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Multimorbidity, Healthcare Processes, and Mortality Among TB/HIV Patients Treated With Antiretroviral Therapy in Uganda

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Walden University
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Abstract

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MPH, Makerere University, 2009

MBChB, Mbarara University of Science and Technology, 2000

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

Globally, Uganda is one of the 30 tuberculosis (TB) and human immunodeficiency virus (HIV) high burden countries with high antiretroviral therapy (ART) coverage, yet mortality is still high among TB/HIV patients on ART. The reasons for the high mortality have not been fully explored. The purpose of this study was to determine the association between multimorbidity, age, sex, marital status, phase of TB treatment, timing of initiation for ART, and type of TB and mortality among TB/HIV patients on ART in Uganda. The health outcomes conceptual framework with 3 domains that directly or indirectly affect the outcome domain was used to guide the study. A quantitative cross-sectional study design was used. The target population of 3,850 deidentified TB/HIV patients on ART, and data were abstracted from 2017, 2018, and 2019 medical records in 9 out of 14 systematically selected regional hospitals in Uganda. Descriptive analysis and binary logistics regression were conducted. TB/HIV patients on ART with 1 or 2 or more multimorbidity were 1.658 times and 1.901 times more likely to die than patients with no multimorbidity. TB/HIV patients on ART who were separated/divorced or single were 1.591 and 1.381 times more likely to die than married patients. The TB/HIV patients on ART who began ART treatment after TB treatment were 1.899 times more likely to die than patients who started ART before TB. The results can support social change by raising awareness among policymakers, national TB program staff, and health workers to implement approaches like patient-family-centered care to prevent deaths among TB/HIV patients on ART.

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Dedication

I dedicate this dissertation to my family, the Nkolo family, my wife Esther Karungi Karamagi Nkolo; my children, Paula Therese Namale Nkolo, Paul Male Jason Nkolo, Priscilla Nansereko Nkolo, Patricia Nantege Nkolo, and Peter Andrew Cyprian Sssewakiryanga Nkolo.

My late father, Erifaazi Ssewakiryanga, taught me the importance of acquiring formal education while being among the best. My mother, Margaret Nakibuuka, and my late Jjajja Nalongo Ssebaduka helped raise me and ingrained hard work.

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I am grateful to Mr. Mbaka Paul for the administrative clearance, the executive directors of the nine regional referral hospitals for the data from the TB registers, ART cards, patient files, and electronic medical records.

Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction to the Study

Introduction

Antiretroviral therapy (ART) improves tuberculosis (TB) treatment outcomes among patients with TB disease who are coinfected with human immunodeficiency virus (HIV). According to Engelbrecht et al. (2017), successful TB treatment outcomes in TB/HIV coinfected patients happens in those with high cluster of differentiation 4 (CD4) cell count (greater than 350) on cotrimoxazole and ART (Engelbrecht et al., 2017). Weldegebreal et al. (2018), in a study conducted in Ethiopia, noted that patients below 18 years of age with extrapulmonary TB and on ART had improved TB outcomes. However, Weldegebreal et al. (2018) also noted that the treatment outcomes were not as high as recommended by the World Health Organization (WHO, 2018) at 90%. According to WHO (2018), 21 out of 27 high TB/HIV burden countries reported treatment outcomes below 85%, yet the global standard is 90%. Poor treatment outcomes include mortality, loss to follow up, failure, transfer out, and not evaluated. Mortality and loss to follow up constitute the poorest treatment outcomes among TB/HIV patients, with a mortality of 9% in the Africa region. Although ART improves TB treatment outcomes among TB/HIV patients on ART, mortality remains high, especially in high burden TB/HIV countries.

According to WHO (2018), in Uganda, mortality among TB/HIV patients is 32/100,000, which is higher than 26/100,000 among TB patients who are HIV negative. High mortality among TB/HIV patients is attributed to several factors, such as delayed testing for TB, delayed start on ART, and anti-TB medicines (WHO, 2018). Furthermore,

Worku et al. (2018) noted that other common opportunistic infections that are not diagnosed may lead to mortality in TB/HIV patients. Generally, multimorbidity is associated with mortality (Academy of Medical Sciences [AMS], 2018; Oni et al., 2015; Smith et al., 2018). However, based on the literature, it is not clear whether multimorbidity, other patient characteristics, and health care processes are associated with mortality among TB/HIV coinfected patients on ART (AMS, 2018; Oni et al., 2015; Smith et al., 2018). There is a need to explore further why mortality remains high among TB/HIV patients on ART. In this study, based in Uganda, I explored the association of multimorbidity and health care processes with mortality among TB/HIV coinfected patients on ART.

The study results could reveal new knowledge of multimorbidity and mortality among TB/HIV patients on ART, which would impact positive social change. Health workers might use this new knowledge to help make decisions on TB/HIV coinfected patients with multimorbidity to avoid mortality. The resulting data could be used in designing policies and guidelines on multimorbidity in Uganda. In Chapter 1, I describe the study's background, problem statement, purpose of the study, research questions, and hypotheses. I also describe the conceptual framework, definitions, nature of the study, assumptions, scope and delimitations, limitations, the significance of the study to theory, practice, and social change. I conclude this chapter with a summary and transition.

Background of the Study

TB/HIV Coinfection

Globally, TB/HIV remains a public health problem, especially in sub-Saharan Africa. WHO listed 30 TB/HIV burden countries, 23 out of 30 countries are found in sub-Saharan Africa, including Uganda (WHO, 2018). In 2005, WHO recommended 12 TB/HIV collaborative activities, which have been adopted by countries. These broadly include setting up mechanisms for TB/HIV collaboration, reducing the burden of TB in HIV patients, and reducing the burden of HIV in TB patients (WHO, 2015).

Additional activities include implementing TB/HIV integrated services using either a one-stop shop, partially integrating services, colocating services with referral between the HIV and TB clinics or referring TB/HV patients between TB and HIV health facilities (WHO, 2015). The integration ensures that TB/HIV patients are managed holistically (WHO, 2018). Although WHO has made recommendations to deal with the persistent global problem of TB/HIV, mortality among TB/HIV patients still needs more attention.

Mortality in TB/HIV Coinfected Patients on ART

It is well known that mortality is reduced in TB/HIV patients when they start ART early. Nagu et al. (2017) indicated that well-planned and highly supervised ART reduces mortality in TB/HIV patients and that death occurs early during TB treatment. According to Engelbrecht et al. (2017), in a retrospective study conducted in South Africa, successful TB treatment outcomes in TB/HIV coinfected patients happens in those with high CD4 cell count (greater than 350), on cotrimoxazole and ART. If well-

supervised, ART administered early in TB/HIV patients reduces mortality among TB/HIV patients. Bruchfeld et al. (2015) highlighted that HIV comorbidities may be responsible for mortality among TB/HIV patients who develop immune reconstitution inflammatory syndrome (IRIS). TB IRIS is one paradoxical phenomenon that must be dealt with when TB/HIV coinfected patients start either ART or anti-TB medicines because it leads to patient deaths.

Uganda started the test and treat policy in 2013, focusing on initiating ART within 4 weeks of starting anti-TB treatment for TB/HIV patients. The ART coverage among TB patients reached 90% in 2016 and is 98% in 2018 (Ministry of Health, Uganda [MoH], 2018). However, the mortality in TB/HIV patients is still high at 12% based on data from MoH (2018), and 15.5% based on research by the Makerere School of Public Health (2018). Even in Uganda, the reasons for high mortality are unknown, although some researchers have pointed out delayed testing for TB, delayed start on ART, and anti-TB medicines (WHO, 2018). For Uganda, mortality among TB/HIV patients on ART is still high, yet the reasons for the high mortality are not well known.

Prevalence and Patterns of Multimorbidity Among TB/HIV Patients on ART

Studies in South Africa have demonstrated a pattern of common comorbidities, including infectious diseases and non communicable diseases. The observed diseases include hypertension, diabetes, HIV, and TB. Oni et al. (2015), in peri-urban South Africa, studied the epidemiology of HIV, TB, and non communicable diseases multimorbidity and found that HIV, TB, diabetes mellitus, and hypertension accounted for 45% of prescription visits, thus reflecting the magnitude of multimorbidity. Pepper et

al. (2015) found similar results in a study conducted in Khayelitsha, South Africa, indicating that TB patients have a comorbidity of about 37% of hypertension and 12% for diabetes mellitus. Hypertension and diabetes mellitus were more prevalent among younger patients on ART than those not on ART.

Epidemiological transition in developing countries is characterized by a double burden of infectious and non infectious diseases. The issue of multimorbidity in this study aligned with the epidemiological transition in developing countries (Oni et al., 2015). Other comorbidities have been noted in TB and HIV patients, including cancers, malaria, pneumonia, malnutrition, and smoking (Marais et al., 2013). The standard patterns for TB/HIV comorbidities were TB/HIV hypertension and TB/HIV diabetes mellitus. The epidemiological transition may explain the double burden of infectious and communicable diseases from infectious to chronic disease (Oni et al., 2015). Comorbidity was known to be lower in TB/HIV patients on ART rather than those not on ART, but higher in the young age ranges of 18–35 years and 36–45 years (Oni et al., 2015). Oni et al. further highlighted the need for research for comorbidities among TB/HIV patients. Although the patterns of infectious and noninfectious diseases have been explored in South Africa, the patterns of multimorbidity among TB/HIV patients still need to be explored beyond South African studies.

Assessment of Comorbidities/Multimorbidity

Tools to measure comorbidities/multimorbidity have been developed focusing on non communicable diseases. These tools have been used to study the magnitude of comorbidities as an indication of the quality of life of patients, especially in developed

countries inpatients and patients over 65 years of age (Brown et al., 2015). These tools have been improved further to include non communicable diseases like HIV and TB (Brown et al., 2015). The tools have evolved, and now there is a functional assessment of chronic illness therapy–tuberculosis (FACIT) tool, which is a TB-specific tool to measure comorbidities and the quality of life among patients with TB (Dujaili et al., 2015).

The health status of an individual can be assessed by counting multimorbidities. The number of comorbidities in an individual is associated with the likelihood of that individual's death (Brown et al., 2015). The score of the count of diseases is called the *comorbidity index*. There are several comorbidity indices: Charlson comorbidity index, RX Risk comorbidity assessment, Elixhauser comorbidity Index, and Johns–Hopkins adjusted clinical group. The Charlson comorbidity index is the most common tool used to measure comorbidity. The tool is based on a list of 17 elements with each condition assigned a weight of 1 to 6, with a 0 indicating no comorbidity (Lix et al., 2016; Wallace et al., 2016).

Effects of Multimorbidity on Mortality

Although the effects of multimorbidity on mortality have been studied, mortality among TB/HIV patients with multimorbidity has not been well described **(**Samuels et al., 2018). The effects of multimorbidity on health care are varied. According to Oni et al. (2015), the effects include failure for the patient to manage themselves because of many diseases, the need for the health care provider to have multiple skills to deal with many diseases, the need for several requirements, equipment, design, and infrastructure of the health system.. The findings indicate that the effects of multimorbidity are at different

levels, including patient level, health system level, and provider level, which all need special attention.

Mortality is a core outcome of multimorbidity. However, the association between multimorbidity and mortality among TB/HIV patients on ART has not been well established. Globally, there is an ongoing debate on multimorbidity and the lacking research in all areas, especially from low-middle-income countries (Catala-Lopez, et al., 2018; Xu et al., 2017). Studies in sub-Saharan Africa have indicated a rise in multimorbidity patterns and the overlap between infectious diseases and non communicable diseases, including, hypertension, diabetes mellitus, cancers, and others (Oni et al., 2015). In Uganda, the mortality in TB/HIV patients is high at 12%, despite the implementation of an HIV test-and-treat policy with ART coverage among TB/HIV patients at 98% (MoH, 2018; WHO, 2018). Understanding the relationship between multimorbidity, health care processes, and mortality among TB/HIV patients is crucial in addressing the high mortality among this population. I explored and tested the association between multimorbidity, health care processes, and mortality among TB/HIV coinfected patients on ART in Uganda. The information could contribute to the ongoing debate of multimorbidity health care processes and their influence on mortality among TB/HIV patients on ART. Health workers could use the information to make appropriate decisions on how to handle TB/HIV patients. Policymakers and managers could further use the results to contribute to developing policies for patients with comorbidities.

Problem Statement

There is high mortality among TB/HIV coinfected patients on ART in Uganda despite high ART coverage. According to MoH, the mortality in TB/HIV patients was 11–12% from 2014 to 2017, despite ART coverage of 60–98% (MoH, 2018; WHO, 2018). The reasons for the high mortality have not been explained but have been associated with a delay in the start of ART, delay in testing TB patients for HIV, and IRIS (WHO, 2018). High mortality among TB/HIV patients is still a challenge at the global level. According to WHO (2018), mortality among TB/HIV patients is 11%. In sub-Saharan Africa, mortality in TB/HIV patients is 9%, whereas in Uganda, it is 12% (WHO, 2018). According to Mchunu et al. (2016), Swaziland has recorded high mortality among TB/HIV patients at 14%. The reasons for mortality are not well understood, but the issues explained relate to failure to decentralize treatment from doctors to nurses (Mchunu et al., 2016).

Global studies have indicated that multimorbidity is an increasing concern and is associated with low quality of care and death. In sub-Saharan Africa, multimorbidity is increasing, as seen from studies conducted in South Africa (Oni et al., 2015). The existing studies on mortality and TB/HIV coinfected populations on ART have indicated inadequate information on the association of multimorbidity and mortality among TB/HIV coinfected patients on ART (Mchunu et al., 2016; Oni et al., 2015; Pepper et al., 2015). There is inadequate information about multimorbidity in middle-income and lower-income countries, including Uganda (Catala-Lopez et al., 2018). Mortality is a known core outcome of multimorbidity. The need to study multimorbidity, health care

processes, and their association to mortality in Uganda was paramount (Catala-Lopez et al., 2018; Smith et al., 2018; Xu et al., 2017). The purpose of the study was to test and analyze the association between multimorbidity, health care processes, and death among TB/HIV patients on ART. The independent variables were multimorbidity, age, sex, marital status, phase of TB treatment, time of initiation of ART, and type of TB. The dependent variable was mortality.

Purpose of the Study

The purpose of this quantitative study was to test and analyze the association between multimorbidity, health care processes, and mortality among TB/HIV patients treated with ART in Uganda. The independent variables were multimorbidity, measured as yes or no. Multimorbidity in this study meant patients with TB/HIV with two or more diseases in addition to TB and HIV. Examples of these diseases are diabetes mellitus, hypertension, malnutrition, pneumonia, and cancers. The other independent variables were age, sex, marital status, the type of TB, phase of TB treatment, and initiation timing for ART measured as *yes* or *no*. The dependent variable was mortality, measured as *yes* or *no*.

Research Questions and Hypotheses

In this study, I addressed the following research questions with corresponding null and alternative hypotheses:

RQ1: What is the association between multimorbidity (disease clusters) and mortality among TB/HIV patients on ART?

$H_0$1: There is no association between multimorbidity (disease clusters) and mortality among TB/HIV patients on ART.

H_a1: There is an association between multimorbidity (disease clusters) and mortality among TB/HIV patients on ART

RQ2: What is the association between demographic factors (sex, age, and marital status) and mortality among TB/HIV patients on ART?

$H_0$2: There is no association between demographic factors (sex, age, and marital status) and mortality among TB/HIV patients on ART.

H_a2: There is an association between demographic factors (sex, age, and marital status) and mortality among TB/HIV patients on ART.

RQ3: What is the association between the phase of TB treatment (initiation and continuation) and mortality among TB/HIV patients on ART?

$H_0$3: There is no association between the phase of TB treatment (initiation and continuation) and mortality among TB/HIV patients on ART.

H_a3: There is an association between the phase of TB treatment (initiation and continuation) and mortality among TB/HIV patients on ART.

RQ4: What is the association between the time of initiation of ART (before the start of TB treatment and after the start of TB treatment) and mortality among TB/HIV patients on ART?

$H_0$4: There is no association between the time of initiation of ART (before the start of TB treatment and after the start of TB treatment) and mortality among TB/HIV patients on ART.

H_a4: There is an association between the time of initiation of ART (before the start of TB treatment and after the start of TB treatment) and mortality among TB/HIV patients on ART.

RQ5: What is the association between type of TB (pulmonary bacteriologically confirmed, pulmonary clinically diagnosed, and extrapulmonary) and mortality among TB/HIV patients on ART?

H_05: There is no association between the type of TB (pulmonary bacteriologically confirmed, pulmonary clinically diagnosed, and extrapulmonary) and mortality among TB/HIV patients on ART.

H_a5: There is an association between the type of TB (pulmonary bacteriologically confirmed, pulmonary clinically diagnosed, and extrapulmonary) and mortality among TB/HIV patients on ART.

Using binary logistics regression, I tested and analyzed the associations between multimorbidity, sex, age, marital status, type of TB, phase of TB treatment, the timing of initiation for ART, and mortality among TB/HIV patients on ART.

Conceptual Framework

The conceptual framework for this study was the health outcomes conceptual framework. The health outcomes conceptual framework relates to a complex interplay between a health system's 4 domains, patient factors, care path, and health outcomes (Canadian Institute for Health Information, 2008; Sbarigia et al., 2016). The health outcomes framework has its origins in the Donabedian model used for quality of care improvement developed in 1967 and implemented in the 1980s (1980, 1986, and 1988).

The Donabedian model includes three levels: (a) the structure or context, which is the setting for health care delivery; (b) the process where medical interventions are implemented; and (c) the outcome, which is the impact of health outcomes (Canadian Institute for Health Information 2008; Sbarigia et al., 2016). Apart from its use in quality improvement, this framework has been used in the study of processes in health care delivery settings and how the processes impact health outcomes.

The framework is also related to outcomes research studies in which researchers focused on chronic issues like mental health and diabetes. The framework has also been used in the Hepatitis C outcomes framework (Canadian Institute for Health Information 2008; Sbarigia et al., 2016). Based on its simplicity in studying patient-level outcomes, the outcomes conceptual framework was used to explore the relations between patient characteristics, multimorbidity, and mortality, contributing to patient-level outcomes. Using this health outcome conceptual framework, I focused on testing and analyzing the association of multimorbidity, age, sex, marital status, phase of TB treatment, time of initiation on ART, and type of TB with mortality among TB/HIV coinfected patients on ART in Uganda (Bates et al., 2015). The health outcomes framework was the most appropriate framework to use because it can be used to explore the relation of mortality and aspects of health structure, patient characteristics, and care process (Canadian Institute for Health Information, 2008).

The critical elements of the framework are the structure or context (health care system structure or context), patient factors, care path, and health outcomes (Canadian Institute for Health Information, 2008; Sbarigia et al., 2016). The health care system

structure is the mechanism patients obtain health care through. There are providers, clinics, and records, so patient characteristics, provider characteristics, and surveillance are necessary. Patient factors include social demographics (age, gender, ethnicity, education, income, marital status, and socioeconomic attributes); risk factors like smoking, drinking, physical activity and diet; and expectations or preferences of the patient. The care path includes interventions. Interventions are what is given to the patient to change the health care status, including prevention, treatment, and care. The processes of care in this study were anti-TB medicines, ART, and cotrimoxazole preventive therapy. The health outcomes were the status achieved after the implementation of interventions. Health outcomes may be either patient-related outcomes or health-system outcomes. Patient-related outcomes include health status, health-related measures, and non-health-related measures. The following are examples of the health-related measures, quality-adjusted life years, disability-adjusted years, health-related measures like hospital admissions, complications, or test results, whereas non-health-related measures include patient satisfaction. At the population level, health system performance measures apply at the national level, and the health outcomes include morbidity prevalence and mortality (Canadian Institute for Health Information, 2008; Sbarigia et al., 2016). In this study, I focused on mortality, which is under patient-level health outcomes (Brown et al., 2016).

The health outcomes conceptual framework provided a logical framework for studying multimorbidity among TB/HIV patients on ART. The conceptual framework also offered a line of thinking from the structure processes to outcomes, emphasizing

what happens rather than what went wrong, as highlighted by Donabedian. That kind of thinking is followed in the quality of care to improve patient health status and, therefore, multimorbidity. Based on this framework, the health outcomes and the health-related outcome (mortality) were the dependent variables. The other categories, like patient characteristics, formed the outcome variable or independent variable (multimorbidity). Several tools, like the Charlson comorbidity index tool and specific TB tools like the FACIT TB tool, could be used to measure TB-related comorbidities (Dujaili et al., 2015; Mamani et al., 2014). TB/HIV documents were reviewed to confirm the different patient characteristics, including multimorbidity. The health outcomes conceptual framework was used to guide the study on multimorbidity, healthcare processes versus mortality among TB/HIV patients on ART in Uganda. The data analyzed were related to the flow of the framework.

Nature of the Study

In this study, I used quantitative research methods with a cross-sectional design, coupled with a retrospective review of medical records to retrieve secondary data (Rudestam & Newton, 2015; van den Akker et al., 2001). Many studies have been conducted on comorbidity and multimorbidity. Researchers have used cross-sectional studies with a review of records (Oni et al., 2015; Peltzer, 2018; Pepper et al., 2015, Weimann et al., 2016). Furthermore, Catala-Lopez et al. (2018) noted that in various systematic studies researchers used a cross-sectional design to study multimorbidity in different countries. Cross-sectional studies are being used in the description of variables, description distribution of multimorbidity patterns, and examination of associations

between predictors and outcomes (Hulley, 2007). Also, cross-sectional studies could be used to provide information on those with a disease or a condition at a given point in time (Hulley, 2007).

To ensure external validity, several issues that affect generalization, like selection bias, were dealt with by ensuring a representative sample was selected from the regional referral hospitals in Uganda that handle TB/HIV patients. The regional referral hospitals in the sample were chosen systematically. All TB/HIV patients on ART were included in the sample to make the minimum required sample for each facility. An adequate sample was maintained by calculating the sample size required to ensure that the study has adequate power (Rudestam & Newton, 2015). The data collected included multimorbidity, sex, age, marital status, type of TB, phase of TB treatment, timing of initiation for ART, and mortality data. The selected variables were based on findings from other studies of comorbidities and multimorbidity in sub-Saharan Africa (Bates et al., 2013; Creswell, 2011, Oni et al., 2015; Pepper et al., 2015).

After authorization by the Walden University Institutional Review Board (IRB; # 01-31-20-0226229), Makerere University Higher Degrees Research Ethical Committee (#772), the Uganda National Council of Science and Technology (#HS692ES), the MoH, and regional referral hospitals, the following were accessed for data abstraction: TB registers, ART cards, patient files, and electronic registers. All patient data were deidentified. I conducted quantitative binary regression to test the associations between multimorbidity, sex, age, marital status, type of TB, phase of TB treatment, timing of initiation for ART, and mortality among TB/HIV patients on ART in Uganda.

Definitions

Antiretroviral therapy (ART): A combination of antiretroviral drugs that suppress HIV and stop the progression of HIV disease (WHO, 2015).

Diabetes mellitus: Diabetes leads to raised blood sugar called hyperglycemia and is a disease of chronic nature (WHO, 2015).

Health care system: A mechanism through which patients get health care from health care providers (Canadian Institute for Health Information 2008; Sbarigia et al., 2016).

Health outcomes: Changes in health that result from the implementation of interventions. Health outcomes may be patient-related outcomes or health system outcomes (Canadian Institute for Health Information 2008; Sbarigia et al., 2016).

Hypertension: A situation in which an individual has high or raised blood pressure. Normal blood pressure is less than 120/80 mm Hg. Elevated blood pressure has systolic readings between 120-129 and diastolic readings less than 80; Stage 1: Systolic between 130-139 or diastolic between 80-89;while Stage 2: Systolic at least 140 or diastolic at least 90 mm Hg; a hypertensive crisis: Systolic over 180 and/or diastolic over 120 (Carey & Whelton, 2018).

Multidrug-resistant TB (MDR-TB): TB resistant to at least rifampicin and isoniazid, the two most effective anti-TB drugs (WHO, 2015).

Multimorbidity: Existence of more than one medical condition or situation in an individual (AMS, 2018).

Noncommunicable diseases: Noninfectious health conditions typically caused by genetic, environmental, and lifestyle factors (Bates et al., 2015).

Patient factors: Characteristics that include social demographics (age, gender, ethnicity, education, income, marital status and social, economic attributes); risk factors like smoking, drinking, physical activity and diet; and expectations or preferences of the patient (Sbarigia et al., 2016).

Process of care: Interventions, including prevention and care interventions (Sbarigia et al., 2016).

TB/HIV coinfected patients: TB disease occurring in someone infected with HIV (WHO, 2015).

Assumptions

The first assumption in this study was that all HIV patients are screened for TB, and all those who had TB were diagnosed. This assumption was based on the WHO recommendation that all HIV patients be screened for TB at every health facility visit. Another assumption was that all multimorbidity in TB/HIV coinfected patients had been recorded on the ART cards and that all records were as complete as possible. At hospitals, there are dedicated records officers who fill in the information in the Unit TB register and the ART cards. Based on ART clinic practice, the record details of any multimorbidity and medications are recorded on the ART card. A third assumption was that all TB/HIV patients are administered both anti-TB medicines and ART. This assumption was based on the WHO recommendation adopted in 2013 in Uganda. All TB/HIV patients should be started on anti-TB treatment immediately after diagnosis and

ART within 2 months or as soon as they can tolerate ART and based on the recent test-and-treat policy (WHO, 2016). However, it was beyond the scope of this study to prove that all TB/HIV coinfected patients in the communities are diagnosed and administered anti-TB treatment and ART.

Scope and Delimitations

The specific aspects of the research problem addressed in the study were related to the selected patients' characteristics. The characteristics included gender, age, type of TB, multimorbidity (diabetes mellitus, hypertension, malnutrition, pneumonia, cancer), and health care processes like phase of TB treatment and timing of initiation for ART among TB/HIV patients on ART. Multimorbidity may be associated with mortality. The multimorbidity, health care processes, and mortality among TB/HIV patients on ART were studied to understand the relationship and support remedial actions.

The study participants included all TB/HIV patients on ART. The study excluded all TB/HIV patients on ART who had missing outcome variables. I used the health outcome conceptual framework for this study, a broad framework with some aspects not included in the study. The framework has three levels, the structure or context representing the health care delivery setup, the process representing how medical interventions occur, and the health outcomes. However, in this study, only parts of the three levels of the conceptual framework were studied. The parts of the conceptual framework that were studied included patient characteristics, which is part of the context, and mortality as the health outcome, the processes of the health outcomes, and mortality as health outcomes. The outcomes framework is so broad that some parameters were not

studied. Population-level outcomes, which include mortality rates and morbidity rates, were not studied. Other elements not studied in the context included the provider characteristics, the surveillance system, and clinic characteristics. This study is generalized to a study population in Uganda of TB/HIV patients on ART, focusing on multimorbidity and mortality.

Limitations

One of the critical limitations of this study was missing data or incomplete records encountered during data retrieval. To ensure that this limitation was minimized, patients were oversampled to cover for these data gaps. There could have been a threat of statistical validity, in which the sample size is too small to show any effect (Harris, 2016). I calculated the sample size to overcome statistical threat validity due to the small sample size. I ensured that more participants beyond the calculated sample were included in the sample to cater for missing data. During analysis, this adequate sample was used to make conclusions.

Significance of the Study

Significance to Theory

The types of multimorbidity among TB and HIV patients are known. However, the multimorbidity and its association with mortality among TB/HIV coinfected patients on ART have not been explicitly studied (AMS, 2018). The results of this study highlight the associations between multimorbidity, health care processes, and TB mortality among TB/HIV patients on ART in Uganda. The results of the study can contribute to new knowledge regarding multimorbidity and mortality among TB/HIV patients on ART.

Significance to Practice

Testing the associations between multimorbidity, health care processes, and mortality has helped to highlight the critical multimorbidities associated with mortality. In alignment with WHO's strategy to end TB and the era of comorbidity, it is essential to know and manage the multimorbidities appropriately for TB/HIV patients on ART (WHO, 2016). Health providers could use this study's results to understand common multimorbidities among TB/HIV patients on ART. The results could also provide insights to national TB program managers to plan appropriately (human resources, medicines, infrastructure, training) in managing and following up TB/HIV patients with various multimorbidities (WHO, 2016).

Significance to Social Change

Regarding positive social change, this study's results could be disseminated to the national TB program and organizations working in communities to plan, manage, monitor, and improve the way multimorbidity is managed among TB/HIV individuals and their families and the general community. Managers could use the results to improve patient health, including networks of TB patients coinfected with TB and who have other comorbidities. The results could also contribute to policies on multimorbidity because it is a new area on the global scene and is likely to be recognized in developing countries.

Summary and Transition

In TB and HIV patients, multimorbidity is associated with poor health outcomes, regardless of whether they are on ART. There is still inadequate information on the prevalence and consequence of multimorbidity among TB/HIV coinfected patients

initiated on ART (Mchunu et al., 2016; Pepper et al., 2015). The purpose of this study was to test the association of multimorbidity, health care processes, and mortality among TB/HIV patients on ART in Uganda. The independent variables were multimorbidity, phase of TB treatment, initiation of ART after the start of TB treatment, and type of TB. The dependent variable was mortality. I used a cross-sectional study design with quantitative methods and secondary data review (Rudestam & Newton, 2015; van den Akker et al., 2001). I analyzed and tested the association between mortality and multimorbidity among TB/HIV patients on ART in Uganda. I analyzed the associations between the independent variables and dependent variables using binary logistics regression. I conducted a multivariate analysis using binary logistics regression (van den Akker et al., 2001).

I am hopeful that managers, policymakers, and community organizations might use the results of this study to improve practice in health facilities and communities. Further, this study's results are likely to impact social change so that patients and networks with multimorbidity are managed by the health care system and in communities. In Chapter 2, I expound on the sections covered in Chapter 1 by reviewing the literature in detail to deepen the understanding about TB/HIV, exploring available literature regarding the independent and dependent variables, conceptual framework, and previous studies.

Chapter 2: Literature Review

Introduction

Uganda is a high-burden country for TB/HIV and is among the 30 TB/HIV high-burden countries with poor TB treatment outcomes. The country still records mortality of about 13% among TB/HIV coinfected patients on ART, despite high ART coverage (MoH, 2018; Musaazi et al., 2019; WHO, 2018). A further review of current studies shows that mortality is a core outcome of multimorbidity. The studies also highlight the inadequate literature on multimorbidity in middle- and low-income countries (Catala-Lopez et al., 2018; Smith et al., 2018; Xu et al., 2017). The studies reviewed on TB/HIV had inadequate information on the association of multimorbidity and mortality among TB/HIV coinfected patients on ART (Mchunu et al., 2016; Oni et al., 2015; Pepper et al., 2015).

Bates et al. (2015) and WHO (2018) have indicated that comorbidity/multimorbidity could be contributing to mortality among TB/HV patients globally. Oni et al. (2015) and Peltzer (2018) have suggested that comorbidity or multimorbidity could be associated with mortality among TB/HIV patients in South Africa. Studies conducted in Uganda show that high mortality among TB/HIV may be associated with extrapulmonary TB, low CD4 cell count, late presentation, several comorbidities, and low Karnofsky score (Kirenga et al., 2014, Musaazi et al., 2019). All the studies I reviewed indicate that multimorbidity among TB/HIV patients may be associated with mortality. However, none of these studies showed any statistical significance that comorbidity or multimorbidity contributes to mortality among TB/HIV

patients on ART (Bates et al., 2015: Kirenga et al., 2014; Musaazi et al., 2019; Oni et al., 2015). This finding highlights the need for research on the association between mortality and multimorbidity among TB/HIV patients on ART in Uganda.

The purpose of this study was to test and analyze the association between multimorbidity, health care processes, and mortality among TB/HIV patients on ART. The independent variables were multimorbidity, age, sex, marital status, type of TB, phase of TB treatment, and timing of initiation for ART. For this study, a patient had multimorbidity if they had any two diseases in addition to TB and HIV. Examples of these diseases are diabetes mellitus, hypertension, malnutrition, pneumonia, and cancers. Multimorbidity was measured as yes or no. The dependent variable was mortality.

This chapter includes the literature search strategy, the conceptual framework, and the literature review. The literature review consists of descriptions, evidence, and synthesis of the current literature for the last 5 years and classic or relevant literature beyond 5 years. The literature review includes topics on TB/HIV coinfection, mortality in TB/HIV coinfected patients on ART, prevalence, and patterns of multimorbidity among TB/HIV patients on ART. Also, the literature review includes an assessment of multimorbidity, the effects of multimorbidity on mortality, and a gap in the mortality and multimorbidity among TB/HIV patients on ART. The last section of this chapter includes a summary and conclusions about key findings and a transition to Chapter 3.

Literature Search Strategy

I searched electronic databases for individual articles in English, using Google search engine, Google Scholar, and Thoreau from Walden University. The electronic

databases included PubMed, CINAHL, Dissertations & Theses at Walden University, EBSCO ebooks, MEDLINE with full text, Open Library, Science Direct, SAGE Knowledge, Thoreau Multi-Database Search, and World Health Organization database. Keywords used during the search included *multimorbidity, comorbidity, TB/HIV, ART, treatment of multimorbidity, opportunistic infections, prevention of comorbidities, TB/HIV integration, TB, TB/HIV Mortality, TB/HIV deaths, TB/HIV outcomes multimorbidity conceptual framework, patient outcomes conceptual framework, multimorbidity,* and *mortality.*

The main articles included in this literature review were published between 2016 and 2020 found mainly in peer-reviewed journals. The journals include *AIDS Research and Treatment, Journal of AIDS and HIV Research, Journal of Infectious Diseases, The Lancet, Transactions of the Royal Society of Tropical Medicine and Hygiene*, and the Biomed Central Pulmonary Medicine open access *New England Journal of Medicine,* and *PLoS ONE*. I also reviewed articles from the *International Journal of Tuberculosis and Lung Disease*, *Public Health Action,* the *Journal of the International Association of Providers of AIDS Care,* the *AIDS Journal*, *International Journal of Mycobacteriology,* and *Journal of Acquired Immune Deficiency Syndromes*. Also, journals from sub-Saharan Africa and India were reviewed: the *South African Medical Journal*, the *Ethiopian Journal of Health Development,* and the *Indian Journal of Medical Research*. I accessed the relevant articles and applied the snowball method with Google Scholar to access other papers that have referenced the article to obtain more articles related to multimorbidity and TB/HIV outcomes. Manuscripts published between 2016 and 2020, within 5 years of

expected publication, were included. Also, a few relevant classical references outside the 5 years were included.

The identified items were entered into the Zotero database in different folders. The conceptual framework and all variables had folders in Zotero to ease the writing processes. Using Zotero, I searched for names of PDF articles that were downloaded but had not been appropriately cited. The Zotero software was used to make corrections to the references that were poorly labeled. Cleaning the Zotero database was coupled with removing duplicates and checking for proper referencing using APA style. The references for excerpts extracted from websites were entered, and I continued to review and remove redundant articles while adding relevant items until the literature review was complete. All folders were merged to form one folder and the reference list was produced using APA style.

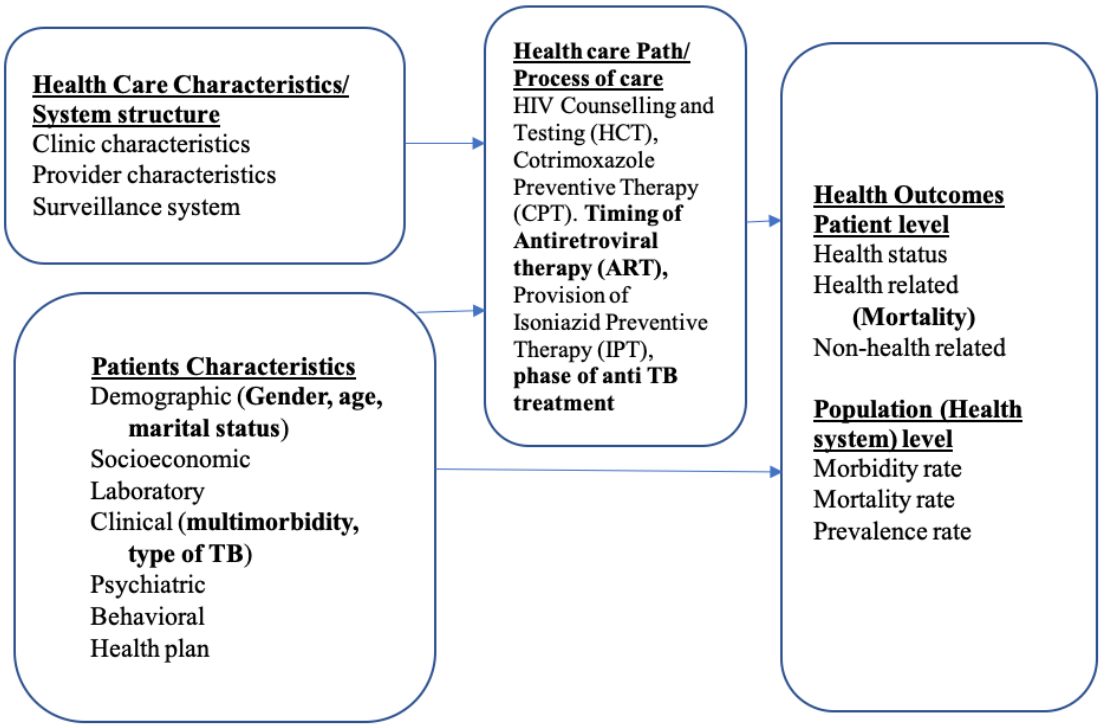
Conceptual Framework

The health outcomes conceptual framework has been used to guide the framework of this study. The health conceptual framework has been used in research outcomes and health services research. The framework has four domains that include (a) characteristics of the health system or health care system, (b) patient characteristics, (c) care/interventions path or process of care, and (d) outcomes (Canadian Institute for Health Information, 2008; Sbarigia et al., 2016). According to Sbarigia et al. (2016), the health system and patient factors are direct predictors of care path (the process of care), which is, in turn, a direct predictor of health outcomes. Also, the patient factors are direct predictors of health outcomes (Sbarigia et al., 2016).

In this section, I explain the four domains of the health outcomes conceptual framework. The characteristics of the health system or health care system structure have the process, structure, and quality related factors; these include clinic characteristics and provider characteristics. The patient characteristics have sociodemographic factors (age, gender, ethnicity, income, education, marital status, socioeconomic status), risk factors (genetics; behavior, e.g., smoking, drinking, physical activity and diet; personal resources, e.g., social support, life stress), laboratory, clinical and health status, and multimorbidity. For care/interventions, path or process of care including preventive, pretreatment, treatment, and treatment monitoring. The outcomes include patient-related issues and health system-related consequences. The patient-related results include health status: e.g., HRQOLTB treatment outcomes (mortality, LTFU, cure + completed = TSR, non evaluated, failure), the health related (proxy measure of the health status), e.g., hospital admissions, complications, increased health service utilization and non health-related, e.g., patient satisfaction. The health system performance-related outcomes include mortality rates and morbidity rates. Figure 2 shows the health system's four domains, patient factors, care path and health outcomes, and the relations and how they affect health outcomes.

Figure 1

The Health Outcomes Conceptual Framework



Comorbidities as health outcomes are significant in three significant areas: (a) clinical care, (b) epidemiology and public health, and (c) health service planning and financing (Valderas, 2009). Comorbidities usually need to be part of the patient outcomes measuring quality of life because it defines health status. In the early 2000s, comorbidities related to TB were measured using general instruments like the Short Form 36 (SF36), Charlson comorbidity index, and the WHO tool (Brown et al., 2015). Specific TB tools are now available to measure TB-related comorbidities—the FACIT-TB (Dujaili et al., 2015; Mamani et al., 2014). Based on this framework, the health outcomes

and health status (comorbidities) were the dependent variable, and the other categories like patient characteristics formed the outcome variable or independent variable.

The health outcomes conceptual framework has elements developed earlier on by the Donabedian quality of care framework with a structure, process, and outcomes (Canadian Institute for Health Information, 2008). Donabedian model refers to the structure as a setting for care delivery, while the process is the medical interventions and outcome as the impact on health status outcomes. The outcomes are the result of the effect of the structure and process. Donabedian's model has been used to measure and evaluate the quality of care and health systems' performance (Canadian Institute for Health Information, 2008; Donabedian, 2005).

The earlier conceptual framework by Donabedian was later used in research study outcomes and by the Canadian Institute for Health Information to focus on the four domains. The four areas include the health system structure, the patient characteristics or factors, the care path, and outcomes (Canadian Institute for Health Information, 2008; Donabedian, 2005; Sbarigia et al., 2016). The framework is also related to outcomes research studies focusing on chronic studies and the hepatitis C outcomes framework (Canadian Institute for Health Information 2008; Sbarigia et al., 2016). Although the framework mentions these social determinants of health, it does not exhaust them. It does not include social determinants for health inequities and political and structural determinants as explained in the new commission for social determinants of health (CSDH) WHO conceptual framework (WHO, 2010). The WHO conceptual framework includes the structural determinants, the social determinants of health inequities and

social determinants of health and how these affect equity in health and well-being, also referred to as health outcomes (WHO, 2016). In the WHO conceptual framework, the health system is one of the social determinants of health. The outcomes conceptual framework is still relevant because of its simplicity in studying the patient level outcomes and, in particular, comorbidities, a contributor to the health status in an individual patient.

The critical statements and definitions of the health outcomes conceptual framework include the health system, the patient factors, care path, and health outcomes. The health care system structure: This is a mechanism through which patients get health careThe patient factors: the patient characteristics include social demographics (age, sex, ethnicity, education, income, marital status, and social, economic attributes), risk factors like smoking, drinking, physical activity and diet, and expectations or preferences of the patient. The care path includes interventions; Interventions are what is given to the patient to change the health care status, and this includes prevention, treatment, and care. The interventions in this study are anti-TB medicines, ART, and cotrimoxazole preventive therapy.

The health outcomes are status achieved after the implementation of interventions (Smith et al., 2017). Health outcomes may be either patient related outcomes or health system outcomes. Patient related outcomes include health status, health-related measures, and non-health related measures (Sbarigia et al., 2016). The examples of the health-related measures include quality-adjusted life years, disability- adjusted years; health-related measures like hospital admissions, complications, or test results; while non-health related measures like patient satisfaction. At the population level, health system

performance measures apply at the national level, and the health outcomes include morbidity prevalence and mortality (Canadian Institute for Health Information, 2008; Sbarigia et al., 2016).

Outcomes research is varied and focuses on quality, the effectiveness of health as measured by attainment of specified outcome (Jefford et al., 2003; Shah et al., 2013). The outcomes include survival, disease status, complications, HRQOL, patient preferences, quality of care, costs, and mortality. In the past, the health outcomes conceptual framework has been used in research studies like the management of hepatitis C virus infection in virology. The framework has also been utilized in the study of chronic diseases like diabetes in noncommunicable diseases, cancers in oncology, and depression in mental health (Oni et al., 2015; Sbarigia et al., 2016). Earlier studies done in the 2000s indicated that the outcomes research was used to assess well-being and satisfaction and economic analysis. The economic analysis includes cost outcome, cost effectiveness, and cost utility. The models used in decision analysis should link research results, patient preferences, and population data (Jefford et al., 2003; Shah et al., 2013). The framework has been used in clinical trials and other studies. The benefits of outcomes research are varied, including the consumer, health care provider, health care organization management, and government (Jefford et al.,2003; Shah et al., 2013).

The benefits include increased participation in decision making for consumers, certainty about interventions by providers, use of the most cost effective interventions by health care organizations, and for governments to be able to plan, save on costs, using effective medicines and research areas (Jefford et al., 2003; Shah et al., 2013). Using this

health outcome conceptual framework, I tested and analyzed the association between multimorbidity, health care processes, and mortality among TB/HIV patients on ART in Uganda. The health outcomes framework was the most appropriate framework to use because it could be used to explore the relation of multimorbidity with mortality among TB/HIV patients on ART (Canadian Institute for Health Information, 2008, Sbarigia et al., 2016).

Literature Review

In this section, I describe the constructs of interest for this study, the chosen methodology, and methods that are consistent with the scope of the study. The constructs include the TB/HIV epidemiology, TB/HIV collaboration and the integration of TB/HIV services, TB/HIV and ART, HIV and TB drug interactions and adverse effects, Mortality among TB/HIV patients, multimorbidity among TB/HIV patients, determinants and patterns of multimorbidity, measures of multimorbidity, and later the methods and methodology consistent with this study.

TB/HIV Epidemiology

In 1993, the WHO declared the DOTS strategy to deal with an increasing TB global epidemic (WHO, 2016). The DOTS strategy was underpinned by five components that included political commitment, diagnosis through microscopy, administration of standardized short course chemotherapy through directly observed therapy, regular supply of anti-TB medicines, recording and reporting (WHO, 2016). Globally, countries started implementing the DOTS strategy to detect 70% of the TB cases and cure 85% of the identified TB patients. There was a noticeably increased TB notifications trend, and

by 2015, countries had saved 43 million people with TB. However, the increasing TB patients' trend was associated with HIV, especially in the 22 high burden countries. It was evident that the DOTS strategy was not adequate to control TB and WHO replaced the DOTS strategy with the STOP TB strategy, which had additional components to deal with the TB/HIV burden and the rising MDR TB (WHO, 2016).

To date, HIV and TB constitute the high burden diseases in low resource settings, especially in sub-Saharan Africa (Bruchfeld et al., 2015; WHO, 2018). WHO has selected the 30 TB/HIV high burden countries focusing on the TB/HIV epidemic in these countries, as showed in the End TB strategy (WHO, 2018). HIV increases the risk of developing TB to 20 to 40-fold and causes 25% of deaths in TB patients (Bates et al., 2015). The TB/HIV coinfection in countries like sub-Saharan Africa was about 70%, and it was inevitable the TB/HIV epidemic needed to be dealt with (Bruchfeld at al., 2015). In the TB high burden areas in low resource settings, HIV increases susceptibility to TB, reinfection with TB, and also reactivation of TB. HIV increases progression to TB, while TB increases the progression from HIV infection to AIDS.

TB/HIV Collaboration and the Integration of TB/HIV Services

To control the dual epidemic, in 2005, WHO developed a TB/HIV framework with 12 collaborative activities. The three objectives of the TB/HIV collaboration were to establish mechanisms for TB/HIV collaboration, reduce the burden of TB in HIV patients and lessen the burden of HIV in TB patients (Ford, & Getahun, 2015; WHO, 2016). Countries have used this framework to test over 80% of TB patients for HIV and start over 30 % of TB /HIV patients on ART (Ford, & Getahun, 2015; WHO, 2018).

Individual countries like Uganda have tested above 90% of TB patients for HIV and started over 80% of TB/HIV patients on ART (WHO, 2018)

Integration of TB/HIV services has been known to improve TB treatment outcomes (Mchunu et al., 2016; Musaazi et al., 2019). Five models of integration have been identified by several studies based on entry at either the TB or HIV service point with a referral for a service at the other aspect and then offering both services at the same point in Uganda (Legido-Quigley et al., 2013). Integration of TB/ HIV services has been found to vary based on the different model's TB/HIV service delivery from full segregation of services through partial integration with referral to full integration. Since no one size fits all, the different models have advantages and disadvantages. The model with complete segregation with a referral is easy to implement. However, the model has risks of losing patients, while the one with full integration needs more space and human resources hosted at the same site. Although the service delivery models have not been comprehensively compared in the different studies to determine the best model for delivering TB/HIV services. Uyei et al. (2012) found that co-location of services is necessary but not sufficient for comprehensive TB/HIV service delivery to occur. Also, treatment outcomes amidst TB/HIV integration affect comorbidities, side effects, delay of patients to access treatment, low serum levels, low patient weight, previous TB treatment, and knowledge on TB treatment (Mchunu et al., 2016; Musaazi et al., 2019). Useful indicators for monitoring integration, like mortality, need to be selected (Mchunu et al., 2016). The researchers and practitioners should be extending the collaborative TB/HIV framework to handle multimorbidity (Oni et al., 2015; WHO, 2018).

TB/HIV and ART

In many studies, ART has been shown to reduce mortality and improve TB treatment outcomes by preventing opportunistic infections and restoring immunity with lifelong viral suppression (Mchunu et al., 2016; WHO, 2018). The TB deaths in TB/HIV coinfected patients, although not sure, seems to be an indicator that can be used to monitor TB/HIV integration (Ansa et al., 2012). Clinical studies indicate that ART does not entirely restore immunity in HIV patients and, therefore, a risk of developing comorbidities, especially in advanced age (WHO, 2018). Some studies have shown that mortality is still high in TB/HIV patients on ART. The mortality may be due to comorbidities and late treatment initiation (Mchunu et al. 2016, Nansera et al., 2012). Other studies indicate that ART has a protective effect against death in TB/HIV patients on ART (Pepper et al., 2015). Also, Oni et al. (2015) found that in South Africa, HIV patients who were on ART had a lower comorbidity index than those not on ART (Oni et al., 2015). Although ART has protective effects in TB/HIV patients on ART, there is a need to determine why some TB/HIV patients on ART still die (Mchunu et al., 2016, Pepper et al., 2015).

HIV and TB Drug Interactions and Adverse Effects

Drug interactions commonly occur in TB/HIV patients on rifampicin. Rifampicin interacts with nevirapine and efavirenz due to induction of CYPP50. This induction reduces the bioavailability of both these drugs (Bruchfeld et al., 2015). To mitigate this effect, the best anti-TB drug to use is rifabutin or the use of efavirenz. Adverse effects are common in TB/HIV patients on anti-TB treatment and HAART. Adverse effects also

occur with the use of anti-TB together with ARVs. The common side effect is hepatotoxicity caused by Rifampicin and Isoniazid; also, ARVs cause this. So, the double effect may be magnified in some patients causing mortality. HIV patients who start ARVs late usually experience IRIS; this leads to worsening TB signs and symptoms and deterioration of the radiographic features on a chest X-ray. Lymphadenopathy is also common. Treatment with corticosteroids helps in managing the IRIS.

Mortality Among TB/HIV Patients

The initiation of ART among TB/HIV patients led to the improvement of treatment outcomes. However, despite ART initiation among TB/HIV patients, the mortality among these patients is high (Mchunu et al., 2016; WHO, 2018). In Swaziland, the evaluation of the 2010–2013 cohort showed similar findings where about 13% of TB/HIV coinfected patients were dying despite ART (Mchunu et al., 2016). Similar findings have also been found in Uganda by Musaazi et al. (2019), where about 10% of TB/HIV coinfection are still dying. However, in all the studies, the risk factors associated with the high case fatality rates are not well known.

Multimorbidity Among TB/HIV Patients

Although the definition of multimorbidity has been differing over the years, the AMS has defined multimorbidity as the coexistence of two or more chronic diseases or conditions (AMS, 2018). Patients with multimorbidity have an increased risk of premature death, high hospitalization, high costs of care, and low quality of life (AMS, 2018; Violan et al., 2014).

The prevalence of multimorbidity is increasing in both developed and developing countries. Oni et al. (2015) showed that multimorbidity is high in TB/HIV patients in South Africa and indicating that NCDs are occurring alongside infectious diseases. HIV is known as comorbidity among TB patients. Patients with HIV usually have other coinfections in addition to TB, leading to multimorbidity. In TB/HIV patients, Multimorbidity is one of the factors postulated to lead to death among TB/HIV patients (Mchunu et al., 2016; Musaazi et al., 2018). The higher the number of comorbidities, the greater the chance of mortality (Lix et al., 2016). According to Nunes et al. (2016). Multimorbidity is associated with an increase in the risk of death mortality. However, Schäfer et al. (2018) indicated that the effect of multimorbidity on mortality is still disputed. Earlier studies by Haregu et al. (2012) showed that mortality may be associated with multimorbidity, gender, age, education status, income, and social, economic status.

Determinants and Patterns of Multimorbidity

There are well known determinants of multimorbidity that include age, gender, and low socioeconomic status. Multimorbidity has been associated with increasing age, although studies in Africa show that young age is also associated with multimorbidity (AMS, 2018; Oni et al., 2015). Females are highly associated with multimorbidity than males, as shown by Violan et al. (2014). However, studies in sub-Saharan Africa show a mixed picture where for some diseases, the prevalence is more in males than females while in others, it is more in females than males (Oni et al., 2015). The low socio-economic status, as measured using the deprivation index, educational level, and health insurance coverage, is significantly associated with multimorbidity (Violan et al., 2014).

Usually, the patterns of multimorbidity are determined by the most prevalent conditions in a given geographical location. In European countries and the US, the typical multimorbidity patterns are hypertension and osteoarthritis or cardiometabolic conditions (Violan et al., 2014). In sub-Saharan Africa, it is becoming clear that there is a dual burden on non communicable and infectious diseases, and this constitutes the patterns of multimorbidity. Oni et al. (2015) observed the typical patterns of multimorbidity in South Africa included hypertension, diabetes, HIV, and TB. (Oni et al., 2015). The high prevalence of chronic and infectious diseases in sub-Saharan Africa confirms the ongoing epidemiological transition in the region and the need to reexamine the way multimorbidity are treated in primary health care centers (Oni et al., 2015)

Measures of Multimorbidity

There are various types of measuring multimorbidity. Haregu et al., (2012) indicated two conventional approaches to measuring multimorbidity, namely using a single condition and clustering of diseases into nonrandom group. According to Lefèvre et al. (2014), there are four types of measures of multimorbidity. The measure includes a simple count of chronic diseases. The second method is grouping diseases from a given list as dyads or triads; identifying common groups with the same diseases and characteristics, the third includes identifying an index disease first, and the fourth includes identifying homogenous groups of people with similar characteristics and similar diseases (Lefevre et al., 2014).

According to Wallace et al., (2016), three standard comorbidity measures have been used in research to measure comorbidities. The measures include the following. (a)

count based morbidity measures involving a simple count of chronic diseases. (b) Charlson comorbidity index, based on a list of 17 conditions (Lix et al., 2016; Wallace, McDowell, Bennett, Fahey, & Smith, 2016). Each condition assigned a weight of 1 to 6, with zero indicating no comorbidity. (c) Other similar measures used to measure comorbidity are RXRisk comorbidity assessment, Elixhauser Comorbidity Index and Johns–Hopkins Adjusted Clinical Group® (ACG®), Chronic Disease Score, Number of Diagnoses and Number of Prescription Drugs Dispensed. The tools use data from patient charts or electronic medical records. Some authors had pointed out that although comorbid measurements have been around for some time, there was no validated tool for TB that measures health status or comorbidities (Brown et al., 2015). However, from the ongoing discourse, there are still varied ways of measuring multimorbidity based on different authors. Therefore, a careful review of the measurements and application would be prudent.

Most of the multimorbidity studies have focused on the prevalence, patterns, and determinants of multimorbidity (Violan et al., 2014). The most common design for studies is the cross-sectional design (AMS, 2018; Oni et al., 2015). Patients in multimorbidity studies have been identified through self-reporting illness or extraction of data from electronic medical records. There are several methods used in multimorbidity studies, as indicated in the following paragraph.

The patterns of multimorbidity in several studies have been analyzed using cluster analysis and factor analysis (Violan et al., 2014). While analyzing determinants like socioeconomic class, the studies have used odds ratios. The test used to test patterns

include λ^2 to measure the difference in the prevalence of chronic disease and multimorbidity. The tests used to test for significance include the Shapiro-Wilk test used to test normality and the Kruskal Wallis test to test for significance of non parametric continuous variables. Significance testing was done in some studies using 2-sided p values and 95% confidence intervals.

An increasing number of research on multimorbidity have been conducted since the 2000s (Oni et al., 2015; Van den Akker et al., 2001). Researchers described how research on multimorbidity should be conducted with a highlight the selection of the set of comorbid diseases to measure, and these should be the more prevalent diseases in a given study setting (Van den Akker et al., 2001; Cassell et al., 2018). The research on multimorbidity has focused on four primary areas the magnitude of multimorbidity (incidence and prevalence), the patterns which focus on the clustering of multimorbidity, the severity that focuses on frailty, and determinants of multimorbidity that include age, gender, and socioeconomic status (Oni et al., 2015; Weimann et al., 2016).

The approach used broadly to investigate these issues is the quantitative approach. The quantitative approach has three broad areas that include data collection, data analysis, and interpretation. Data collection for multimorbidity has been done either through self-report, interview questionnaires, or data extraction from existing databases (Casell et al., 2018). The following methods are used in data analysis, counts, analysis using multiple regression, stratified analysis according to Mantel Haenzel, or stepwise multiple logistic regression (Van den Akker et al., 2001). Also, relative risk or odds ratio, confounding variables like age, socioeconomic status, environmental factors, and

psychological factors should be taken care of as confounders and effect modifiers (Van den Akker et al., 2001).

In recent research, researchers have mostly used retrospective cross-sectional designs to explore comorbidities (Casell et al., 2018; Creswell et al., 2011; Oni et al., 2015; Pepper et al., 2015). There are some strengths in using retrospective cross-sectional designs. The use of retrospective cross-sectional designs may be attributed to the fact that prospective designs take a long time, and an instant study would have limited data. Therefore, retrospective designs are used because they are quick to perform as compared to prospective studies. In multimorbidity studies, researchers usually require large sample sizes that are difficult to obtain with prospective studies within a short period. The retrospective cross-sectional studies have the advantage of collecting large volumes of data in a short time (Casell et al., 2018; Weimann et al., 2018). Also, retrospective studies require a lower cost as compared to prospective studies. Usually, the costs of prospective designs as compared to retrospective designs are high and inhibitive (Creswell et al., 2011).

Although retrospective studies have been used to examine multimorbidity, they have inherent weaknesses like a lack of variables that may be useful to consider (Umanah et al., 2015). Retrospective designs usually depend on already collected data from medical records and may collect all the relevant variables, including confounders (Umanah et al., 2015; Weimann et al.; 2016). However, some previous studies extracting data from electronic registers may have lacked variables like CD4 cells, date of initiation of treatment because these were missing in those databases (Oni et al., 2015). In this

study, because of the limitations of time and cost of the survey, I used retrospective cohort records to review the design with the quantitative design. In the past, multimorbidity has been defined in various ways, and therefore, it was difficult to compare studies. After 2018, the AMS (2018) has defined multimorbidity to mean the coexistence of two or more chronic conditions of long duration physical non communicable disease, mental condition on infectious disease (AMS, 2018). The new definition means that the comparison of studies would no longer be a limitation to multimorbidity studies.

Justification of Selected Variables or Concepts

The selection of independent and dependent variables was based on gaps observed in the existing literature of the variables as elaborated in the conceptual framework and the literature reviewed on multimorbidity (Oni et al., 2015; Weimann, et al., 2016). Also, the variables were best on the best predictors of outcomes based on previous literature.

The independent variables are multimorbidity, and a group of multimorbidity was selected: diabetes mellitus, hypertension, malnutrition, pneumonia, cancers. The author based the multimorbidity selection on the frequent multimorbidities documented in TB patients in sub-Saharan Africa and Uganda (Oni et al., 2015; WHO, 2018). The dependent variable is mortality. This variable was selected because mortality is associated with multimorbidity. However, there is no study for TB/HIV that has associated mortality with multimorbidity (Mchunu et al., 2016). This study is likely to give insights into the association between mortality and multimorbidity. Covariables for

this study selected include age, gender, income, education, marital status, and social, economic status (Mchunu et al., 2016; Pepper et al., 2015). These covariables are always included in other studies of multimorbidity (AMS, 2018). Most multimorbidity is attributed to gender, age, and low socioeconomic class. (Violan et al., 2014). The next section comprises the literature on each of the variables. Independent variables included multimorbidity, age, sex, marital status, phase of TB treatment, the timing of ART initiation, and type of TB. The dependent variable was mortality.

This section describes the literature for all the study variables that are within the last 5 years. However, important literature that goes beyond 5years is also included. The literature covers, what is known, the gap, and what this study may contribute to the existing body of knowledge for TB/HIV patients on ART. The variables of the study include mortality, which is a dependent variable. The rest of the variables are independent variables. They include multimorbidity, demographic factors (sex, age, and marital status), the phase of TB treatment (Initiation and continuation), the time of initiation of ART, and the type of TB.

Mortality Among TB/HIV Patients on ART

An increasing number of researches on mortality have been conducted since the 2000s (Mchunu, et al., 2016; Oni et al., 2015;). The research on TB/HIV mortality has focused on TB/HIV patients in general and not necessarily on ART alone, socio-demographics clinical and immunological information as independent variables, and mortality as the dependent variable (Mchunu et al., 2016; Musaazi et al., 2019; Stijnberg et al., 2019; Tola et al., 2019;). The primary outcomes of these study show that ART is

protective for TB patients, and death is usually associated with patients who are not on ART, with adverse effects, and who begin ART late variable (Mchunu et al., 2016; Musaazi et al., 2019; Stijnberg et al., 2019; Tola et al., 2019;).

The initiation of ART among TB/HIV patients led to the improvement of treatment outcomes. However, despite ART initiation among TB/HIV patients, the mortality among these patients is high (Mchunu et al., 2016; Musaazi et al., 2019; WHO, 2018). In Swaziland, the evaluation of the 2010 – 2013 cohort showed similar findings where about 13% of TB/HIV coinfected patients were dying despite ART (Mchunu et al., 2016). Similar findings have also been found in Uganda by Musaazi et al. (2019), where about 10% of TB/HIV coinfection are still dying. However, in all the studies, the risk factors associated with the high case fatality rates are not well known.

Mortality as a Dependent Variable

Mortality has been indicated as an outcome of multimorbidity (AMS, 2018; Smith et al., 2017). Multimorbidity has worse consequences, including mortality, disability, institutionalization, greater use of health care, miserable quality o life, and high side effects (Vetrano et al., 2017). Mortality in TB/HIV coinfected patients remains high globally despite the implementation of the test and treat policy for ART among TB/HIV patients. The link between mortality and multimorbidity among TB/HIV patients is not well understood. I explored the link between multimorbidity, health care processes, and mortality among TB/HIV patients on ART. One of the studies conducted in Denmark showed high death among people with multimorbidity was male, single or unmarried, low income status, and high age of 60 to 70 years (Taleshan et al., 2018).

Multimorbidity Among TB/HIV Patients

Although the definition of multimorbidity has been differing over the years, the AMS (2018) defines multimorbidity as the coexistence of two or more chronic diseases or conditions (AMS, 2018). Patients with multimorbidity have an increased risk of premature death, high hospitalization, high costs of care, and low quality of life (AMS, 2018; Violan et al., 2014). According to Nunes et al. (2016), multimorbidity is associated with an increase in the risk of mortality. However, Schäfer et al. (2018) indicate that the effect of multimorbidity on mortality is still disputed. The prevalence of multimorbidity is increasing in both developed and developing countries. Oni et al. (2015) showed that multimorbidity is high in TB/HIV patients in South Africa and indicating that NCDs are occurring alongside infectious diseases. HIV is known as comorbidity among TB patients. Patients with HIV usually have other coinfections in addition to TB, leading to multimorbidity. In TB/HIV patients, multimorbidity is one of the factors postulated to lead to death among TB/HIV patients (Mchunu et al., 2016; Musaazi et al., 2018). The higher the number of multimorbidities, the greater the chance of mortality (Lix et al., 2016). The gap in this study is that there is little literature that multimorbidity is associated with mortality among TB/HIV patients on ART (Mchunu et al., 2016; Musaazi et al., 2019; Stijnberg et al., 2019; Tola et al., 2019;). In this study, I determined the association between multimorbidity (non communicable disease clusters like diabetes, hypertension, malnutrition, cancers, and others.) and mortality among TB/HIV patients on ART.

Several patterns of multimorbidity exist in different parts of the world. In Europe and the USA, several studies indicated the most common multimorbidity patterns. The most common multimorbidity patterns were cardiometabolic and cardiovascular. Others included metabolic, cardiorespiratory pattern, metabolic pattern, neuropsychiatric, and musculoskeletal (Vetrano et al., 2017; Violan et al., 2014). In developing countries where both infectious and non communicable diseases exist the especially in sub-Saharan Africa, because of the ongoing epidemiological transition, the multimorbidity pattern was mixed with hypertension, diabetes, HIV, and TB (Oni et al., 2015). For this study, which was conducted in Uganda found in sub-Saharan Africa, the independent variables were multimorbidity, age, sex, marital status, phase of TB treatment, the timing of ART initiation, and type of TB, while the dependent variable is mortality (Mchunu et al., 2016; Pepper et al., 2015). The following sections describe the essential constructs and variables that were used in this study.

Diabetes Mellitus

Globally, the prevalence of diabetes is increasing, and patients with diabetes are at higher risk of multimorbidity. Patients with diabetes are at increased risk of cardiovascular, cerebrovascular diseases, pulmonary TB, kidney disease, dementia, and depression leading to premature illness and death (Chen et al., 2016). In countries with limited resources, the incidence of TB is declining while the number of notified cases of diabetes mellitus is rising, giving rise to a double burden (Bates et al.,2015; Kapur & Harries, 2013; Reis-Santos et al., 2013; Ugarte-Gil & Moore, 2014). The WHO studies reveal that diabetes is the second common comorbidity after HIV in patients with TB

(WHO, 2015). There could be variations by country based on the prevalence of TB; high TB burden countries are likely to have HIV as comorbidity, while in those countries where the HIV prevalence is low, diabetes is likely to be the most prevalent comorbidity, especially in populations above 65 years (Brown et al., 2015). In Asia, Ko et al. (2016) found that the prevalence of TB among TB patients had increased by 27% over the 10 years 2000 to 2010 (Ko et al., 2016). To manage the TB and diabetes comorbidity, WHO has created a framework similar to the TB/HIV framework (Sharma et al., 2014). The primary objectives are, establish mechanisms for collaboration, detect and manage TB in patients with diabetes, and identify and manage diabetes in patients with TB. Also, a monitoring framework has been developed to ensure surveillance (Bates et al., 2015). Brown et al. (2015) explained the misdistribution of fat (lipodystrophy) in HIV patients on non nucleoside reverse transcriptase inhibitors in patients with diabetes, hyperglycemia, and obesity are some of the comorbidities that manifest in the HIV patients on ART. (Brown et al., 2015). Higher mortality is observed in patients with more types of comorbidities (Oni et al., 2015).

Hypertension

TB and cardiovascular diseases have been noted to have links, although cardiovascular conditions are not direct risk factors for TB (Creswell et al., 2011). The effects of TB on the lungs have been known to give rise to pulmonary hypertension (Creswell et al., 2011). In studies conducted in South Africa, hypertension was found to be the most prevalent comorbidity in both diabetic and HIV patients (Oni et al., 2015; Weimann et al., 2016). The most common comorbidity among TB patients was

HIV/ART, followed by hypertension and diabetes (Oni et al., 2015; Weimann et al., 2016). The epidemiological transition is eminent in low-resource settings, where more non communicable diseases, including hypertension, are becoming prevalent with an equally high burden of communicable or infectious diseases (Creswell, 2011; Weimann et al., 2016). The dual burden of infectious and non infectious diseases may indicate the need to conduct more studies. Such e studies should explore the links of hypertension with TB focusing on high TB burden settings (Weimann et al., 2016).

Malnutrition

Malnutrition is associated with mortality in patients with multimorbidity, contributing to 10-85% of patients with multimorbidity. Mini nutritional assessment may be an easier way of measuring nutritional status in patients with multimorbidity. Usually, there are 18 items, but these are reduced to 7, including weight loss, mobility, body mass index, number of full meals, mode of feeding, fluid consumption, and health status. The new indices are 12.5–15 represents well-nourished, 9–12 represents those at risk of malnutrition, and less than nine those who are malnourished.

Pneumonia

Pneumonia is one of the comorbid diseases found in patients with multimorbidity, especially the elderly. The elderly with multimorbidity have pneumonia called community-acquired pneumonia. The risk of pneumonia is high in frail elderly hospitalized patients. The most frequent type of pneumonia that affects the adult is *Streptococcus pneumonia.* About 45% of all the cases of community-acquired pneumonia occur in the elderly above 65 years. To avoid pneumonia in the elderly, issues around

lifestyle, including immunization in the elderly, have to be considered. Mortality due to pneumonia in the elderly is 25% higher than in the general population.

Cancers and Mental Health

Cancers increases with age, and the increase in age is associated with multimorbidity. In patients above 65 years, more cancers and other multimorbid diseases are usually common (AMS, 2018). However, there are few studies on cancers and multimorbidity. Taking care of multimorbidity in cancer patients could be crucial since multimorbidity increases in patients with cancer and risk factors such as smoking, obesity, and alcohol use (AMS, 2018). The common multimorbidity includes myocardial infarction, osteoporosis, stroke, and metabolic syndrome. Mortality, quality of care, and treatment complications need to be taken care of in such cancer patients. Multimorbidity is associated with mental health. People with mental health have a 25-year life expectancy less than the other individuals. Mental health can be measured using depression (AMS, 2018). There is a detailed questionnaire that has been developed over time used to assess mental health.

Age, Gender, and Socioeconomic Status and Mortality

There are well known determinants of mortality that include age, gender, and low socioeconomic status. Earlier studies by Haregu et al. (2012) showed that mortality may be associated with gender, age, education status, income, and social, economic status . Mortality has been associated with increasing age, although studies in Africa show that young age is also associated with mortality in TB/HIV patients (AMS, 2018; Oni et al., 2015). Females are highly associated with mortality than males, as shown by Violan et al.

(2014). However, studies in sub-Saharan Africa show a reversed picture where males die more than females in TB/HIV patients (Oni et al., 2015). The low socioeconomic status, as measured using the deprivation index, educational level, and health insurance coverage, is significantly associated with mortality (Violan et al., 2014). The current gap is that there is little evidence in sub-Saharan Africa about the association of mortality with age, mortality, and marital status among TB/HIV patients on ART (Mchunu et al., 2016; Musaazi et al., 2019; Stijnberg et al., 2019; Tola et al., 2019;). In this study, I analyzed the association between demographic factors (sex, age, and marital status) and mortality among TB/HIV patients on ART.

TB Treatment Phase and Mortality

Patients diagnosed with susceptible TB take treatment for 6 months during the initial phase and continuation phase. The initial phase of TB treatment consists of 2 months of treatment. The initial phase has 4medicines: a fixed dose of rifampicin, isoniazid, pyrazinamide, and ethambutol (WHO, 2018). The combination of medicines kills the tubercle bacilli rapidly, and the patient becomes non infectious in about 2 weeks, and symptoms subside (WHO, 2013). PBC patients rapidly become sputum negative by the end of 2 months. These medicines are highly effective in HIV and non-HIV patients who may harbor a sizeable bacillary load. The continuation phase is given for 4 months with rifampicin and Isoniazid (WHO, 2018). Studies indicated that mortality is high in patients in the initial phase, especially at 2 months (Musaazi et al., 2019; Stijnberg et al., 2019; Tola et al., 2019;). However, these studies do not necessarily comment on the

initial or continuation phase (Mchunu et al., 2016; Musaazi et al., 2019; Tola et al., 2019).

Most of these studies point out that these patients with high mortality at 2 months may not be on ART. Mortality at 2 months may also be due to delayed diagnosis and the start of TB treatment (Stijnberg et al., 2019; Tola et al., 2019;). This finding indicates a gap in the knowledge of what happens in the era of ART, test, and treat policy. Are patients still dying at 2 months in the initial phase, or are they dying in the continuation phase? There is a need to explore when mortality happens in patients initiated on ART and then develop TB, and even those who begin ART after TB treatment. This study analyzed the association between TB treatment (Initiation and continuation phase) and mortality among TB/HIV patients on ART. The phase of TB treatment was the independent variable, while mortality was the dependent variable, and all these were categorical variables. Also, the analysis indicates those who died either in the initial or continuation phase and when they started ART.

Time of initiation of ART and Mortality Among TB/HIV Patients

Delay in ART initiation is one of the associations of mortality in TB/HIV patients, yet accelerated ART initiation improves clinical outcomes (Ford et al., 2018; Lisboa et al., 2019). Some earlier studies had shown that health workers could delay ART in those with less risk of IRIS and adverse reactions (Tola et al., 2019; Lisboa et al., 2019). However, in those studies, ART was only indicated in patients with a CD4 cell count of less than 200. However, mortality has continued to be high among patients with TB/HIV on ART (Gatechompol et al., 2019; Musaazi et al., 2019; WHO, 2018). During 2012, the

recommendation of when to start ART in TB/HIV patients became very important (Gatechompol et al., 2019).

In 2013, WHO produced a test and treat policy, and for all TB/HIV patients, ART was to begin within 8 weeks of the TB patients beginning TB treatment (Gatechompol et al., 2019). On the other hand, patients who have HIV and are on ART can still develop TB. However, no known studies were found which indicate the association between time of initiation of ART (before the start of TB treatment and after the start of TB treatment) and mortality among TB/HIV patients on ART, and this is a gap. This study was used to determine the association between time of initiation of ART, before the start of TB treatment and after the start of TB treatment, and mortality among TB/HIV patients on ART. The results could contribute to the body of knowledge of the time of initiation of ART and mortality.

Type of TB and Mortality Among TB/HIV Patients

TB is either extrapulmonary or pulmonary TB (WHO, 2019). Most of the patients with TB are usually pulmonary. The pulmonary TB patients are either pulmonary bacteriologically confirmed (PBC) or pulmonary clinically diagnosed (PCD). The pulmonary bacteriologically confirmed that people with TB include diagnosis using microscopy GeneXpert, culture, and other molecular tests. The diagnosis of a pulmonary clinically diagnosed patient is based on the appearance of radiological abnormalities suggestive of TB. The patient is usually bacteriologically negative. Also, the PCD diagnosis can be made based on the judgment of a health worker who decides to start

treatment with a high suspicion of TB. High mortality among TB/HIV patients was usually associated with PCD and extrapulmonary TB (Lisboa et al., 2019; WHO, 2006).

Mortality in EPTB and PCD is associated with the delay in diagnosis and delay in treatment of TB (Lisboa et al., 2019). However, the findings are now mixed, with some studies showing an association of high mortality with PBC, PCD, and EPTB, while other studies show the contrary (Lisboa et al., 2019; Tola et al., 2019). A significant number of these studies were conducted when ART was only recommended in patients with a CD4 cell count of less than 200 (Lisboa et al., 2019; Stijnberg et al., 2019: Tola et al., 2019). The current literature gap points out inadequate information about the type of TB and its association among TB/HIV patients on ART during the test and treats all TB/HIV patients on ART (Tola et al., 2019). This study examined the association of type of TB with mortality among TB/HIV patients on ART. The study provided new information to add to the body of existing knowledge for TB/HIV associated mortality.

Summary and Conclusions

Uganda is a high TB/HIV country among the 30 high burden TB/HIV countries in the world with poor TB treatment outcomes (WHO, 2018). The country still records high mortality of about 13% among TB/HIV coinfected patients on ART despite the high ART coverage (MoH, 2018; Musaazi et al., 2019; WHO (2018). The current studies on multimorbidity show that mortality is a core outcome of multimorbidity. The studies also highlight the fact that there is inadequate literature on multimorbidity in middle- and low-income countries (Catala-Lopez et al., 2018; Smith et al., 2018; Xu, Mishra, & Jones, 2017). The studies reviewed on TB/HIV had inadequate information on the association of

multimorbidity and mortality among TB/HIV coinfected patients on ART (Mchunu et al., 2016; Oni et al., 2015; Pepper et al., 2015).

In studies conducted globally by Bates et al. (2015) and WHO (2018) indicate that multimorbidity could be contributing to the mortality among TB/HV patients. Oni et al. (2015) and Peltzer (2018) suggest that comorbidity or mortality could be associated with mortality among TB/HIV patients in South Africa. Studies conducted in Uganda show that high mortality among TB/HIV may be associated with several factors. The factors include extrapulmonary TB, low CD4 cell count, late presentation, several comorbidities, low Karnofsky score (Kirenga et al., 2014, Musaazi et al., 2019). All the studies reviewed indicate that multimorbidity among TB/HIV patients may be associated with mortality. However, none of these studies shows any statistical significance that comorbidity or multimorbidity contributes to mortality among TB/HIV patients on ART (Bates et al., 2015: Kirenga et al., 2014; Musaazi et al., 2019; Oni et al., 2015). The preliminary finding highlights the need for research on the association between mortality and multimorbidity among TB/HIV patients on ART in Uganda.

The purpose of the study was to test and analyze the association between multimorbidity, health care processes, and death among TB/HIV patients on ART. One of the independent variables is multimorbidity. In this study, a patient has multimorbidity if they have any two diseases in addition to TB and HIV. Examples of these diseases are diabetes mellitus, hypertension, malnutrition, pneumonia, cancers. Multimorbidity was measured as yes or no. The other independent variables include demographic factors

(age, sex, and marital status), phase of TB treatment time of initiation of ART. The dependent variable is mortality.

In this study, the health outcomes conceptual framework has been used. The framework has four domains: health care system, patient characteristics, care or interventions, and outcomes, and has components derived from the Donabedian model of quality improvement. (Canadian Institute for Health Information, 2008; Sbarigia et al., 2016). In the past, multimorbidity in TB was measured using TB non specific tools. The tools used are the counting method, SF-36, Charleson comorbidity index, among others. However, new tools specific to measuring multimorbidity in TB like FACIT –TB are now available and should be utilized and refined.

Worldwide a significant proportion of TB/HIV patients has been started on ART. However, many of them still die; this highlights the gap that warrants further investigation, mainly focusing on multimorbidity as one of the likely causes of the associated mortality. This study could fill the literature gap by the author testing the association between multimorbidity and mortality among TB/HIV patients on ART and make recommendations that can be taken up by the policymakers and practitioners. The literature review would guide the next chapter on research methods, including the research design and rationale, the methodology, sampling and sampling procedures, procedures for recruitment, participation, and data collection.

Chapter 3: Research Method

Introduction

TB/HIV coinfected patients are initiated on life saving ART. However, mortality has remained high among TB/HIV patients globally and in sub-Saharan Africa (Mchunu et al., 2016; Oni et al., 2015; Pepper et al., 2015; WHO, 2018). There is inadequate information about multimorbidity in middle-income and lower-income countries, including Uganda (Catala-Lopez et al., 2018). As stated in Chapter 1, the purpose of this quantitative study was to test and analyze the association between multimorbidity, health care processes, and mortality among TB/HIV patients on ART in Uganda. The major sections of this chapter include research design and rationale, the methodology, sampling and sampling procedures, procedures for recruitment, participation, data collection for secondary data, instrumentation and operationalization of constructs, data analysis plan, threats to validity, and ethical procedures. This chapter concludes with an overall summary of the research methods.

Research Design and Rationale

In this study, the independent variables were multimorbidity, age, sex, marital status, phase of TB treatment, initiation of ART after the start of TB treatment, and type of TB. Multimorbidity included diabetes, hypertension, malnutrition, cancers, and other multimorbidities. These multimorbidities were selected based on their occurrence in sub-Saharan Africa, as indicated in the literature review (Oni et al., 2016; Peltzer, 2018). The dependent variable was mortality. I used a quantitative cross-sectional design with a review of medical records. The medical records have data elements for TB and HIV

patients in all hospitals and some health centers in Uganda. The records are collected during the clinical review of patients by hospital staff. The HIV data are first collected on the patient ART card and later entered into electronic medical records. TB patients' data are entered into the Unit TB register after a patient is diagnosed with TB and initiated on treatment. The following are the research questions studied using the cross-sectional design and review of records:

RQ1: What is the association between multimorbidity (disease clusters) and mortality among TB/HIV patients on ART?

RQ2: What is the association between demographic factors (sex, age, and marital status) and mortality among TB/HIV patients on ART?

RQ3: What is the association between the phase of TB treatment (initiation and continuation) and mortality among TB/HIV patients on ART?

RQ4: What is the association between time of initiation of ART (before the start of TB treatment and after the start of TB treatment) and mortality among TB/HIV patients on ART?

RQ5: What is the association between type of TB (pulmonary bacteriologically confirmed, pulmonary clinically diagnosed, and extrapulmonary) and mortality among TB/HIV patients on ART?

The constraints associated with the cross-sectional design and review of records are varied and include missing data elements. This constraint is compensated for by using large volumes of data and eliminating the data with missing variables. Usually, accessing secondary data that needs extraction is cumbersome because it needs approvals at many

levels. However, this challenge was sorted out by ensuring the MoH issued a letter of introduction to the regional referral hospitals. The letter identified the request for the data for research.

The cross-sectional design, coupled with a secondary review of the medical records, ensured easy access to large volumes of data collected over a long period. The costs to collect primary data were saved. Also, it is ethical to use the existing secondary data instead of trying to collect primary data from patients affecting their physical or mental well-being (Laureate, 2012). Over the last two decades, multimorbidity data have been collected through either interview of patients or review of medical records. For example, recent multimorbidity studies by Peltzer (2018), Weimann et al. (2016), Oni et al. (2015), and Pepper et al. (2015) were conducted using cross-sectional designs and reviews of records. Cross-sectional studies are known for describing variables and distribution of patterns and examining associations between predictors and outcomes (Hulley, 2007). Cross-sectional studies and reviews of records have been used to build the body of existing knowledge on multimorbidity and therefore were suitable for this study (AMS, 2018; Rudestram & Newton, 2015).

Methodology

Population, Sampling, and Sampling Procedures

The target population of this study was TB/HIV patients on ART in Uganda. In a year, about 17,000 TB/HIV patients are notified in Uganda (WHO, 2016). For this study, the accessible population was the TB/HIV patients on ART in the Unit TB register and ART cards or HIV electronic medical records at the national and regional referral

hospitals in Uganda. The intended sample of the study was TB/HIV patients enrolled on ART in selected hospitals in Uganda. The patients were registered in TB and ART cards or HIV electronic medical records in Uganda between January 2017 and December 2019. Systematic sampling was conducted to reach the intended number of regional hospitals. Nine out of the 14 regional referral hospitals with the corresponding sample size of available patients were selected. Data for TB/HIV patients on ART were extracted for all TB/HIV adults and children from January 2017 to December 2019 from the selected nine hospitals.

Inclusion and Exclusion Criteria

The sampling included TB/HIV patients on ART in selected regional referral hospitals registered in the Unit TB registers and ART client cards between 2017 and 2019. All TB/HIV patients on ART were included in the sample. The data were abstracted from the TB registers and ART cards for 2017–2019 for all TB/HIV patients. For TB/HIV patients whose records were missing some vital data, elements were excluded from the study. The patients who did not meet the criteria were excluded from the study.

Using Power Analysis to Determine Sample Size

I used G Power Version 3.1.9.2 to determine the minimum sample size for logistic regression for a dichotomous predictor, a significant predictor of a binary outcome (mortality), with or without other covariates (Faul et al., 2009). The following information, including statistical power, alpha, and effect size, was used. Usually, the statistical power of 80% (0.8) is recommended to test a relationship between the

independent and dependent variables. For alpha, I used a predetermined figure of 0.05 to maintain the high power of the study. Pr (Y = 1 | X = 1) H1, and I assumed the probability of mortality for TB/HIV patients on ART with multimorbidity is $H_1 = 0.18$. Then Pr (Y = 1 | X = 1) H_0 = the probability of mortality (Y = 1) when someone has no multimorbidities. If the probability of mortality for patients without multimorbidity is $H_0 = 0.09$ (TB patients without HIV), the two probabilities give an odds ratio of 2.524. Then R squared (R^2 other X) = the expected squared multiple correlation coefficient (R squared) between the main categorical predictor (multimorbidity status) and all other covariates. R squared represents the amount of variability in the main predictor (multimorbidity) that is accounted for by the covariates. X param π = The proportion of multimorbidity cases and are dead; this is estimated at 0.5. The sample size was 2,405. Assuming 20% (481) of the data were missing variables, the sample size would be adjusted to compensate for the missing variables. The new sample size was adjusted to 2,886, representing 62,362 TB/HIV patients on ART in Uganda from 2017–2019. Table 1 shows the output of the G Power.

Table 1

Calculation of Sample Size using G Power

No.	Parameter	Result
1	Tails	2
2	Pr(Y=1/X=1) H1	0.18
3	Pr(Y=1/X=1) H0	0.09
4	Alpha	0.05
5	R2 other X	0.81
6	X distribution	binomial
7	X Parm π	0.5
8	Critical z	1.9596640
9	Total sample	2,405

Archival Data/Secondary Data

Recruitment, Participation, and Data Collection

In the study, I used existing secondary data at the regional referral hospitals as medical records for TB and HIV patients. These secondary data were from the Unit TB register and ART cards. The primary data are usually collected during routine evaluations of TB and HIV patients; a clinician enters the data on the ART card or Unit TB registers. The Unit TB register has the following variables: (a) name and contact of the person, (b) health worker, (c) age, (d) sex, and (e) address (district, county, subcounty, parish, village). There is a column for disease classification—in this case, type of TB. Pulmonary bacteriologically confirmed (PBC) TB occurs in the lungs and is identified through smear microscopy or molecular technology. Pulmonary clinically diagnosed (PCD) TB occurs in the lungs but cannot be identified through smear microscopy or molecular technology. Extrapulmonary (EP) TB occurs outside the lungs. There is also a column for the type of patient (new, relapse, failure; loss to follow up; treatment history unknown); date treatment started and regimen, transfer in, results of sputum and other results, TB/HIV activities (CT, HIV result, CPT, ART) IPT, treatment model (community or facility), issue of anti-TB drugs (intensive/continuation phase), treatment outcome (cured, completed, failure, died, transferred out, loss to follow up, diagnosed with DR–TB). Among the data elements listed, a few data elements were collected from the Unit TB registers at the regional referral hospitals. The data on independent variables and the dependent variable were collected from the Unit TB register and ART cards.

Study Variables

The selection of independent and dependent variables for this study was based on gaps observed in the existing literature of the variables as elaborated in the conceptual framework and the literature reviewed on multimorbidity (Oni et al., 2015; Weimann et al., 2016). Also, the variables of the best predictors of outcomes were based on previous literature. In the section below, I describe all the variables. The variables include measurement, type of variable, and the tool used to extract it.

Dependent Variables

The dependent variable is mortality and is measured by yes or no and is a categorical variable.

Table 2

The dependent variable, measure, type, and tool

Dependent variable	Measurement	Type of variable	Tools to use
Mortality	Yes/No	Categorical/nominal	Data retrieval form

Independent Variables

The independent variables are multimorbidity, age, sex, marital status phase of TB treatment, initiation of ART after the start of TB treatment, and type of TB. Multimorbidity includes diabetes, hypertension, malnutrition, cancers, asthma, peptic ulcer disease, and others. The different multimorbidities were selected based on their occurrence in sub-Saharan Africa, as indicated in the literature review (Oni et al., 2016; Peltzer, 2018).

Table 3

Independent Variables, Measurements, Types, and Tools

S/N	Independent variable	Measurement	Variable type	Tools to use
	Multimorbidity (diabetes, malnutrition, cancers, and others)	Yes/No outcome	Categorical/ nominal	Data retrieval form
	Age	Years	Ratio	Data retrieval form
	Sex	Male/ female	Nominal/ categorical	Data retrieval form
	Marital status	Married/widow/ divorced/separated	Nominal/ categorical	Data retrieval form
	The phase of TB treatment	Initial/continuation	Categorical/ nominal	Data retrieval form
	Initiation of ART after the start of TB treatment	Before starting TB treatment	Categorical/ nominal	Data retrieval form
		After TB treatment		
		Unknown		
	Type of TB	Pulmonary TB (clinically diagnosed and bacteriogically diagnosed)	Categorical/ nominal	Data retrieval form
		Extrapulmonary TB		

Additional data were extracted from the ART cards of TB/HIV patients on ART. The presence of multimorbidity was recorded as Yes, and recorded in the column labeled, "other medications dispensed," including nutritional supplements (Peltzer, 2018). This data on medicines were used to come up with the most frequent chronic diseases in TB/HIV patients, namely, diabetes mellitus, hypertension, malnutrition, pneumonia, cancers, and others (Putnam et al., 2002). An expert physician provided the commonly prescribed medicines in Uganda for selected chronic diseases, and this was triangulated with the same chronic disease medical prescriptions in Uganda's clinical guidelines. The prescriptions from the expert and the Uganda clinical guidelines were merged and are as indicated below:

Table 4

Examples of some chronic diseases and their treatment

Chronic disease	Medicines	Type of variable	Tools to use
Diabetes mellitus	Insulin, metformin, pioglitazone, Glipizide, glibenclamide, Tolbutamide, gliclazide, Acarbose, chlorpromide	Categorical/nominal	Data retrieval form
Hypertension	propranolol, captopril, nifedipine, atenolol, lisinopril, losartan H; furosemide, methyl dopa, Bendrofluazide, propranolol, enalapril, amlodipine hydralazine	Categorical/nominal	Data retrieval form
Malnutrition	Diet supplements, for example, RUTF	Categorical/nominal	Data retrieval form
Pneumonia	ceftriaxone, Levofloxacin, ampicillin, azithromycin, Benzylpenicillin (xpen), Amoxycillin, chloramphenicol, erythromycin	Categorical/nominal	Data retrieval form
Asthma	Beta agonist inhalers(salbutamol), steroid inhalers, aminophylline injections, Salbutamol, hydrocortisone, aminophylline.	Categorical/nominal	Data retrieval form
Cancers	Methotrexate, actinomycin D; cyclophosphamide, Vincristine, Vinblastine, Chlorambucil, Busulfan	Categorical/nominal	Data retrieval form
Peptic ulcer disease	omeprazole, lansoprazole, pantoprazole, cimetidine, magnesium	Categorical/nominal	Data retrieval form

Using a letter from the MoH, permission was sought from regional referral hospitals to access TB/HIV data from the clinics. The formal request for data use is a

standard procedure set by the MoH to gain access to the data from health facilities in the country. Several types of research have been conducted in regional referral hospitals. The practice has been to usually access this data without restrictions once the letter seeking authorization is presented. Once permission was granted, data was accessed from the Unit TB register and ART card. The data accessed was de-identified.

The Unit TB register and ART card are the best sources of TB/HIV data. These are the tools where patient data is recorded daily when patients are attended to TB clinics and ART clinics. The medical health workers usually clerk, examine, investigate, diagnose, prescribe medicines, and conduct health education. The results from the medical processes are written in the Unit TB register and the ART card. The TB/HIV data is cheap to collect since it can be located easily in the clinics at the regional referral hospitals. The TB/HIV data from the ART card can also be accessed from the electronic medical record system in the regional referral hospitals, and this is a quick and easy to access process.

Operationalization of the Variables

This section highlights the operational definitions of both the independent and dependent variables. The section includes how each variable was measured. The section also includes how the scale or core was calculated. An example of how each item was measured and calculated is illustrated.

Definitions of Independent Variables

- Multimorbidity: Existence of more than one medical condition or situation an individual other than TB/HIV (AMS, 2018).

- Age: Period from the date of birth and time of when the patient had TB/HIV coinfection.
- Sex: A differentiation between male and female.
- Marital status: This is a legally defined marital state. It can be married, widowed, divorced, separated, or none.
- The phase of TB treatment: The phase can be the initiation phase or continuation phase. The initiation (intensive) phase is 2 months and consists of four drugs: rifampicin, isoniazid, pyrazinamide, and ethambutol. The initiation phase regimen kills rapidly multiplying bacteria or semi dormant bacteria (WHO, 2014). The continuation phase is 4 months and consists of two drugs: rifampicin and isoniazid. The continuation phase regimen eliminates bacteria and reduces failure and relapse (WHO, 2014).
- The timing of initiation for ART: This is whether the patient started antiretroviral treatment either before TB treatment or after the start of TB treatment.
- Type of TB: TB is either extrapulmonary or pulmonary. The pulmonary TB is either pulmonary bacteriologically confirmed (PBC) or pulmonary clinically diagnosed (PCD).

Nature of Scales

For independent variables, the natures of scales are indicated in the paragraph below. All the independent variables were categorical except age; they include multimorbidity, sex, marital status, phase of TB treatment, initiation of ART before or after the start of TB treatment, and type of TB. The following independent variables were

collected from the secondary data source, the Unit TB register, ART cards, patient files, or electronic medical records. They were recorded as dichotomous variables as follows.

- Multimorbidity: No multimorbidity = 1 and the presence of multimorbidity = 0
- The different multimorbidities were further categorized and coded as follows: No multimorbidity = 0; Cancer =1, Cardiovascular =2, Dermatological =3, Endocrine =3, ENT =4, GIT =5, Hematological =6, Immunological =7, Infectious =8, Liver =9, Lymphatic =10, Musculoskeletal =11, Neurological =12, Nutritition =13 , Reproductive =14, Respiratory =15, Psychological = 16
- Age was recorded as a continuous variable 0,1, 2,3,4 --------95 years
- Sex was recorded as a dichotomous variable male = 0 and female = 1
- Marital status was recorded as a categorical variable, married = 0, Widowed = 1, Divorced/separated = 2, Single = 3, Child =4
- Phase of TB treatment, Initial phase =0, continuation = 2 and alive =3
- Initiation of ART after the start of TB treatment Before or with TB treatment =0, after TB treatment = 1,
- Type of TB, Pulmonary bacteriologically confirmed (PBC) =0, Pulmonary clinically diagnosed (PCD) =1, Extra pulmonary tuberculosis (EP TB) =2

Data Analysis Plan

SPSS Software, Data Collection, and Research Questions and Hypotheses

The statistical package for the social sciences (SPSS) for Windows Version 25 was used to analyze data. Data of the Unit TB register and electronic medical records from the regional referral hospitals were retrieved into a data retrieval form. A copy of

the data retrieval form and codebook are included in the appendix. The data collected in the retrieval forms were cleaned and maintained in an excel file as codes and then exported to SPPS; and analyzed. I checked the database for missing data, outliers, and inconsistencies. In case of such inconsistencies, original documents were checked and corrected. An audit log for all data changes was maintained. Priority for data cleaning and editing was given, especially for the dependent variables, to ensure no data is missing. Editing procedures were repeated to ensure all errors and missing variables are corrected, and the database was declared final and locked.

Research Questions and Hypotheses

The following are research questions with corresponding null and alternative hypotheses as written in chapter 1:

RQ1: What is the association between multimorbidity (disease clusters) and mortality among TB/HIV patients on ART?

$H_0$1: There is no association between multimorbidity (disease clusters) and mortality among TB/HIV patients on ART.

H_a1: There is an association between multimorbidity (disease clusters) and mortality among TB/HIV patients on ART

RQ2: What is the association between demographic factors (sex, age, and marital status) and mortality among TB/HIV patients on ART?

$H_0$2: There is no association between demographic factors (sex, age, and marital status) and mortality among TB/HIV patients on ART.

H_a2: There is an association between demographic factors (sex, age, and marital status) and mortality among TB/HIV patients on ART.

RQ3: What is the association between the phase of TB treatment (initiation and continuation) and mortality among TB/HIV patients on ART?

$H_0$3: There is no association between the phase of TB treatment (initiation and continuation) and mortality among TB/HIV patients on ART.

H_a3: There is an association between the phase of TB treatment (initiation and continuation) and mortality among TB/HIV patients on ART.

RQ4: What is the association between the time of initiation of ART (before the start of TB treatment and after the start of TB treatment) and mortality among TB/HIV patients on ART?

$H_0$4: There is no association between the time of initiation of ART (before the start of TB treatment and after the start of TB treatment) and mortality among TB/HIV patients on ART.

H_a4: There is an association between the time of initiation of ART (before the start of TB treatment and after the start of TB treatment) and mortality among TB/HIV patients on ART.

RQ5: What is the association between type of TB (pulmonary bacteriologically confirmed, pulmonary clinically diagnosed, and extrapulmonary) and mortality among TB/HIV patients on ART?

$H_0$5: There is no association between the type of TB (pulmonary bacteriologically confirmed, pulmonary clinically diagnosed, and extrapulmonary) and mortality among TB/HIV patients on ART.

H_a5: There is an association between the type of TB (pulmonary bacteriologically confirmed, pulmonary clinically diagnosed, and extrapulmonary) and mortality among TB/HIV patients on ART.

Variables, Types of Data, and Statistical Tests

The data analysis was focused on analyzing the relationship /association between the different variables in each of the research questions. Analysis for hypothesis one was focused on the analysis of multimorbidity as an independent variable and mortality as a dependent variable. To ensure proper data analysis, new/dummy independent variables were derived. All the data on multimorbidity was changed into codes. The coded data were entered in the TB/HIV coded form (see appendix). The data was converted into dichotomous variables, yes or no. The new variable “yes” l represented the presence, and “no” represented the absence of multimorbidity.

All available data for the key variables is categorical except for age. For example, the data for the independent variable of multimorbidity is yes or no. The data for the dependent variable of mortality is also “yes” or “no.” Age is a continuous variable and was recorded in years. The data for sex was represented as “male” or “female.” The marital status data was coded as married, widow, separated or divorced, single or child. The table below shows the types of variables, independent and dependent variables,

including the statistical tests used to test each of the corresponding hypothesis/research questions.

Table 5

Type of Variable and Statistical Tests

Research question/ Hypothesis	Independent variable (type of variable)	Dependent variable (type of variable)	Statistical test
1	Presence /absence of multimorbidity (categorical)	mortality (categorical)	Descriptive analysis, Chi-square logistic regression
2	Demographic Age (ratio) Sex (categorical) Marital status (categorical)	mortality (categorical)	Descriptive analysis, binary logistic regression
3	Phase of TB (categorical)	mortality (categorical)	Descriptive analysis, binary logistic regression
4	ART Initiation (categorical)	mortality (categorical)	Descriptive analysis, binary logistic regression
5	Type of TB (categorical)	mortality (categorical)	Descriptive analysis, binary logistic regression

Data Analysis and Interpretation

The analysis included univariate analysis, bivariate and multivariable analysis., Descriptive measures like the mean, median, mode, interquartile range were used for univariate analysis. Also, a full range for continuous data and frequencies for categorical

data were used. The confidence intervals were set at 95%, and values were considered statistically significant at p= < 0.05.

According to Creswell (2009), logistics regression measures the relationship between categorical dependent variables and one or more independent variables (Creswell,2009). To test the hypothesis, logistic regression was used to measure the relationship between the presence or absence of multimorbidity, age, sex, marital status, phase of TB treatment, the timing of ART initiation, and type of TB, which are independent variables, and mortality, which is the dependent variable. The odds ratio was used to measure the IVs and mortality as the dependent variable. The confounders were tested for using binary logistics regression analysis.

The potential confounders (covariates) for inclusion in the study were age, sex, and marital status (Sangha at al., 2003). Descriptive results were interpreted based on the mean, median, frequency, and mode. In this study, the confidence interval was set at 95%, and all results were interpreted as statistically significant when P=< 0.05. For interpretation of the outputs of logistics regression, the odds ratio was used. If the odds ratio was higher than one, this meant multimorbidity or other IV is associated with mortality than expected. If the odds ratio is less than one, multimorbidity or the other IVs were less associated with mortality (Van den Akker et al., 2001).

Threats to Validity

Validity is concerned with whether the study can achieve all it is intended to achieve through measuring. Is the observed result of the dependent variable (mortality) associated with the independent variable's changes (multimorbidity)? The study is likely

to face some threats to validity, including external, internal, and construct validity. These threats to validity were controlled to ensure the study results are correct and can be used to the general population of TB/HIV patients on ART (Creswell, 2009). The next sections elaborate on how external validity, internal validity, and construct validity are likely to affect this study and how the threats to validity were minimized.

External Validity

External validity relates to whether the study findings were generalizable to the general population. The study had external validity if the findings in the selected regional referral hospitals could be easily related to the findings in other regional referral hospitals (Creswell, 2009). Using a sample that is not representative of the general population arising from, for example, selection bias is a critical threat to external validity (Frankfort-Nachmias & Nachmias, 2008). The attrition of the selected participants during the study could lead to having a nonrepresentative sample. The use of secondary data with access to a large data sample ensures that the challenge of non representative is overcome. A sample size estimation was conducted using G Power Version 3.1.9.2 to obtain an adequate sample size for logistic regression for a dichotomous predictor, a significant predictor of a binary outcome (mortality), with or without other covariates. . A sample size of 2,405 was obtained. The study has adequate power to ensure the results are generalizable.

Internal Validity

Internal validity is the level to which a researcher can say that the independent variable was the cause of the dependent variable. There are several threats to internal

validity during the study that affect experimental studies, including history, maturation, statistical regression, experimental mortality, and selection-maturation interaction. These threats did not affect this study directly since the study is based on secondary data. Some issues that are likely to affect this study include the missing data and missing variables. For missing data, some statistical calculations have been developed to ensure this is not a problem. In the case of missing variables, there was oversampling to cater for the missing variables. Also, all the data captured was as complete as possible.

Construct Validity

According to Frankfort-Nachmias and Nachmias, construct validity is where the instrument can measure a concept or hypothetical variable or the extent to which the measure is theoretically sound (Frankfort-Nachmias & Nachmias, 2008). Statistical conclusion validity refers to a situation where the sample size is too small to show any effect (Harris, 2010). To overcome the challenge of construct validity, a literature review was conducted on the variables to improve the conceptualization of the variables and their impact on the measurement. The independent variables multimorbidity, age, sex, marital status, phase of TTB treatment, the timing of ART initiation, and type of TB were studied and their effect on the mortality dependent variable. The dependent variable for this study is the presence or absence of multimorbidity.

Ethical Procedures

Permission was obtained from the directors of the regional referral hospitals to access TB patient data in the Unit TB registers and, where necessary, ART cards for patients. The records were accessed, and data abstracted. All the patient data was de-

identified. The data will be stored for at least 5 years if any further analysis needs to be done. In this study, patients were not interviewed, and therefore, there was no need for using informed consent.

Regarding secondary data extraction, each participant was given a different unique identification number recorded on the data collection tool. During data entry, the unique identification number was used, and patient names were deleted. The data was kept under lock and key and only be accessed to analyze it for the study purpose. The data will be kept for at least 5 years to enable future analysis and only be accessed under restricted circumstances.

Before collecting data, permission was sought from the IRB of Walden University (# 01-31-20-0226229) to conduct this study. Also, permission was sought from a local IRB Makerere University Higher Degrees Research Ethical Committee (#772). The Uganda National Council of Science and Technology (UNCST) is mandated to approve any research in the country. Permission was sought from the UNCST (# HS692ES) to conduct the study in addition to the local IRB and Walden University IRB. I signed data agreements with all the executive directors in all the nine regional referral hospitals.

Summary

This section contains a summary of the methodology that was used for this study. The purpose of the study was to test and analyze the association between multimorbidity, health care processes, and mortality among TB/HIV patients on ART in Uganda. The independent variable is multimorbidity, age, sex, marital status, phase of TB treatment, time of initiation of ART, and type of TB. The dependent variable was mortality. The

study used a quantitative cross-sectional design and applied the review of records in nine out of the 14 regional referral hospitals. The target population of the study was TB/HIV patients on ART in Uganda. The sample size result was 2,405. Since the response rate from previous studies is about 80%, the sample size to use was 2,886 patients. G Power was used to calculate the sample size.

The statistical package for the social sciences (SPSS) for windows version 25 was used for data analysis. The data analysis was focused on analyzing the relationship /association between the different variables in each of the research questions. The data analysis included descriptive and binary logistics regression. The confounders were tested using binary logistic regression. Central tendency measures and standard deviation were used to interpret descriptive data.

Straight forward interpretation of data was displayed using tables, graphs, and pie charts. Inferential conclusions were drawn from data using the confidence interval set at 95% and significance level set at P =< 0.05. Any statistically significant results with data with P <=0.05 were subjected to biological or social plausibility. Before collecting data, permission was sought from the IRB of Walden University, a local IRB, and UNCST as required by the country's laws and regulations. In this study, patients were not interviewed, and there was no need for using informed consent. The results are presented in Chapter 4.

Chapter 4: Results

The purpose of the study was to analyze the association between multimorbidity, health care processes, and mortality among TB/HIV patients on ART in Uganda. I used the health outcomes conceptual framework that allays a complex interplay between the health system's four domains, patient factors, care path, and health outcomes. The independent variables were multimorbidity, age, sex, marital status, phase of TB treatment, the timing of initiation for ART, and type of TB. The dependent variable was mortality. I tested and analyzed the association between multimorbidity, health care processes, and mortality among TB/HIV patients on ART. The following were the research questions and hypotheses of the study.

Research Questions and Hypotheses

RQ1: What is the association between multimorbidity (disease clusters) and mortality among TB/HIV patients on ART?

$H_0$1: There is no association between multimorbidity (disease clusters) and mortality among TB/HIV patients on ART.

H_a1: There is an association between multimorbidity (disease clusters) and mortality among TB/HIV patients on ART

RQ2: What is the association between demographic factors (sex, age, and marital status) and mortality among TB/HIV patients on ART?

$H_0$2: There is no association between demographic factors (sex, age, and marital status) and mortality among TB/HIV patients on ART.

H_a2: There is an association between demographic factors (sex, age, and marital status) and mortality among TB/HIV patients on ART.

RQ3: What is the association between the phase of TB treatment (initiation and continuation) and mortality among TB/HIV patients on ART?

$H_0 3$: There is no association between the phase of TB treatment (initiation and continuation) and mortality among TB/HIV patients on ART.

$H_a 3$: There is an association between the phase of TB treatment (initiation and continuation) and mortality among TB/HIV patients on ART.

RQ4: What is the association between the time of initiation of ART (before the start of TB treatment and after the start of TB treatment) and mortality among TB/HIV patients on ART?

$H_0 4$: There is no association between the time of initiation of ART (before the start of TB treatment and after the start of TB treatment) and mortality among TB/HIV patients on ART.

$H_a 4$: There is an association between the time of initiation of ART (before the start of TB treatment and after the start of TB treatment) and mortality among TB/HIV patients on ART.

RQ5: What is the association between type of TB (pulmonary bacteriologically confirmed, pulmonary clinically diagnosed, and extrapulmonary) and mortality among TB/HIV patients on ART?

$H_0$5: There is no association between the type of TB (pulmonary bacteriologically confirmed, pulmonary clinically diagnosed, and extrapulmonary) and mortality among TB/HIV patients on ART.

H_a5: There is an association between the type of TB (pulmonary bacteriologically confirmed, pulmonary clinically diagnosed, and extrapulmonary) and mortality among TB/HIV patients on ART.

In Chapter 4, I describe the data collection methods, the study findings in detail, including descriptive results and results from the binary logistics regression. I provide a summary of the research questions and a transition to Chapter 5.

Data Collection

Several institution review boards approved this study: Walden University IRB (# 01-31-20-0226229), Makerere University Higher Degrees Research Ethical Committee (#772), and the Uganda National Council of Science and Technology (#HS692ES). The MoH provided administrative clearance for the study, and the executive directors of the regional referral hospitals signed data use agreements for each hospital. Also, the research committees of three hospitals provided additional ethical approval. All these documents were presented to the respective hospital authorities at the time of data abstraction.

The experienced health workers in different hospitals abstracted data from Unit TB registers, ART cards, and patients' files onto a data abstraction tool starting in August 2020, and abstraction was completed on November 20, 2020. The data included a hospital's name, year, unique ID, age, sex, marital status, DR TB status, type of TB, TB

treatment outcome, ART number, other medications, and other diseases diagnosed other than TB or HIV. The abstraction tool did not include direct identifiers, and patient names were not included in the data set. There were no discrepancies in the data collection plan. WHO (2020) estimated about 35,000 people living with HIV fell ill with TB in Uganda in 2019, with 25,125 notified to WHO, and 25,125 were on ART.

I used G Power Version 3.1.9.2 to determine the minimum sample size for logistic regression for a dichotomous predictor. The following information, including statistical power, alpha, and effect size, was used in calculating sample size. The statistical power of 80% (0.8) was used to test a relationship between the independent and dependent variables. For alpha, I used a predetermined figure of 0.05 to maintain the high power of the study. Pr (Y = 1 | X = 1) *H*1, and I assumed the probability of mortality for TB/HIV patients on ART with multimorbidity was $H_1 = 0.18$. Then Pr (Y = 1 | X = 1) H_0 = the probability of mortality (Y = 1) when someone has no multimorbidities. If the probability of mortality for patients without multimorbidity is $H_0 = 0.09$ (TB patients without HIV), the two probabilities give an odds ratio of 2.524. Then R squared (R^2 other X) = the expected squared multiple correlation coefficient (R squared) between the main categorical predictor (multimorbidity status) and all other covariates. R squared represents the amount of variability in the main predictor (multimorbidity) that is accounted for by the covariates. X param π = The proportion of multimorbidity cases and are dead; this was estimated at 0.5. The calculated sample size was 2,405. The sample size was adjusted to 2,886 to compensate for the 20% missing variables. However, during data abstraction, all data on all eligible TB/HIV patients on ART were abstracted from

the 9 regional referral hospitals, making 3,580 records. The 3,580 records were adequate to answer the research questions. The data were used to make conclusions about the mortality, multimorbidity, and health care processes among TB/HIV patients on ART in Uganda.

Results

The representative sample of the study was 2,880 TB/HIV patients on ART in Uganda. As shown in Table 6, 3,580 TB/HIV patients on ART in Uganda were abstracted from the nine hospitals. The majority of the TB/HIV patients (95%; 3,402) had susceptible TB; only 5% (178) had DR–TB. One hospital had the majority of patients at 763, while the last had the least patients at 151. A total of 749 (20.9%) of TB/HIV patients were dead, while 1016 (28.4%) had at least one multimorbidity, and 344 (30%) of those who were dead had multimorbidity. The top five most common multimorbidities were gastrointestinal, nutritional, respiratory, neurological, and infectious diseases (see Table 7).

Table 6

Regional Referral Hospital Statistics

Regional referral hospital	Code	Frequency	Percent
Regional Referral hospital A	0	763	21.3
Regional Referral hospital B	1	426	11.9
Regional Referral hospital C	2	490	13.7
Regional Referral hospital D	3	408	11.4
Regional Referral hospital E	4	388	10.8
Regional Referral hospital F	5	316	8.8
Regional Referral hospital G	6	405	11.3
Regional Referral hospital H	7	151	4.2
Regional Referral hospital I	8	233	6.5
	Total	3,580	100.0

Table 7

Multimorbidities in TB/HIV Patients on ART

	Disease category	Frequency	%
1	GIT	275	27.1
2	Nutrition	127	12.5
3	Respiratory	119	11.7
4	Neurological	101	9.9
5	Infectious	74	7.3
6	Musculoskeletal	44	4.3
7	Cardiovascular	42	4.1
8	Renal	36	3.5
9	Hematological	33	3.2
10	Dermatological	30	3.0
11	Endocrine	23	2.3
12	Reproductive	23	2.3
13	Immunological	22	2.2
14	Otorhinolaryngology	18	1.8
15	Cancer	17	1.7
16	Liver	16	1.6
17	Psychological	10	1.0
18	Lymphatic	6	0.6
	Total	1016	

The study had one dependent variable, mortality, and seven independent variables: (a) sex, (b) age, (c) marital status, (d) type of TB, (e) ART initiation, (f) TB treatment phase, and (g) multimorbidity clusters. All variables were categorical except age. Age was measured in years and was the only independent continuous variable. The minimum age was 0.42 years; the maximum age was 95 years; the mean age was 36.3 years, the median age was 36 years, and the mode age was 30 years. Table 8 shows the details of the dependent and independent categorical variables. The total sample size was 3,580 for each variable except age and marital status with 3,579 and 3,245, respectively.

All variables met the criteria for evaluation of statistical assumptions for binary logistics regression.

Table 8

Descriptive Statistics for Categorical Variables

	N Statistic	Type of variable	Categories	Code	Frequency Statistic	Frequency %
Mortality	3580	Dependent	Alive	0	2831	79.1
			Dead	1	749	20.9
Sex	3580	Independent	Male	0	2087	58.3
			Female	1	1493	41.7
Marital status	3,245	Independent	Married	0	1646	46.0
			Widowed	1	210	5.9
			Divorced/Separated	2	667	18.6
			Single	3	507	14.2
			Child	4	215	6.0
			Missing system	-	335	9.4
Type of TB:	3580	Independent	PBC	0	1452	40.6
			PCD	1	1870	52.2
			EPTB	2	258	7.2
ART Initiation	3580	Independent	Before TB treatment	0	2907	81.2
			after TB treatment	1	673	18.8
Phase of TB treatment	3500	Independent	Initial phase	0	564	15.8
			Continuation phase	1	105	2.9
			NA	3	2831	79.1
			Missing system		80	2.2
Multimorbidity clusters	3580	Independent	MM0	0	2564	71.6
			MM1	1	824	23.0
			MM2ormore	2	192	5.4

Evaluating Statistical Assumptions

I used binary logistic regression to analyze the data set on TB/HIV patients on ART in Uganda. As a recommendation, the data should meet all the seven assumptions of binary logistics regression before applying the analysis (Laerd, 2017). The first four assumptions are concerned with the study's design, while the other three assumptions are

concerned with the nature of data (Laerd, 2017). The requirement is for the data to meet all seven assumptions before analyzing using binary logistics regression.

The study met the assumption1. The first assumption requires that a dichotomous dependent variable (DV). The DV for this study is mortality, and it is dichotomous, with mortality coded as one and no mortality coded as zero. Assumption 2 was met. Assumption 2 required that the independent variables (IV) should either be continuous or categorical. This study had seven IVs, one of which was continuous, age measured in years. The rest of the six IVs are categorical multimorbidity clusters, sex, marital status, time of ART initiation, phase of TB treatment, and type of TB. The study met assumption 3. Assumption 3 required independent observations and mutually exclusive and exhaustive variables. Each observation captured in its row, and the observations have no relationship between each and mutually exclusive. All seven variables met this assumption. The study met the assumption 4 for only six out of the seven IVs. Assumption 4 required that each of the independent variables have at least 15 cases (Laerd, 2017). All the independent variables in this study have more than 15 cases each except phase of TB treatment. The static count was 3580 for sex, time of art initiation, phase of TB treatment and type of TB, and multimorbidity clusters, while marital status was 3,245 and age was 3,579. The phase of TB treatment IV had zero cases in the binary outcome, as shown in Table 9. To address this, I answered RQ3 using descriptive statistics.

Table 9

The Phase of TB Treatment With Fewer Than 15 Cases in the Binary Outcome

	Code	Initial	Continuation	Completion	Total
No mortality	0	0	0	2831	2831
Mortality	1	564	105	0	669
Total		564	105	2831	3500

Assumption 5 was met. Assumption 5 assumed that there should be a linear relationship between the independent continuous variables and the logit transformation of the categorical dependent variable (Box & Tidwell, 1962). I tested this assumption using the Box Tidwell approach. The only continuous independent variable in this study is age. I conducted a Box Tidwell procedure to assess the linearity of age (continuous variable) against the logit transformation of mortality as a dependent variable (Box & Tidwell, 1962). The assessment showed that ln -age was not significant ($p > 0.05$), meaning there is a linear correlation between age and the logit transformation of mortality (Laerd, 2017). Assumption 6 related to multicollinearity was not tested since it is only tested when there are many independent study variables. This study had only bivariate independent variables without multivariate independent variables. The study satisfied Assumption 6.

The study satisfied Assumption 7 that there no significant outliers. I tested this using case wise diagnostics and analyzed each IV against the dependent variable mortality. The output did not produce a case wise plot since it had no outliers for the independent variables.

Statistical Analysis by Research Question

This section details the statistical analysis of each research question. The following is research question one, the null and alternate hypothesis.

RQ1: What is the association between multimorbidity (disease clusters) and mortality among TB/HIV patients on ART?

$H_0$1: There is no association between multimorbidity (disease clusters) and mortality among TB/HIV patients on ART.

H_a1: There is an association between multimorbidity (disease clusters) and mortality among TB/HIV patients on ART

I conducted a binomial logistic regression to test an association between multimorbidity (disease clusters) and mortality among TB/HIV patients on ART in Uganda. The outcome variable was mortality, while the independent variable was multimorbidity. The IV had three levels: (1) no multimorbidity, (2) one multimorbidity, and (3) two or more multimorbidities. Mortality was classified as 1 for dead and 0 for alive. The logistics regression model was also significant with $\chi 2$ (2) = 37.167, $p<0.0001$. The model explained 1.6% (Nagelkerke) of the variance in mortality and correctly classified 79.1% of the mortality cases.

Table 10 shows that the two levels of the independent variables in the model were statistically significant. The two levels of the independent variables were one multimorbidity cluster and two or more multimorbidity clusters. The TB/HIV patients on ART with one multimorbidity were 1.658 times more likely to die ($P<0.0001$ for each at 95% CI (1.388 – 1.992) compared to patients with no multimorbidity. The TB/HIV

patients on ART with two or more multimorbidities were 1.901 times more likely to die (p<0001, 95% CI (1.373 -2.633) compared to TB/HIV patients on ART with no multimorbidity.

Table 10

Logistics Regression Predicting the Likelihood of Mortality Based on Multimorbidity Clusters in TB/HIIV Patients on ART in Uganda

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
No multimorbidity (MM0)			38.217	2	.000			
One multimorbidity cluster (MM1)	.506	.094	29.209	1	.000	1.658	1.380	1.992
Two or more multimorbidity cluster (MM2+)	.642	.166	14.943	1	.000	1.901	1.373	2.633
Constant	–1.497	.051	859.066	1	.000	.224		

Note. The reference variable multimorbidity clusters is no multimorbidity.

RQ2: what the association between demographic factors (sex, age, and marital status) and mortality among TB/HIV patients on ART?

$H_0$2: There is no association between demographic factors (sex, age, and marital status) and mortality among TB/HIV patients on ART.

H_a2: There is an association between demographic factors (sex, age, and marital status) and mortality among TB/HIV patients on ART.

The second research question was answered using a binomial logistic regression to test for an association between demographic factors (sex, age, and marital status) and mortality among TB/HIV patients on ART in Uganda. The outcome variable was mortality, while the independent variables were sex, age, and marital status. Sex coded as

male 0 female 1, Age is a continuous variable measure in years, while marital status was coded as married 0, widowed 1, separated/divorced 2, single 3, and child 4. Mortality is classified as 0 for dead and 1 for alive 0. The logistics regression model was significant with $\chi 2$ (6) = 10.339, p>0.001 (0.001). The model explained 0.11% (Nagelkerke) of the variance in mortality and correctly classified 80.5% of the mortality cases.

Table 11 shows that the two predictor variables in the model, separated or divorced, and single were statistically significant. The TB/HIV patients on ART that were separated or divorced were 1.591 times more likely to die (P<0.0001) (0.000); (95% CI: 1.279 -1.98)1 as compared to married patients. The TB/HIV patients on ART that were single were 1.381 times more likely to die (P<0.0001) (0.000); (95% CI: 1.069 -1.782) as compared to married patients.

Table 11

Logistics Regression Predicting the Likelihood of Mortality Based on Sex, Marital Status, and Age

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B) Lower	Upper
Sex: M = 0, F = 1 (1)	–.031	.092	.117	1	.732	.969	.809	1.160
Marital status								
Married			22.006	4	.000			
Widowed	–.110	.215	.263	1	.608	.896	.588	1.364
Divorced/separated	.465	.112	17.309	1	.000	1.591	1.279	1.981
Single	.322	.130	6.106	1	.013	1.380	1.069	1.782
Child	.053	.227	.055	1	.815	1.055	.676	1.645
Age	–.002	.004	.166	1	.684	.998	.990	1.007
Constant	–1.492	.189	62.562	1	.000	.225		

Note. The reference variable for sex is male and for marital status is married.

RQ3: What is the association between the phase of TB treatment (initiation and continuation) and mortality among TB/HIV patients on ART?

$H_0$3: There is no association between the phase of TB treatment (initiation and continuation) and mortality among TB/HIV patients on ART.

H_a3: There is an association between the phase of TB treatment (initiation and continuation) and mortality among TB/HIV patients on ART.

This question violated the third assumption, which states that each independent variable should have more than 15 cases (Laerd, 2017). Three variables had zero alive cases for the initial continuation and zero dead cases for completion. The results shown in Table 12 are descriptive statistics of TB/HIV patients n the different phases of TB treatment.

Table 12

The Phase of TB Treatment With Less Than 15 Cases in the Binary Outcome

	Code	Frequency	Percent
Initial phase	0	564	15.8
Continuation	1	105	2.9
Completed treatment	3	2831	79.1
Missing system	-	80	2.2
Total		3500	97.8

RQ4: What is the association between the time of initiation of ART (before the start of TB treatment and after the start of TB treatment) and mortality among TB/HIV patients on ART?

$H_0$4: There is no association between the time of initiation of ART (before the start of TB treatment and after the start of TB treatment) and mortality among TB/HIV patients on ART.

H_a4: There is an association between the time of initiation of ART (before the start of TB treatment and after the start of TB treatment) and mortality among TB/HIV patients on ART.

For research question four, a binomial logistic regression was conducted to test for an association between the time of initiation of ART (before the start of TB treatment and after the start of TB treatment) and mortality among TB/HIV patients on ART. The outcome variable was mortality, while the independent variable was the time of initiation of ART. The time of initiation of ART was categorized as before the start of TB treatment coded as 0 and after the start of TB treatment coded as 1. Mortality was classified as 1 for dead and 0 for alive. The logistics regression model was also significant with $\chi 2$ (1) = 31.011(P = 0.000), p<0.001. The model explained 1.3% (Nagelkerke) of the variance in mortality and correctly classified 79.1% of the mortality cases.

Table 13 shows that the predictor variables in the model, time of initiation of ART, was statistically significantly associated with mortality of TB/HIV patients on ART. The TB/HIV patients on ART who began ART treatment after TB treatment were 1.899 times more likely to die (P<0.0001); (95% CI: 1.496 -2.410) than patients who started ART before TB treatment.

Table 13

Logistics Regression Predicting the Likelihood of Mortality Based on ART Initiation in TB/HIV Patients

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Time of initiation of ART	.641	.122	27.810	1	.000	1.899	1.496	2.410
Constant	–1.868	.113	272.161	1	.000	.154		

Note. The reference variable for the time of initiation on ART is initiation after TB treatment.

RQ5: What is the association between type of TB (pulmonary bacteriologically confirmed, pulmonary clinically diagnosed, and extrapulmonary) and mortality among TB/HIV patients on ART?

$H_0$5: There is no association between the type of TB (pulmonary bacteriologically confirmed, pulmonary clinically diagnosed, and extrapulmonary) and mortality among TB/HIV patients on ART.

H_a5: There is an association between the type of TB (pulmonary bacteriologically confirmed, pulmonary clinically diagnosed, and extrapulmonary) and mortality among TB/HIV patients on ART.

To answer the fifth research question, I conducted a binomial logistic regression to test an association between Type of TB and mortality among TB/HIV patients on ART. The outcome variable was mortality, while the independent variable Type of TB. The variable type of TB was coded into three, pulmonary bacteriologically confirmed (PBC) = 0, pulmonary clinically diagnosed (PCD) =1 and extrapulmonary (EPTB) =2. The logistics regression model was also significant with $\chi 2$ (2) = 41.486, $p<0.001$. The

model explained 1.4% (Nagelkerke) of the variance in mortality and correctly classified 79.1% of the mortality cases.

Table 14 shows that the two predictor variables in the model, PCD, and EP TB, were statistically significant. The TB/HIV patients on ART with PCD were 1.275 times more likely to die (P<0.0001 for each; 95% CI: 1.072 -1.518) than patients with PBC. The TB/HIV patients on ART with EP TB were 2.355.087 times more likely to die (P<0.0001 for each; 95% CI: 1.760 – 3.150) than patients with PBC.

Table 14

Logistics Regression Predicting the Likelihood of Mortality Based on the Type of TB Treatment for TB/HIV Patients on ART

Category	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Pulmonary bacteriologically positive (PBC)			33.778	2	.000			
Pulmonary clinically diagnosed (PCD)	.243	.089	7.516	1	.006	1.275	1.072	1.518
Extrapulmonary (EP)	.856	.149	33.249	1	.000	2.355	1.760	3.150
Constant	–1.532	.069	498.006	1	.000	.216		

Note. The reference for the type of TB variable was PCD.

Summary

This study used cross sectional data from nine out of 14 regional referral hospitals. The nine hospitals were systematically selected. The data were extracted from all TB/HIV patients on ART registered in 2017, 2018, and 2019 from the Unit TB registers and ART cards or ART electronic medical records. The final records collected and cleaned were 3,580 records. The study showed significant results for all objectives

except objective 3. The study showed that TB/HIV patients on ART, with one multimorbidity and two or more multimorbidities, were 1.658 and 1.901 times more likely to die than patients with no multimorbidity. The TB/HIV patients on ART that were separated or divorced and single were 1.591 and 1.381 times, respectively, more likely to die than married patients. Age and sex were not significantly associated with mortality. The TB/HIV patients on ART who began ART treatment after TB treatment were 1.899 times more likely to die than patients who started ART before TB treatment. The TB/HIV patients on ART with PCD and EPTB were 1.275and 2.087 times, respectively, more likely to die than patients with PBC. In chapter 5, I interpreted the results of the findings, highlight the limitations, significance, and made recommendations for future research.

Chapter 5: Discussion, Conclusions, and Recommendations

The purpose of the study was to analyze the association between multimorbidity, health care processes, and mortality among TB/HIV patients on ART in Uganda. The independent variables were multimorbidity, age, sex, marital status, type of TB, phase of TB treatment, and timing of initiation for ART. The dependent variable was mortality. This study was designed to use quantitative research methods with a cross-sectional design, coupled with a retrospective review of medical records from the Unit TB register, ART cards, patient files, and electronic medical records.

The data were cross sectional from nine out of 14 regional referral hospitals. The nine hospitals were systematically selected. The data were from all TB/HIV patients on ART registered in 2017, 2018, and 2019, in the Unit TB registers and ART cards, patient files, or ART electronic medical records. The total of final records collected and cleaned were 3,580. The study showed significant results for all objectives except Objective 3. TB/HIV patients on ART with one multimorbidity, two or more multimorbidities, separated or divorced, and single were associated with mortality. Age and sex were not significantly associated with mortality. TB/HIV patients on ART who began ART treatment after TB treatment were more likely to die than patients who started ART before TB treatment. TB/HIV patients on ART with PCD were more likely to die than patients with PBC. TB/HIV patients on ART with EPTB were more likely to die than patients with PBC. In Chapter 5, I interpreted the results, highlighted the limitations, implications of the study, made future research recommendations, and concluded the study.

Interpretation of Findings

In general, multimorbidity increases premature death risk (AMS, 2018). Studies in high-income and middle-income countries have shown that the higher the number of multimorbidities, the higher the chances of death (Lix et al., 2016; Nunes et al., 2016; Willadsen et al., 2018). There is little literature about multimorbidity and its association with mortality among TB/HIV patients on ART (Mchunu et al., 2016; Musaazi et al., 2019; Stijnberg et al., 2019; Tola et al., 2019). In TB/HIV patients, multimorbidity has been postulated to lead to death. However, findings have not always been definitively backed by inferential statistics (Mchunu et al., 2016; Musaazi et al., 2019; Stijnberg et al., 2019; Tola et al., 2019).

In my study, the results showed that TB/HIV patients on ART with one multimorbidity were 1.658 times more likely to die than patients with no multimorbidity. The TB/HIV patients on ART with two or more multimorbidities were 1.901 times more likely to die than patients with no multimorbidity. The results are aligned to the general literature from high-income countries that show that the higher the number of multimorbidities, the higher the chances of death (Lix et al., 2016; Nunes et al., 2016; Willadsen et al., 2018). However, studies conducted in Africa have concentrated on prevalence and multimorbidity patterns rather than their association with mortality (Oni et al., 2016; Peltzer et al., 2018). The results of this study add new knowledge to the existing body of literature for TB/HIV patients on ART, showing that an increase in multimorbidity is associated with mortality. The top 10 multimorbidity clusters included gastrointestinal disease, nutritional, respiratory, neurological, infections, musculoskeletal,

renal, cardiovascular, hematological, and dermatological diseases. There is a need to reexamine current practices, including integrated TB/HIV patient care models and care for people with advanced HIV/AIDS disease (WHO, 2017). Stakeholders need to improve the screening, diagnostic, and management algorithms to address multimorbidity in TB/HIV patients.

Generally, researchers of marital status have consistently shown that unmarried people have poorer health outcomes than married people do (Hilz & Wagner, 2018; Kaplan & Kronick, 2006). In this study, the mortality of unmarried individuals, except for the widowed, was more likely to happen as compared to married people. The unmarried people included those who were divorced, separated, and single. However, the widowed population's mortality compared to the married population was not significant. Based on previous research, unmarried people tend to have issues with income, physical activity, and social networks, which may predispose them to high mortality (Hilz & Wagner, 2018). Several studies have shown that married people use health services more than people who are not married (Rutaremwa & Kabagenyi, 2016). In Uganda, widowed people could be excluded from this group because they usually have income left by their deceased spouse (Rutaremwa & Kabagenyi, 2016). There is a need to pay attention to the separated and single if mortality among TB/HIV patients is averted.

Age and sex were not associated with mortality among TB/HIV patients on ART in this study. This finding departs from earlier findings on studies that reflect that sex and age are associated with mortality in TB/HIV patients (Englebrecht et al., 2017; Haregu et al., 2012). However, some studies have shown no association between mortality, gender,

and age (Lisboa, 2019; Tabarsi et al., 2012). Increasing age is generally associated with mortality in developed countries, while some studies in Africa indicate that young age is associated with mortality among TB/HIV patients on ART (Englebrecht et al., 2017; Oni et al., 2015). Generally, being female is associated with death in developed countries, whereas being male is associated with death in TB/HIV patients in Africa (Hood et al., 2019; Teklu et al., 2017).

In this study, I also included a variable for the phase of TB treatment (initiation and continuation) in testing for mortality among TB/HIV patients on ART. The majority of patients completed treatment (79.1%). Among TB/HIV patients on ART who did not complete treatment, 15.8% died in the initial phase and 2.9% died in the continuation phase. These findings are similar to results in other studies in which more TB/HIV patients died in the initial phase of TB treatment than in the continuation phase (Hood et al., 2019; Musaazi et al., 2019; Stijnberg et al., 2019). Delay in diagnosis, delay in initiation of TB and ART, and IRIS could contribute to mortality (Stijnberg et al., 2019; Tola et al., 2019). The results reconfirm that the majority of patients die in the initial phase than in the continuation phase. However, it is not clear whether the initial phase or continuation phase is statistically associated with mortality.

Many researchers have found that ART is protective among TB/HIV patients (Musaazi et al., 2019; Nagu et al., 2017; Torrens et al., 2016). In this study, the TB/HIV patients on ART who began ART treatment after TB treatment were 1.899 times more likely to die than patients who started ART before TB treatment. This finding is similar to findings in other studies and implies that the earlier the ART begins, the more protective

it will be to patients (Musaazi et al., 2019; Nagu et al., 2017; Torrens et al., 2016). Delay in the initiation of ART is associated with high mortality, and ART initiation improves clinical outcomes (Ford et al., 2018). However, the reasons for high mortality among TB/HIV patients on ART need to be explored at the clinical intervention level.

TB/HIV patients on ART with PCD or EPTB in this study were more likely to die than patients with PBC. In this study, I found that TB/HIV patients on ART with PCD or EPTB were 1.275 and 2.087 times, respectively, more likely to die than patients with PBC. The results are similar to results from researchers in Uganda and Ethiopia who found that patients with PCD and EPTB were more likely to die than patients with PBCs (Biruk et al., 2016; Lisboa et al., 2019; Musaazi et al., 2019; Tola et al., 2019). The higher mortality among PCD and EPTB than PBC may be due to delay in diagnosing PCD and EPTB, which may take more than a month (Lisboa et al., 2019).

In this study, I used the health outcomes model with four domains: characteristics of the health care system, patient characteristics, health care path, and patients outcomes(Canadian Institute for Health Information, 2008). The health outcomes conceptual framework was used because of its simplicity in studying patient-level outcomes. The independent variables were part of only two domains of the study, patient characteristics (sex, age, marital status, multimorbidity) and health care path (timing of ART and phase of TB treatment) that were direct predictors of patient outcomes (mortality). However, patient characteristics (sex, age, marital status, and multimorbidity) were also indirect predictors of patient outcomes (Sbagiria et al., 2016).

The study results are in line with the health outcomes conceptual framework. The independent variables—patient characteristics (marital status, multimorbidity) and health care path (timing of ART and phase of TB treatment)—were direct predictors of mortality as reflected in the statistically significant results. In this study, age and sex were not statistically significant and therefore not predictors of mortality. Age and sex could have been indirect predictors of mortality; however, this prediction was not proven in this study. The health outcomes model is used in public health to predict and improve patient outcomes. The conceptual framework is also used as a TB/HIV framework to monitor and evaluate TB/HIV activities (WHO, 2015). The framework has also been used in health outcomes research, primarily for the Hepatitis C virus (Sbagiria et al., 2016).

Limitations of the Study

In this study, the health outcomes conceptual framework was used that has four domains. However, only three domains were used to study patient characteristics, health care path, and patient outcomes. The health systems care domain was not studied. In addition, a few factors from the three domains were studied as represented by the independent variables (multimorbidity, age, sex, marital status, type of TB, phase of TB treatment, and timing of initiation for ART) and dependent variable (mortality). Despite this limitation, the study brought out new findings on the association of multimorbidities and mortality. The study has also shown consistent results with other studies (Musaazi et al., 2019; Nagu et al., 2017; Torrens et al., 2016;). The need for future studies to be designed to include more factors that are missing in this study is conspicuous.

This study used routine data from Unit TB registers, ART cards, HIV patient files, and electronic medical records. Secondary routine data usually have missing records. Patients who had incomplete data on the outcome variable were left out, especially for patients registered at the regional referral hospital for TB care but receiving ART at peripheral health facilities. Also, patients with other unfavorable outcomes like the loss to follow-up and non evaluated were left out since the outcome variable was binary with dead or alive. However, all independent variables were captured, including marital status and age, which had missing data. Another limitation could be about diagnostic errors. The diagnostic tests depended on the equipment used to make the diagnostic tests during routine care. The accurate and correct records depended on the clinician. To minimize this error, the health workers abstracted data from primary data tools filled by the clinician during service delivery.

Although these limitations exist, this study's strength was using the large sample size of 3,580 patients and systematic sampling from nine out of 14 patients. The large sample size and systematic sampling improved the internal and external validity of the study. The study design was appropriate for the research questions to highlight the significant findings related to death among TB/HIV on ART. The study findings can be generalized to TB/HIV patients on ART with associated mortality in Uganda and similar settings.

Recommendations

Mortality for TB/HIV patients on ART is an outcome with some known confounders that were not part of the TB and ART tools. These included socioeconomic

characteristics and behavioral factors (Tola et al., 2019). The socioeconomic factors left out include income, social support, and education status. The behavioral factors left out were alcohol consumption and cigarette smoking. These variables would have further supported the explanation of mortality on TB/HIV patients on ART. In the future, prospective studies collecting primary data should include all the relevant variables on all socioeconomic factors (income, social support, education status) and behavioral factors (alcohol consumption, cigarette smoking).

I did not include some treatment and disease related factors like adherence of patients on ART and TB treatment, CD4 cell testing, and viral load. There is a need for future research to check for an association between patient adherence to ART and TB treatment, CD4 cell testing, viral load, and mortality in TB/HIV patients on ART. The results would inform HIV and TB programs on interventions to protect TB/HIV patients from death and interventions to protect HIV patients on ART from developing advanced HIV disease. A prospective rather than a retrospective research study could be conducted with a clear intention to follow up the well-documented multimorbidities among TB/HIV patients on ART.

In this study, I did not cover individual multimorbidities. Multimorbidity was studied as disease clusters. There is a need to understand further the individual diseases and how they are associated with mortality in TB/HIV patients on ART. Such a study would provide vital information on how patient-family-centered care can be delivered to improve mortality among TB/HIV patients on ART in Uganda.

Implications

Health stakeholders can use the significant findings that arise from the study to influence positive social change with an impact on the lives of patients, families, and communities. This study showed significant findings that several multifaceted factors are associated with mortality among TB/HIV patients on ART in Uganda. The policymakers, managers in governments, and NGOs should advocate for change in policy, practice, and research at different levels, including networks of TB patients coinfected with TB. This study has developed new knowledge; there is an association between multimorbidity (disease clusters) and mortality among TB/HIV patients on ART. All patients with multimorbidity need appropriate care to avoid mortality. In previous studies, patient–family-centered care was beneficial to patients with multimorbidity (Boyd & Fortin, 2010). The dually infected TB/HIV patients on ART that have multimorbidity will need patient-family-centered care. The health managers need to advocate for patient – family-centered care at all healthcare levels, including the patient, family, and healthcare teams (Boyd& Fortin, 2010).

Furthermore, the study showed that mortality in TB/HIV patients on ART was associated with those who were separated or divorced and single (Robards et al., 2012). The health workers managing patients have to think about the families and making sure those who are either separated, divorced, and single are given appropriate nonclinical care at the TB/HIV clinics. Also, the TB/HIV patients on ART who began ART treatment after TB treatment were 1.899 times more likely to die than patients who started ART before TB treatment. Care providers should prioritize and closely monitor all patients

who start ART late for care at the health facilities to make sure they do not die. The TB/HIV patients on ART with PCD and EPTB were 1.275 and 2.087 times, respectively, more likely to die than patients with PBC. Extra care has to be taken by health care workers to screen for PCD and EPTB in TB/HIV patients on ART in patient-family-centered care. Also, community TB/HIV services have to target patients with multimorbidity, separated/ divorced or single, with PCD or EPTB, and those who start ART after TB treatment.

The TB and HIV programs should implement patient-family-centered care at the health facility and community levels in line with universal health coverage principles described by WHO under the sustainable development goals. The TB and HIV programs should screen and treat all TB/HIV patients with advanced HIV disease who have other diseases, including GIT, nutritional, respiratory, neurological, and infections, musculoskeletal, renal, cardiovascular. The two programs should endeavor to identify patients who are single, separated, or divorced, with EPTB or PCD, who started ART after TB treatment and ensure they get appropriate care. Finally, sexual contacts of people with HIV may have HIV and TB. The HIV programs should screen for HIV among all sexual contacts of TB/HV patients, which helps identify new HIV patients early and start treatment before they get TB. Screening household contacts of all TB/HIV patients for TB is already a practice that should continue.

Conclusions

This study contributed to new knowledge, confirmed the findings from previous studies, and presented findings that differed from the findings of other studies about

multimorbidity, health care processes, and mortality among TB/HIV patients on ART. The new knowledge: TB/HIV patients on ART with one or more multimorbidities were more likely to die than patients with no multimorbidity. Based on the existing literature, no TB/HIV study brought out this critical finding. The policymakers and practitioners should use this new knowledge to guide the management of multimorbidities among TB/HIV patients on ART to prevent premature deaths.

The study has also confirmed the findings from previous studies. The TB/HIV patients on ART that were separated/divorced or single were 1.591 and 1.381 times, respectively, more likely to die than married patients. This finding is similar to knowledge generated from other general studies and studies on TB and TB/HIV. Looking out for unmarried people to minimize mortality among TB/HIV patients on ART is a priority. More to this finding, TB/HIV patients on ART who began ART treatment after TB treatment were 1.899 times more likely to die than patients who started ART before TB. ART has always been protective in HIV and TB/HIV patients, especially when it started early (Musaazi et al., 2019). The practitioners should endeavor to start ART as soon as possible in TB/HIV patients (WHO, 2017).

The study has also presented findings that differed from the findings of other studies. Age and sex were not significantly associated with mortality, unlike in other studies, where mortality was associated with age and sex. All these findings highlight the need for implementation of patient-family-centered care at the health facility and community levels. More studies are needed to understand further the individual

multimorbidities associated with mortality and how patient-family-centered care can be delivered to improve mortality among TB/HIV patients on ART in Uganda.

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Appendix

TB/HIV Data Extraction Form

TB/HIV Data Extraction form Years: January 2017 - December 2019

TB/Unit Register														ART Card		
(1) Serial number	(2) Name of hospital	(3) Year	(4) Age	(5) Sex: Male, Female , others	(6) Marital status: Married, Widowed, separated, Others	(7) DR TB / susceptible TB	(8) Type of TB: PBC, PCD,EP	(9) Date TB treatment started	(10) ART Start Date	(11) TB Treament outcomes (Cured, Completed, Dead, failure, loss to follow up, not evaluated) & Date	(12) Date of Treatment outcome	(13) If Dead Phase of TB treatment when patient died , initial phase/Continuation phase	(14) ART Number	(15) Other Meds	(16) Date of Other Meds	(17) Disease: Cancers, Diabetes,Hypertension, malnutrition, others specify (Ulcers, HT)

TB/HIV Code Book

Code Book: Multimorbidity, Healthcare Processes, and Mortality Among TB/HIV Patients Treated With Antiretroviral Therapy in Uganda		
No	**Variable**	**Variable Content**
		Name of Hospital
		RRH= 1,2 3,4,5,6,7,8,9
		Years
		January - December 2017 =0
		January - December 2018=1
		January - December 2019 =2
	Age (IV)	**Age**
		0- 95 years
	Gender (IV)	**Gender**
		Male = 0
		Female= 1
	Marital status (IV)	**Marital status**
		Married =0
		Widowed=1
		Divorced=2
		Separated=3
		Child= 4
		TB disease
		Susceptible TB =0
		MDR TB= 1
	TB Type (IV)	**TB Type**
		Pulmonary Bateriologically confirmed (PBC) = 0
		Pulmonary Clinically Diagnosed (PCD)= 1
		Extrapulmonary (EP) = 2
	ART Timimg (IV)	**ART Timimg**
		Before TB Treatment =1
		After TB treatment= 2
	mortality (D)	**TB treatment outcome**
		Dead =1
		Alive =0
	Phase of TB treatment (IV)	**Phase of TB treatment Initial phase/Continuation phase**
		Initial = 0
		Continuation =1
		Completed trement = 2
		Other meds
	Diabates mellitus=1	Tolbutamide, gliclazide, glibenclamide, metformin, Acarbose, insulin,chlorpromide =1
	Hypertension =2	Furosemide, methyl dopa, Nifedine, Bendrofluazide, atenolol, propranolol, lesinopril, enalapril, amlodipine hydralazine = 2
	Malnutrition = 3	RUTF = 3
	pneumonia = 4	Asthma= Salbutamol, hydrocotisone, amininophylline. Pneumonia= Benzyl penicillin, amoxycillin, chloraphenical , erythromycin, cepharosporins = 4
	Cancers = 5	Methotrexate, actinomycin D, Cyclophosphamide, vincristine, vin blastine, chlor ambucil, busulfan = 5
	Duodenal/petic Ulcers = 6	Magnesium trisilicate, cimetidine, Ranitidine =6
	Others: Specify..... = 7, 8,9 ....n	Others = 7
		None = 0
		Disease category
	Disease cluster (IV)	MMCluster 1; No =0, Cancer =1, Cardiovascular =2,Endocrine =3, ENT =4, GIT =5, Hematological =6, Immulogical =7, Infectious =8, Liver =9, Lymphatic =10, Musculoskeletal =11, Neurological =12, Nutritition =13 , Reproductive =14, Respiratory =15, Psychological = 16 Renal =17 Dermatological =18
		Disease cluster
		No Multimorbidity =0
		One multimorbidity = 1
		Two or more multimorbidity = 2