infection if we are to achieve national and global targets of drug resistant TB/HIV eradication, improving patient outcomes, and curbing drug resistant TB/HIV related mortality following the 2019 world TB report recording an increase in drug resistant TB/HIV progress in high burden countries inclusive of Uganda(WHO, 2019b).However, these findings

were different from those reported in South Africa (23.4%)(Farley et al., 2011), 19% in a multicenter cohort done in Abkhazia, Armenia, Colombia, Kenya, Kyrgyzstan, Swaziland and Uzbekistan (Bastard et al., 2018), 18% in a systematic review done sub-Saharan Africa(Van Hout & Hope, 2019b)and 11.4% among children (Singh et al., 2020). All these mortality rates were much lower than that recorded in our study. The observed difference could be due to the difference in time, study population characteristics, DR-TB treatment practices/regimens in Uganda as they differ from these studies, and improved compliance in documentation of patient outcomes, different comprehensive model of DR-TB/HIV care and expertise through trainings as well as continued efforts in implementation of drug resistant TB/HIV management policies in the country. Another study from KwaZulu-Natal Province, South Africa reported a 42% mortality which was different from findings in our study (Yuengling et al., 2018). This mortality rate was higher than that reported in our study and the observed difference could have been due to the fact that this study was done between 2001 to 2007 compared to ours that was done in 2019, and there has been a lot of changes in the DR-TB regimens and management. However, this mortality rate that was found in this study is higher than that that would be observed in the other Ugandan regions because Mulago is a national referral hospital, so all patients who fail on treatment countrywide are referred there. Secondly, these patients are very sick with other comorbidities, thus are more likely to die despite the proper treatment.

## 5.2 Factors associated with mortality among drug resistant TB/HIVco-infected patients in Mulago Hospital.

Inorder to understand and curb mortality among DR-TB/HIV co-infected patients, we need to have a clear understanding of the factors associated and then devise means to mitigate them. From our study, mortality was majorly associated with sociodemographics and clinical factors. Risk factors to mortality were age, hospitalization, having an adverse event, patient's phone contact, body mass index, starting ART, history of TB treatment and mid upper arm circumference.

## Adverse events

Our study found an association between adverse events and mortality. Presence of an adverse event was protective and thus reduced the risk of death among patients taking DR-TB treatment. In our study there was a 19% reduced likelihood of death among patients with an adverse event compared to those without any adverse event. This was consistent with findings from a study done in India (Dela et al., 2017).However these findings were different from another study that was done in South Africa(Umanah et al., 2015) that found no significant association between having and adverse event and mortality, however there was infrequent documentation of specific drug associated events. This observed difference could possibly be due to the fact that participants in our study were monitored more frequently than those in previous studies, thus increasing the chance of detecting adverse events. More still, patients who experienced adverse events were adherent to DR-TB therapy and could have been monitored more closely by physicians, and thus were more likely to achieve favorable treatment outcomes. In addition, it's also more likely that patients experiencing an adverse event were adherent to their medication hence having a higher dose exposure, thus likely to have more dose dependent TB adverse events but treatment outcomes could be better. Other explanation would be that, patients who were on more drugs including cotrimoxazole, ART and DR-TB drugs, had a larger number of drugs that exposed them to a high frequency of adverse events although the adverse events were not very severe and life threatening.

## Patient's Phone contact

This study found an association between mortality and patient's phone contact. There was a 14.6%reduction in the likelihood of mortality among patients with phone contacts documented as compared to patients without phone contacts. This is because presence of the phone contact would ease tracing and communication with the patient to ensure complete follow up, monitoring and ensuring proper adherence and compliance as well as tracing lost to follow up patients. It also ensured creation of a relationship and social support by the health care provider and the patient. These study findings were consistent with a study carried in Malawi (Weigel et al., 2011).The availability

of phone contacts was an effective way of identifying outcomes of LTFU patients and following up patients if they missed their drug and review appointment dates thus enhancing adherence in turn reducing death. Additionally, via telephone, patients were more likely to be located on a first attempt, admit leaving the clinic, and reveal their outcome status. More still, although not directly, having a phone is an indication of a better socio-economic status that also reduces mortality.

## Baseline body mass index (BMI)

Our study found an association between mortality and body mass index. This study found a 9% reduced likelihood in mortality among patients who had a bmi ≥18.5kg/m2 than patients who had a bmi<18.5kg/m2. This was consistent with findings from different previous studies by (Isaakidis et al., 2011; Johnston, Shahidi, Sadatsafavi, & Fitzgerald, 2009; Palacios et al., 2012; Satti, McLaughlin, Hedt-Gauthier, et al., 2012; Waisman et al., 2001)in Mumbai, South Africa, Lesotho and Europe respectively. This is explained by the fact that HIV and TB are linked to malnutrition and wasting syndrome, a hallmark of severity of TB and HIV infection, therefore its strong association as a predictor of mortality is not surprising. Additionally, on DR-TB treatment experienced severe gastrointestinal intolerance (nausea, vomiting and gastritis) and drug toxicities during treatment that causes malnutrition and this may reduce the survival probability of the participants. This is scientifically supported that anti-TB drugs have serious adverse effects including nausea, vomiting and electrolyte disturbance which leads to poor prognosis. Additionally, BMI is a very important aspect in starting DR-TB therapy thus influences patient treatment outcomes.

## Starting ART

Our study found a significant association between starting ART and mortality. Starting ART was protective against mortality compared to not having started ART.This study found out that there was a21% reduced likelihood of death among patient who had started ART as compared to those that hadn't started ART.Our findings were consistent with those of Blanc et al that found out that the risk of death was significantly reduced in patients receiving

ART earlier(Blanc et al., 2011).This is because by the time this study was undertaken, antiretroviral treatment (ART) was rolled out countrywide and was available in Uganda. This can also be explained by the fact that having started ART reduces immunosuppression and opportunistic infections thus improving the health status (Dereje et al., 2019).Additionally, there has been increased voluntary HIV testing and counseling (VCT) at all entry point for patients to receive ART, and social support has been given by clinicians due to stigma that was associated with HIV, most patients are now willing to be tested to know their HIV infection. This is reflected by 100% of the patients in our study with a known HIV status. Indeed, the wide availability of ARVs in this period must have greatly reduced mortality levels of this cohort of DR-TB/HIV patients.

## Mid upper arm circumference (MUAC) at baseline

Our study found a significant association between mid-arm upper circumference (MUAC) and mortality. There was a 17% reduced likelihood of death among patients that had a MUAC of ≥24.5CM as compared to those that had a MUAC of<24.5cm. This could be explained by the fact that MAUC estimates the nutritional state of a patient thus results into a very good stable environment for the patient to take their medication well as they are being monitored by the clinician. Additionally, MUAC is a very important parameter while initiating patient on DR-TB drugs and affects treatment outcome before and after. These findings were consistent with a study done in Philippines that established that there was an association between under-nutrition assessed using MUAC with risk of death (Lee et al., 2019).Additionally, another possible explanation might be that DR-TB causes secondary malnutrition as the participants' loss of appetite, nutrient, and micro-nutrient. This is also evidenced by fact that malabsorption and altered metabolism resulted in poor survival. In turn, under nutrition could lead to secondary immunodeficiency which exacerbates poor survival of DR-TB patients (Jayasuriya et al., 2013).

## TB History

Contrary to the some study that reported an association between previously TB treated DR-TB patients, patients with a history of treatment relapse and re-treatment failure and mortality (Olaleye & Beke, 2018), our study found no association between mortality and TB history. However, our study findings were similar to a South African study done by Manda et al that reported no association between mortality and history of previous TB treatment. This could be explained by the fact that may be history of TB treatment is not an important predictor of mortality in this population.

## Age of the patient.

Despite various studies reporting an association between drug resistant TB/HIV mortality and age, there was no association between age of a patient and DR-TB/HIV mortality in our study. This was consistent with a South African study by Manda et al that also reported no association between mortality and age of the patient. However, our findings differed from a South African and Ethiopian study that reported a higher risk of mortality among patients that were ≥60 years and on DR-TB/HIV treatment (Gandhi et al., 2012; Gesesew et al., 2016).This observed difference could be because drug resistant TB/HIV co-infected patients with ≥60 years of age in our sample were too few (6 patients) to detect a significant difference.

## ART regimen

Our study hypothesized that switching from the first line regimen to second line regimen in-creased mortality. This is because switching from first to second-line ART is associated with a low CD4 cell count and virological failure (Landier et al., 2011; Palombi et al., 2009; Petersen et al., 2014). Furthermore, delays in switching may contribute to accumulated drug resistance, advanced immunosuppression, increased morbidity. Therefore, delayed switching was not only associated with death as previously documented (Keiser et al., 2009; Keiser et al., 2010; Petersen et al., 2014), but also was associated with deteriorating immunologic status of patients which exposed them to opportunistic infections (Ramadhani et al., 2016), the risk of developing resistance and potential onward

transmission to partners. However, our study found no association between the ART regimen and mortality. This could be due to the fact that most of our patients were on first line regimen (369) versus second line regimen (21) and thus we couldn't detect any significant difference. Additionally, despite the fact that patients were on first line and second line drugs, there were difference in there drug combination that could explain the no association found.

### Viral load

We hypothesized that having an undetectable viral load would reduce the likelihood of death among DR-TB/HIV patients. This is because viral load is a measure of adherence to ART and it determines the need for treatment change in case on regimen fails (Shoko & Chikobvu, 2019).However, there was no association between viral load and mortality. This could be because the patients that had an undetectable viral load documented in this study (55) were too few to detect a significant difference. Majority of the participants (289) in this study had missing values of viral load thus we couldn't detect any association.

## 5.3 Strengths of the study

Mortality was confirmed in the hospital and for patients who died at home, regular tracing and reminders for visits helped in ascertaining home-related DR-TB/HIV mortality.

Certain variables like BMI, MUAC and sputum culture were collected at baseline to prevent different exposure duration thus preventing over or under-estimation of the effect size.

Modified poisson Regression with robust standard errors was used in analysis and it provided unbiased estimates of IRRs.

## 5.4 Limitations of the study

This was a retrospective study that used secondary cohort analysis of routinely reported data with gaps in reporting that could hardly be addressed by file review or contacting patients. The missing information on some variables like CD4 cell counts and co-morbidities, was one of the biggest limitation of the data thus underscoring the significant challenges of performing real life retrospective studies. There was missing data on very important variables e.g. viral load that reduced statistical power of a study thus giving biased estimates of the mortality, leading to invalid conclusions.

This study was prone to misclassification bias and this leads to drawing incorrect conclusions about the relationship between different variables studied and mortality.

The study was prone to confounding because other risk factors to DR-TB/HIVmortality like alcohol use, comorbidities were not measured and this could affect the conclusions drawn from the study.

The study was conducted in national referral hospital where most patients were referred from other regional facilities and health centers that could lead to referral bias. This therefore limits the generalizability of our findings to this particular hospital. The high mortality observed may have been overestimated in Mulago because most of the patients referred there had failed on treatment in other regional hospitals and some of them were very sick and thus could have died during the course of treatment.

Different participants were analyzed at different categories i.e. for sputum culture at baseline (n=281) and of the 281 participants, only 161(57.3%) were culture positive. This implied that the rest of the participants might not have had DR-TB since culture was negative thus affecting the outcome in this study.

# Chapter 6: Conclusions and Recommendations

## 6.0 Conclusions

Despite all the effort to fight TB and HIV by different stake holders, our study reported a high mortality rate of 32.8%.Mortality was mainly driven by clinical factors that could be modified to reduce the mortality. Having an adverse event, patient's phone number, body mass index, starting antiretroviral therapy, and mid upper arm circumference were protective against mortality among DR-TB/HIV co-infected patients

## 6.1 Recommendations

The nutritional status of DR-TB/HIV patients based on BMI and MUAC should be monitored by clinicians and all healthcare workers regularly so as to achieve favorable treatment outcomes. Proper diets should be given to the patients to enhance weight gain and appetite.

All patients' phone contacts should be documented for easy follow up and tracing as well as carrying out wellness visits.

Clinicians and all health care workers should initiate all DR-TB/HIV co-infected patients on antiretroviral therapy (ART) because it's protective against mortality.

Clinicians and all other healthcare workers should monitor and manage adverse-events among DR-TB/HIV co-infected patients because patients with adverse events actually have high treatment success thus reducing mortality.

A prospective cohort study should be done to fully assess and understand all possible factors associated with mortality among DR-TB/HIV patients as well as address the gaps of the retrospective study like reporting bias

## References


Aljadani, R., Ahmed, A. E., & Al-Jahdali, H. (2019). Tuberculosis mortality and associated factors at King Abdulaziz Medical City Hospital. *BMC Infect Dis, 19*(1), 427. doi:10.1186/s12879-019-4063-7

Arentz, M., Pavlinac, P., Kimerling, M. E., Horne, D. J., Falzon, D., Schünemann, H. J., . . . Walson, J. L. J. P. o. (2012). Use of anti-retroviral therapy in tuberculosis patients on second-line anti-TB regimens: a systematic review. *7*(11), e47370.

Baluku, J. B., Mugabe, P., Mulwana, R., Nassozi, S., Katuramu, R., & Worodria, W. J. B. R. I. (2020). High Prevalence of Rifampicin Resistance Associated with Rural Residence and Very Low Bacillary Load among TB/HIV-Coinfected Patients at the National Tuberculosis Treatment Center in Uganda. *2020*.

Bastard, M., Sanchez-Padilla, E., du Cros, P., Khamraev, A. K., Parpieva, N., Tillyashaykov, M., . . . Dlamini, T. J. P. o. (2018). Outcomes of HIV-infected versus HIV-non-infected patients treated for drug-resistance tuberculosis: Multicenter cohort study. *13*(3), e0193491.

Bei, C., Fu, M., Zhang, Y., Xie, H., Yin, K., Liu, Y., . . . Zhou, J. (2018). Mortality and associated factors of patients with extensive drug-resistant tuberculosis: an emerging public health crisis in China. *BMC Infect Dis, 18*(1), 261. doi:10.1186/s12879-018-3169-7

Brust, J. C., Shah, N. S., Van Der Merwe, T. L., Bamber, S., Ning, Y., Heo, M., . . . Friedland, G. H. J. J. o. a. i. d. s. (2013). Adverse events in an integrated, home-based treatment program for MDR-TB and HIV in KwaZulu-Natal, South Africa. *62*(4), 436.

Chingonzoh, R., Manesen, M. R., Madlavu, M. J., Sopiseka, N., Nokwe, M., Emwerem, M., . . . Kuonza, L. R. J. P. o. (2018). Risk factors for mortality among adults registered on the routine drug resistant tuberculosis reporting database in the Eastern Cape Province, South Africa, 2011 to 2013. *13*(8), e0202469.

Chung-Delgado, K., Guillen-Bravo, S., Revilla-Montag, A., & Bernabe-Ortiz, A. J. P. o. (2015). Mortality among MDR-TB cases: comparison with drug-susceptible tuberculosis and associated factors. *10*(3), e0119332.

Daftary et al. (2014). Preferential adherence to antiretroviral therapy over tuberculosis treatment: a qualitative study of drug-resistant TB/HIV co-infected patients in South Africa. *9*(9), 1107-1116.

Edelman, E. J., Gordon, K. S., Glover, J., McNicholl, I. R., Fiellin, D. A., Justice, A. C. J. D., & aging. (2013). The next therapeutic challenge in HIV: polypharmacy. *30*(8), 613-628.

Farley, J. E., Ram, M., Pan, W., Waldman, S., Cassell, G. H., Chaisson, R. E., . . . Van der Walt, M. J. P. o. (2011). Outcomes of multi-drug resistant tuberculosis (MDR-TB) among a cohort of South African patients with high HIV prevalence. *6*(7), e20436.

Gandhi, N. R., Andrews, J. R., Brust, J. C., Montreuil, R., Weissman, D., Heo, M., . . . Disease, L. (2012). Risk factors for mortality among MDR-and XDR-TB patients in a high HIV prevalence setting. *16*(1), 90-97.

Gandhi, N. R., Moll, A., Sturm, A. W., Pawinski, R., Govender, T., Lalloo, U., . . . Friedland, G. J. T. L. (2006). Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *368*(9547), 1575-1580.

Gandhi, N. R., Shah, N. S., Andrews, J. R., Vella, V., Moll, A. P., Scott, M., . . . medicine, c. c. (2010). HIV coinfection in multidrug-and extensively drug-resistant tuberculosis results in high early mortality. *181*(1), 80-86.

Heysell, S., Ogarkov, O., Zhdanova, S., Zorkaltseva, E., Shugaeva, S., Gratz, J., . . . Disease, L. (2016). Undertreated HIV and drug-resistant tuberculosis at a referral hospital in Irkutsk, Siberia. *20*(2), 187-192.

Hicks, R., Padayatchi, N., Shah, N., Wolf, A., Werner, L., Sunkari, V., . . . disease, l. (2014). Malnutrition associated with unfavorable outcome and death among South African MDR-TB and HIV co-infected children. *18*(9), 1074-1083.

Hirasen, K., Berhanu, R., Evans, D., Rosen, S., Sanne, I., & Long, L. (2018). High rates of death and loss to follow-up by 12 months of rifampicin resistant TB treatment in South Africa. *PLoS One, 13*(10), e0205463. doi:10.1371/journal.pone.0205463

Isaakidis, P., Varghese, B., Mansoor, H., Cox, H. S., Ladomirska, J., Saranchuk, P., . . . Udwadia, Z. J. P. o. (2012). Adverse events among HIV/MDR-TB co-infected patients receiving antiretroviral and second line anti-TB treatment in Mumbai, India. *7*(7), e40781.

Kawai, V., Soto, G., Gilman, R. H., Bautista, C. T., Caviedes, L., Huaroto, L., . . . hygiene. (2006). Tuberculosis mortality, drug resistance, and infectiousness in patients with and without HIV infection in Peru. *75*(6), 1027-1033.

Kidenya, B. R., Webster, L. E., Behan, S., Kabangila, R., Peck, R. N., Mshana, S. E., . . . Fitzgerald, D. W. J. T. (2014). Epidemiology and genetic diversity of multidrug-resistant tuberculosis in East Africa. *94*(1), 1-7.

Kliiman, K., & Altraja. (2010). Predictors and mortality associated with treatment default in pulmonary tuberculosis. *J The international journal of tuberculosis*

*lung disease, 14*(4), 454-463.

Kurbatova, E. V., Taylor, A., Gammino, V. M., Bayona, J., Becerra, M., Danilovitz, M., . . . Leimane, V. J. T. (2012). Predictors of poor outcomes among patients treated for multidrug-resistant tuberculosis at DOTS-plus projects. *92*(5), 397-403.

Lehloenya, R. J., & Dheda, K. J. E. r. o. a.-i. t. (2012). Cutaneous adverse drug reactions to anti-tuberculosis drugs: state of the art and into the future. *10*(4), 475-486.

Manda et al. (2013). Risk of death among HIV co-infected multidrug resistant tuberculosis patients, compared to mortality in the general population of South Africa. 7.

Mollel, E. W., & Chilongola, J. O. (2017). Predictors for Mortality among Multidrug-Resistant Tuberculosis Patients in Tanzania. *J Trop Med, 2017*, 9241238. doi:10.1155/2017/9241238

Musa, B. M., Adamu, A. L., Galadanci, N. A., Zubayr, B., Odoh, C. N., & Aliyu, M. H. J. P. O. (2017). Trends in prevalence of multi drug resistant tuberculosis in sub-Saharan Africa: a systematic review and meta-analysis. *12*(9), e0185105.

Nkolo et al. (2018a). USAID Defeat TB Annual Report October 1, 2017–September 30, 2018.

.

Nkolo et al. (2018b). USAID Defeat TB Annual Report.

Nkolo et al. (2019). NATIONAL TUBERCULOSIS AND LEPROSY PROGRAM REPORT.

NTLP. (2018). A Bulletin of the National Tuberculosis and Leprosy Program. *2*(4).

O'Donnell, M. R., Padayatchi, N., Kvasnovsky, C., Werner, L., Master, I., & Horsburgh Jr, C. R. J. E. i. d. (2013). Treatment outcomes for extensively drug-resistant tuberculosis and HIV co-infection. *19*(3), 416.

Okethwangu, D., Birungi, D., Biribawa, C., Kwesiga, B., Turyahabwe, S., Ario, A. R., & Zhu, B.-P. J. B. i. d. (2019). Multidrug-resistant tuberculosis outbreak associated with poor treatment adherence and delayed treatment: Arua District, Uganda, 2013–2017. *19*(1), 1-10.

Otu, J., Gehre, F., Zingue, D., Kudzawu, S., Forson, A., Mane, M., . . . Adebiyi, E. J. B. G. H. (2017). MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB): AN EMERGING PROBLEM IN WEST AFRICA. *2*(Suppl 2), A32-A33.

Palacios, E., Franke, M., Munoz, M., Hurtado, R., Dallman, R., Chalco, K., . . . disease, l. (2012). HIV-positive patients treated for multidrug-resistant tuberculosis: clinical outcomes in the HAART era. *16*(3), 348-354.

Podlekareva, D., Schultze, A., Panteleev, A., Skrahina, A., Miro, J., Rakhmanova, A., . . . Losso, M. J. A. (2017). One-year mortality of HIV-positive patients treated for rifampicin-and isoniazid-susceptible tuberculosis in Eastern Europe, Western Europe, and Latin America. *31*(3), 375.

Sagwa, E., Mantel-Teeuwisse, A. K., Ruswa, N., Musasa, J. P., Pal, S., Dhliwayo, P., & van Wyk, B. J. S. m. r. (2012). The burden of adverse events during treatment of drug-resistant tuberculosis in Namibia. *5*(1), 6.

Salinas, J. L., Armstrong, L. R., Silk, B. J., Haddad, M. B., & Cegielski, J. P. (2017). Factors Associated With All-Cause Mortality Among Patients With Multidrug-Resistant Tuberculosis-United States, 1993-2013. *Clin Infect Dis, 65*(11), 1924-1926. doi:10.1093/cid/cix667

Satti et al. (2012). Outcomes of multidrug-resistant tuberculosis treatment with early initiation of antiretroviral therapy for HIV co-infected patients in Lesotho. *7*(10), e46943.

Satti, H., McLaughlin, M. M., Omotayo, D. B., Keshavjee, S., Becerra, M. C., Mukherjee, J. S., & Seung, K. J. J. P. O. (2012). Outcomes of comprehensive care for children empirically

treated for multidrug-resistant tuberculosis in a setting of high HIV prevalence. *7*(5), e37114.
Schnippel, K., Berhanu, R. H., Black, A., Firnhaber, C., Maitisa, N., Evans, D., & Sinanovic, E. J. B. i. d. (2016). Severe adverse events during second-line tuberculosis treatment in the context of high HIV Co-infection in South Africa: a retrospective cohort study. *16*(1), 1-10.
Schnippel, K., Firnhaber, C., Berhanu, R., Page-Shipp, L., & Sinanovic, E. J. J. o. A. C. (2017). Adverse drug reactions during drug-resistant TB treatment in high HIV prevalence settings: a systematic review and meta-analysis. *72*(7), 1871-1879.
Schnippel, K., Firnhaber, C., Ndjeka, N., Conradie, F., Page-Shipp, L., Berhanu, R., & Sinanovic, E. (2017). Persistently high early mortality despite rapid diagnostics for drug-resistant tuberculosis cases in South Africa. *Int J Tuberc Lung Dis, 21*(10), 1106-1111. doi:10.5588/ijtld.17.0202
Shean, K., Streicher, E., Pieterson, E., Symons, G., van Zyl Smit, R., Theron, G., . . . Victor, T. C. J. P. o. (2013). Drug-associated adverse events and their relationship with outcomes in patients receiving treatment for extensively drug-resistant tuberculosis in South Africa. *8*(5), e63057.
Singh et al. (2020). Drug-Resistant Tuberculosis and HIV Infection: Current Perspectives. *12*, 9.
Umanah et al. (2015). Treatment outcomes in multidrug resistant tuberculosis-human immunodeficiency virus Co-infected patients on anti-retroviral therapy at Sizwe Tropical Disease Hospital Johannesburg, South Africa. *15*(1), 478.
USAID. (2018). USAID-URC DEFEAT TB ANNUAL REPORT.
van der Walt et al. (2016). Tuberculosis case fatality and other causes of death among multidrug-resistant tuberculosis patients in a high HIV prevalence setting, 2000-2008, South Africa. *11*(3), e0144249.
Van Hout, M. C., & Hope, V. J. B. i. d. (2019). Treatment outcomes and antiretroviral uptake in multidrug-resistant tuberculosis and HIV co-infected patients in Sub Saharan Africa: a systematic review and meta-analysis. *19*(1), 1-8.
Viana, P. V. S., Redner, P., & Ramos, J. P. (2018). Factors associated with loss to follow-up and death in cases of drug-resistant tuberculosis (DR-TB) treated at a reference center in Rio de Janeiro, Brazil. *Cad Saude Publica, 34*(5), e00048217. doi:10.1590/0102-311x00048217
Walls, G., Bulifon, S., Breysse, S., Daneth, T., Bonnet, M., Hurtado, N., & Molfino, L. J. G. h. a. (2015). Drug-resistant tuberculosis in HIV-infected patients in a national referral hospital, Phnom Penh, Cambodia. *8*(1), 25964.
WHO. (2013). *Definitions and reporting framework for tuberculosis–2013 revision* (9241505346). Retrieved from
WHO. (2020a). Global Tuberculosis Report.

WHO. (2020b). WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-resistant tuberculosis treatment.

Yuengling, K. A., Padayatchi, N., Wolf, A., Mathema, B., Brown, T., Horsburgh, C. R., & O'Donnell, M. R. J. J. o. a. i. d. s. (2018). Effect of antiretroviral therapy on treatment outcomes in a prospective study of extensively drug resistant tuberculosis (XDR-TB) HIV co-infection treatment in KwaZulu-Natal, South Africa. *79*(4), 474.

# Appendices

## Appendix 1: Request for waiver of Consent

22nd October 2019
To the Chairman,
School of Medicine Research and Ethics Committee, Makerere University College of Health Sciences,
P.O. Box 7072 Kampala Uganda.
Dear Sir,

**RE: Request for a waiver of consent for a study entitled "Mortality rate and associated factors among drug resistant TB/HIV co-infected patients at Mulago Hospital".**

I am writing to request a waiver of consent for my proposed above medical records review study. This is a retrospective chart review that involves no more than minimal risk to the participants. The study will use records whose owners may be impossible to contact including loss to follow-up and even those who may be dead. Moreover no medical procedures or interventions will be performed as part of this study, and no new medical conditions will be discovered that could increase economic, legal, or social risks for study participants. In an effort to protect patient confidentiality, each subject will be assigned a unique identification number. All study related documentation will be stored under lock and key with restricted access. Access to computer records will be strictly controlled and will require simultaneous knowledge of the database structure, language, and multiple passwords. Names and other identifying information from subjects will be obtained for quality assurance purposes only, and will be kept separately as an electronic file protected by multiple passwords. No individual will be identified by any study reports or publications. The risks to subjects are minimal, and the findings are of potential benefits to society in general. I appreciate your consideration of my request for a waiver.

Thank you

Bayowa Joan Rokani

# Appendix 2: Data abstraction form

**MORTALITY RATE AND ASSOCIATED FACTORS AMONG DRUG RESISTANT TUBERCULOSIS/HIV CO-INFECTED PATIENTS IN MULAGO HOSPITAL**

**Initials of Research Assistant/ data collector ……**

**Participant's ID No……**

***(Write in bold or tick where appropriate)***

| | Data abstraction Form | |
|---|---|---|
| | **Questions** | **Coding Category** |
| | **Patient Sociodemo- graphics** | |
| 1 | Sex | • Male=1<br>• Female=2 |
| 2 | Age (should be completed in years) | …… |
| 3 | Marital status | • Married=1<br>• Single=2<br>• Widowed=3<br>• Separated=4<br>• Divorced=5 |
| 4 | Occupation(state the occupation) | …….. |

| | | |
|---|---|---|
| 5 | Highest level of Education attained | • Unspecified=1<br>• Primary=2<br>• Secondary=3<br>• Tertiary =4 |
| 6 | Weight | ……. |
| 7 | Height | …….. |
| 8 | Nationality | • Non Ugandan=1<br>• Ugandan=2 |
| 9 | Place of residence | • Within Kampala<br>• Away from Kampala |
| 10 | Type of TB case | • New=1<br>• Relapse=2<br>• Failurecat1=3<br>• Failurecat2=4<br>• Return after LTFU=5<br>• Failurecat4=6 |
| | | • Others=7 |
| 11 | Patient phone contact | • Yes=1<br>• No=2 |
| 12 | Next of kin's phone contact | • Yes=1<br>• No=1 |
| | **Clinical Factors** | |
| 13 | Initial MUAC(state value in figures) | …….. |
| 14 | Site of TB | • PTB=1<br>• EPTB=2<br>• Both=3<br>• Unspecified=4 |
| 15 | ART Treatment start date | ---/----/----- |
| 16 | Inpatient at treatment initiation | • Yes=1<br>• No=2 |
| 17 | HIV testing done | • Yes=1<br>• No=2<br>• Unknown=3 |
| 18 | Date of test | ---/---/---- |
| 19 | Started ART | • Yes=1<br>• No=2 |
| 20 | ART regimen | …….. |
| 21 | Started CPT and start date | • Yes=1 ---/---/-----<br>• No=2 |
| 22 | Viral load (state value in figures) | ……<br>• missing |
| | DR-TB factors | |

| | | |
|---|---|---|
| 23 | Patient started on second line drugs | • Yes=1<br>• No=2 |
| 24 | Reason for entering second line | • Bacteriologically confirmed(RR/MDR/XDR)=1<br>• Presumptive(RR/MDR/XDR)=2 |
| 25 | TB treatment start date | ---/---/---- |
| 26 | TB regimen | • Kanamycin<br>• Capreomycin<br>• Amikacin<br>• Levofloxacin<br>• Moxifloxacin<br>• Ciprofloxacin<br>• Ofloxacin<br>• Ethionamide |
| | | • Prothionamide<br>• P-aminosalicyclic acid<br>• Bedaquiline<br>• Cycloserine<br>• Clofazimine<br>• Delamanid<br>• Linezolid<br>• Impenem<br>• Terizidone |
| 27 | Treatment Modality | • Facility DOTs=1<br>• Community DOTs=2 |
| 28 | Sputum culture results at baseline | • Positive=1<br>• Negative=2 |
| | **Drug related factors** | |
| 29 | Adverse drug reactions | • Gastrointestinal<br>• Hepatotoxicity<br>• Renal toxicity<br>• Musculoskeletal<br>• Ototoxicity<br>• Vision changes<br>• Dsyglycemia<br>• Dermatological<br>• Hematologic<br>• New onset seizure<br>• Electrolyte abnormality<br>• Hypothyroid<br>• Cardiovascular<br>• Psychiatric |

| | | |
|---|---|---|
| 30 | Specify adverse reaction according to category | …… |
| 31 | Severity | • Grade1=1<br>• Grade2=2<br>• Grade3=3<br>• Grade 4=4<br>• Grade 5=5 |
| 32 | Died | • Yes=1<br>• No=2 |
| 33 | Date of Death | ---/---/----- |

# Appendix 3: REC Approval

MAKERERE 1832

MAKERERE UNIVERSITY
P.O. Box 7072 Kampala, Uganda
E-mail: rresearch9@gmail.com
Phone: 256 414 533541
Fax: 256 414 541036/0414 532204

**COLLEGE OF HEALTH SCIENCES**
**SCHOOL OF MEDICINE**

RESEARCH ETHICS COMMITTEE

February 11, 2020

Ms. Bayowa Joan Rokani
Clinical Epidemiology Unit

**Category of Review**
[X] Initial review
[X] Full board review
[ ] Expedited review
[ ] Continuing review
[ ] Amendment
[ ] Termination of study
[ ] SAEs

Dear Dr. Bayowa,

**Re: Approval of proposal #REC REF 2020-063**

**"Mortality rate and associated factors among drug resistant Tuberculosis/HIV Co-infected patients at Mulago Hospital"**

Thank you for submitting an application for approval of the above – referenced **proposal**. The committee reviewed it and granted approval for one year, effective February 11, 2020. Approval will expire on February 10th, 2021.

**Continuing Review**
In order to continue work on this study (including data analysis) beyond the expiration date, the School of Medicine Research and Ethics Committee must reapprove the protocol after conducting a substantive, meaningful, continuing review. This means that you must submit a continuing report form as a request for continuing review. To best avoid a lapse, you should submit the request six (6) weeks before the lapse date. Please use the forms supplied by our office.

**Amendments**
During the approval period, if you propose any change to the protocol such as its funding source, recruiting materials, or consent documents, you must seek School of Medicine Research and Ethics Committee approval before implementing it.
Please summarize the proposed change and the rationale for it in a letter to the School of Medicine Research and Ethics Committee. In addition, submit three (3) copies of an updated version of your

original protocol application- one showing all proposed changes in bold or 'track changes,' and the other without bold or track changes.

**Reporting**

Other events which must be reported promptly in writing to the School of Medicine Research and Ethics Committee include:

Suspension or termination of the protocol by you or the grantor

Unexpected problems involving risk to participants or others

Adverse events, including unanticipated or anticipated but severe physical harm to participants.

Do not hesitate to contact us if you have any questions. Thank you for your cooperation and commitment to the protection of human subjects in research.

Documents approved for use along with the protocol

- English and translated informed consent form
- Data collection tool

**Please Note:**

1. Final approval is to be granted by Uganda National Council for Science and Technology.
2. All the study documents including the revised proposal, Informed Consent Forms, Data Collection Tools and any other study documents should be stamped by the REC.
3. Approval from National Drug Authority should be sought where applicable.
4. Approval for use of research devices should be sought from the Ministry of Health/Uganda National Council for Science and Technology where applicable.
5. Administrative clearance should be sought from the various study sites.
6. This study will be monitored by the School of Medicine Research Ethics Committee to assess for compliance to both national and international research guidelines for protecting the rights and welfare of research participants.
7. The REC should be involved in the dissemination of study findings to the different stakeholders. (This applies to staff research, collaborative research and PhD students).
8. The REC should be informed and involved in the process of study closure.

Yours sincerely,

MAKERERE UNIVERSITY
SCHOOL OF MEDICINE
APPROVED
VALID UNTIL
10 FEB 2021
RESEARCH & ETHICS COMMITTEE
P.O. BOX 7072, KAMPALA

Assoc. Prof. Ponsiano Ocama
**Chairperson School of Medicine Research and Ethics Committee**

# Appendix 4: Approval of waiver of consent

MAKERERE UNIVERSITY
P.O. Box 7072 Kampala, Uganda
**E-mail**: rresearch9@gmail.com
**Phone:** 256 414 533541
**Fax:** 256 414 541036/0414 532204

COLLEGE OF HEALTH SCIENCES
SCHOOL OF MEDICINE

RESEARCH ETHICS COMMITTEE

13 February, 2020

Ms. Bayowa Joan Rokani
Clinical Epidemiology Unit

Dear Ms. Bayowa,

**RE: APPROVAL OF CONSENT WAIVER**

In your request dated 22nd October 2019, you requested the committee to waive off consent for your study participants for the study entitled **"Mortality rate and associated factors among drug resistant Tuberculosis/HIV Co-infected patients at Mulago Hospital"** for the given ethical reasons.

The committee has waived the requirement for consent because this is a retrospective chart review, you will use records whose owners may be impossible to contact including loss to follow-up. No medical procedures or interventions will be performed as part of this study.

On behalf of the committee, I am glad to inform you that the committee has granted a waiver of the informed consent process.

Final approval is to be granted by the Uganda National Council of Science and Technology.

Yours sincerely,

Assoc.Prof.Ponsiano Ocama
**Chairperson, School of Medicine Research and Ethics Committee**

Page 1 of 1

# Appendix 5: Mulago administrative clearance

TELEPHONE: +256-41554008/1
FAX: +256-414-5325591
E-mail: admin@mulago.or.ug
Website: www.mulago.or.ug

IN ANY CORRESPONDENCE ON THIS SUBJECT PLEASE QUOTES NO…

MULAGO NATIONAL REFERRAL HOSPITAL
P.O. Box 7051
KAMPALA, UGANDA

Dr. Nakwagala
Plse handle
4/3/20

MULAGO NATIONAL REFERRAL HOSPITAL
20 FEB 2020
EXECUTIVE DIRECTOR
RECEIVED
MULAGONATIONALREFERRALHOSPITAL

17th February, 2020.

The Executive Director
Mulago National Referral Hospital

Dear Sir,

**RE: RECOMMENDATION FOR ADMINISTRATIVE CLEARANCE.**

The Mulago Hospital Research & Ethics Committee has reviewed the protocol entitled **MHREC 1832: "Mortality Rate and Associated Factors among Drug Resistant Tuberculosis/HIV Co-Infected Patients at Mulago Hospital"** by Dr. Joan Bayowa Rokani as the lead Principal Investigator.

The study got an initial approval from Makerere University School of Medicine Research & Ethics Committee for a period of one (1) year from 11th Feb, 2020, 2019 to 10th Feb, 2021.

The study has met the following obligations;

1. Paid MHREC Administrative review fees of 20,000/=
2. Agreed to comply with all institutional policies and regulations of Mulago National Referral Hospital
3. Agreed to provide end of study report and acknowledge Mulago hospital in all publications

Administrative clearance is valid for one (1) year effective from 17th February, 2020 to 16th February, 2021.

The study is therefore recommended for your provision of administrative clearance by Mulago National Referral Hospital.

Yours sincerely;

DR. NAKWAGALA FREDERICK NELSON
**CHAIRMAN- MULAGO HOSPITAL RESEARCH & ETHICS COMMITTEE.**

JOAN BAYOWA ROKANI
ADM CLEARANCE
PROVIDED BY MNRH
6/3/2020

**Copied to;**
1. **In – charge Ward 5/6**

**Vision: "To be the leading centre of Health Care Services"**